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Expert review of Merck's HPV vaccine studies

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Contents

Qualifications

I received a Master of Science in biology and chemistry in 1974 and my Medical Degree in 1984, both from the University of Copenhagen. My Doctoral Thesis was titled "Bias in double-blind trials," which included six papers, two of which were published in the British Medical Journal (BMJ) and The Lancet.

I worked with clinical trials and regulatory affairs in the pharmaceutical industry from 1975 to 1983 and as a clinician at hospitals in Copenhagen between 1984 and 1995.

I co-founded the Cochrane Collaboration and established the Nordic Cochrane Centre in 1993. The Cochrane Collaboration is an international not-for-profit organization that aims to help people make well-informed decisions about health care by preparing, maintaining and promoting the accessibility of systematic reviews of the effects of healthcare interventions. Cochrane reviews of randomised trials have been widely regarded as some of the most rigorous reviews that exist.

Due to my expertise in randomised trials and research methodology more generally, I became a professor of Clinical Research Design and Analysis in 2010 at the University of Copenhagen. I am officially retired but currently work as a researcher, lecturer, author, and independent consultant.

I have published over 100 papers in "the big five" (British Medical Journal/BMJ, Lancet, Journal of the American Medical Association/JAMA, Annals of Internal Medicine and New England Journal of Medicine/NEJM) and my scientific works have been cited over 190,000 times. Overall, I have authored over 350 peer reviewed papers, over 850 other scientific publications, and I am also the author of several books and book chapters. I have been a peer reviewer for dozens of medical journals, including for the BMJ, JAMA, NEJM, Clinical Trials, Clinical Trials and Meta-analysis, European Journal of Neurology, International Journal of Cancer, Journal of Clinical Epidemiology, Journal of Medical Ethics, and Science.

I have written or co-written several papers published in peer-reviewed journals about Merck's HPV vaccines.[1]

I have written many papers, taught numerous courses, and given numerous lectures on randomised clinical trial methodology, evidence-based medicine, trial protocols, blinding of test subjects, statistics, relative risks and odds ratios, systematic reviews and metanalyses, reporting harms in clinical trials, data access, bias and conflicts of interest in scientific research, and ethics in science and medicine.

I have been an examiner of instances of scientific misconduct for the Oxford Health Alliance and have been a member of ad hoc committees for the Danish Office of Scientific Integrity.

I have co-authored guidelines for good reporting that many prestigious medical journals refer to in their instructions to authors: CONSORT for randomised trials, STROBE for observational studies, PRISMA for systematic reviews and meta-analyses, and SPIRIT for trial protocols. I was an editor in the Cochrane Methodology Review Group from 1997 to 2014 and am the author of 19 Cochrane reviews.

My current CV accompanies this report, which includes a listing of legal cases in which I have either testified in court or at a deposition.

[1] Jørgensen L, Gøtzsche PC, Jefferson T. Benefits and harms of the human papillomavirus (HPV) vaccines: systematic review with meta-analyses of trial data from clinical study reports. Syst Rev 2020;9:43; Jørgensen L, Doshi P, Gøtzsche PC, Jefferson T Challenges of independent assessment of potential harms of HPV vaccines. BMJ 2018;362;k3694; Jørgensen L, Gøtzsche PC, Jefferson T. Index of the human papillomavirus (HPV) vaccine industry clinical study programmes and non-industry funded studies: a necessary basis to address reporting bias in a systematic review. Syst Rev 2018;7:8; Gøtzsche PC, Jørgensen KJ. EMA's mishandling of an investigation into suspected serious neurological harms of HPV vaccines. BMJ Evid Based Med 2022;27:7-10; Gøtzsche PC. What do we know about the safety of the HPV vaccines? Tidsskr Nor Laegeforen 2017;137:11-2; Jørgensen L, Gøtzsche PC, Jefferson T. The Cochrane HPV vaccine review was incomplete and ignored important evidence of bias. BMJ Evid Based Med 2018;23:165-8.; Jørgensen L, Gøtzsche PC, Jefferson T. The Cochrane HPV vaccine review was incomplete and ignored important evidence of bias: Response to the Cochrane editors. BMJ Evidence-Based Medicine 2018; 17 Sept.

I charge $400 per hour independent of what the task is, and $1500 per day when traveling to and from a venue (not while at the venue, in which case the hourly rate applies).

Methodology

I have systematically examined in detail the preclinical (animal) and clinical (human) study reports for the Merck-sponsored studies of Gardasil (monovalent, quadrivalent, and Gardasil 9), including appendices to these reports, and other related reports on Merck's HPV vaccines, all of which were produced to plaintiffs by Merck. I also compared the Gardasil study reports with the study results published in the medical literature, clinical trial registries in the US and UK, and Gardasil labels. The methodology I employed in reviewing Merck's clinical trials is the same I have used throughout my career and in numerous Cochrane drug reviews (see the Cochrane Handbook for Systematic Reviews of Interventions).[2]

I have also performed a number of meta-analyses of the clinical trials. The biggest ones include 14 trials, and 48,962 patients treated with either the quadrivalent vaccine (Gardasil), the 9 valent vaccine (Gardasil 9), the aluminium adjuvant or placebo (only 889 patients, or 2% of the total). Apart from a few dose-response studies with very few patients, I did not include patients treated with monovalent vaccine, as these vaccines have not been marketed. I used the Comprehensive Meta Analysis program version 2.2.064 (fixed effect analyses), which is explained in more detail in a separate document in Appendix A ("Meta-analyses and attempts at meta-analyses"). Since there was considerable heterogeneity in some of the analyses, I checked the robustness of the results by also using a random effects model. This made no difference to my conclusions. I preferred fixed effect analyses because they weigh large trials with many events more than random effects analyses. According to the Cochrane Handbook, this is an accepted method when the studies are similar, which is the case for Merck's HPV vaccine studies.

I entered the data in Excel and double-checked that the numbers were correct before I transferred them to the statistical software to do meta-analyses. As I explain below, double counting of adverse events could not always be avoided because of the way Merck had entered adverse events in its tables, but this problem did not affect the conclusions I made based on my meta-analyses.

In the tables and meta-analysis graphs contained in Appendix A, P013, P015 and P019 are the three pivotal Future 1, 2 and 3 trials, respectively, of quadrivalent vaccine against the vaccine adjuvant. Other pivotal trials are the two "placebo-controlled" trials, P018 of Gardasil (quadrivalent vaccine v aluminium adjuvant) and P006 of Gardasil 9 (nine-valent vaccine), and P001, which is a large trial comparing Gardasil 9 with Gardasil. Pivotal trials are those trials that are supposed to provide sufficient data to determine whether a new drug or vaccine is safe and effective enough to be approved by regulators for marketing.

I also examined the studies to find out what they showed about symptoms of POTS or Complex Regional Pain Syndrome (CRPS). As many patients (2.9%) experienced serious adverse events in study P001 that compared Gardasil 9 with Gardasil, I copied the MedDRA terms (MedDRA means the Medical Dictionary for Regulatory Activities) from p827ff in the main trial report (V503 P001 CSR) into a spreadsheet and asked an investigator with expertise in POTS to assess which ones she considered might be associated with POTS and CRPS, in a blinded fashion, i.e. without knowing which of the two groups they came from.

There were 165 MedDRA subterms, grouped under MedDRA headings (e.g. nervous system disorders). The investigator considered that eight and four of these subterms could be associated with POTS or CRPS, respectively (for POTS: vertigo positional, non-cardiac chest pain, headache, migraine, presyncope, syncope, tension headache and dyspnoea; for CRPS: fibromyalgia, myalgia, hypoaesthesia and sensory disturbance). I searched in the study reports using these terms and also "orthostatic," "tilt table test" and "tilt test" (to find

[2] Higgins JPT, Thomas J, Chandler J, et al. (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.4. Cochrane Collaboration; 2023.

occurrences of postural orthostatic tachycardia syndrome), “complex regional pain syndrome,” “chronic regional pain syndrome,” POTS and CRPS. Lastly, I went through all the study reports again to ensure I had not overlooked anything.

In addition to Appendix A, which contains my meta-analyses and attempts at meta-analyses, I also attach additional appendices, which further explain my methodology, opinions, and references. Appendix B consists of my review notes of Merck’s animal studies; Appendix C are my review notes of the monovalent and quadrivalent Gardasil vaccine trials; and Appendix D are my review notes for Gardasil 9 clinical trials. Appendix E contains my narrative review of Merck’s clinical trials.

List of Materials Reviewed / Reliance Material

Animal Studies (monovalent and quadrivalent):

TT 97-2545 & TT 97-2546, acute toxicity in 10 mice and 10 rats
TT 97-2633 & TT 97-2634, acute toxicity in 10 mice and 10 rats
TT 99-2637 & TT 99-2638, acute toxicity in 10 mice and 10 rats
TT 99-2667 & TT 99-2668, acute toxicity in 10 mice and 10 rats
TT 01-0260, ten-week intramuscular toxicity in 60 vs 60 mice
TT 03-7030, immunogenicity and toxicity in 250 female rats with post weaning evaluation
TT 07-7110, immunogenicity and fertility in 100 male rats
TT 02-7066, immunogenicity in 25 non-pregnant rats
TT 03-7036, immunogenicity in 5 rats
TT 99-2639, acute intramuscular irritation in 16 rabbits
TT 97-2548, fifteen-day intramuscular irritation in 16 rabbits
TT 97-2632, fifteen-day intramuscular irritation in 16 rabbits
TT 99-2669, fourteen-day intramuscular irritation in 16 rabbits
PD001, immunogenicity in 3 vs 3 rhesus macaques
PD003, immunogenicity in 4 green monkeys
PD004, immunogenicity in 34 green monkeys, 6-8 animals per group
Animal studies of 9-valent vaccine
V503 TT 07-1006_rat study unsigned, three-month toxicity in 200 rats
V503 TT 12-6017_rat study, three-month toxicity in 60 rats
V503 TT 07-7400, pregnancy, 90 rats
V503 TT 09-7320_rat study, offspring, 50 female rats
V503 PD001, immunogenicity in 6 rhesus macaques
Animal or in vitro studies, adjuvant versus control
PD002_adjuvant studies, immunogenicity in 6 chimpanzees
TT 11-8051, mutagenesis in bacteria
T 11-8635 & TT 11-8639, chromosomal aberrations in hamster cells
TT 11-8636 & TT 11-8637, micronucleus induction in rat bone marrow

"Placebo-controlled" study of quadrivalent HPV vaccine (Gardasil):

V501 P018 V1 CSR
V501 P018 LTFU CSR_ w protocols P018-05, -06, -10 and -11

Dose-response studies of monovalent vaccine:

V501 P001 CSR, monovalent HPV 11 L1 VLP vaccine
V501 P002 CSR, monovalent HPV 16 L1 VLP vaccine
V501 P004 CSR, monovalent HPV 16 L1 VLP vaccine

Other comparisons of monovalent vaccine with adjuvant:

V501 P005 CSR, monovalent HPV 16 L1 VLP vaccine
V501 P026 Clinical Report
V501 P006 CSR, monovalent HPV 18 L1 VLP vaccine

Dose-response studies of quadrivalent HPV vaccine (Gardasil):

V501 P007 CSR protocol amendments
V501 P016 V1 CSR
V501 P016 V2 CSR

Comparisons of quadrivalent vaccine (Gardasil) with adjuvant and other studies:

Future 1, study P013
- V501 P013 CSR with P013-10
- V501 P013 V1 CSR
- V501 P011 CSR
- V501 P012

Future 2, study P015
- V501 P015 CSR protocol P005-10
- V501 P015 V1 CSR
- V501 P015 V2 CSR
- V501 P015-20 CSR
- V501 P015-21_Report #4

Future 3, study P019
- V501 P019 CSR
- V501 P019 V1 CSR
- V501 P019 x02 (aka P019-21) CSR

Other studies
- V501 P020 CSR protocols P020-04
- V501 P020 V1_protocol P020-04
- V501 P020-21 LTFU Analysis #1
- V501 P020-21 LTFU Analysis #2
- V501 P023 CSR
- V501 P024 CSR
- V501 P025 CSR
- V501 P028 CSR
- V501 P029 CSR India
- V501 P030_Statistical Analysis China
- V501 P031
- V501 P031-02_Final Report
- V501 P031-02_Revised Final Report
- V501 P033-00_Final Study Report

V501 P035 CSR China
V501 P041 CSR synopsis only China
V501 P046 CSR Africa
V501 P059_Korea
V501 P070 qHPV
V501 P070-01 3rd report
V501 P070-01 4th report
V501 P070-01 5th report
V501 P110 CSR Japan, qHPV
V501 P122 V01 CSR Japan, qHPV
V501 P125 CSR qHPV
V501 P200 V01 Japan qHPV
V501_Extension Safety Summaries_P005-10, 007-20, 013-10, 015-10, and 016-10, qHPV

V501 Protocol GDS03E, qHPV

Gardasil 9 studies:

V503 P002
V503 P003
V503 P005
V503 P007
V503 P009
V503 P010
V503 P020

Other material:

Merck lists of Gardasil studies
Marchev Declaration
eCTD for Gardasil

Selection of electronic Case Report Forms (CRFs):

MRKGAR_E00002063 AN 40007	V501 P015 Site 0012
MRKGAR_E00000526 AN 42366	V501 P015 Site 0014
MRKGAR_E00002986 AN 42548	V501 P015 Site 0089
MRKGAR_E00006785 AN 83917	V501 P019 Site 0040
MRKGAR_E00027246 AN 11017	V503 P001 Site 0004
MRKGAR_E00027418 AN 17568	V503 P001 Site 0006
MRKGAR_E00020073 AN 68191	V503 P001 Site 0027
MRKGAR_E00020109 AN 68443	V503 P001 Site 0027
MRKGAR_E00024267 AN 11237	V503 P001 Site 0028
MRKGAR_E00024292 AN 18065	V503 P001 Site 0028
MRKGAR_E00015345 AN 18091	V503 P001 Site 0040
MRKGAR_E00020977 AN 21343	V503 P001 Site 0053
MRKGAR_E00021728 AN 73675	V503 P001 Site 0053
MRKGAR_E00013426 AN 74925	V503 P001 Site 0057
MRKGAR_E00013453 AN 17698	V503 P001 Site 0058
MRKGAR_E00024666 AN 72941	V503 P001 Site 0088
MRKGAR_E00022088 AN 67647	V503 P001 Site 0090
MRKGAR_E00022762	
MRKGAR_E00023761	
MRKGAR_E00022761	
MRKGAR_E00023801 AN 73689	V503 P001 Site 0091

MRKGAR_E00016345	AN 69263	V503 P001 Site 0097
MRKGAR_E00017226	AN 68223	V503 P001 Site 0102
MRKGAR_E00014491		
MRKGAR_E00014522	AN 69903	V503 P001 Site 0105
MRKGAR_E00023353	AN 70545	V503 P001 Site 0109
MRKGAR_E00023790	AN 73643	V503 P001 Site 0109
MRKGAR_E00033905	AN 37974	V503 P006 Site 0012
MRKGAR_E00033608	AN 37083	V503 P006 Site 0021
MRKGAR_E00013259.	AN #?	V503 P006
MRKGAR_E00019617	AN 19756	V503 P001 Site 0027
MRKGAR_E00000938		
MRKGAR_E00000153		

CRPS and POTS submitted to EMA:

MRKGAR04837135
MRKGAR04837137
MRKGAR04837138
MRKGAR04837260
MRKGAR04837432
MRKGAR04837632
MRKGAR04837820

Other Merck Documents:

MRKGAR07594764
MRKGAR03270584
MRKGAR03490537
MRKGAR02719446
MRKGAR02719449
MRKGAR01211162
MRKGAR00847940
MRKGAR02788011
MRKGAR02788012
MRKGAR03555494
MRKGAR03438445
MRKGAR03437178
MRKGAR03437180
MRKGAR03566033
MRKGAR03459830
MRKGAR02853188
MRKGAR02853226
MRKGAR01038009
MRKGAR01052355
MRKGAR01050857
MRKROBI_0000001.XLSX
MRKROBI_0000002.XLSX
MRKROBI_00000023.XLSX
MRKGAR05916415
MRKGAR05916417
MRKGAR05916411

2009 Gardasil label
2011 Gardasil label

Robi verified Supplemental Form Interrogatory Responses
Robi Proposed MARRS search, Attachment 5/16/19 email from counsel for Merck

Deposition Transcripts:

Mary Ann Goss
Fabio Lievano
Alain Luxembourg 30(b)(6)
Alain Luxembourg Vol I
Alain Luxembourg Vol II

See also citations identified throughout report, and appendices.

Summary of opinions

I found numerous flaws in Merck's clinical trials of its HPV vaccines - in its study reports, in the published clinical trial reports, and in its package inserts for Gardasil. The issues I found, which are explained more fully below and in the attached appendices, are so pervasive that Merck's clinical trials cannot be used to fully assess Gardasil's risks because of the design and conduct of the studies, and because Merck seriously underreported the potential harms of its vaccines and split the data in so many ways that it would be difficult if not impossible for any scientist, including regulators, to assemble them in a way that would allow a full evaluation of the risks.

The primary flaws include failure to use a true placebo in comparison to Gardasil in the clinical trials with the exception of one small study, which was flawed in its own right (see Appendix D, pp 1-15; Appendix E, pp 42-56), and another small study using a highly immunogenic aluminium adjuvant, which Merck misleadingly called a placebo, thus obscuring the vaccine's harms; counting adverse events only if deemed by a "study coordinator" as vaccine-related; counting adverse events only if they occurred within 14 days, thus the exclusion of (by as much as 90%) adverse events that take longer to manifest; calling adverse events that occurred after 14 days "new medical conditions," rather than adverse events; and failure to delineate whether adverse events were mild, moderate, or severe contrary to the study protocols.

It is indefensible that Merck avoided comparing its vaccine with placebo. The World Health Organization has stated that using adjuvant or another vaccine as comparator instead of placebo makes it difficult to assess the harms of a vaccine and that placebo can be used in trials of vaccines against diseases for which there are no existing vaccines.[3]

Despite all the flaws, in my review of the HPV vaccine trials, I found clear signals of long-lasting, serious, systemic harms, including harms related to dysautonomia[4] (see also below). Such nervous system harms can be difficult to identify. Symptoms of dysautonomia are diffuse and widespread because the autonomic nervous system innervates, monitors and controls most of the tissues and organs in the body.[5] Dr. Louise Brinth, who is an expert on postural orthostatic tachycardia syndrome (POTS), has argued that POTS should probably be considered a symptom secondary to another, yet unidentified, condition rather than as a disease entity of its own.[6]

It is remarkable that drug regulators accepted Merck's contradictory, biased and misleading reports based on trials that were already flawed by design (using adjuvant as "placebo" and using many manoeuvres that avoided

[3] Expert consultation on the use of placebos in vaccine trials. WHO 2013. https://apps.who.int/iris/bitstream/handle/10665/94056/9789241506250_eng.pdf?sequence=1.
[4] Jørgensen L, Gøtzsche PC, Jefferson T. Benefits and harms of the human papillomavirus (HPV) vaccines: systematic review with meta-analyses of trial data from clinical study reports. Syst Rev 2020;9:43.
[5] Science Direct, Autonomic Nervous System, Encyclopaedia of Cardiovascular Research and Medicine, 2018.
[6] Brinth L, Theibel AC, Pors K, et al. Suspected side effects to the quadrivalent human papilloma vaccine. Dan Med J 2015;62:A5064.

reporting possible harms of the vaccine). It is well known that regulatory agencies are understaffed, which means it is unlikely they would be able to undertake a thorough review of Merck's data as presented. It confirms observations made by many researchers that drug regulation is insufficient.[7]

Drug regulators rely on drug companies to provide truthful information even though there are many examples of why they should not be so trusting.[8] When Denmark had raised concerns in 2015 about the harms of the HPV vaccines, EMA asked the manufacturers to evaluate whether their vaccines are safe, review cases of CRPS and POTS in their trials, go through their postmarketing surveillance data, use these data to produce "observed versus expected" analyses of adverse events, and review and assess the published scientific literature.[9]

Weaknesses in the scientific strategy employed by Merck and GlaxoSmithKline were obvious. EMA's official report did not mention that the search strategies the manufacturers used to search their databases were inadequate and must have overlooked many cases. The companies did not search for *headache* even though all of Brinth's patients had headaches, and *dizziness* needed to occur together with *orthostatic intolerance* or *orthostatic heart rate response increased* in order to count. EMA nonetheless uncritically reproduced the incidence rates of CRPS and POTS constructed by the manufacturers.[10]

Animal and *in vitro* studies

These studies cannot be used to reliably assess the toxicity of the vaccine or its adjuvant, as biased designs and omission of essential data in the reports were common.

When the studies showed that both the vaccine and its adjuvant caused harm, including many changes at the injection site and beyond at autopsy, Merck concluded that, "None of these changes was treatment related" even though they could not have occurred without the injections (Appendix B, p. 10, Study TT 01-0260).

Merck admitted that its adjuvant causes harm but argued that, since the harms were similar to those caused by a high-dose vaccine, this meant that they had "minimal toxicological significance." See e.g., Appendix B, p. 19, Study V503 TT 07-1006. This conclusion is unsupported and is like saying that cigars are safe because they cause similar harms as cigarettes.

Merck's statement that, "in general, there were no differences" between the adjuvant control and the saline control groups, was inaccurate (Appendix B, p. 19 Study V503 TT 07-1006). In many cases, Merck simply ignored the findings in the saline control groups. In other cases, Merck attempted to dismiss what they found. About an increase in spleen weight, which is expected for a vaccine, Merck concluded that, "Owing to the low magnitude of the change and in the absence of any histomorphologic correlate, these were not considered test article-related" and that, "the difference in mean adrenal weights relative to controls was considered within the expected biological variation and therefore not related to administration of the test article" (Appendix B, p. 26 Study V503 TT 12-6017). In an earlier, larger study, Merck had concluded that the increase in spleen weight was caused by the vaccine. It was inappropriate to first do a study that shows an effect, and then do another, smaller study and say there is no effect, without quoting the first study.

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[7] Topol, Failing the Public Health – Rofecoxib, Merck, and the FDA, New England Journal of Medicine (October 31, 2004); Testimony of David J. Graham, MD, MPH, November 18, 2004, accessible at https://www.finance.senate.gov/imo/media/doc/111804dgtest.pdf Kesselheim AS, Avorn J. The role of litigation in defining drug risks. JAMA 2007;297:308-11; see also Riva and Spinosa. Has the HPV vaccine approval ushered in an era of over-prevention? J Scientific Practice and Integrity 2020;2.

[8] Gøtzsche PC. Vaccines: truth, lies, and controversy. New York: Skyhorse; 2021; Gøtzsche PC. Deadly medicines and organised crime: How big pharma has corrupted health care. London: Radcliffe Publishing; 2013.

[9] Briefing note to experts. EMA/666938/2015. 2015; 13 Oct. https://ijme.in/pdf/g-briefing-note-to-the-experts-ema-oct-2015-unredacted.pdf.

[10] Gøtzsche PC, Jørgensen KJ. EMA's mishandling of an investigation into suspected serious neurological harms of HPV vaccines. BMJ Evid Based Med 2022;27:7-10.

In one study, the intramuscular injection "appeared not to have been done in the quadriceps muscles sampled for histopathologic examination," but the autopsy nonetheless showed changes on the wrong side. This suggests that what Merck found were not local but systemic harms (Appendix B, p. 26, Study V503 TT 12-6017).

An *in vitro* study showed that the aluminium adjuvant is not harmless. At a dose of 45 pg/mL, the adjuvant reduced cell growth to 49% of solvent controls and induced significant increases in chromosomal aberrations compared to the solvent controls (Appendix B, p. 34, Study TT 11-8635 & TT 11-8639).

Some of the problematic issues in the animal studies were also issues in the human studies. The objective of one study was to "demonstrate the general tolerability" of the vaccine (Appendix B, p. 31 Study PD002). Merck falsely called the adjuvant placebo, and in a study where one group received the adjuvant and another group received phosphate buffered saline, Merck described these groups as "placebo and PBS control groups," even though the correct description is the opposite, "adjuvant control and PBS placebo groups." The dose of the adjuvant was given with excessive precision, but it was not the same in the compared formulations, or from study to study, which makes it difficult to compare the various studies (Appendix B, p. 14 Study TT 07-7110). By increasing the amount of adjuvant, Merck also made it difficult to evaluate if the dose-response relationship that was reported for harms was solely caused by an increasing number of antigens, or if the adjuvant also contributed to it.

Clinical trials - wide variety of systems for collecting, analysing and reporting adverse events

Merck's methods for collecting, analysing and reporting adverse events were highly problematic. Even after I had examined a total of 43,211 pages describing the three pivotal Future trials, corresponding to about 200 medium-sized books, I still did not know in sufficient detail how Merck collected data on clinical adverse events and reported on them, not even when they were serious or deadly. The various messages were often contradictory or unclear and the ambiguity left the door wide open to biased reporting, as there were many ways in which possible harms could have been hidden, ignored, suppressed, or left out (See Appendix C and D).

Merck used many systems and methods for collecting, analysing and reporting adverse events and did not clarify what the differences were and when to use which system or method, apart from stating that anything untoward that happened outside three arbitrary two-week periods after each vaccination should not be called adverse events but new medical history, unless it was a serious adverse experience (Appendix C and D).

The instructions to the investigators were opaque, e.g. "new medical conditions not present at baseline and not reported as an adverse experience were to be collected throughout the study" (Appendix D, p27). Understandably, the investigators did not always adhere to this scientifically inappropriate rule. Nor did Merck, as the company sometimes lumped the two categories in its tables, e.g. for autoimmune disorders, or simply equated safety with new medical history.

Merck operated with a "Condition of Particular Attention" and with the "Sanofi Pasteur MSD Specification 005261 List of Adverse Event of Special Interest (AESIs)" without explaining what this was and when to use what (Appendix D, p48).

Merck operated with at least eleven different procedures for reporting adverse events: Tables with date of onset in relation to vaccination dates, severity, and a little more information; tables with MedDRA terms (Medical Dictionary for Regulatory Activities); new medical history; "other important medical event;" CIOMS adverse experience reports" which, despite the name, seemed to include only serious adverse events; "NWAES - New Worldwide Adverse Experience System database. The WAES database was the company global safety database that held all Adverse Experience information" (mentioned on p1367 in the final study report for Future 1); the Clinical Trials Systems (CTS) database; "Subjects With Non-serious Adverse Events, to be Reported to www.clinicaltrials.gov;" ICH Subject Data Listings; case report forms; and narratives in the text.

The WAES reports of serious adverse events were much more detailed than other narratives, but most of them were about pregnancy complications, which was puzzling.

Most of the narratives for serious adverse events only appeared in interim reports, which was inappropriate, as the final report may be the only one that is read by drug regulators and researchers.

A Gardasil 9 report for study P010 mentioned that, "Serious Adverse Event Reports in [16.2.7] are derived from data in the safety database. For the complete subject data, see the data tabulations from the clinical database." It is my understanding that this database and other clinical trial databases are no longer accessible because they have been "decommissioned," and thus there is no opportunity for any scientist to examine the raw data, which is deeply concerning (see Marchev Declaration). Importantly, "raw data from clinical trials most closely reflect the study observations. The analyzable data set, by contrast, is the result of many decisions made by clinical trialists … If there are errors, flaws, or biases in the processing of raw data, such problems will not necessarily be identified in the analyzable data set. Examples of the value of raw data include the detection of serious errors or biases as well as fraud uncovered by detailed and intense audits of raw data conducted by central statistical centers when inconsistencies or anomalies have been noted in analyzable data sets (Fisher et al. 1995; Soran et al., 2006; Temple and Pledger, 1980[11]

In another Gardasil 9 report, for study P001, I searched for these concepts and one more, a "Data Definition File page." In the CIOMS reports, the patient identifier was not the AN number as in other narratives, but patient initials, country and birth date (which was redacted). There was no check box on the form for the intensity of the events, although, according to the protocol, all events should be classified as mild, moderate or severe.

Merck operated with many intervals for reporting adverse events: First five days after each vaccination; first two weeks after each vaccination; "vaccination period" (which could be five days, three times two weeks, or up to 7 months, which it was in the Future 3 trial); after day 1; after day 16; after 7 months; or divided on several intervals in long-term follow-up studies. The reporting period was often unclear because the language was unclear and inconsistent. In tables, it could be called "from Day 1 through visit cut-off" (e.g. in the report for the large Gardasil 9 study, (P001), which might be the same as from day 1 to the "study completion date," but as many studies operated with both a randomised phase and a follow-up phase, which could also involve visits, it was often unclear what this meant. "Day 1 to Cut-Off Date" (in study P122) and "After day 1" were also confusing. I first thought that "after day 1" meant the interval up to one month after the third vaccination, as there was usually another table that only included events after month 7. I checked this in the Future 1 study and found out that "after day 1" must include data collected after month 7: For "new medical history," there were 104 pregnancy events after day 1 but only 93 after month 7, even though the latter period was much longer, as it ended after four years.

In the Future 3 study, the data were split even more than in Future 1 and 2. New medical history was now split in two mutually exclusive groups, events recorded before and after month 7. By doing this, Merck made it even more difficult than in Future 1 and 2 to find out which harms its vaccine causes. It is not possible to avoid double counting, as a patient may appear in both sets of tables, even with the same type of event.

The subdivision in arbitrary intervals led to much confusion and even absurdities. In study 122, for example, a death was omitted from the serious adverse events in a summary table because it occurred outside the two-week interval for reporting.

Merck's clinical study reports

[11] The Committee on Strategies for Responsible Sharing of Clinical Trial Data, Board on Health Sciences Policy; Institute of Medicine, Sharing Clinical Trial Data: Maximizing Benefits, Minimizing Risk, 2015.

Merck concluded in its study reports for all its pivotal randomised trials of its two vaccines that they were "generally well tolerated." This conclusion was already formulated in the primary objectives or hypotheses for the studies, and it was unaffected by the data Merck assembled in its studies even when they showed that the vaccines were poorly tolerated. In science, it is inappropriate to write the conclusion before the research has been carried out. An appropriate primary objective or hypothesis cannot be to "determine that" a vaccine "is generally well-tolerated." In science we *investigate if* a vaccine is safe.

Merck's study reports were written in such a way that obfuscated and downplayed the harms of its vaccines.

The three Future studies of Gardasil versus adjuvant are essential.

The study reports contained numerous errors, omissions of data (even on deaths and other serious adverse events), obfuscations, ambiguous language, lack of definition of essential concepts, and contradictions.

The tables in the large Gardasil 9 vs Gardasil trial (P001), including a little interspersed text, took up over 2000 pages, and they were quite disorganized. The tables of vaccine-related systemic adverse events started by showing only those that had occurred after visit 1 and only if recorded during two weeks, which was a subgroup of a subgroup. After tables of systemic adverse events with an incidence of at least 1% during two weeks, there were tables of temperature during five days, tables of systemic adverse events with an incidence of at least 1% during two weeks (this time judged vaccine related), serious adverse events, pregnancy related events, new medical history conditions, autoimmune disorders, patients never randomised, patient characteristics, a lot about the patients' sexual and gynaecological history and contraceptive use, and efficacy results. Then, after 1659 pages of various tables, there were suddenly tables again about adverse events.

The effect of this is to drown and confuse the reader with unnecessary detail, which means important results might easily pass unnoticed. Many of the tables provided very similar information, with slightly different headings, in a confusing order, which would make it easy for a reader to miss important details if one is not extremely careful.

I also found that, after 1448 pages of copies of scientific papers, as printed in medical journals, which were not derived from Merck's study, suddenly additional safety tables popped up, on page 7135 onwards.

Sometimes, table headers were erroneous or misleading, e.g. a table in the report for the placebo-controlled study of Gardasil 9 (P006) described "subjects with adverse events," which was not correct, as the table only included patients with systemic adverse events and not those with injection-site adverse events.

In a sub-study in Future 2, data were presented for only 207 (14%) of the 1514 randomised patients. There was no explanation why and the reporting was obfuscated: "Detailed safety summaries and analyses will appear in the CIN 2/3 Efficacy CSR." To write this in a 5000+ page main study report suggests to the readers that this information is not available in the report but perhaps somewhere else. Where that information is will remain obscure for all but the most tenacious reader (Appendix C, p. 92, Study PO15).

The only trial report that provided case report forms was study P009 that compared Gardasil 9 with Gardasil in 600 girls. Even though only three patients developed serious adverse events, there were 2094 pages with case report forms. When I tried to find a girl with epilepsy, I discovered there were three different identifiers for that patient: AN 51128, baseline number 0603-00017, and case reference number E2011-02911. Although the event was serious for two reasons: the patient was hospitalised and it was "Persistent or significant disability/ incapacity," the investigator had ticked "no" to the question: "Is the AE [adverse event] an event of clinical interest?" There were also two narratives, of which the most comprehensive one did not have the AN identifier, in contrast to the other one, but the case reference number was E2011-02911.

Merck's obfuscation of evidence of harm in study reports

Merck effectively concealed evidence of Gardasil harms by a multitude of methods: not using MedDRA terms in key tables though they were used for other types of events; leaving out a significant amount of data including tables of adverse experiences even though the missing tables appeared in an index; reporting data for only the two weeks after each vaccination; splitting the data in many ways, e.g. in a subgroup of a subgroup of a subgroup, that made it impossible to ensure that the same person was not counted more than once, which is a prerequisite for statistical analyses; avoiding describing what the events were, e.g. under "Ear and labyrinth disorders," even though such disorders included, for example, "vertigo positional," which is a key symptom for POTS; using a cut-off for reporting events of 1%; and confusing adverse events with new medical history.

The Future 1 study

In the study reports for Future 1, there were lists of deaths, discontinuations, serious adverse events, pregnancy adverse events, and new medical conditions, often with MedDRA terms. I did not find a single table of systemic adverse events with MedDRA terms or even one without these terms.

Such tables existed in the two reports for substudies P011 and P012 but they were also wanting. For P011, 17 events were listed under the MedDRA heading "Ear and labyrinth disorders," but as there were no MedDRA subheadings, it was obscure what these 17 patients had experienced even though this could be highly relevant. For example, the study report for the large Gardasil 9 study (P001) mentioned in a table of serious adverse events under this MedDRA heading a patient on Gardasil 9 with "vertigo positional," which is a key symptom for POTS. Also, for "Vascular disorders," there were no MedDRA subheadings; the only information was that there were 14 patients with such disorders.

For P012, in the two main groups (Gardasil and adjuvant), 41 patients had experienced "Ear and labyrinth disorders" and 48 patients had experienced "Eye Disorders," but there was no information about what these events were.

The Future 2 study

There was no table of systemic adverse experiences for all the patients. An announced listing of "All clinical adverse experiences" in the main report did not exist; another report was not helpful either, and in a third report, systemic adverse events were subdivided in many ways, with separate tables for the USA, the UK and "Non-U.S. and Non-U.K. Study Sites," which only showed data for two weeks after each injection, with other tables showing data from day 16 and beyond. It would therefore be impossible to avoid double counting of patients.

In the third report, there was a relevant table with MedDRA terms, but it was a subgroup of a subgroup of a subgroup. It was only about events occurring within the first two weeks after each vaccination, only in the United States (only 889 patients (7%) out of the total of 12,050 with data), and only if the incidence was at least 1% in one or more vaccination groups.

Much later in the third report, there was a table on non-US and non-UK data, still for only the three two-week periods, which showed that only 5 patients (2 on the vaccine and 3 on adjuvant) had any "Ear And Labyrinth Disorders" (1 patient with tinnitus and 4 with vertigo out of 11,002 patients).

As I had serious concerns about the veracity of these data, I compared them with a similar table from the large Gardasil 9 trial (P001), also with events occurring within the three two-week periods. The table showed that 106 of 14,149 patients had experienced "Ear And Labyrinth Disorders," and of these, 7 had tinnitus, 26 had vertigo and 1 had positional vertigo. The difference between the two studies was so large that it cannot have occurred by chance. This is seen most clearly if we compare like with like, those patients in both studies that received Gardasil. There were 2 of 5509 vs 49 of 7078 with "Ear And Labyrinth Disorders," $p = 2 \times 10^{-10}$.

The Future 3 study

As for Future 1 and Future 2, a table of serious clinical adverse experiences had no MedDRA terms. Since I could not find any list with MedDRA terms, I looked up an earlier report. However, as for Future 2, an announced listing of "All adverse experiences" did not exist. The next line in the text was about "New Medical History," as if this were the same as all adverse experiences.

I found a table of all "Systemic Clinical Adverse Experiences," but only for the three two-week periods after each vaccination. Considering how important this table was, it is remarkable that it came after a huge amount of irrelevant information, and not in the final report but in an earlier report. This table was number 381 out of the total of 399 tables and it came on page 6754 out of 7000+ pages.

The table showed that 20 of 1908 patients on Gardasil experienced "Ear And Labyrinth Disorders," of which 1 was tinnitus and 14 were vertigo. The p-value for the difference to the 2 of 5509 patients in the Future 2 study was 2×10^{-10}, exactly the same as for the difference between Future 2 and the large Gardasil 9 study (P001) (see just above).

Flawed study designs and reporting

Although it was a primary objective in Merck's trials to study safety, Merck did not compare Gardasil with placebo but with its adjuvant, apart from a study a drug regulator had requested; it was not Merck's idea.

Merck's justification for using adjuvant instead of placebo is unfounded. The adjuvant was not needed to preserve the blinding; the safety of Merck's adjuvant has never been tested in comparison with an inert substance in humans; Merck's claim that, "The safety profile of Merck's aluminum adjuvant is well characterized" is false because the adjuvant varies from batch to batch; adjuvants are not perfectly safe as they are strongly immunogenic substances, which is the reason for using them to bolster the immune response to a non-live vaccine.[12] Even according to Merck's own definition, an aluminium adjuvant is not a placebo: "A placebo is made to look exactly like a real drug but is made of an inactive substance, such as a starch or sugar."[13]

My research group has investigated whether the safety of Merck's adjuvant, amorphous aluminium hydroxyphosphate sulfate (AlHO9PS-3 or just AAHS), has ever been tested in comparison with an inert substance in humans. We have been unable to find any evidence of this. Merck's adjuvant has a confidential formula; its properties are variable from batch to batch and even within batches. The harms caused by the adjuvant therefore likely vary.[14] [15]

Other adjuvants than Merck's have similarly been implicated in other vaccines. For instance, the influenza vaccine Pandemrix caused narcolepsy in over 1300 people, a life-long, seriously debilitating condition with poor treatment options where people suddenly fall asleep, with an onset from about two months after vaccination and up to at least two years later.[16] [17] Its manufacturer, GlaxoSmithKline, acknowledged the causal link,[18] and the likely mechanism is an autoimmune cross-reaction in people with a particular tissue type

[12] Petersen and Gluud. Was amorphous aluminium hydroxyphosphate sulfate adequately evaluated before authorisation in Europe? BMJ Evidence, December 2021 Vol. 26, Number 6; Doshi et al. Call to Action: RIAT Restoration of Previously Unpublished Methodology in Gardasil Vaccine Trials, 346 Brit. Med. J. 2865 (2019).
[13] Merck: Placebos. https://www.merckmanuals.com/home/drugs/overview-of-drugs/placebos.
[14] Jørgensen L, Gøtzsche PC, Jefferson T. The Cochrane HPV vaccine review was incomplete and ignored important evidence of bias: Response to the Cochrane editors. 2018; 17 September. https://ebm.bmj.com/content/early/2018/07/27/bmjebm-2018-111012.responses#the-cochrane-hpvvaccine-review-was-incomplete-and-ignored-important-evidence-of-bias-response-to-the-cochraneeditors.
[15] Thiriot DS, Ahl PL, Cannon J, et al. Method for preparation of aluminium hydroxyphosphate adjuvant. Patent WO2013078102A1. 2013; 30 May. https://patents.google.com/patent/WO2013078102A1/en.
[16] Institutet för Hälsa och Välfärd. Förhöjd narkolepsirisk i två år efter Pandemrix-vaccinationen. 2014; June.
[17] Nohynek H, Jokinen J, Partinen M, et al. AS03 adjuvanted AH1N1 vaccine associated with an abrupt increase in the incidence of childhood narcolepsy in Finland. PLoS One 2012;7:e33536.
[18] Vogel G. Why a pandemic flu shot caused narcolepsy. Science 2015; July 1.

between the active component of the vaccine and receptors on brain cells controlling the day rhythm. Jens Lundgren, Professor of virology at the University of Copenhagen, suspected it was the adjuvant, thimerosal, also called thiomersal, that caused the narcolepsy, and stated that, "It is unlikely that it was the active part of the vaccine that in itself caused the side effects. There was the same virus in all vaccines, and it is only Pandemrix that has given this type of problems."[19]

Since adjuvants can produce significant harm, the use of adjuvant as "placebo" in Merck's trials was inappropriate. Merck effectively concealed the fact that it was using its adjuvant as comparator and its statement that the vaccine is well tolerated when it has almost exclusively been tested against a harmful vaccine adjuvant was highly inappropriate. On top of this, Merck gave the impression that its adjuvant was safe, and Merck's claim, in its study reports, consent forms, published trial reports and package inserts, that the adjuvant was a placebo, was false.[20]

My research group complained to the European Ombudsman in October 2016 about the European Medicines Agency's (EMA) handling of the issue of suspected serious harms of the HPV vaccines and in the ensuing correspondence, EMA's Executive Director Guido Rasi explained to the Ombudsman that, "all studies submitted for the marketing authorisation application for Gardasil were placebo controlled."[21] EMA's official 2015 report about the safety of the HPV vaccines also gave this impression and mentioned "placebo cohorts" for the Gardasil trials.[22]

As already noted, the WHO has stated that using adjuvant or another vaccine as comparator instead of placebo makes it difficult to assess the harms of a vaccine, and that placebo can be used in trials of vaccines against diseases for which there are no existing vaccines, which was the case here.[23]

The three pivotal Future trials were designed in the same way and suffered from the same flaws. The important safety measures were severe injection-site reactions and *vaccine related* serious adverse experiences. However, *all* adverse events are important, and it is subjective to decide if an adverse experience is vaccine related and most of the key investigators making these decisions had financial conflicts of interest with Merck, thus interjecting potential bias.

Systemic adverse experiences that were not considered serious were reported very selectively. In half of the trials, they were only reported for the three two-week periods after each vaccination, and in the other half, they were also reported selectively because the investigators had been instructed not to report such events as adverse events beyond the two-week periods but to call them new medical history. This was scientifically inappropriate, and the Future 3 study illustrates how misleading this was. Within the three two-week intervals after each vaccination, 2249 patients had systemic adverse experiences with at least a 1% incidence, and during the full four-year period of the study, only five more patients had such experiences.

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[19] Villesen K. "Jeg drømmer at jeg dør." Information 2015 Dec 19.

[20] Doshi et al., Call to Action: RIAT Restoration of Previously Unpublished Methodology in Gardasil Vaccine Trials. BMJ 2019; Jan 11; Petersen SB, Gluud C. Was amorphous aluminium hydroxyphosphate sulfate adequately evaluated before authorisation in Europe? BMJ Evid Based Med 2021;26:285-9.

[21] Gøtzsche PC, Jørgensen KJ, Jefferson T, et al. Our comment on the decision by the European Ombudsman about our complaint over maladministration at the European Medicines Agency related to safety of the HPV vaccines. Deadlymedicines.dk 2017; 2 Nov. http://www.deadlymedicines.dk/wp-content/uploads/2019/02/1.-2017-11-02-Our-assessment-on-the-Ombudsmans-decision.pdf.

[22] European Medicines Agency. Assessment report. Review under Article 20 of Regulation (EC) No 726/2004. Human papilloma virus (HPV) vaccines. 2015; 11 Nov. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/HPV_vaccines_20/Opinion_provided_by_Committee_for_Medicinal_Products_for_Human_Use/WC500197129.pdf

[23] Expert consultation on the use of placebos in vaccine trials. WHO 2013. https://apps.who.int/iris/bitstream/handle/10665/94056/9789241506250_eng.pdf?sequence=1.

The design of the studies no doubt resulted in fewer reports of adverse reactions than those that occurred. For instance, in the Future 2 study, non-serious adverse experiences "could be reported based on investigator discretion. Adverse experience reports received from these investigators were only captured if they occurred during the 14 days following each vaccination."

This provision sends a message to investigators that there is no need to report anything unless the event is serious (e.g. the patient died, experienced a life-threatening adverse event, went to hospital or experienced a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions). Merck also sent a signal to the investigators via its case report forms that it was acceptable to not report the harms of its vaccine, not even the serious ones. On one such form, two serious adverse events could be listed, with just one line for the narrative and the text, "Brief description of SAE [serious adverse event] (if necessary)" (Appendix C, p. 81 & 85, Future 2, study PO15). It is *always* necessary and required to describe serious adverse events.

Another form, for non-serious adverse events, was miniscule but could nonetheless be used for three different events and yet again, the tiny space at the bottom for up to three narratives was only to be used "if necessary" (Appendix C, p. 80, Future 2, study PO15).

The investigators were not encouraged to ask questions, and there was no guide as to how they should ask if they insisted on asking despite Merck's apparent disinterest. Yet another form should only be filled out "If any safety information was received" (Appendix C, p. 82, Future 2, study PO15). This is like saying: "Merck does not want you to report anything but if you are desperate to do so, here is your opportunity."

A US substudy in Future 2 showed how easy it would be to demonstrate that the vaccine causes harms, compared to its adjuvant, if one takes an interest in studying harms. This substudy had a particular focus on non-serious adverse events and was called "Detailed safety cohort." It was the only time I saw Merck take an interest in finding out what the harms of its vaccines were. Even though the US substudy was very small, only 895 patients (7%) of the 12,050 with data in the trial, more patients on Gardasil than on adjuvant experienced injection-site adverse events of moderate or severe intensity ($p = 0.0005$).

The text and tables about blood pressure and pulse were contradictory, and it was impossible to know if the study investigators measured but did not report them. On a case report form for day 1, there were entries for blood pressure and pulse but also the text: "Was exam performed?" It was well known when Merck planned its studies that vaccinations can lead to changes in blood pressure and pulse, and to fainting and near-fainting. It was therefore unacceptable that Merck did not require investigators to measure blood pressure and pulse at each visit and to use a tilt test, if they suspected orthostatic hypotension, which is a decisive test for POTS.

The Data and Safety Monitoring Board (DSMB) meetings told a similar story about a lack of interest in detecting harms. These meetings mostly addressed efficacy, and when harms were discussed, it was not in a systematic fashion, and sometimes they were not even presented for each treatment group separately. Early on, the DSMB was concerned about syncope, also if it occurred in the intervals between the vaccinations and were therefore not the result of the needle prick, but Merck did not change its procedures to make it more likely that the company detected such possible, serious harms of its vaccine, which could be a symptom of POTS, even though Merck made many protocol amendments during the trials.

Most patient narratives of serious adverse events were only available in an earlier report, e.g. 9 of the 12 deaths in the Future 2 study. This piecemeal type of reporting is not transparent and makes it difficult to try to find out what the harms of the vaccines are.

Because study coordinators could veto serious adverse experiences, some SAEs very likely were excluded from the study reports. For instance, for the three Future trials, the clinical study report stated: "This CSR [clinical study report] focuses on summarizing [or summarizes] all serious clinical adverse experiences, including any deaths or any serious adverse experience *determined by the study coordinator* to be related to the study vaccine or a study procedure" (Appendix C, p. 59, Future 1, Study P013; p. 75, Future 2, Study P015; p. 96, Future 3 Study PO19).

As explained in more detail below and in Appendices C and D, Merck's approach to reporting adverse events was also highly flexible in terms of cut-offs for reporting. In study P020 of Gardasil 9 versus Gardasil, Merck compared systemic adverse events only if they occurred in at least 4 people in either group, which meant that events with an incidence below 1.6% did not count. Merck normally used a 1% cut-off, but there were also examples of 2% and 5%.

There were tables of systemic adverse events by system organ class in the three Future trials, but I could not find one for the more recent, large Gardasil 9 study (P001). I searched for "systemic adverse events" and found 24 such tables, but they showed only selected data: from just one vaccination visit, or from just the two weeks after each vaccination, or only for those events with an incidence of at least 1%. The table that came closest included "clinical adverse events" for the whole trial period with no incidence limitation, but it had not separated injection-site events from systemic events.

Merck was very generous with providing statistical testing of benefits but parsimonious when it came to harms. In the large Gardasil 9 trial (P001), I had seen countless confidence intervals, all related to the benefit of the vaccine, with a few exceptions such as the acquisition of new sexual partners and the incidence of chlamydia and gonorrhoea, before I found the first 95% confidence interval related to adverse events on page 757 in the report.

Contradictory numbers of randomised patients, deaths, and other events

In reviewing the Gardasil clinical trials, it was sometimes close to impossible to check if the numbers of patients randomised and analysed were correct, as the explanations were scattered around in huge study reports and were sometimes unclear or contradictory. There were no flow charts of in- and excluded patients, with reasons, even though this has been the scientific standard for reporting randomised trials since 1996 (see the CONSORT guidelines for good reporting of randomised trials).

My calculations for the large Gardasil 9 (P001) trial led to four different numbers of randomised people. Some females from a dose-ranging substudy were included in the main study, but the only place in the whole report that described the number of females randomised de novo for the main study was in the Discussion section, 902 pages into the 8000+ page report.

In an extension study for Future 2, there were discrepancies of up to nine patients between the text and the tables, and Merck violated basic scientific rules about comparing like with like, which led to seriously flawed results in favour of the vaccine.

The reported number of deaths also varied, with no explanations for the discrepancies. In the Future 3 study, there were 8 vs 4 deaths in the US trial register, 7 vs 1 in the study report, and none in the trial publication in the *Lancet*. In the large Gardasil 9 (P001) trial, which compared Gardasil 9 with Gardasil, 5 vs 5 patients died according to Merck's study report and to the published trial report, but in the EU trial register, there were 6 vs 5 deaths, and in the US trial register, which Merck updated in November 2018, I could only find 1 vs 1 deaths (apart from a foetal death).

The reports for Future 3 stated in various places that there were narratives for 14 patients, 30 patients, 31 patients, and 32 patients, but through all the checks I did, I found out that the correct number was 33. Cases were missing in tables, even of deaths, and one patient was stated to have developed symptoms one year after she died (Appendix C, p. 98).

In Future 3, eight patients died, but even though death by definition is a serious adverse event, and even though one cannot continue in a trial after one's death, there were only two discontinuations due to serious adverse events in the same table, which covered the whole trial period ("Days 1 to 9999," p566 in the study report).

The number of patients with adverse events was not always the same even in the same study report, e.g. a table in study P009 stated that only one patient had experienced a serious adverse event even though another, similar table with the same follow-up described three patients. In the report for the Future 2 trial, the events varied by one or two patients in two tables, separated by 3972 pages, even though they had exactly the same headings.

Study P030 was quite misleading, which was easy to see. Not only were some results about the lack of adverse events too good to be true, but they were also contradicted by data elsewhere in the report.

The proportion of patients with adverse events differed widely even for trials with the same design and follow-up period. In the three Future trials, the percentage of patients with adverse events varied from 11% to 92%. This heterogeneity is so extreme (χ^2 = 12,582 with 2 df) that standard statistical software does not compute exact p-values. There were similar extreme discrepancies in the proportions of other events in the Future trials, apart from serious adverse events.

The large Gardasil 9 (P001) trial reported systemic adverse events considered vaccine related 7 times as often as the Future 2 trial, even though they were collected in the same way.

These observations suggest that a significant amount of data on adverse events in the Future 2 trial were never collected, were lost, or were suppressed after they had been reported to Merck.

In the publication of the Gardasil 9 placebo-controlled trial (PO18), 316 patients had mild injection site pain for the whole trial period whereas 368 had such pain already after the first vaccine dose, which is a mathematical impossibility. In the study report, 368 patients had mild pain "post-vaccination 1" in one table while it was 473 patients in another table, an unexplained difference of 105 patients.

In a post marketing surveillance study, non-serious adverse events were reported for only 0.5%, as compared to 92% in the Future 1 trial. This illustrates how unreliable observational studies can be, but Merck nonetheless included an observational study in its package inserts for Gardasil, even without telling its readers which one it was (see below).

New medical history

Even though Merck emphasized the category "new medical history" in its trials, I could not find any definition in any of Merck's protocols about what this was supposed to be. I did not find any descriptions either on blank case report forms, apart from one, which was related to pregnancies. It was only about serious events and there were no instructions about how to use the form.

In contrast, Merck was highly specific when it came to injection-site adverse events, which were explored in great detail even though they are short-lived and far less important than systemic adverse events.

In the large Gardasil 9 trial (P001), investigators were told what new medical history *was not*, instead of what it was: "… new medical conditions that were not considered adverse experiences (i.e., they occurred outside the Day 1 through Day 15 post-vaccination visit period and/or were not considered by the study investigator to be SAEs [serious adverse events]). New medical history was collected from Day 1 through the end of the study" (Appendix D, p28).

These instructions to investigators were confusing and contradictory. Investigators were not allowed to use the new medical history category for events that occurred within two weeks after each vaccination, but investigators were nevertheless told to collect new medical history events from day 1. This was also the case for Future 2 and Future 3.

Furthermore, what should investigators do if they were convinced that an event beyond a two-week interval was a Gardasil harm and wanted to call it an adverse experience? This was explicitly forbidden by Merck unless the event was serious.

By calling adverse events new medical history, Merck not only concealed important adverse events but also their severity, as they were not assessed as to their maximum intensity like the two-week adverse experiences were. In the published reports of the large pivotal trials, there was no mention of what these events were, even though they spanned years, in contrast to the two-week periods.

New medical history was not used in all Merck's trials. I focussed on seven trials and found these data:

	n vaccine	N vaccine	n control	N control	Per cent with events
P018, qHPV vs placebo	520	1179	280	594	45
P006, Gardasil 9 vs placebo	175	613	99	305	30
P013, qHPV vs adjuvant	2328	2713	2311	2724	85
P015, qHPV vs adjuvant	4357	6075	4399	6076	72
P019, qHPV vs adjuvant	756	1908	702	1902	38
P020, qHPV vs adjuvant	498	2020	463	2029	24
P001, Gardasil 9 vs qHPV	5096	7099	5069	7105	72

The percentage of patients with one or more new medical history events differed hugely, from 24% in study P020 to 85% in Future 1. This is deeply concerning because the study protocols were very similar, and for all studies, the events shown in the table are those registered from day 1 until month 7. These large differences cannot have occurred by chance, e.g. for the difference between Future 2 (72%) and Future 3 (38%), $p = 8 \times 10^{-305}$. This means that there are 303 additional zeros after 0.0 before the digit 8 appears, which is the lowest p-value I have ever seen. For comparison, the weight of the earth, when measured in µg, is only 6×10^{33}.

A tabulation of patients with adverse events and with new medical history also shows how extreme the discrepancies were between the three Future studies, even though they had the same design:

	Patients with events		
	Future 1	Future 2	Future 3
Any adverse event	92%	11%	84%
New medical history	85%	72%	38%
Ratio	1.08	0.15	2.21

Something is terribly wrong. The ratio between patients with adverse events and patients with new medical history is 18 times larger for Future 3 than for Future 2.

Risk ratios for adverse events were increased

It is important to look at the totality of the evidence and its consistency. In my meta-analyses of Merck's data, I found that the risk ratio was increased for all types of adverse events:

	Risk ratio	No. of events	p-value
all adverse events	1.045	32010	< 0.001
injection-site adverse events	1.095	28155	< 0.001
systemic adverse events	1.017	20123	0.08
systemic adverse events, vaccine related	1.060	10370	< 0.001
serious adverse events	1.088	761	0.24
deaths	1.061	49	0.85

These results were highly consistent. It is therefore of less importance that some of them were not statistically significant because, whether a signal of harm is statistically significant or not, depends on the number of events.

For systemic adverse events, a non-significant p-value of 0.08 became significant ($p < 0.001$) when only vaccine related events were included, which halved the number of events. This may seem counterintuitive but

the “background noise” of irrelevant events decreased, which caused the risk ratio to increase from 1.017 to 1.060. The number needed to harm was only 167 for vaccine related systemic events, which are the ones Merck emphasized in its study reports.

The risk ratio for serious adverse events was about the same as that for injection-site adverse events, and the risk ratio for deaths was the same as that for vaccine related systemic events. This does not mean, however, that Merck’s vaccines increase total mortality. First, there were very few deaths, only 26 vs 23. Second, the number of deaths is highly uncertain, as the numbers were contradictory. We do not know what the effect of the vaccines are on total mortality and will probably never be able to answer this question because most of the females who received adjuvant in the trials were later vaccinated. In several trials, they were offered the vaccine when the follow-up of typically four years was over.

Only 14 (2%) of the 761 serious adverse events were considered vaccine related by the investigators while they considered 52% of the systemic adverse events vaccine related. Even though abortions were considered serious adverse events, they cannot explain this huge difference. I consider it unlikely that only 2% of the serious adverse events were vaccine related while 52% of the systemic adverse events were vaccine related.

Severity of systemic adverse events

In the major trials, the adverse events were evaluated as to their maximum intensity. As noted above, Merck downplayed the severity of systemic adverse events.

In the large trial that compared Gardasil 9 with Gardasil, Merck concluded that, “The majority of subjects across the vaccination groups experienced systemic adverse experiences, most of which were of mild or moderate intensity.” This is misleading. I calculated that, for moderate or severe events, $p = 0.007$, and the number needed to harm was only 45.

Mild events are not a problem, as they are easily tolerated, according to Merck’s own definition:

Mild: awareness of sign or symptom, but easily tolerated
Moderate: discomfort enough to cause interference with usual activities
Severe: incapacitating with inability to work or do usual activity.

Merck also reported the severity data selectively. There wasn’t a single table about the severity of the events in Merck’s report on a dose-response study of Gardasil even though these data had been collected. In the study reports for Future 1 and 2, only subsets of these data were presented (for 66% and 7% of the patients, respectively). In addition to this - and in contrast to injection-site reactions, which were always considered vaccine related - there was no information in any of Merck’s study reports about which of the systemic adverse events of moderate or severe intensity the investigators considered vaccine related, even though such information was collected.

For my meta-analysis, I could only find data from 8 of the 14 studies I included in other meta-analyses. The risk ratio was significantly increased for severe or moderate systemic adverse events, 1.038 (95% confidence interval 1.007 to 1.070, $p = 0.015$). The risk difference was also increased, but the difference was not statistically significant, 0.007 (-0.003 to 0.017), $p = 0.15$). This is not important. In my meta-analyses, I used risk ratios, which is the preferred statistical method for binary data because the result does not depend on the prevalence of the adverse events. I supplemented with the risk difference only because we use this to calculate the number needed to treat to harm one person (NNT), which is the inverse of the risk difference. The Cochrane Handbook notes that the clinical importance of a risk difference may depend on the underlying risk of events. For example, a risk difference of 0.02 (or 2%) may represent a small, clinically insignificant change from a risk of 58% to 60% or a proportionally much larger and potentially important change from 1% to 3%.

Meta-analyses

As indicated above, I used the Comprehensive Meta Analysis program version 2.2.064. I carried out fixed effect meta-analyses because they weigh large trials with many events more than random effects analyses. However, since there was considerable heterogeneity in some of the analyses, I checked the robustness of the results with a random effects model and showed these as well. This made no difference to my conclusions.

I have explained in detail why Merck's data on adverse events are highly unreliable. Merck underestimated the harms of its HPV vaccines by the way it designed, interpreted, analysed and reported its randomised trials.

Therefore, when I found vaccine harms in my meta-analyses, despite all the flaws in Merck's trials, my results likely underestimated the real harms.

In the tables and graphs in my metanalyses, P013, P015 and P019 are the three pivotal Future 1, 2 and 3 trials, respectively, that compared the quadrivalent vaccine with the vaccine adjuvant. Other pivotal trials are the two "placebo-controlled" trials, P018 of quadrivalent vaccine (Gardasil) and P006 of nine-valent vaccine (Gardasil 9), and P001, which is by far the largest trial that compared Gardasil 9 with Gardasil.

In the tables and graphs, the two placebo-controlled trials come at the top, as they are the most relevant ones. Next come the Gardasil versus adjuvant trials and last the Gardasil 9 versus Gardasil trials.

Dose-response studies

Different vaccine doses were used in three studies of monovalent vaccine and in two studies of quadrivalent vaccine. I merged the data in order to have three groups for all five studies: low, medium and high dose. For convenience, as there were very few patients in all studies, I added the adverse events across the studies to get an idea of whether any dose-response relationship was apparent:

	low	medium	high
subjects with follow-up	1426	1449	1431
with one or more adverse events	1277	1294	1319
injection-site adverse events	1131	1190	1217
systemic adverse events	949	909	896
systemic adverse events, vaccine related	509	502	491

There was a clear dose-response relationship for injection-site adverse events, χ^2 for trend = 16.02; p = 0.0003. A more formal meta-analysis is not needed, at it would yield a similar result, given this strong signal.

For systemic adverse events, there was no dose-response relationship. I consider this a false negative finding caused by the many flaws in Merck's trials because the more antigens and amount of adjuvant there is in a vaccine, the more systemic adverse events it will cause. In agreement with this obvious fact, my analyses showed that Gardasil 9 is more harmful than Gardasil, which was expected because Gardasil 9 contains five more antigens and more than double as much adjuvant as Gardasil (500 µg vs 225 µg) (see below). In the large trial that compared Gardasil 9 with Gardasil (P001), a supplementary appendix to the trial publication revealed that there were more serious systemic adverse events in girls receiving the 9-valent vaccine than in those receiving the 4-valent vaccine (3.3% vs. 2.6%, p = 0.01).[24] The number needed to harm was only 141, and it would undoubtedly have been even smaller if the control group had not received Gardasil, too.

In this trial, more patients on Gardasil 9 than on Gardasil experienced nervous system disorders (p = 0.01), headache (p = 0.02) and dizziness (this difference was not statistically significant, p = 0.12, but when events are subdivided, a true signal might not be statistically significant). The number needed to harm for nervous system disorders was only 50. The corresponding table for new medical history also showed that more patients on Gardasil 9 than on Gardasil had nervous system disorders, 515 vs 481.

[24] Joura EA, Giuliano AR, Iversen OE, et al. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. N Engl J Med 2015;372:711-23.

Extreme variations in number of patients with adverse events

The proportion of patients with adverse events differed hugely from trial to trial, even though their design and follow-up periods were very similar. As the three Future trials had the same design, it is particularly concerning that the percentage of patients with adverse events varied from 11% in Future 2 to 84% in Future 3 and 92% in Future 1. This heterogeneity is extreme (χ^2 = 12,582 with 2 df). With a chi-square value this high, standard statistical software does not compute exact p-values. Already when χ^2 = 25 with 2 df, the p-value is very low (p < 0.00001,[25] or less than one per 100,000). A chi-square value of twelve thousand is so extreme that it means – beyond any doubt - that the reporting of adverse events in the Future trials cannot be trusted.

Something must be wrong with Future 2 where only 11% of the patients had adverse events, but I have not found any explanation of this in Merck's study reports, let alone a comment.

There were similar extreme discrepancies in the proportions of other events in the Future trials, apart from serious adverse events where the proportion was the same in Future 3 as in Future 2 (0.8%) and only double as high in Future 1 (numbers are in per cent, Gardasil 9 is the large trial comparing Gardasil 9 with Gardasil):

Subjects with adverse events	Future 1	Future 2	Future 3	Gardasil 9
all adverse events	91.7	11.4	84.2	92.6
injection-site	83.9	8.2	70.5	88.0
systemic	64.5	7.5	59.7	56.6
vaccine-related	88.3	9.5	78.2	89.9
injection-site, vaccine related	83.9	8.2	70.5	88.0
systemic, vaccine related	42.1	3.8	38.2	28.4
serious adverse events	1.8	0.8	0.8	2.9
serious adverse events, vaccine-related	0.0	0.0	0.0	0.0

It is noteworthy that in these four trials, serious adverse events were so rarely considered vaccine related that the percentage was 0.0% for all the trials. A total of 642 serious adverse events were reported, among a total of 21,173 patients (3.0%) in these four trials, but only 10 patients (0.05%) were considered to have experienced vaccine related serious adverse events.

The extreme heterogeneity was concerning in other ways. As noted above, the Gardasil 9 trial reported systemic adverse events considered vaccine related 7 times as often as the Future 2 trial, even though almost all the systemic adverse events were collected in the three two-week periods after each vaccination in both studies because the investigators were instructed to call what was reported to them by the patients outside these two-week periods, "new medical history."

These observations suggest that a huge amount of data on adverse events in the Future 2 trial were never collected, were lost, or were suppressed after they had been reported to Merck. I cannot see any other explanations.

I noted that the table of adverse events in the synopsis of the Future 2 trial on p11 did not show the same numbers of patients as the same table 3972 pages later in the same report, even though the table headings were exactly the same. There was no explanation in the report why the numbers differed by 1 or 2 patients (Appendix A).

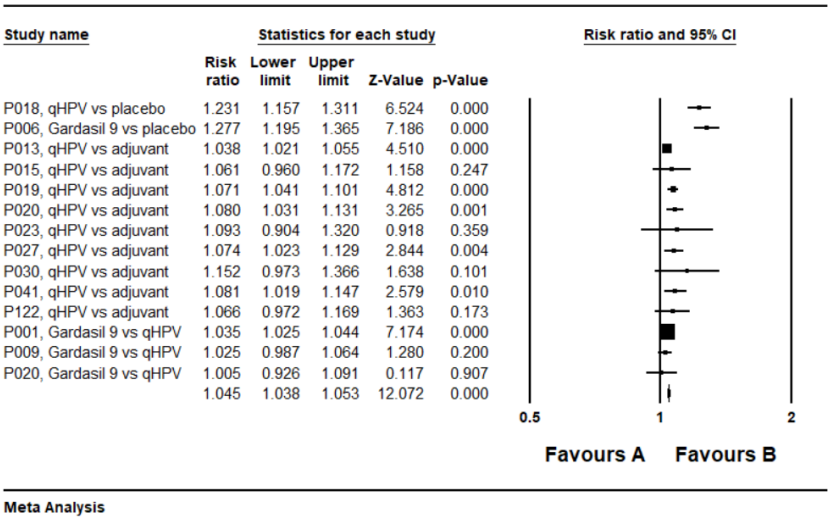
All adverse events

Fourteen studies (48,962 patients) contributed to this meta-analysis. The risk ratio was 1.045, with a narrow 95% confidence interval (1.038 to 1.053; p < 0.001). This means that the HPV vaccines caused more harm than

[25] https://www.socscistatistics.com/pvalues/chidistribution.aspx

the comparator, which was placebo in two trials, the adjuvant in nine trials and the quadrivalent HPV vaccine in three trials.

It is easy to see on the graph that the results were heterogeneous. The risk of harm was much greater in the two placebo-controlled trials than in the adjuvant-controlled trials, and lowest in the three vaccine-controlled trials.



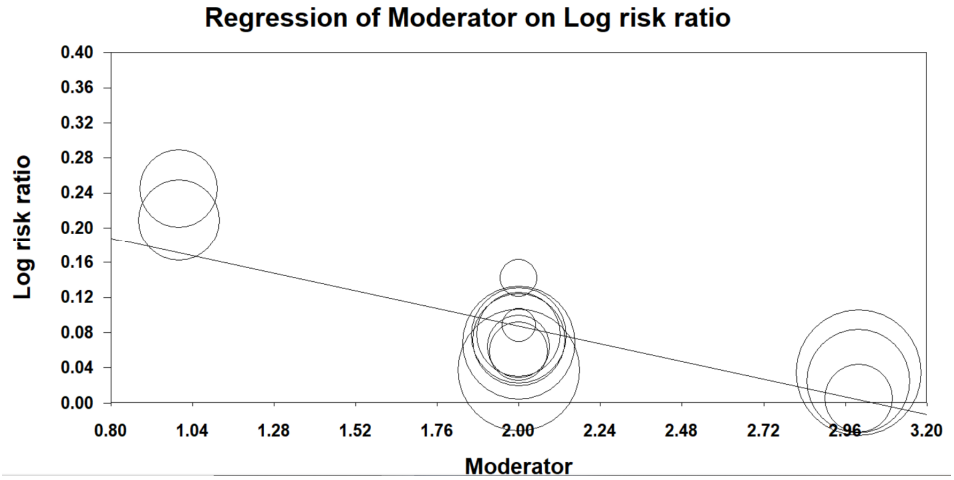
In meta-analyses, heterogeneity can be quantified by I^2, which is the proportion of the total variance that is due to between study variance, i.e. I^2 = between study variance/ (between study variance + within study variance). To put it differently, I^2 describes the percentage of the variability in effect estimates that is due to heterogeneity (differences between studies) rather than sampling error (chance).

In this meta-analysis, there was huge heterogeneity, $I^2 = 83\%$. It is therefore both relevant and appropriate to analyse the results for each type of comparator separately. The vaccine harm is highly statistically significant ($p < 0.001$) also for each group taken separately:

Control group	Risk ratio	95% confidence interval
Placebo	1.253	1.197 to 1.311
Adjuvant	1.047	1.032 to 1.062
qHPV	1.034	1.025 to 1.043

The three confidence intervals are far from overlapping. When this is the case, the estimates differ much more than expected by chance, i.e. the differences between the three estimates are highly statistically significant and can therefore be considered to be real.

A more formal way of showing this is to do a meta-regression, with moderator variables 1, 2 and 3 for the placebo, adjuvant and qHPV comparators, respectively. The graph shows a mixed effects regression (unrestricted maximum likelihood). The circles are proportional to the weights the study have, which are determined by the number of events; thus, a study with few events contribute less to the meta-regression than a study with many events. The differences between the three estimates were highly statistically significant ($p < 0.00001$ for the slope of the line).



This, and other analyses, show that Gardasil 9 is more harmful than Gardasil, which was expected because Gardasil 9 contains five more antigens and more than double as much adjuvant as Gardasil (500 µg vs 225 µg).

It is more clinically relevant to compute the risk difference than the risk ratio because the inverse of the risk difference (one divided by the risk difference) is the number needed to harm:

Control group	Risk difference	95% confidence interval	Number needed to harm
Placebo	0.178	0.144 to 0.211	6
Adjuvant	0.027	0.020 to 0.035	37
qHPV	0.031	0.022 to 0.039	32

For every 6 patients treated with an HPV vaccine instead of placebo, one experiences an adverse event.
For every 37 patients treated with Gardasil instead of adjuvant, one experiences an adverse event.
For every 32 patients treated with Gardasil 9 instead of Gardasil, one experiences an adverse event.

The true harms of Merck's HPV vaccines are not known because Merck conducted only two small, "placebo-controlled" trials (one of the so-called placebo-controlled trials did not use a true placebo), but these two trials show that the harms are very common.

Merck's view that its adjuvant is harmless is clearly not true. The number needed to harm increased from 6 to 37 when the adjuvant was used as control instead of placebo and concealed the harms.

Of course, not all patients who experience an adverse event have been harmed by the vaccine or the adjuvant, as adverse events occur for many other reasons. But as this is true for both compared groups, it is both correct and relevant to calculate the number needed to harm, which is a relative measure.

Systemic adverse events

Merck reported these data very selectively. In 7 of the 14 trials (one placebo-controlled, four adjuvant-controlled, and two vaccine-controlled), systemic adverse events were only reported for the three two-week periods after each vaccination. In the other 7 trials, systemic adverse events were also reported very selectively because the investigators had been instructed not to report such events as adverse events beyond the two-week periods but to call them new medical history, which was scientifically inappropriate.

There was no heterogeneity, $I^2 = 0$. The risk ratio was increased, 1.017, but the lower limit of the 95% confidence interval was slightly below 1 (0.998 to 1.036), which means that the difference was not statistically significant ($p = 0.08$). As explained just above, this illustrates that Merck concealed the systemic adverse events in their trials so effectively that my meta-analysis result was not statistically significant. See also next section.

Vaccine related systemic adverse events

Merck reported these data very selectively. There was no heterogeneity, $I^2 = 0$. The risk ratio for systemic adverse events considered vaccine related by the investigators was significantly increased, 1.060 (95% confidence interval 1.029 to 1.093, $p < 0.001$). As noted just above, the risk ratio was also increased for all systemic adverse events, but less so, 1.017.

There were about double as many patients with systemic adverse events (20,123), as those the investigators considered vaccine related (10,370) (Appendix A, p9-12). Thus, when the "background noise" became reduced by half, it was apparent that the vaccines increase systemic adverse events significantly.

The risk difference is more meaningful and relevant than the risk ratio. The number needed to harm was 167 (Appendix A, p12).

Serious adverse events

Two of the 14 studies had no events in either group. There was very little heterogeneity, $I^2 = 2\%$ (Appendix A, p13). The risk ratio for serious adverse events was increased, 1.088, but the difference was not statistically significant (95% confidence interval 0.945 to 1.254; $p = 0.24$). This result should be interpreted in light of the low number of patients with serious adverse events, only 761. Whether a signal of harm is statistically significant or not, depends on the number of events. The increased risk ratio for serious adverse events should therefore not be dismissed just because the p-value was not statistically significant. It should be compared with the other risk ratios:

	Risk ratio	No. of events	p-value
all adverse events	1.045	32010	< 0.001
injection-site adverse events	1.095	28155	< 0.001
systemic adverse events	1.017	20123	0.08
systemic adverse events, vaccine related	1.060	10370	< 0.001
serious adverse events	1.088	761	0.24

The risk ratio for serious adverse events was larger than for all adverse events and for vaccine related systemic adverse events and was about the same as that for injection-site adverse events. According to these data, Merck's HPV vaccines cause substantial harm, no matter in which way this harm is being assessed. Since all risk ratios are greater than 1, it means that it is more than 50% likely that the vaccines cause these events, including the serious ones.

Severe systemic adverse events

Merck reported these data selectively, in two ways. As for injection-site events, a lot of data from the Future 1 and 2 trials had been left out. In addition to this - and in contrast to injection-site reactions, which were always considered vaccine related - there was no information in any of Merck's study reports about which of the systemic adverse events of moderate or severe intensity the investigators considered vaccine related, even though such information was collected in all the trials that collected information about severity. This was scientifically inappropriate, particularly considering that Merck provided hundreds of tables in their study reports and emphasized those events the investigators considered vaccine related.

The risk ratio was not increased, 0.998 (95% confidence interval 0.934 to 1.067; $p = 0.95$). As explained above, this should be considered a false negative finding.

Severe and moderate systemic adverse events

Merck reported these data selectively (see just above).

The risk ratio was significantly increased, 1.038 (1.007 to 1.070; p = 0.015). The risk difference was also increased but the difference was not statistically significant, 0.007 (-0.003 to 0.017), p = 0.15). As explained above, this is immaterial.

Autoimmune events

Nine of the 14 studies provided data about potential autoimmune events but there were several issues about how Merck had handled these data (Appendix A, p23).

I used the largest numbers for my meta-analysis. The risk ratio was increased, 1.019 (95% CI 0.907 to 1.146), but the difference was not statistically significant (p = 0.75). Because of the many flaws in the way Merck handled adverse events, this is likely a false negative finding.

POTS and CRPS

My attempts at finding out if Merck's vaccines might cause POTS or CRPS by examining Merck's deficient clinical trials proved futile. As I have described, a great deal of data were missing, and the data Merck presented were split in so many ways, in many hundreds of tables, that it was impossible to collect them in a way that ensured that the same person was not counted more than once, which is a prerequisite for statistical analyses. Nevertheless, my research group found a clear signal of neurological harms from the HPV vaccines[26] (see also below).

It is noteworthy that, in an expert assessment report for Gardasil 9 written on behalf of the European Medicines Agency (EMA),[27] the rapporteurs were concerned that Sanofi (Merck) had avoided identifying possible cases of serious harms of the vaccine. Their concerns were shared by EMA's own trial inspectors[28] who criticised adverse events only being reported for 14 days after each vaccination; that any new symptoms at other times were reported as "new medical events" without medical assessments or final outcomes being recorded; and that the reporting of serious adverse events was not required during the full course of the trial even though systemic side effects could appear long after the vaccinations were given (see Dunder in the footnote). For example, even though symptoms of POTS may appear early, it can take years before the diagnosis is objectively established by a tilt test.[29]

The inspectors also criticised that three people had been diagnosed with POTS in the clinical safety database after receipt of Gardasil 9 but that these were not reported as adverse events; that a case of POTS after Gardasil was called "new medical history" instead of an adverse event; that hospitalisation for severe dizziness was not reported as a serious adverse event (against the rules); and that, for another person, the term "dysautonomia" was not included in the list of events.

Meanwhile, an investigative journalist (see Joelving in the footnote) reported that three Danish Future 2 study participants had experienced serious adverse events after Gardasil, but their complaints were never registered as adverse events. One of the three women had brought up her symptoms with study personnel at every visit during the four-year trial and had even told them that her illness had forced her to quit school. But no one took

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[26] Jørgensen L, Gøtzsche PC, Jefferson T. Benefits and harms of the human papillomavirus (HPV) vaccines: systematic review with meta-analyses of trial data from clinical study reports. Syst Rev 2020;9:43.

[27] Dunder K, Mueller-Berghaus J. Rapporteurs' Day 150 Joint Response Assessment Report. Gardasil 9. 2014; 23 Nov.

[28] Joelving F. What the Gardasil testing may have missed. Slate 2017; 17 Dec.

[29] Blitshteyn S, Brinth L, Hendrickson JE, Martinez-Lavin M. Autonomic dysfunction and HPV immunization: an overview. Immunol Res 2018;66:744-54.

her seriously. The journalist was able to obtain the case report forms and checked them together with the patient many years later. The only checked box on all the forms was the one that said "None," even though she was incapacitated and therefore had a serious adverse event.

A press officer from the Danish Medicines Agency, which approved Merck's Future 2 protocol in 2002, pointed out that it contained no mention of "new medical history" or "new medical conditions" (see Joelving).

I checked the trial protocol for Future 2 and amendments. I did not find any mention that "new medical history" or "new medical conditions" was a safety metric for the vaccine.

In an email, the Danish press officer wrote, "We are also not aware of whether this category has been used in other clinical trials with drugs, as these are not terms that are used according to guidelines" (see Joelving). In their final report recommending conditional approval of Gardasil 9, the EMA rapporteurs asked Merck to "discuss the impact of [its] unconventional and potentially suboptimal method of reporting adverse events and provide reassurance on the overall completeness and accuracy of safety data provided in the application." However, in EMA's publicly available assessment of Gardasil 9, there was no mention of the safety concerns.

Danish POTS cases

In 2014, the Danish drug regulator instructed Sanofi Pasteur MSD, which manufactured Gardasil, on how to search on specific symptoms in its database including dizziness, palpitations, rapid heart rate, tremor, fatigue and fainting. Despite the clear instructions, Sanofi only searched *postural dizziness*, *orthostatic intolerance* and *palpitations and* dizziness. The Danish authorities discovered this because only 3 of 26 registered Danish reports of POTS showed up in Sanofi's searches.[30]

I have indirect knowledge that, at the Danish Syncope Centre, a patient who was a participant in the pivotal trial that compared Gardasil 9 with Gardasil was diagnosed with POTS, and a clinical investigator attempted to report this to Merck, but her report was rebuffed. I obtained this information directly from the investigator. This same investigator saw a total of three cases with POTS in the Gardasil 9 study, two of which had been hospitalized and which were therefore by definition serious adverse events that must be reported. The patients could not say exactly when the POTS symptoms started but they started long before the last two weeks of the obligatory recordings on the vaccination report card, i.e. within the first 6-7 months of the study. The investigator sent reports of the two serious adverse events to Merck, and Merck's Danish monitor agreed that this was appropriate.

The investigator struggled to get the cases reported, and Merck USA reportedly became involved, and did not want them reported. As the symptoms appeared gradually, it was impossible for the patients to give an exact date for the onset of symptoms, so the investigator wrote a time interval instead of a date on the forms, which was a year or more before the patients were admitted to hospital. Merck would not accept the reports because of the time lag between the vaccinations and the diagnosis. Merck determined that the starting date for the onset of symptoms was the date of hospitalization, which fell outside the reporting period.

I searched the Gardasil 9 study report and did not find these cases.

EMA asked Merck and GlaxoSmithKline to assess 83 POTS cases that had been identified by Dr. Louise Brinth from the Danish Syncope Centre (for Gardasil and Cervarix). Although the companies considered only 33 of the cases to have met the case definition criteria,[31] it was still a significant number of cases from just one country that were missing in the study reports of Merck's trials. An EMA rapporteur concluded that, "the HPV case reports from Denmark are distinguished from those from other countries by the fact that they contain an

[30] Weber C, Andersen S. Firma bag HPV-vaccinen underdrev omfanget af alvorlige bivirkninger. Berlingske 2015; 26 Oct.
[31] European Medicines Agency. Assessment report. Review under Article 20 of Regulation (EC) No 726/2004. Human papilloma virus (HPV) vaccines. 2015; 11 Nov. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/HPV_vaccines_20/Opinion_provided_by_Committee_for_Medicinal_Products_for_Human_Use/WC500197129.pdf.

increased amount of clinical information and that certain, specific diagnostic PTs [preferred terms] are more commonly used."[32] This important information was not mentioned in EMA's official report [33]

I, along with colleagues, have criticized EMA's handling of these issues.[34]

Publication of Gardasil studies in major journals

The published trial reports are of overriding importance because this is where doctors, patients, and scientists get information about what the trials showed.

Merck's publications of its pivotal trials in major medical journals were misleading. The abstract of the main publication of Merck's only placebo-controlled trial of Gardasil[35] stated that the control group received "saline placebo." Water for injection is not saline; Merck's carrier solution is not a saline placebo; and some of the authors knew this was inaccurate, as 6 of the 12 authors were Merck employees (there were no conflicts of interest statements in the article). Merck also concluded that Gardasil was "generally well tolerated," which was inaccurate.

New medical history was not explained under Methods. The only mention was under Results: "Through month 18, the proportions of subjects reporting new medical conditions were comparable between the 2 vaccination groups. In both groups, the most common new condition was influenza." It was thus unclear how Merck used this category of adverse events.

In Merck's publications of the three Future trials and the large Gardasil 9 trial in *New England Journal of Medicine* and *Lancet*, there was no mention of new medical history at all even though this is about adverse events; even though Merck put great emphasis on this in its study reports; and even though there were more such events than what Merck categorised as adverse events (25,018 vs 22,156 in the four trials).

Most of the authors on the published reports of the three Future trials and the large Gardasil 9 trial were current or former employees of Merck, with financial conflicts of interest, likely leading to selective reporting. On top of this, the US trial register showed that the principal investigators had an agreement with Merck that restricted their rights to discuss or publish trial results after the trial was completed.

In Merck's publication of the Future 1 trial in the *New England Journal of Medicine,*[36] the study was called "placebo-controlled," which was plainly false. Although safety was a primary objective, there was nothing in the abstract about safety. Numbers of patients with various types of adverse events contradicted similar tables in Merck's study reports even though the total number of patients were the same, with differences of up to 3 patients, apart from pyrexia, where the largest difference was 79 patients, and injection-site events, where the largest difference was 377 patients, when compared with another of Merck's tables.

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[32] Briefing note to experts. EMA/666938/2015. 2015; 13 Oct. http://ijme.in/pdf/g-briefing-note-to-the-experts-ema-oct-2015-unredacted.pdf.

[33] European Medicines Agency. Assessment report. Review under Article 20 of Regulation (EC) No 726/2004. Human papilloma virus (HPV) vaccines. 2015; 11 Nov. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/HPV_vaccines_20/Opinion_provided_by_Committee_for_Medicinal_Products_for_Human_Use/WC500197129.pdf.

[34] Gøtzsche PC, Jørgensen KJ. EMA's mishandling of an investigation into suspected serious neurological harms of HPV vaccines. BMJ Evid Based Med 2022;27:7-10.

[35] Reisinger KS, Block SL, Lazcano-Ponce E, Samakoses R, Esser MT, Erick J, Puchalski D, Giacoletti KE, Sings HL, Lukac S, Alvarez FB, Barr E. Safety and persistent immunogenicity of a quadrivalent human papillomavirus types 6, 11, 16, 18 L1 virus-like particle vaccine in preadolescents and adolescents: a randomized controlled trial. Pediatr Infect Dis J 2007;26:201-9.

[36] Garland SM, Hernandez-Avila M, Wheeler CM, Perez G, Harper DM, Leodolter S, Tang GW, Ferris DG, Steben M, Bryan J, Taddeo FJ, Railkar R, Esser MT, Sings HL, Nelson M, Boslego J, Sattler C, Barr E, Koutsky LA; Females United to Unilaterally Reduce Endo/Ectocervical Disease (FUTURE) I Investigators. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. N Engl J Med 2007;356:1928-43.

Merck's publication of the Future 2 trial in the *New England Journal of Medicine*[37] stated that the control group had received placebo, which again was untrue. As for Future 1, although safety was a primary objective, there was nothing in the abstract about safety.

Indiana University and Merck had a confidential agreement that paid the university "on the basis of certain landmarks regarding the HPV vaccine" and one of the investigators received "a portion of these structured payments." As noted above, it is remarkable that only 11% of the patients experienced adverse events in this trial, compared with 92% in Future 1 and 84% in Future 3.

In Merck's publication of the Future 3 trial in *Lancet,*[38] the study was called "placebo-controlled," which was once again untrue. Although safety was a primary objective, the only mention in the abstract was: "We recorded no vaccine-related serious adverse events." As noted above, in the large Gardasil 9 trial, 99.95% of the patients with systemic adverse events disappeared when only vaccine related serious adverse events were accounted for.

The Statistical Analysis section contained nothing about testing for safety. The Results section only mentioned serious adverse events, and only if they had occurred within the first two weeks after each vaccination, even though the US trial register noted that the time frame for reporting serious adverse events was four years. In the large Gardasil 9 trial, 90% of the serious adverse events occurred outside the two-week intervals.

Compared with Merck's study report, there were discrepancies for adverse events, with differences of up to 4 patients, and even more for serious adverse events. Merck reported 3 vs 7 patients in *Lancet*, within the two-week periods after each vaccination, but this was inaccurate. I checked the dates for all the events, and the correct numbers were 3 vs 6 (the other events had occurred from day 44 until day 1059 after a vaccination). Merck reported 14 vs 16 patients in its summary table in the study report but also noted in the text that two additional cases "were mistakenly not incorporated into the Clinical Trials Systems (CTS) database but were reported in the worldwide adverse experience system (WAES) database," and there were 15 vs 17 in the trial register. Thus, there were four sets of data for serious adverse events: 15 vs 17, 14 vs 16, 3 vs 7 and 3 vs 6.

There were no p-values or confidence intervals in the table of adverse events, even though safety was a primary objective, and there were no comments about the huge difference in injection-site adverse events ($p = 6 \times 10^{-17}$) or the non-significant difference in systemic adverse events considered vaccine related ($p = 0.11$) (my calculations).

There was nothing about safety in the Discussion and no conclusion other than one sentence in the abstract: "We recorded no vaccine-related serious adverse events."

There was no mention that some patients died. Whether considered drug related or not, deaths must always be reported in a clinical trial. In the trial register, no deaths were listed under "All-cause mortality" whereas 8 vs 4 were listed elsewhere, in contrast to the 7 vs 1 in Merck's study report.

The large trial that compared Gardasil 9 with Gardasil (P001) was published in the *New England Journal of Medicine*.[39] The only mention of adverse events in the abstract was: "Adverse events related to injection site were more common in the 9vHPV group than in the qHPV group."

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[37] FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med 2007;356:1915-27.

[38] Muñoz N, Manalastas R Jr, Pitisuttithum P, Tresukosol D, Monsonego J, Ault K, Clavel C, Luna J, Myers E, Hood S, Bautista O, Bryan J, Taddeo FJ, Esser MT, Vuocolo S, Haupt RM, Barr E, Saah A. Safety, immunogenicity, and efficacy of quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine in women aged 24-45 years: a randomised, double-blind trial. Lancet 2009;373:1949-57.

[39] Joura EA, Giuliano AR, Iversen O-E,et al. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. N Engl J Med 2015;372:711-23.

The Cochrane Collaboration conducted a review of Merck's clinical trials based on what was published in the literature. I and my colleagues have criticized Cochrane's review of HPV vaccines.[40]

Gardasil package inserts

The FDA approved package inserts for Gardasil are very important, as this is where patients and doctors can get information about the vaccine, apart from the published trial reports, and they are freely available on the Internet. They should convey the knowledge the company has about common drug harms and also about rare but severe harms, which can be important for decision-making about whether taking the drug (or vaccine) is worthwhile.

The package inserts from 2009 and 2011 noted that post-vaccination syncope, sometimes with seizure-like activity, is not always transient and that nausea and dizziness (which are also key symptoms for POTS), are more common on Gardasil than on the adjuvant or "saline placebo." Again, the claim that a trial was "saline placebo-controlled" was factually incorrect and misleading. The patients in the control group had received the carrier solution, which contains active substances and water for injection.

The 2009 package insert reviewed six clinical trials and an unreferenced and unknown uncontrolled study. Regarding "systemic adverse reactions," there was no division between the adjuvant control and the carrier solution placebo; these two groups were lumped together. Furthermore, the table for females was erroneous. Even though headache was the most commonly reported adverse reaction, headache was entirely missing from the table of common systemic adverse reactions for females. Merck did not mention in the package inserts that Gardasil increases significantly the occurrence of systemic adverse events considered vaccine related.

Merck's 2011 package insert was updated by adding the 3810 patients from the Future 3 trial, but most of the numbers of patients with adverse events did not change, or changed very little, despite this addition.
About serious adverse events, Merck provided a sentence that stated 129 patients had a "serious adverse reaction" on placebo, which was false, as virtually all the 129 events were on the adjuvant, which by far most patients in the control groups had received.

In the 2011 package insert, the number of patients with serious adverse reactions had increased by only 3, which is a mathematical impossibility, as the Future 3 trial had 32 such reactions. Merck's reporting of deaths was also unreliable. In the 2011 package insert, the number of deaths had increased by only 3, even though there were 8 deaths in the Future 3 trial: another mathematical impossibility.

Review of Gardasil package inserts

I shall review the Gardasil package insert from 2009 (26 pages long) in the following and shall also compare it with the package insert from 2011 (28 pages). The first page has this information:

[40] Jørgensen L, Gøtzsche PC, Jefferson T. The Cochrane HPV vaccine review was incomplete and ignored important evidence of bias. BMJ Evid Based Med 2018;23:165-8 and Jørgensen L, Gøtzsche PC, Jefferson T. The Cochrane HPV vaccine review was incomplete and ignored important evidence of bias: Response to the Cochrane editors. BMJ Evidence-Based Medicine 2018; 17 Sept.

----------CONTRAINDICATIONS----------

- Hypersensitivity, including severe allergic reactions to yeast (a vaccine component), or after a previous dose of GARDASIL. (4) (11)

----------WARNINGS AND PRECAUTIONS----------

- Because vaccinees may develop syncope, sometimes resulting in falling with injury, observation for 15 minutes after administration is recommended. Syncope, sometimes associated with tonic-clonic movements and other seizure-like activity, has been reported following vaccination with GARDASIL. When syncope is associated with tonic-clonic movements, the activity is usually transient and typically responds to restoring cerebral perfusion by maintaining a supine or Trendelenburg position. (5.1)

---------- ADVERSE REACTIONS----------

The most common adverse reaction was headache. Common adverse reactions (frequency of at least 1.0% and greater than AAHS control or saline placebo) are fever, nausea, dizziness; and injection-site pain, swelling, erythema, pruritus, and bruising. (6.1)

This information is important. A severe allergic reaction to yeast is a contraindication for usage because the vaccine contains yeast. Thus, Merck admitted, at least indirectly, that what it called placebo in its only placebo-controlled trial of Gardasil is not placebo, as it contained the carrier solution, including yeast. A genuine placebo cannot cause a severe allergic reaction because saline is a physiological fluid that cannot cause allergic reactions. Merck misrepresented that its carrier solution was saline, both in its published trial report and in the package insert.

Merck wrote that post-vaccination syncope, sometimes with seizure-like activity, is not always transient. Syncope and pre-syncope are key symptoms for POTS. Merck admitted that two other key symptoms for POTS,[41] nausea and dizziness, are more common on the vaccine than on the adjuvant or "saline placebo." The text about headache was ambiguous, as it did not say explicitly that headache is more common on the vaccine.

There was an 8-page section on adverse reactions where Merck mentioned that, "In 6 clinical trials (4 Amorphous Aluminum Hydroxyphosphate Sulfate [AAHS]-controlled, 1 saline placebo-controlled, and 1 uncontrolled), 14,273 individuals were administered GARDASIL or AAHS control or saline placebo."

Not a single patient received a saline placebo in the controlled Gardasil trials, and it is a violation of generally accepted research practices to lump data from randomised trials with data from an unreferenced and therefore unknown observational study when providing information about drug harms. We do randomised trials because they are far more reliable for assessing harms than observational studies. The lack of information about which trials Merck had included made it difficult to check the veracity of Merck's information.

Although the introductory text was about both genders, "Studies in Girls, Women, Boys, and Men 9 Through 26 Years of Age," the next page in the package insert is only about females:

[41] Brinth L, Theibel AC, Pors K, et al. Suspected side effects to the quadrivalent human papilloma vaccine. Dan Med J 2015;62:A5064.

Table 1
Injection-Site Adverse Reactions in Girls and Women 9 Through 26 Years of Age*

Adverse Reaction (1 to 5 Days Postvaccination)	GARDASIL (N = 5088) %	AAHS Control** (N = 3470) %	Saline Placebo (N = 320) %
Injection Site			
Pain	83.9	75.4	48.6
Swelling	25.4	15.8	7.3
Erythema	24.7	18.4	12.1
Pruritus	3.2	2.8	0.6
Bruising	2.8	3.2	1.6

*The injection-site adverse reactions that were observed among recipients of GARDASIL were at a frequency of at least 1.0% and also at a greater frequency than that observed among AAHS control or saline placebo recipients.
**AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate

With respect to the 320 patients who should have received a saline placebo, I found a table in the study report for the carrier solution-controlled trial (V501 P018 V1) on page 252 that was divided by gender and where the number 320 appeared among the females:

	Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Vacine		Non-Alum Placebo	
	Boys 9 to 15 Years of Age (N=564)	Girls 9 to 15 Years of Age (N=615)	Boys 9 to 15 Years of Age (N=274)	Girls 9 to 15 Years of Age (N=320)
	n (%)	n (%)	n (%)	n (%)
Subjects in analysis population	564	615	274	320

There was a similar table for males as the one for females:

Table 2
Injection-Site Adverse Reactions in Boys and Men 9 Through 26 Years of Age*

Adverse Reaction (1 to 5 Days Postvaccination)	GARDASIL (N = 3092) %	AAHS Control ** (N = 2029) %	Saline Placebo (N = 274) %
Injection Site			
Pain	61.5	50.8	41.6
Erythema	16.7	14.1	14.5
Swelling	13.9	9.6	8.2

*The injection-site adverse reactions that were observed among recipients of GARDASIL were at a frequency of at least 1.0% and also at a greater frequency than that observed among AAHS control or saline placebo recipients.
**AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate

By splitting the data, Merck made it more difficult to understand what the harms were and their incidence, particularly because the symptoms listed for the two genders were not the same.

There were tables of the severity of pain, swelling and erythema, also divided per gender:

Table 3
Postdose Evaluation of Injection-Site Adverse Reactions in Girls and Women 9 Through 26 Years of Age (1 to 5 Days Postvaccination)

	GARDASIL (% occurrence)			AAHS Control* (% occurrence)			Saline Placebo (% occurrence)		
Adverse Reaction	Post-dose 1 N** = 5011	Post-dose 2 N = 4924	Post-dose 3 N = 4818	Post-dose 1 N = 3410	Post-dose 2 N = 3351	Post-dose 3 N = 3295	Post-dose 1 N = 315	Post-dose 2 N = 301	Post-dose 3 N = 300
Pain	63.4	60.7	62.7	57.0	47.8	49.6	33.7	20.3	27.3
Mild/Moderate	62.5	59.7	61.2	56.6	47.3	48.9	33.3	20.3	27.0
Severe	0.9	1.0	1.5	0.4	0.5	0.6	0.3	0.0	0.3

Merck lumped mild and moderate reactions and wrote that, “Of those girls and women who reported an injection-site reaction, 94.3% judged their injection-site adverse reaction to be mild or moderate in intensity.”

Merck downplayed the harms of Gardasil. I calculated that the number needed to harm compared to placebo for injection-site reactions was only 3, and it was only 4 for moderate or severe injection-site adverse reactions.

In two tables, one for each gender, Merck described those systemic adverse reactions that were observed in at least 1% of the patients on Gardasil and at a greater rate than those observed in the adjuvant or "saline placebo group." In contrast to local reactions, the data were obfuscated, as there was no longer any division between the adjuvant control and the carrier solution placebo; these two groups were lumped.

To find out if there were any statistically significant differences, the reader would need to calculate numbers from percentages and add them for females and males, as there were no such numbers or significance tests in the package insert:

Table 5
Common Systemic Adverse Reactions in Girls and Women 9 Through 26 Years of Age (GARDASIL ≥ Control)*

Adverse Reactions (1 to 15 Days Postvaccination)	GARDASIL (N = 5088) %	AAHS control** or Saline Placebo (N = 3790) %
Pyrexia	13.0	11.2
Nausea	6.7	6.5
Dizziness	4.0	3.7
Diarrhea	3.6	3.5
Vomiting	2.4	1.9
Cough	2.0	1.5
Toothache	1.5	1.4
Upper respiratory tract infection	1.5	1.5
Malaise	1.4	1.2
Arthralgia	1.2	0.9
Insomnia	1.2	0.9
Nasal congestion	1.1	0.9

Table 6
Common Systemic Adverse Reactions in Boys and Men 9 Through 26 Years of Age (GARDASIL ≥ Control)*

Adverse Reactions (1 to 15 Days Postvaccination)	GARDASIL (N = 3092) %	AAHS control** or Saline Placebo (N = 2303) %
Headache	12.3	11.2
Pyrexia	8.2	6.5
Pharyngolaryngeal pain	2.8	2.1
Diarrhea	2.7	2.2
Nasopharyngitis	2.6	2.6
Nausea	2.0	1.0
Upper respiratory tract infection	1.5	1.0
Abdominal pain upper	1.4	1.4
Myalgia	1.3	0.7
Dizziness	1.2	0.9
Vomiting	1.0	0.8

When I tried to calculate total numbers for the three most common adverse events related to POTS (headache, nausea and dizziness), I observed that the table for females was erroneous. Although Merck stated that, in females, "Headache was the most commonly reported systemic adverse reaction in both treatment groups (GARDASIL = 28.2% and AAHS control or saline placebo = 28.4%), headache was entirely missing in the table of common systemic adverse reactions for females, even though it showed 12 symptoms, of which the most common was pyrexia (13.0% vs 11.2%) (see the table just above).

In the package insert from 2011, the same information appeared, and the error was repeated. That package insert referred to one more adjuvant-controlled trial than the earlier package insert, and the total number of patients had increased from 14,273 to 18,083, an increase of 3810 patients. The additional 3810 patients are the number in the analysis population in the Future 3 trial, which was therefore the new trial included in the package insert from 2011.

In Merck's two package inserts, there was no mention that Gardasil increased significantly the occurrence of systemic adverse events considered vaccine related. I found a risk ratio of 1.060 (95% confidence interval 1.029 to 1.093), $p < 0.001$. When I restricted the analysis to the Gardasil trials (excluding the Gardasil 9 trials), I confirmed this result (risk ratio 1.049, $p = 0.015$). Even when I restricted the analysis to those 5 Gardasil trials for which Merck had clinical study reports available in 2009 (assuming that these were P018, P013, P015, P020, and P023, as the other Gardasil trials were more recent), the result was the same (risk ratio 1.054, p =

0.053). The 2011 package insert had included the Future 3 trial, and when I added this trial to my meta-analysis, the result was the same (risk ratio 1.058, p = 0.012).

There were two tables about fever, split in three ways (by gender, vaccine visits and two thresholds for reporting the temperature):

Table 7
Postdose Evaluation of Fever in Girls and Women 9 Through 26 Years of Age
(1 to 5 Days Postvaccination)

	GARDASIL (% occurrence)			AAHS Control* or Saline Placebo (% occurrence)		
Temperature (°F)	Postdose 1 N** = 4945	Postdose 2 N = 4804	Postdose 3 N = 4671	Postdose 1 N = 3681	Postdose 2 N = 3564	Postdose 3 N = 3467
≥100 to <102	3.7	4.1	4.4	3.1	3.8	3.6
≥102	0.3	0.5	0.5	0.2	0.4	0.5

I added the numbers from the first vaccination: 287 of 7917 patients had fever on Gardasil and 178 of 5875 on the adjuvant or carrier solution, p = 0.056. This suggests that Gardasil causes fever, but Merck obscured this by splitting the data; did not perform any statistical tests; and did not provide any comment on these tables.

About serious adverse reactions in the "Entire Study Population," Merck wrote:

"Across the clinical studies, 255 individuals (GARDASIL N = 126 or 0.8%; placebo N = 129 or 1.0%) out of 29,323 (GARDASIL N = 15,706; AAHS control N = 13,023; or saline placebo N = 594) individuals (9- through 45-year-old girls and women; and 9- through 26-year-old boys and men) reported a serious systemic adverse reaction."

This sentence is misleading. It stated that 129 patients had serious reactions on placebo, which is false, as virtually all the 129 reactions were on the adjuvant, which by far most patients in the control group received. It was also false to state that 594 patients received saline placebo. Since the word "placebo" appeared in both places, it appears that 22% (129/594) had serious reactions on placebo compared to only 0.8% on Gardasil.

The similar statement in the 2011 package insert was equally misleading:

"Across the clinical studies, 258 individuals (GARDASIL N = 128 or 0.8%; placebo N = 130 or 1.0%) out of 29,323 (GARDASIL N = 15,706; AAHS control N = 13,023; or saline placebo N = 594) individuals (9- through 45-year-old girls and women; and 9- through 26-year-old boys and men) reported a serious systemic adverse reaction."

Furthermore, it is a mathematical impossibility that the number of patients with serious systemic adverse reactions can increase by only 2 vs 1, after inclusion of the Future 3 trial for which Merck reported 14 vs 16 serious adverse events in its summary table (and two more in the text). On top of this, the total number of patients was 29,323 in both package inserts even though the Future 3 trial had been added, which is also mathematically impossible.

I have not in any of Merck's study reports seen the concept serious *systemic* adverse reactions, only serious adverse reactions, but by far most of these are systemic. Local reactions only occur right after the injections; they are rarely serious; and about 90% of the serious systemic adverse reactions occur beyond the two-week periods after each injection.

These are the data I have on serious adverse events for the six trials in 2011 the package insert:

Study	Patients with events	
P018, qHPV vs placebo	5	0
P013, qHPV vs adjuvant	49	45
P015, qHPV vs adjuvant	46	56
P019, qHPV vs adjuvant	14	16
P020, qHPV vs adjuvant	8	11
P023, qHPV vs adjuvant	0	1
Total	122	129

My totals when Future 3 (P019) is included, 122 vs 129, are not too far from Merck's two data sets in its package inserts, but they are not the same: 126 vs 129 and 128 vs 130.

Merck's reporting of deaths in its package inserts is also unreliable. In the 2009 package insert, there were 18 vs 19 deaths in the "entire study population across the clinical studies" among 29,323 patients, which increased by three deaths on Gardasil in 2011 (21 vs 19 deaths), in the same study population with the same number of patients, 29,323, even though the Future 3 trial had been added, with its 7 vs 1 deaths and 3810 patients. This is yet another mathematical impossibility.

I could not confirm any of the two sets of postulated deaths, 18 vs 19, and 21 vs 19, as my data were these (see Appendix A):

Study name	Group-A Events	Group-A Total N	Group-B Events	Group-B Total N
P018, qHPV vs placebo	0	1165	0	584
P006, Gardasil 9 vs placebo	0	608	0	305
P013, qHPV vs adjuvant	2	2673	2	2672
P015, qHPV vs adjuvant	7	6019	5	6031
P019, qHPV vs adjuvant	7	1890	1	1888
P020, qHPV vs adjuvant	3	2020	10	2029
P023, qHPV vs adjuvant	0	117	0	59
P027, qHPV vs adjuvant	0	480	0	468
P030, qHPV vs adjuvant	0	302	0	298
P041, qHPV vs adjuvant	2	1499	0	1498
P122, qHPV vs adjuvant	0	554	0	559
P001, Gardasil 9 vs qHPV	5	7071	5	7078
P009, Gardasil 9 vs qHPV	0	299	0	300
P020, Gardasil 9 vs qHPV	0	248	0	248

In the five Gardasil studies that Merck referred to in its 2009 package insert, there were no deaths in the "placebo-controlled" study, and only 12 vs 17 deaths in the remainder, which I believe must have been P013, P015, P020 and P023. Even though I used Merck's own study reports for my attempted verification, it was impossible to confirm Merck's numbers on serious adverse reactions and deaths. The unknown uncontrolled study cannot explain this mystery, as there is, by definition, only one group in an uncontrolled study; therefore, the additional 6 vs 2 deaths in 2009 cannot have come from this study. Furthermore, this unknown study cannot explain either that there were only three more deaths in 2011 after Future 3 was included with its eight deaths.

I constructed this table of included patients based on the 2009 package insert:

Page	Gardasil	Control	Comment	Age group
4	8180	6093	Used vaccination report card	9 to 26
5	8180	6093	Injection-site adverse reactions	9 to 26
6	8013	5944	Injection-site adverse reactions post-dose 1	9 to 26
6	7821	5768	Injection-site adverse reactions post-dose 2	9 to 26
6	7643	5653	Injection-site adverse reactions post-dose 3	9 to 26
7	8180	6093	Systemic adverse reactions	9 to 26
8	7916	5875	Temperature post-dose 1	9 to 26
8	7651	5643	Temperature post-dose 2	9 to 26
8	7462	5513	Temperature post-dose 3	9 to 26
8	15706	13617	Serious systemic adverse reactions	9 to 45 vs 9 to 26
8	15706	13617	Deaths	9 to 45 vs 9 to 26
10f	13798	11715	Systemic autoimmune disorders (new medical conditions)	9 to 26

For comparison, these are the numbers of randomised patients in the six studies:

Study	Numbers randomised	
P018, qHPV vs placebo	1179	594
P013, qHPV vs adjuvant	2713	2724
P015, qHPV vs adjuvant	6075	6076
P019, qHPV vs adjuvant	1908	1902
P020, qHPV vs adjuvant	2032	2033
P023, qHPV vs adjuvant	117	59
Total	14024	13388

It is impossible to make sense out of the many significantly differing numbers Merck presented. Merck's numbers as shown in the table on the previous page were the same for the 2011 package insert as for the 2009 package insert even though Merck had included an additional 3810 patients from Future 3, which is mathematically impossible.

When I used the total number of randomised patients as shown in Merck's study reports, I arrived at 12,116 patients in the Gardasil groups and 11,486 patients in the control groups for the 2009 package insert and 14,024 vs 13,388 for the 2011 package insert. Both sets of numbers are very far from what Merck presented in its package inserts.

This means that the information Merck provided in its two package inserts was unreliable and scientifically inappropriate. Furthermore, the package inserts inappropriately gave readers the impression that the adjuvant is so harmless that the data obtained with it could be lumped with the data obtained with placebo.

Conclusions

It is my opinion, to a reasonable degree of medical and scientific certainty and based on my education, training, professional experience, review of Merck's clinical trials and the materials identified above and in the accompanying appendices to this report, that Merck's clinical trials of Gardasil were seriously flawed making any scientist, including regulators, attempting to accurately determine its risks, much less specific or rare risks, difficult if not impossible.

Merck was in the very best position and had the responsibility to honestly assess Gardasil's risks. Merck squandered the opportunity to legitimately study the safety of Gardasil in the multiple studies conducted, involving tens of thousands of study participants (mostly young girls). The significant and elevated risks identified in my meta-analyses would almost certainly be higher than what I calculated because vaccine harms were not adequately collected by Merck, not to mention the other inadequacies I have identified in this report.

Because of the studies' numerous flaws, Merck's clinical trials also cannot be used to claim that Gardasil is generally safe or that specific risks do not exist. Notwithstanding the flaws, I found a clear signal of serious harms, including neurological harms, from Merck's HPV vaccines, which almost certainly would have been

even larger than what I found had Merck's studies been properly conducted and reported. This risk is consistent with my and my colleague's systematic review of the HPV vaccine trials,[42] wherein we concluded that: "The serious harms that were judged 'definitely associated' with POTS or CRPS by the blinded physician were increased by the HPV vaccines, both for POTS (56 vs. 26, RR 1.92 [95% CI 1.21 to 3.07], NNH 1073, P = 0.006, I^2 = 0%) and CRPS (95 vs. 57, RR 1.54 [95% CI 1.11 to 2.14], NNH 906, P = 0.010, I^2 = 0%). The new onset diseases that were judged 'definitely associated' with POTS were also increased by the HPV vaccines (3675 vs. 3352, RR 1.08 [95% CI 1.01 to 1.15], NNH 144, P = 0.03, I^2 = 29%)."As noted above, in the trial that compared Gardasil 9 with Gardasil, more patients on Gardasil 9 than on Gardasil experienced nervous system disorders (p = 0.01), headache (p = 0.02) and dizziness (p = 0.12).

The Uppsala Monitoring Centre, a WHO collaborating centre that accepts reports of suspected harms of vaccines and other drugs, found that POTS was reported 82 times more often for HPV vaccines than for other vaccines.[43] In 2017,[44] researchers from the centre published a paper that showed that, for the largest clusters they identified in the WHO VigiBase(R), the combination of headache and dizziness with either fatigue or syncope was more commonly reported in HPV vaccine reports than in other vaccine reports for females aged 9–25 years.
This disproportionality remained when countries reporting the signals of CRPS (Japan) and POTS (Denmark) were excluded. Even though the researchers reduced the possible influence of media attention by including only cases reported before the media attention, they identified a greater number of potentially undiagnosed cases than the *total* number of cases labeled with one of these diagnoses by the drug companies.

There is a considerable public health interest in finding out if patients who have developed POTS, CRPS, autoimmune diseases and other debilitating diseases after vaccination have acquired destructive autoantibodies. If the HPV vaccine causes dysautonomia, for example, we would expect to find autoantibodies against the autonomic nervous system more often in those patients than in other patients. In one study, such autoantibodies were found in most of 17 patients with POTS, whereas 7 patients with vasovagal syncope and 11 healthy controls did not have them.[45] Another, larger study was carried out at the Danish Syncope Centre. It showed that, after vaccination, autoantibodies were identified in most girls with POTS combined with other symptoms of dysautonomia but only in a minority of those vaccinated girls who were healthy, and in even fewer healthy controls.[46] There are additional such studies.[47]

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[42] Jørgensen L, Gøtzsche PC, Jefferson T. Benefits and harms of the human papillomavirus (HPV) vaccines: systematic review with meta-analyses of trial data from clinical study reports. Syst Rev 2020;9:43.
[43] Briefing note to experts. EMA/666938/2015. 2015; 13 Oct. https://ijme.in/pdf/g-briefing-note-to-the-experts-ema-oct-2015-unredacted.pdf
[44] Chandler RE, Juhlin K, Fransson J, et al. Current safety concerns with human papillomavirus vaccine: a cluster analysis of reports in Vigibase (R). *Drug Saf* 2017;40:81-90.
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[46] Mehlsen J, Brinth L, Pors K, et al. Autoimmunity in patients reporting long-term complications after exposure to human papilloma virus vaccination. J Autoimmun 2022;133:102921.
[47] Chandler RE. Modernising vaccine surveillance systems to improve detection of rare or poorly defined adverse events. BMJ 2019;365:l2268.

4

Appendix A

Meta-analyses and attempts at meta-analyses

Contents

Introduction

The meta-analyses I present in this document were made with the Comprehensive Meta Analysis program version 2.2.064 (fixed effect analyses) based on the data I extracted from Merck's clinical study reports on its HPV vaccines. I entered the data in Excel and double-checked that the numbers were correct before I transferred them to the statistical software to do meta-analyses. Since there was considerable heterogeneity in some of the analyses, I checked the robustness of the results by also using a random effects model. This made no difference to my conclusions. I preferred fixed effect analyses because they weigh large trials with many events more than random effects analyses.

First, Merck's clinical trial data are not reliable because Merck designed, conducted, analysed and reported their HPV vaccine trials in a way that seriously underestimated the harms of the vaccines.

This means that, when I find significant vaccine harms in my meta-analyses, despite all the flaws in Merck's trials that include omission of essential data, these are strong signals of true vaccine harms. It also means that, when I find non-significant, but elevated harms, had Merck properly conducted and reported on its studies, these could very well have become significant. Even when I did not find an elevated risk, that does not mean no risk exists because Merck's studies were poorly conducted and reported.

In the tables and meta-analysis graphs, P013, P015 and P019 are the three pivotal Future 1, 2 and 3 trials, respectively, of quadrivalent vaccine against the vaccine adjuvant. Other pivotal trials are the two "placebo-controlled" trials, P018 of Gardasil (quadrivalent vaccine) and P006 of Gardasil 9 (nine-valent vaccine), and P001, which is a large trial comparing Gardasil 9 with Gardasil.

In the tables and graphs, the two "placebo-controlled" trials come at the top, as they are the most relevant ones, despite their small size. Next come the Gardasil versus adjuvant trials and last the Gardasil 9 versus Gardasil trials.

Vaccine compared with control

Extreme variations in numbers of patients with adverse events

The proportion of patients with any adverse event, i.e. including both local, injection-site reactions and systemic adverse events, differed widely from trial to trial, even though their design was very similar, also in terms of how adverse events were to be collected and for how long. This can easily be seen by tabulating the percentage of patients with adverse events (I used the data sources shown in the table for all analyses, unless stated otherwise):

	Vaccine		Control		with events	Data source	Page
	n	N	n	N	in per cent		
P018, qHPV vs placebo	963	1165	392	584	77	V501 P018 V1 CSR_missing P018-05 and -06	140
P006, Gardasil 9 vs placebo	583	608	229	305	89	V503 P006 CSR Appendices Section 16 missing	8
P013, qHPV vs adjuvant	2497	2673	2405	2672	92	V501 P013 CSR_with P013-10 pg 712	13
P015, qHPV vs adjuvant	704	6019	665	6031	11	V501 P015 CSR_protocol P005-10 pg 1917	11
P019, qHPV vs adjuvant	1645	1890	1535	1888	84	V501 P019 CSR	566
P020, qHPV vs adjuvant	1346	2020	1252	2029	64	V501 P020 CSR_protocols P020-04 pg 958	348
P023, qHPV vs adjuvant	91	117	42	59	76	V501 P023 CSR_missing Appendices forms	6
P027, qHPV vs adjuvant	433	480	393	468	87	V501 P027 CSR-revision_only synopsis	9
P030, qHPV vs adjuvant	153	302	131	298	47	V501 P030_Statistical Analysis_China	16
P041, qHPV vs adjuvant	926	1499	856	1498	59	V501 P041 CSR_synopsis only_Chinese	20
P122, qHPV vs adjuvant	354	554	335	559	62	V501 P122 V01 CSR_Japan	21
P001, Gardasil 9 vs qHPV	6661	7071	6444	7078	93	V503 P001 CSR	25
P009, Gardasil 9 vs qHPV	287	299	281	300	95	V503 P009 CSR	8
P020, Gardasil 9 vs qHPV	204	248	203	248	82	V503 P020 CSR	9

As the three Future trials had the same design, it is particularly concerning that the percentage of patients with adverse events varied from 11% in Future 2 to 84% in Future 3 and 92% in Future 1.

This extreme heterogeneity can be tested statistically, with a chi-square test of the tree proportions, which yields $\chi^2 = 12{,}582$ with 2 df. This is not a printing error, where I happened to use a comma instead of a full stop. The chi-square value is over twelve thousand. Standard statistical software does not compute exact p-values for such high numbers of chi-square. Already when $\chi^2 = 25$ with 2 df, $p < 0.00001$,[1] less than one per 100,000. A chi-square value of twelve thousand is so extreme that it means – beyond any doubt - that the reporting of adverse events in the Future trials cannot be trusted.

Something must be terribly wrong in the Future 2 trial where only 11% of the patients had adverse events. As the three Future trials were also similar in terms of the countries that contributed patients, cultural differences cannot explain the extreme heterogeneity (Europe contributed about half the patients for Future 2). I have not seen any explanation of this in Merck's study reports.

There were similar extreme discrepancies in the proportions of other events in the Future trials, apart from serious adverse events where the proportion was the same in Future 3 as in Future 2 and only double as high in Future 1 (numbers are in per cent, Gardasil 9 is P001, the large trial comparing Gardasil 9 with Gardasil):

Subjects with adverse events	Future 1	Future 2	Future 3	Gardasil 9
all adverse events	91.7	11.4	84.2	92.6
injection-site	83.9	8.2	70.5	88.0
systemic	64.5	7.5	59.7	56.6
vaccine-related	88.3	9.5	78.2	89.9
injection-site, vaccine related	83.9	8.2	70.5	88.0
systemic, vaccine related	42.1	3.8	38.2	28.4
serious adverse events	1.8	0.8	0.8	2.9
serious adverse events, vaccine-related	0.0	0.0	0.0	0.0

It is noteworthy that, in all four pivotal trials, where the active vaccine was compared with either a strongly immunogenic adjuvant or with another vaccine (study P001), serious adverse events were so rarely

[1] https://www.socscistatistics.com/pvalues/chidistribution.aspx

considered vaccine related that the percentage was 0.0% for all the trials. A total of 642 serious adverse events were reported in these four trials, among a total of 21,173 patients (3.0%), but only 10 patients (0.05%) were considered to have experienced vaccine related serious adverse events.

Whatever the explanation is, the extreme heterogeneity is disturbing. The Gardasil 9 trial reported systemic adverse events considered vaccine related 7 times as often as the Future 2 trial. This is not because of longer follow-up because in both studies, virtually all the systemic adverse events were collected in the three two-week periods after each vaccination. In fact, the investigators were instructed not to collect adverse events outside the three two-week periods, but to call what was reported to them by the patients "new medical history." Furthermore, the whole period for collecting any adverse event (almost exclusively the serious ones) were described in the table headings as "Day 1 through Visit Cut-OffDate" for Gardasil 9 and "Days 1 to 9999" for Future 2, which meant 42 months and 48 months, respectively.

At one of the Data and Safety Monitoring Board meetings for the Future 2 trial, it was noted that many cases of serious adverse events were from Denmark. This is supported by a table of "Composite Serious Adverse Experiences:" 4 of the 19 events came from Denmark whereas only 15 came from Peru, Colombia, Finland, Iceland, United States, Mexico or Singapore. This suggested that other countries substantially underreported serious adverse events. The reporting of "Composite Nonserious Adverse Experiences" was strikingly different. In this case, 218 of the 252 events came from the United States and only 11 from Denmark.

Future 2 enrolled 72% of its subjects from Europe and North America, compared to 54% in the Gardasil 9 trial.[2] One would therefore not expect Future 2 to report adverse events in only 11% of the patients, compared to 93% in the Gardasil 9 trial.

These observations suggest that a large amount of data on adverse events in the Future 2 trial were never collected, were lost, or were suppressed after being reported to Merck. I can see no other explanations.

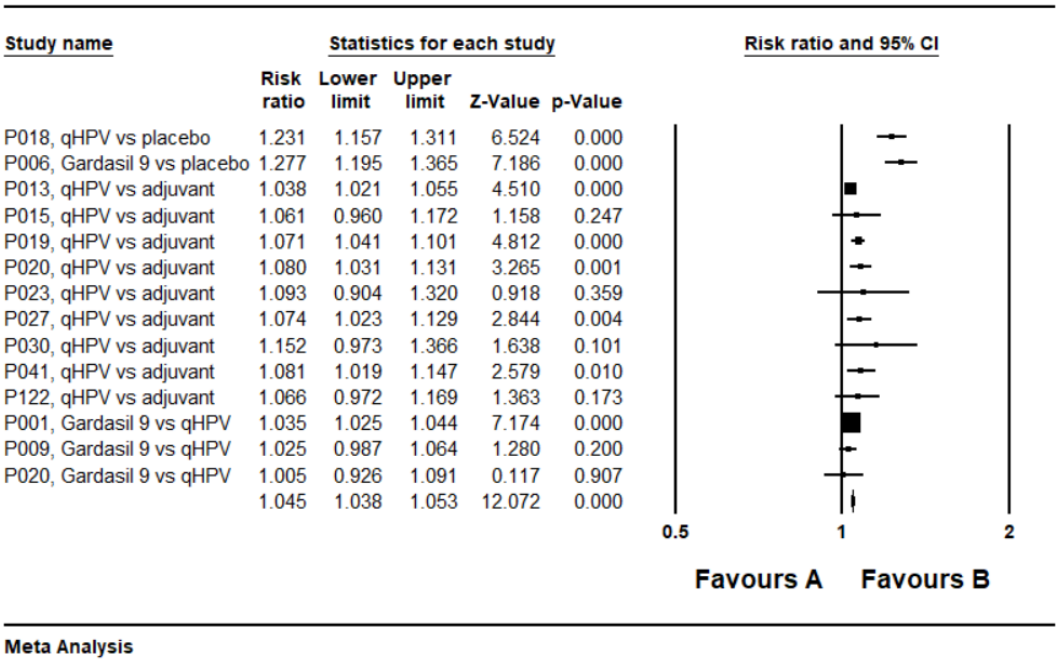
I noted that the table of adverse events in the synopsis of the Future 2 trial (V501 P015 CSR_protocol P005-10 pg 1917, p11) did not show the same numbers of patients as the same table on p3983 in the same study report. Subjects with adverse events were given as 704 and 665 vs 703 and 663; for systemic adverse events, the numbers were 448 and 453 vs 447 and 451; and for serious adverse events, they were 46 and 56 vs 45 and 54. Since the heading for the two tables was the same, "Clinical Adverse Experience Summary (Days 1 to 9999 Following Any Vaccination Visit)," the numbers should have been exactly the same. There was no explanation in the report why the numbers differed slightly, but such observations show that the numbers Merck provided in their clinical study reports cannot be trusted as they are not even internally consistent in the same report. I found several such examples also in other study reports.

All adverse events

The 14 studies already mentioned (48,962 patients) contributed to this meta-analysis. Data sources are listed on page 2 above.

[2] Data from V501 P015 CSR_protocol P005-10 pg 1917 (p339ff) and V503 P001 CSR (p974ff)

Study name	Group-A Events	Group-A Total N	Group-B Events	Group-B Total N
P018, qHPV vs placebo	963	1165	392	584
P006, Gardasil 9 vs placebo	583	608	229	305
P013, qHPV vs adjuvant	2497	2673	2405	2672
P015, qHPV vs adjuvant	704	6019	665	6031
P019, qHPV vs adjuvant	1645	1890	1535	1888
P020, qHPV vs adjuvant	1346	2020	1252	2029
P023, qHPV vs adjuvant	91	117	42	59
P027, qHPV vs adjuvant	433	480	393	468
P030, qHPV vs adjuvant	153	302	131	298
P041, qHPV vs adjuvant	926	1499	856	1498
P122, qHPV vs adjuvant	354	554	335	559
P001, Gardasil 9 vs qHPV	6661	7071	6444	7078
P009, Gardasil 9 vs qHPV	287	299	281	300
P020, Gardasil 9 vs qHPV	204	248	203	248



The risk ratio was 1.045, with a narrow 95% confidence interval (1.038 to 1.053), and $p < 0.001$. This means that the HPV vaccines caused more harm than the comparator, which was "placebo" in two trials (one of the so-called placebo studies used a potentially immunogenic carrier solution), the adjuvant in nine trials and the quadrivalent HPV vaccine in three trials.

It is easy to see on the graph that the results were heterogeneous. The risk of harm was much greater in the two placebo-controlled trials than in the adjuvant-controlled trials, and lowest in the three vaccine-controlled trials.

In meta-analyses, this is called heterogeneity. It can be quantified by I^2, which is the proportion of the total variance that is due to between study variance, i.e. I^2 = between study variance/ (between study variance + within study variance). To put it differently, I^2 describes the percentage of the variability in effect estimates that is due to heterogeneity (differences between studies) rather than sampling error (chance).

In this meta-analysis, there was significant heterogeneity, as $I^2 = 83\%$:

Model	Number Studies	Point estimate	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared
Fixed	14	1.045	1.038	1.053	12.072	0.000	77.205	13	0.000	83.162
Random	14	1.081	1.053	1.109	5.895	0.000				

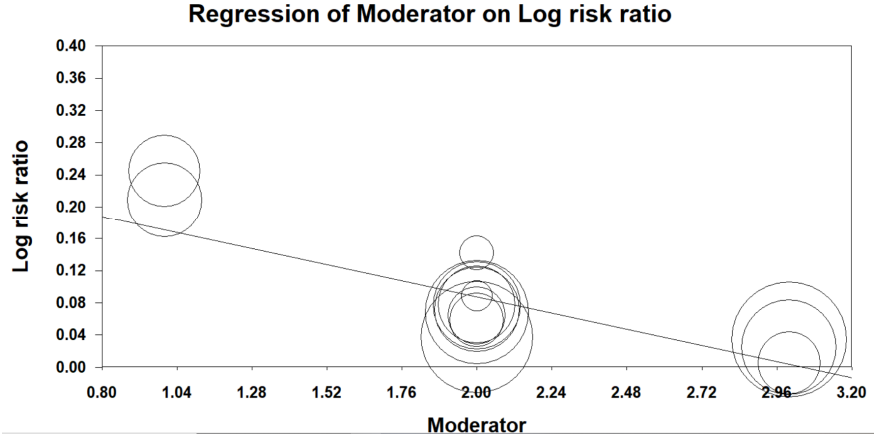
I have also, for completeness, shown the result with a random effects model that takes the between study variance into account. The risk ratio in this analysis is larger, 1.081.

Since there were three types of studies, it is highly relevant and appropriate to analyse the results for each type of comparator separately. This analysis shows that the overall result of vaccine harm is highly statistically significant ($p < 0.001$) also for each group taken separately:

Control group	Risk ratio	95% confidence interval
Placebo	1.253	1.197 to 1.311
Adjuvant	1.047	1.032 to 1.062
qHPV	1.034	1.025 to 1.043

The three confidence intervals are far from overlapping. When this is the case, it may be concluded without any statistical testing that the estimates differ much more than expected by chance, i.e. the differences are highly statistically significant.

A more formal way of showing this is to do a meta-regression. I used moderator variables 1, 2 and 3 for the "placebo," adjuvant and qHPV comparators, respectively. The graph shows a mixed effects regression (unrestricted maximum likelihood). The circles are proportional to the weights the studies have, which are determined by the number of events; thus, a study with few events contribute less to the meta-regression than a study with many events). The differences between the three estimates were highly statistically significant ($p < 0.00001$ for the slope of the line).



It is more clinically relevant to compute the risk difference than the risk ratio because, by definition, the inverse of the risk difference is the number needed to harm:

Control group	Risk difference	95% confidence interval	Number needed to harm
Placebo	0.178	0.144 to 0.211	6
Adjuvant	0.027	0.020 to 0.035	37
qHPV	0.031	0.022 to 0.039	32

Thus, the two "placebo-controlled" trials show that for every 6 subjects (= 1/0.178) treated with an HPV vaccine instead of placebo, one experiences an adverse event.

For every 37 subjects who get Gardasil instead of adjuvant, one experiences an adverse event.

For every 32 subjects who get Gardasil 9 instead of Gardasil, one experiences an adverse event.

The true harms of Merck's HPV vaccines are not known because, apart from the two small, placebo-controlled trials, Merck compared Gardasil with the adjuvant, and Gardasil 9 with Gardasil.

The results are nonetheless remarkable and important. Merck's view is that its adjuvant is harmless, but my meta-analyses show that Merck's adjuvant is harmful: The number needed to harm increased from 6 to 37 when the adjuvant was used as control instead of placebo. Thus, not only is Merck's vaccine harmful, but its vaccine adjuvant is also harmful.

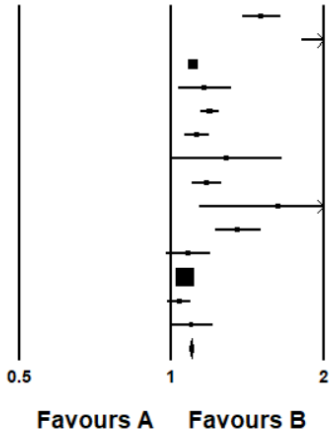
Of course, not all patients who experience an adverse event have been harmed by the vaccine or the adjuvant, as adverse events occur for many other reasons. But as this is true for both compared groups, it is correct and relevant to calculate the number needed to harm, which is a relative measure. My meta-analyses also show that Gardasil 9 is more harmful than Gardasil. This was expected because Gardasil 9 contains five more antigens and more than double as much adjuvant as Gardasil (500 µg vs 225 µg).

Injection-site adverse events

The same 14 studies already mentioned contributed also to this meta-analysis; data sources are listed on page 2. In all studies, adverse reactions at the injection site were automatically considered vaccine related, so it would make no difference to analyse all injection-site adverse reactions (the numbers occasionally differed, but only by one person).

Study name	Group-A Events	Group-A Total N	Group-B Events	Group-B Total N
P018, qHPV vs placebo	877	1165	292	584
P006, Gardasil 9 vs placebo	554	608	135	305
P013, qHPV vs adjuvant	2353	2673	2132	2672
P015, qHPV vs adjuvant	531	6019	457	6031
P019, qHPV vs adjuvant	1449	1890	1213	1888
P020, qHPV vs adjuvant	1169	2020	1046	2029
P023, qHPV vs adjuvant	84	117	33	59
P027, qHPV vs adjuvant	408	480	338	468
P030, qHPV vs adjuvant	66	302	40	298
P041, qHPV vs adjuvant	564	1499	416	1498
P122, qHPV vs adjuvant	330	554	308	559
P001, Gardasil 9 vs qHPV	6422	7071	6024	7078
P009, Gardasil 9 vs qHPV	274	299	265	300
P020, Gardasil 9 vs qHPV	196	248	179	248

Study name	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
P018, qHPV vs placebo	1.506	1.379	1.643	9.163	0.000
P006, Gardasil 9 vs placebo	2.059	1.811	2.341	11.025	0.000
P013, qHPV vs adjuvant	1.103	1.077	1.130	8.141	0.000
P015, qHPV vs adjuvant	1.164	1.033	1.312	2.487	0.013
P019, qHPV vs adjuvant	1.193	1.144	1.244	8.278	0.000
P020, qHPV vs adjuvant	1.123	1.061	1.188	4.029	0.000
P023, qHPV vs adjuvant	1.284	0.996	1.654	1.931	0.053
P027, qHPV vs adjuvant	1.177	1.100	1.259	4.723	0.000
P030, qHPV vs adjuvant	1.628	1.137	2.331	2.664	0.008
P041, qHPV vs adjuvant	1.355	1.220	1.504	5.697	0.000
P122, qHPV vs adjuvant	1.081	0.977	1.197	1.505	0.132
P001, Gardasil 9 vs qHPV	1.067	1.054	1.080	10.402	0.000
P009, Gardasil 9 vs qHPV	1.037	0.983	1.094	1.346	0.178
P020, Gardasil 9 vs qHPV	1.095	0.990	1.211	1.771	0.077
	1.095	1.085	1.106	18.277	0.000



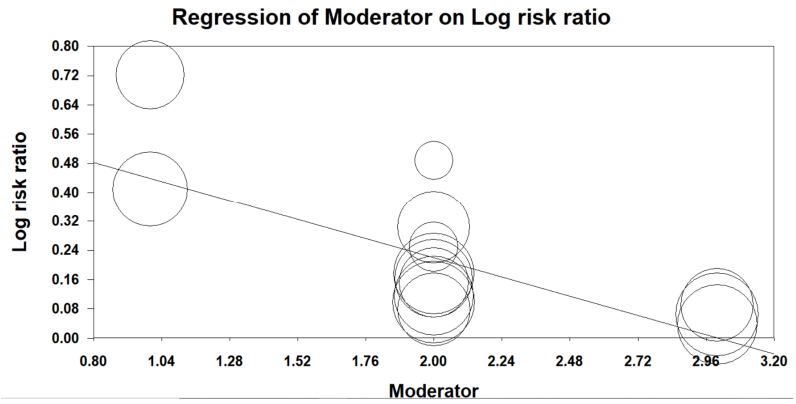
Meta Analysis

Model	Number Studies	Point estimate	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared
Fixed	14	1.095	1.085	1.106	18.277	0.000	209.671	13	0.000	93.800
Random	14	1.215	1.149	1.285	6.823	0.000				

These results are also remarkable. The risk ratio was 1.095, with a narrow 95% confidence interval (1.085 to 1.106), and $p < 0.001$. This means that the HPV vaccines caused more injection-site harms than the comparator. There was significant heterogeneity, $I^2 = 94\%$. It is easy to see on the graph where most of the heterogeneity comes from. The risk of harm was much greater in the two placebo-controlled trials than in the adjuvant-controlled trials, and lowest in the three vaccine-controlled trials:

Control group	Risk ratio	95% confidence interval
Placebo	1.663	1.547 to 1.787
Adjuvant	1.135	1.115 to 1.155
qHPV	1.066	1.053 to 1.079

For all three comparators, the result was highly statistically significant ($p < 0.001$). A meta-regression showed that the differences between the three estimates were highly statistically significant, $p < 0.00001$:



The number needed to harm was even less than for all adverse events:

Control group	Risk difference	95% confidence interval	Number needed to harm
Placebo	0.336	0.298 to 0.373	3
Adjuvant	0.043	0.035 to 0.051	23
qHPV	0.056	0.046 to 0.067	18

There was one more important finding. In the only two placebo-controlled trials, the risk ratio for injection-site adverse events was much higher, 2.06 (95% confidence interval 1.81 to 2.34) for the nine-valent vaccine (Gardasil 9) than for the quadrivalent vaccine (Gardasil), 1.51 (1.38 to 1.64). The confidence intervals were far apart, and this difference was therefore highly statistically significant (p = 0.00009). This shows that the combined effect of giving the patients many antigens (nine vs four), a high dose of adjuvant (500 µg vs 225 µg) and many vaccine doses (six vs three, as all patients in the Gardasil 9 study had received three doses of Gardasil earlier) increase the harms.

These observations lead to the following conclusions:

1) It was inappropriate for Merck to expose healthy children and young people in the control groups of their Gardasil (qHPV) trials apart from one (which a drug regulator had requested; it was not Merck's idea) to a harmful adjuvant. On top of this, Merck gave the impression that its adjuvant was safe. Merck stated in its main study reports that "The safety profile of the Sponsor's aluminum adjuvant is well characterized" and did not at any point admit that its adjuvant is harmful.

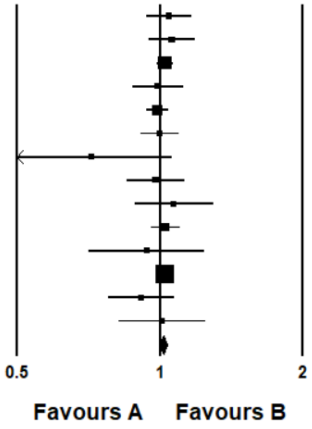
2) Merck's use of its adjuvant as a comparator was inappropriate and resulted in undisclosed harms.

Systemic adverse events

The same 14 studies already mentioned also contributed to this meta-analysis; data sources are listed on page 2. Merck reported these data very selectively. In 7 trials, systemic adverse events were only reported for the three two-week periods after each vaccination. These 7 trials were a "placebo-controlled" trial (P018), four adjuvant-controlled trials (P023, P027, P030 and P122), and two vaccine-controlled trials (P009 and P020). In the other 7 trials, systemic adverse events were also reported selectively because the investigators had been instructed not to report such events as adverse events beyond the two-week periods but to call them new medical history. In my opinion, this was scientifically inappropriate.

Study name	Group-A Events	Group-A Total N	Group-B Events	Group-B Total N
P018, qHPV vs placebo	541	1165	260	584
P006, Gardasil 9 vs placebo	374	608	177	305
P013, qHPV vs adjuvant	1746	2673	1701	2672
P015, qHPV vs adjuvant	448	6019	453	6031
P019, qHPV vs adjuvant	1121	1890	1135	1888
P020, qHPV vs adjuvant	617	2020	622	2029
P023, qHPV vs adjuvant	37	117	26	59
P027, qHPV vs adjuvant	212	480	211	468
P030, qHPV vs adjuvant	129	302	119	298
P041, qHPV vs adjuvant	770	1499	750	1498
P122, qHPV vs adjuvant	80	554	86	559
P001, Gardasil 9 vs qHPV	4052	7071	3957	7078
P009, Gardasil 9 vs qHPV	142	299	156	300
P020, Gardasil 9 vs qHPV	101	248	100	248

Study name	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
P018, qHPV vs placebo	1.043	0.935	1.164	0.754	0.451
P006, Gardasil 9 vs placebo	1.060	0.945	1.188	0.999	0.318
P013, qHPV vs adjuvant	1.026	0.986	1.068	1.268	0.205
P015, qHPV vs adjuvant	0.991	0.874	1.124	-0.142	0.887
P019, qHPV vs adjuvant	0.987	0.936	1.040	-0.504	0.614
P020, qHPV vs adjuvant	0.996	0.908	1.093	-0.077	0.939
P023, qHPV vs adjuvant	0.718	0.485	1.062	-1.659	0.097
P027, qHPV vs adjuvant	0.980	0.850	1.129	-0.285	0.776
P030, qHPV vs adjuvant	1.070	0.884	1.295	0.691	0.489
P041, qHPV vs adjuvant	1.026	0.956	1.101	0.712	0.476
P122, qHPV vs adjuvant	0.939	0.709	1.243	-0.442	0.658
P001, Gardasil 9 vs qHPV	1.025	0.996	1.055	1.678	0.093
P009, Gardasil 9 vs qHPV	0.913	0.777	1.073	-1.102	0.271
P020, Gardasil 9 vs qHPV	1.010	0.816	1.250	0.091	0.927
	1.017	0.998	1.036	1.739	0.082



Meta Analysis

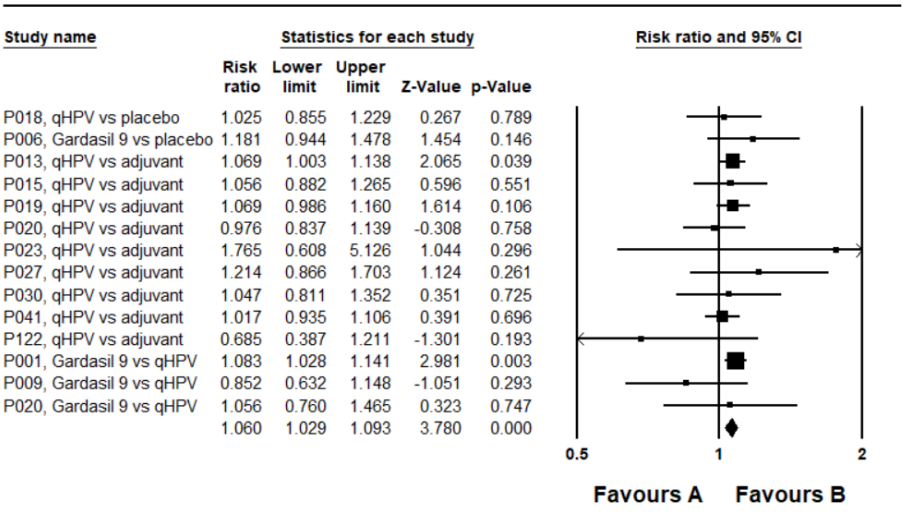
Model	Number Studies	Point estimate	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared
Fixed	14	1.017	0.998	1.036	1.739	0.082	8.483	13	0.811	0.000
Random	14	1.017	0.998	1.036	1.739	0.082				

There was no heterogeneity in this analysis, $I^2 = 0$. The risk ratio was increased, 1.017, but the lower limit of the 95% confidence interval was slightly below 1 (0.998 to 1.036), which means that the difference was not statistically significant (p = 0.08). Given that Merck selectively reported its results and underreported substantially the adverse events with Gardasil, it is not important that the p-value is not formally statistically significant. See also the other results I found in my meta-analyses, which confirm that Gardasil causes systemic adverse events.

Vaccine related systemic adverse events

The same 14 studies already mentioned contributed also to this meta-analysis; data sources are listed on page 2. As just noted, Merck reported these data very selectively.

Study name	Group-A Events	Group-A Total N	Group-B Events	Group-B Total N
P018, qHPV vs placebo	274	1165	134	584
P006, Gardasil 9 vs placebo	186	608	79	305
P013, qHPV vs adjuvant	1162	2673	1087	2672
P015, qHPV vs adjuvant	233	6019	221	6031
P019, qHPV vs adjuvant	746	1890	697	1888
P020, qHPV vs adjuvant	275	2020	283	2029
P023, qHPV vs adjuvant	14	117	4	59
P027, qHPV vs adjuvant	66	480	53	468
P030, qHPV vs adjuvant	87	302	82	298
P041, qHPV vs adjuvant	639	1499	628	1498
P122, qHPV vs adjuvant	19	554	28	559
P001, Gardasil 9 vs qHPV	2088	7071	1930	7078
P009, Gardasil 9 vs qHPV	62	299	73	300
P020, Gardasil 9 vs qHPV	57	248	54	248



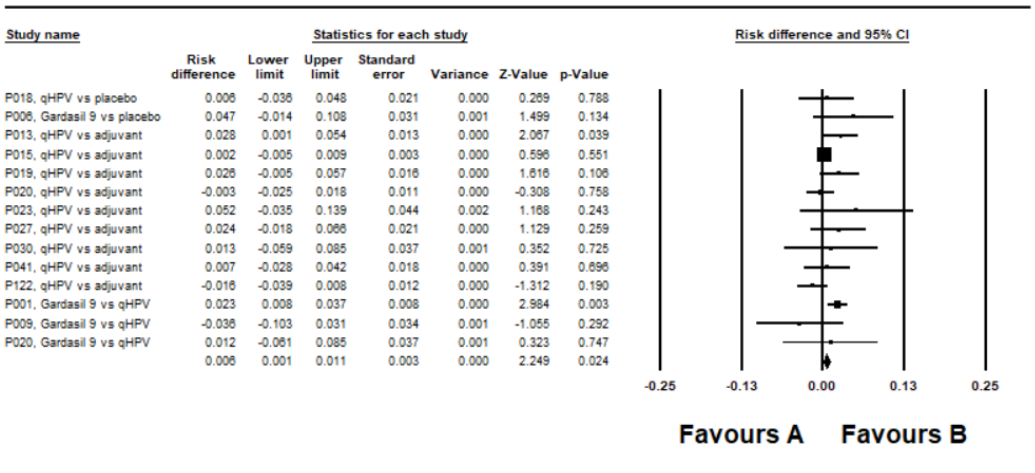
Meta Analysis

Model	Number Studies	Point estimate	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared
Fixed	14	1.060	1.029	1.093	3.780	0.000	9.640	13	0.723	0.000
Random	14	1.060	1.029	1.093	3.780	0.000				

There was no heterogeneity in this analysis, $I^2 = 0$. The risk ratio for systemic adverse events the investigators considered vaccine related was significantly increased, 1.060 (95% confidence interval 1.029 to 1.093, $p < 0.001$). As noted just above, the risk ratio was also increased for all systemic adverse events, but less so, 1.017 (95% confidence interval 0.998 to 1.036).

The total number of patients with systemic adverse events in the 14 trials was 20,123, about double as many as those the investigators considered vaccine related, 10,370. Thus, when the "background noise" became reduced by half, it was apparent that the vaccines increase systemic adverse events significantly.

The risk difference is more meaningful and relevant than the risk ratio:



Meta Analysis

Model	Number Studies	Point estimate	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared
Fixed	14	0.006	0.003	0.000	0.001	0.011	2.249	0.024	19.350	13	0.113	32.816
Random	14	0.009	0.005	0.000	0.000	0.019	1.979	0.048				

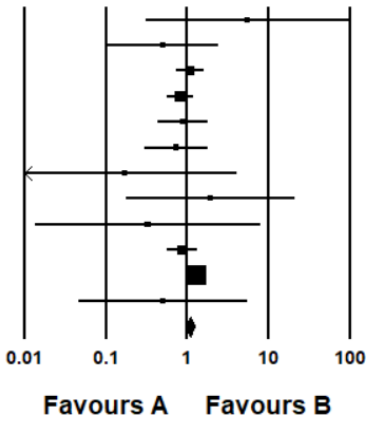
This analysis shows that the number needed to harm is 167.

Serious adverse events

The same 14 studies already mentioned contributed also to this meta-analysis; data sources are listed on page 2. Two of the 14 studies had no events in either group and therefore do not appear in the meta-analysis. I excluded a case of cervical carcinoma in the vaccine group from study.

Study name	Group-A Events	Group-A Total N	Group-B Events	Group-B Total N
P018, qHPV vs placebo	5	1165	0	584
P006, Gardasil 9 vs placebo	3	608	3	305
P013, qHPV vs adjuvant	49	2673	45	2672
P015, qHPV vs adjuvant	46	6019	56	6031
P019, qHPV vs adjuvant	14	1890	16	1888
P020, qHPV vs adjuvant	8	2020	11	2029
P023, qHPV vs adjuvant	0	117	1	59
P027, qHPV vs adjuvant	2	480	1	468
P030, qHPV vs adjuvant	0	302	1	298
P041, qHPV vs adjuvant	38	1499	43	1498
P122,qHPV vs adjuvant	0	554	0	559
P001, Gardasil 9 vs qHPV	233	7071	183	7078
P009, Gardasil 9 vs qHPV	1	299	2	300
P020, Gardasil 9 vs qHPV	0	248	0	248

Study name	Statistics for each study					Risk ratio and 95% CI
	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value	
P018, qHPV vs placebo	5.519	0.306	99.636	1.157	0.247	
P006, Gardasil 9 vs placebo	0.502	0.102	2.471	-0.848	0.396	
P013, qHPV vs adjuvant	1.088	0.729	1.626	0.414	0.679	
P015, qHPV vs adjuvant	0.823	0.558	1.214	-0.983	0.326	
P019, qHPV vs adjuvant	0.874	0.428	1.786	-0.369	0.712	
P020, qHPV vs adjuvant	0.731	0.294	1.812	-0.677	0.498	
P023, qHPV vs adjuvant	0.169	0.007	4.098	-1.092	0.275	
P027, qHPV vs adjuvant	1.950	0.177	21.432	0.546	0.585	
P030, qHPV vs adjuvant	0.329	0.013	8.042	-0.682	0.495	
P041, qHPV vs adjuvant	0.883	0.574	1.358	-0.566	0.571	
P001, Gardasil 9 vs qHPV	1.274	1.053	1.542	2.492	0.013	
P009, Gardasil 9 vs qHPV	0.502	0.046	5.503	-0.564	0.572	
	1.088	0.945	1.254	1.173	0.241	



Meta Analysis

Model	Number Studies	Point estimate	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared
Fixed	12	1.088	0.945	1.254	1.173	0.241	11.218	11	0.425	1.942
Random	12	1.075	0.926	1.248	0.953	0.341				

There was very little heterogeneity in this analysis, I^2 = 2%. The risk ratio for serious adverse events was increased, 1.088, but the difference was not statistically significant (95% confidence interval 0.945 to 1.254; p = 0.24). This result needs to be interpreted in the light of the low number of patients who reportedly experienced serious adverse events, only 761, as well as the other limitations referenced throughout my report. Whether a signal of harm is statistically significant or not, depends on the number of events. The increased risk ratio for serious adverse events should therefore not be dismissed just because the p-value was not statistically significant. It should be compared with the other risk ratios:

	Risk ratio	No. of events	p-value
all adverse events	1.045	32010	< 0.001
injection-site adverse events	1.095	28155	< 0.001
systemic adverse events	1.017	20123	0.08
systemic adverse events, vaccine related	1.060	10370	< 0.001
serious adverse events	1.088	761	0.24

The risk ratio for serious adverse events was larger than for all adverse events and for vaccine related systemic adverse events and was about the same as that for injection-site adverse events.

These data show that Merck's HPV vaccines cause substantial harm, no matter in which way this harm is being assessed. The harms are also more severe than those in the control groups (see below).

Vaccine related serious adverse events

The same 14 studies already mentioned contributed also to this meta-analysis; data sources are listed on page 2. Only 14 of the 761 (2%) serious adverse events were considered vaccine related by the investigators (n1: number of patients with serious adverse events, n2: number of patients with vaccine related serious adverse events):

	Vaccine		Control	
	n1	n2	n1	n2
P018, qHPV vs placebo	5	0	0	0
P006, Gardasil 9 vs placebo	3	1	3	1
P013, qHPV vs adjuvant	49	1	45	0
P015, qHPV vs adjuvant	46	3	56	2
P019, qHPV vs adjuvant	14	0	16	0
P020, qHPV vs adjuvant	8	0	11	0
P023, qHPV vs adjuvant	0	0	1	1
P027, qHPV vs adjuvant	2	0	1	0
P030, qHPV vs adjuvant	0	0	1	0
P041, qHPV vs adjuvant	38	0	43	1
P122, qHPV vs adjuvant	0	0	0	0
P001, Gardasil 9 vs qHPV	233	2	183	2
P009, Gardasil 9 vs qHPV	1	0	2	0
P020, Gardasil 9 vs qHPV	0	0	0	0
Total	**399**	**7**	**362**	**7**

In contrast, the investigators considered 52% of the systemic adverse events vaccine related. By definition, abortions were considered serious adverse events, but the occurrence of abortions cannot explain the large difference in events considered vaccine related by the investigators. It is concerning that this percentage dropped from 52% to 2% for those systemic events that were serious. I consider it unlikely that only 2% of serious adverse events are vaccine related while 52% of the systemic adverse events are vaccine related. In my experience, clinical trial investigators sometimes avoid reporting such events. For example, when I reported to a company conducting a trial of an AIDS drug that a patient had experienced a serious adverse event, I was convinced was drug related, it resulted in significant additional work, with considerable negotiations with the company and the filling out of many forms. The general sentiment at the department was that we should avoid calling an event drug related, as we did not have the time for all the follow up it caused.

I did not find it meaningful or reliable to meta-analyse the 14 events.

Severe injection-site adverse events

In some of the trials, the adverse events were graded as mild, moderate and severe:

Mild: awareness of sign or symptom, but easily tolerated
Moderate: discomfort enough to cause interference with usual activities
Severe: incapacitating with inability to work or do usual activity.

As easily tolerated adverse events are not a problem, the two most important categories are obviously moderate and severe adverse events.

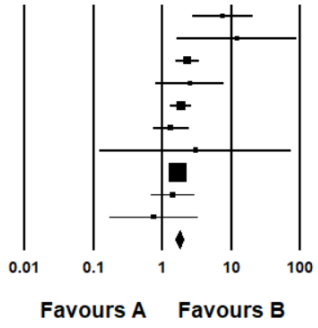
Merck reported these data selectively. At first, I considered data from only 8 of the 14 studies could be included. However, there were partial data from Future 1 and Future 2. Substudy P012 under P013 had data from 3502 of the 5345 patients (66%) in the trial, and a substudy of US patients in P015 had data from 895 of the 12,050 patients (7%) in the trial.

The data sources for these events are not in all cases the same as those for the meta-analyses above:

Data sources for data on severity of adverse events			
		Injection site	Systemic
	Data source	Page	Page
P018, qHPV vs placebo	V501 P018 V1 CSR_missing P018-05 and -06	151	163
P006, Gardasil 9 vs placebo	V503 P006 CSR Appendices Section 16 missing	148	156
P013, qHPV vs adjuvant	V501 P012	171	186
P015, qHPV vs adjuvant	V501 P015 V2 CSR	299	315
P019, qHPV vs adjuvant	V501 P019 V1 CSR_missing Appendices	423	452
P020, qHPV vs adjuvant	V501 P020 CSR_protocols P020-04 pg 958	738	749
P122, qHPV vs adjuvant	V501 P122 V01 CSR_Japan	126	132
P001, Gardasil 9 vs qHPV	V503 P001 CSR	775	810
P009, Gardasil 9 vs qHPV	V503 P009 CSR	175	208
P020, Gardasil 9 vs qHPV	V503 P020 CSR	87	189

Study name	Group-A Events	Group-A Total N	Group-B Events	Group-B Total N
P018, qHPV vs placebo	60	1165	4	584
P006, Gardasil 9 vs placebo	24	608	1	305
P013, qHPV vs adjuvant	85	1752	37	1750
P015, qHPV vs adjuvant	10	448	4	447
P019, qHPV vs adjuvant	89	1890	48	1888
P020, qHPV vs adjuvant	25	2020	19	2029
P122, qHPV vs adjuvant	1	554	0	559
P001, Gardasil 9 vs qHPV	315	7071	190	7078
P009, Gardasil 9 vs qHPV	17	299	12	300
P020, Gardasil 9 vs qHPV	3	248	4	248

Study name	Statistics for each study					Risk ratio and 95% CI
	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value	
P018, qHPV vs placebo	7.519	2.746	20.588	3.926	0.000	
P006, Gardasil 9 vs placebo	12.039	1.636	88.574	2.444	0.015	
P013, qHPV vs adjuvant	2.295	1.569	3.356	4.281	0.000	
P015, qHPV vs adjuvant	2.494	0.788	7.894	1.555	0.120	
P019, qHPV vs adjuvant	1.852	1.312	2.616	3.500	0.000	
P020, qHPV vs adjuvant	1.322	0.730	2.392	0.921	0.357	
P122, qHPV vs adjuvant	3.027	0.124	74.146	0.679	0.497	
P001, Gardasil 9 vs qHPV	1.660	1.390	1.981	5.609	0.000	
P009, Gardasil 9 vs qHPV	1.421	0.691	2.924	0.955	0.339	
P020, Gardasil 9 vs qHPV	0.750	0.170	3.316	-0.379	0.704	
	1.793	1.566	2.053	8.449	0.000	



Meta Analysis

Model	Number Studies	Point estimate	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared
Fixed	10	1.793	1.566	2.053	8.449	0.000	16.816	9	0.052	46.480
Random	10	1.939	1.490	2.522	4.934	0.000				

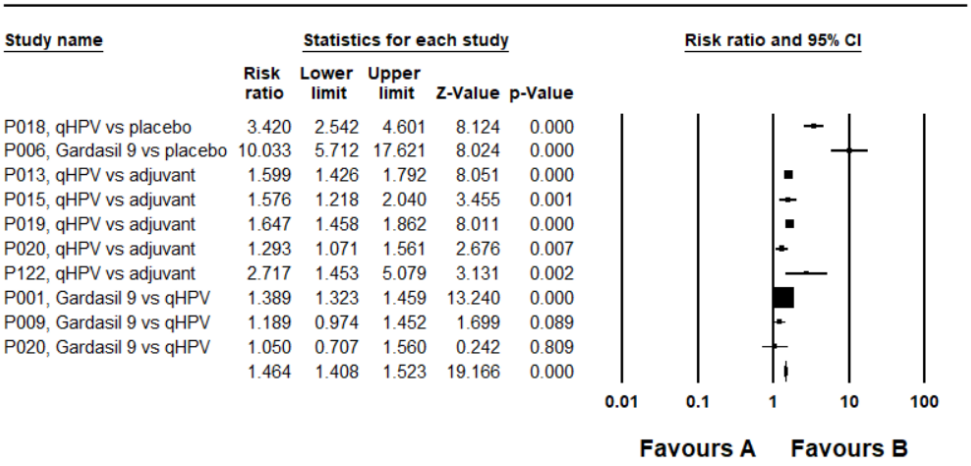
The vaccines increased the occurrence of severe injection-site adverse events (risk ratio 1.79 (1.57 to 2.05), $p < 0.001$) and there was a large difference between the placebo-controlled trials and the trials with adjuvant or vaccine as control. The risk ratio for the two placebo-controlled trials was 8.27 (3.37 to 20.33), with a confidence interval very far from that for the risk ratio of 1.93 (1.54 to 2.43) for the five adjuvant-controlled trials and 1.63 (1.37 to 1.93) for the three vaccine-controlled trials.

The risk difference for the two placebo-controlled trials was 0.041 (0.030 to 0.052), which means that for every 24 subjects injected with a vaccine, one will experience severe harm (incapacitating with inability to work or do usual activity).

Severe or moderate injection-site adverse events

Merck reported these data selectively (see above).

Study name	Group-A Events	Group-A Total N	Group-B Events	Group-B Total N
P018, qHPV vs placebo	307	1165	45	584
P006, Gardasil 9 vs placebo	240	608	12	305
P013, qHPV vs adjuvant	573	1752	358	1750
P015, qHPV vs adjuvant	119	448	75	447
P019, qHPV vs adjuvant	536	1890	325	1888
P020, qHPV vs adjuvant	224	2020	174	2029
P122, qHPV vs adjuvant	35	554	13	559
P001, Gardasil 9 vs qHPV	2654	7071	1912	7078
P009, Gardasil 9 vs qHPV	128	299	108	300
P020, Gardasil 9 vs qHPV	42	248	40	248



Meta Analysis

Model	Number Studies	Point estimate	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared
Fixed	10	1.464	1.408	1.523	19.166	0.000	99.189	9	0.000	90.926
Random	10	1.764	1.474	2.112	6.184	0.000				

The vaccines increased the occurrence of severe or moderate injection-site adverse events (risk ratio 1.46 (1.41 to 1.52), $p < 0.001$) and there was a large difference between the placebo-controlled trials and the trials with adjuvant or vaccine as control. The risk ratio for the two placebo-controlled trials was 4.32 (3.32 to 5.62), with a confidence interval very far from that for the risk ratio of 1.58 (1.47 to 1.69) for the five adjuvant-controlled trials and 1.37 (1.31 to 1.44) for the three vaccine-controlled trials.

The risk difference for the two placebo-controlled trials was 0.25 (0.22 to 0.27), which means that for every 4 subjects injected with a vaccine, one will experience severe or moderate harm (incapacitating with inability to work or do usual activity, or discomfort enough to cause interference with usual activities).

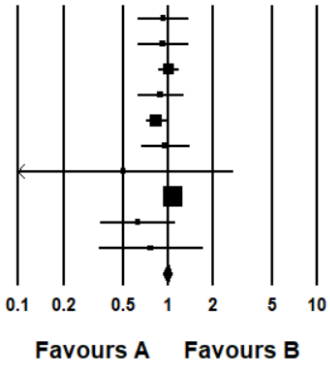
Severe systemic adverse events

Merck reported these data selectively, in two ways. As for injection-site events, a significant amount of data from the Future 1 and 2 trials had been left out (see above). In addition to this - and in contrast to injection-site reactions, which were always considered vaccine related - there was no information

anywhere in Merck's study reports which of the severe systemic adverse events the investigators considered vaccine related, even though such information was collected in all the trials that collected information about severity. This is scientifically inappropriate, particularly considering that Merck provided hundreds of irrelevant tables in their study reports.

Study name	Group-A Events	Group-A Total N	Group-B Events	Group-B Total N
P018, qHPV vs placebo	69	1165	37	584
P006, Gardasil 9 vs placebo	63	608	34	305
P013, qHPV vs adjuvant	251	1752	246	1750
P015, qHPV vs adjuvant	51	448	57	447
P019, qHPV vs adjuvant	233	1890	278	1888
P020, qHPV vs adjuvant	51	2020	53	2029
P122, qHPV vs adjuvant	2	554	4	559
P001, Gardasil 9 vs qHPV	826	7071	761	7078
P009, Gardasil 9 vs qHPV	17	299	27	300
P020, Gardasil 9 vs qHPV	10	248	13	248

Study name	Statistics for each study					Risk ratio and 95% CI
	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value	
P018, qHPV vs placebo	0.935	0.635	1.376	-0.341	0.733	
P006, Gardasil 9 vs placebo	0.930	0.627	1.378	-0.364	0.716	
P013, qHPV vs adjuvant	1.019	0.866	1.199	0.228	0.819	
P015, qHPV vs adjuvant	0.893	0.626	1.272	-0.628	0.530	
P019, qHPV vs adjuvant	0.837	0.712	0.984	-2.149	0.032	
P020, qHPV vs adjuvant	0.967	0.661	1.413	-0.176	0.861	
P122, qHPV vs adjuvant	0.505	0.093	2.743	-0.792	0.428	
P001, Gardasil 9 vs qHPV	1.086	0.990	1.192	1.752	0.080	
P009, Gardasil 9 vs qHPV	0.632	0.352	1.134	-1.538	0.124	
P020, Gardasil 9 vs qHPV	0.769	0.344	1.721	-0.638	0.523	
	0.998	0.934	1.067	-0.061	0.951	



Meta Analysis

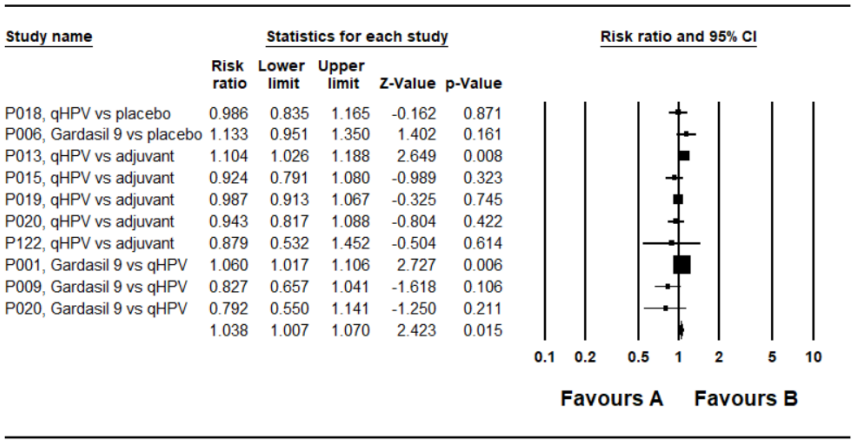
Model	Number Studies	Point estimate	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared
Fixed	10	0.998	0.934	1.067	-0.061	0.951	11.811	9	0.224	23.802
Random	10	0.963	0.875	1.059	-0.785	0.432				

Merck's trials showed the risk ratio was not increased, 0.998 (95% confidence interval 0.934 to 1.067, p = 0.95). As explained above, this should be considered a false negative finding.

Severe and moderate systemic adverse events

Merck reported these data selectively (see just above, for severe systemic adverse events).

Study name	Group-A Events	Group-A Total N	Group-B Events	Group-B Total N
P018, qHPV vs placebo	303	1165	154	584
P006, Gardasil 9 vs placebo	253	608	112	305
P013, qHPV vs adjuvant	828	1752	749	1750
P015, qHPV vs adjuvant	178	447	193	448
P019, qHPV vs adjuvant	750	1890	759	1888
P020, qHPV vs adjuvant	307	2020	327	2029
P122, qHPV vs adjuvant	27	554	31	559
P001, Gardasil 9 vs qHPV	2780	7071	2625	7078
P009, Gardasil 9 vs qHPV	89	299	108	300
P020, Gardasil 9 vs qHPV	42	248	53	248



Meta Analysis

Model	Number Studies	Point estimate	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared
Fixed	10	1.038	1.007	1.070	2.423	0.015	16.739	9	0.053	46.234
Random	10	1.011	0.958	1.067	0.399	0.690				

The risk ratio was significantly increased, 1.038 (1.007 to 1.070, p = 0.015). The risk difference was also increased but the difference was not statistically significant, 0.007 (-0.003 to 0.017), p = 0.15) per Merck's reporting of its trials. As explained above, this should be considered a false negative finding.

Deaths

The data sources are listed on page 2 above. It is not clear if all deaths were accounted for. As one example, 5 vs 5 patients died in the large Gardasil 9 vs Gardasil trial according to Merck's study report and the published trial report,[3] but according to the EU trial register,[4] 6 vs 5 patients died:

Serious adverse events	Base Study: Low-dose V503	Base Study: Mid-dose V503	Base Study: High-dose V503	Base Study: Gardasil	Extension Study: Mid-dose V503 (Cohort 1)	Extension Study: Mid-dose V503 (Cohort 2)
Total subjects affected by serious adverse events						
subjects affected / exposed	4 / 310 (1.29%)	233 / 7071 (3.30%)	5 / 305 (1.64%)	184 / 7078 (2.60%)	1 / 150 (0.67%)	25 / 3049 (0.82%)
number of deaths (all causes)	0	6	0	5	0	0

[3] Joura EA, Giuliano AR, Iversen O-E, et al. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. N Engl J Med 2015;372:711-23.

[4] https://www.clinicaltrialsregister.eu/ctr-search/trial/2007-003528-39/results#moreInformationSection

In the US trial register clinicaltrials.gov,[5] which Merck last updated in November 2018, I could only find 1 vs 1 deaths (apart from one foetal death). I checked my findings by searching on death and mortality on the website but did not find more deaths. Even more curious, a table about total mortality had no information although it seemed to include all the patients (the next item was serious adverse events):

All-Cause Mortality

	Base Study: Low-Dose V503		Base Study: Mid-dose V503		Base Study: High-dose V503		Base Study: Gardasil		Extension Study: Mid-dose V503 (Cohort 1)		Extension Study: Mid-dose V503 (Cohort 2)	
	Affected / at Risk (%)		Affected / at Risk (%)		Affected / at Risk (%)		Affected / at Risk (%)		Affected / at Risk (%)		Affected / at Risk (%)	
Total	--/--		--/--		--/--		--/--		--/--		--/--	

Serious Adverse Events

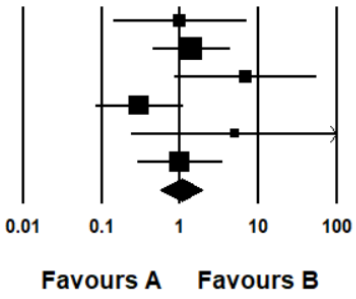
	Base Study: Low-Dose V503		Base Study: Mid-dose V503		Base Study: High-dose V503		Base Study: Gardasil		Extension Study: Mid-dose V503 (Cohort 1)		Extension Study: Mid-dose V503 (Cohort 2)	
	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events
Total	4/310 (1.29%)		233/7071 (3.30%)		5/305 (1.64%)		184/7078 (2.60%)		1/150 (0.67%)		25/3049 (0.82%)	

There was also one more patient in the US trial register with a serious adverse event in the Gardasil group than reported by Merck in its study report and published trial report. These discrepancies have not been explained.

Study name	Group-A Events	Group-A Total N	Group-B Events	Group-B Total N
P018, qHPV vs placebo	0	1165	0	584
P006, Gardasil 9 vs placebo	0	608	0	305
P013, qHPV vs adjuvant	2	2673	2	2672
P015, qHPV vs adjuvant	7	6019	5	6031
P019, qHPV vs adjuvant	7	1890	1	1888
P020, qHPV vs adjuvant	3	2020	10	2029
P023, qHPV vs adjuvant	0	117	0	59
P027, qHPV vs adjuvant	0	480	0	468
P030, qHPV vs adjuvant	0	302	0	298
P041, qHPV vs adjuvant	2	1499	0	1498
P122, qHPV vs adjuvant	0	554	0	559
P001, Gardasil 9 vs qHPV	5	7071	5	7078
P009, Gardasil 9 vs qHPV	0	299	0	300
P020, Gardasil 9 vs qHPV	0	248	0	248

[5] https://www.clinicaltrials.gov/ct2/show/results/NCT00543543

Study name	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
P013, qHPV vs adjuvant	1.000	0.141	7.091	-0.000	1.000
P015, qHPV vs adjuvant	1.403	0.445	4.417	0.578	0.563
P019, qHPV vs adjuvant	6.993	0.861	56.779	1.820	0.069
P020, qHPV vs adjuvant	0.301	0.083	1.093	-1.824	0.068
P041, qHPV vs adjuvant	4.997	0.240	103.990	1.039	0.299
P001, Gardasil 9 vs qHPV	1.001	0.290	3.456	0.002	0.999
	1.061	0.571	1.969	0.186	0.852



Meta Analysis

Model	Number Studies	Point estimate	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared
Fixed	6	1.061	0.571	1.969	0.186	0.852	8.020	5	0.155	37.652
Random	6	1.164	0.509	2.664	0.359	0.719				

The risk of death was increased, risk ratio 1.061, but the confidence interval was very wide, 0.571 to 1.969, and p = 0.85.

Dose-response studies

Different vaccine doses were used in five studies:

1) V501 P001 CSR: monovalent HPV 11 L1 VLP vaccine
2) V501 P002 CSR: monovalent HPV 16 L1 VLP vaccine
3) V501 P004 CSR: monovalent HPV 16 L1 VLP vaccine
4) V501 P007 CSR_protocol amendments_pg 2047: quadrivalent HPV L1 VLP vaccine
5) V501 P016 V2 CSR: quadrivalent HPV L1 VLP vaccine

The doses and number of subjects randomised were:

1	**adjuvant**	**10 mcg**	**20 mcg**	**50 mcg**	**100 mcg**
	28	28	28	28	28
2	**adjuvant**	**10/40 mcg**	**40 mcg**	**80 mcg**	
	27	13	45	24	
3	**adjuvant**	**10 mcg**	**20 mcg**	**40 mcg**	**80 mcg**
	52	112	105	104	107
4	**adj 225 mcg**	**adj 450 mcg**	**low**	**medium**	**high**
	135	140	275	272	280
5	**20%**	**40%**	**60%**	**100%**	
	503	514	507	1015	

I merged the data in order to have three groups for all five studies: low, medium and high dose. High dose was the highest dose for each study, medium dose was the next category (apart from study 5, where 40% and 60% were combined), and low dose was the rest. For convenience, as there were very few patients in

all studies, I added the adverse events across the studies to get an idea of whether any dose-response relationship was apparent:

	low	medium	high
subjects with follow-up	1426	1449	1431
with one or more adverse events	1277	1294	1319
injection-site adverse events	1131	1190	1217
systemic adverse events	949	909	896
systemic adverse events, vaccine related	509	502	491

There was a clear dose-response relationship for injection-site adverse events. I did a chi-square test for trend, which yielded $\chi^2 = 16.02$ (2 df), or $p = 0.0003$.[6] A more formal meta-analysis is not needed, at it would yield a similar result, given this strong signal.

For systemic adverse events, I did not find a dose-response relationship. I consider this a false negative finding caused by the many flaws in Merck's trials because the more antigens and amount of adjuvant there is in a vaccine, the more systemic adverse events it will cause. In agreement with this obvious fact, my analyses showed that Gardasil 9 is more harmful than Gardasil, which was expected because Gardasil 9 contains five more antigens and more than double as much adjuvant as Gardasil (500 µg vs 225 µg) (see below). In the large trial that compared Gardasil 9 with Gardasil (P001), a supplementary appendix to the trial publication revealed that there were more serious systemic adverse events in girls receiving the 9-valent vaccine than in those receiving the 4-valent vaccine (3.3% vs. 2.6%, $p = 0.01$).[7] The number needed to harm was only 141, and it would undoubtedly have been even smaller if the control group had not received Gardasil, too.

Other meta-analyses and attempts at meta-analyses

To explore whether there were signals of harms related to POTS, CRPS and autoimmune disorders in Merck's study reports, I did several additional meta-analyses or attempted to do them.

Those reports that described randomised trials had included a total of 62,640 subjects but numbers with follow-up data, which are the ones I used for my meta-analyses, were lower than this. In some of the trials, some subjects had been randomised to monovalent vaccine. The five biggest trials had randomised 40,025 subjects: 25,801 to a quadrivalent vaccine (Gardasil) or adjuvant (four trials), and 14,215 to Gardasil 9 or Gardasil (one trial). I included data from these five trials and also data from the only two trials that had a "placebo control" (2,705 subjects).

New medical history

This category of events was not used in all Merck's trials. For the seven trials I focused on, these are the data sources:

[6] Altman DG. Practical statistics for medical research. London: Chapman & Hall; 1991:p261.
[7] Joura EA, Giuliano AR, Iversen OE, et al. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. N Engl J Med 2015;372:711-23.

	Data source	Page
P018, qHPV vs placebo	V501 P018 V1 CSR_missing P018-05 and -06	354
P006, Gardasil 9 vs placebo	V503 P006 CSR Appendices Section 16 missing	426
P013, qHPV vs adjuvant	V501 P013 CSR_with P013-10 pg 712	559
P015, qHPV vs adjuvant	V501 P015 CSR_protocol P005-10 pg 1917	407
P019, qHPV vs adjuvant	V501 P019 CSR	684
P020, qHPV vs adjuvant	V501 P020 CSR_protocols P020-04 pg 958	852
P001, Gardasil 9 vs qHPV	V503 P001 CSR	2123

And these were the number of events:

	n vaccine	N vaccine	n control	N control	Per cent with events
P018, qHPV vs placebo	520	1179	280	594	45
P006, Gardasil 9 vs placebo	175	613	99	305	30
P013, qHPV vs adjuvant	2328	2713	2311	2724	85
P015, qHPV vs adjuvant	4357	6075	4399	6076	72
P019, qHPV vs adjuvant	756	1908	702	1902	38
P020, qHPV vs adjuvant	498	2020	463	2029	24
P001, Gardasil 9 vs qHPV	5096	7099	5069	7105	72

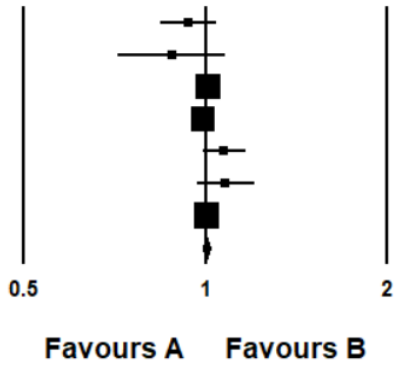
The percentage of patients with one or more events called new medical history differed significantly, from 24% to 85%, which is deeply concerning because the study protocols were very similar, and the events in the table are those registered in all studies from day 1 until month 7. These huge differences cannot have occurred by chance, e.g. a comparison of the rates in Future 2 with Future 3 gives $p = 8 \times 10^{-305}$. This means 0.00 … 8 (with 304 zeros after the full stop before the digit 8 appears), which is the lowest p-value I have ever seen. For comparison, the weight of the earth is 6×10^{33} even when measured in µg.

This shows once again that what Merck has reported about possible harms of its vaccines cannot be trusted. Gender differences, for example, cannot explain the extreme heterogeneity. The lowest event rate was from a study conducted in males, but all other studies were conducted in females, apart from P018 where about half the subjects were males.

I did a meta-analysis for the sake of completeness:

Study name	Group-A Events	Group-A Total N	Group-B Events	Group-B Total N
P018, qHPV vs placebo	520	1179	280	594
P006, Gardasil 9 vs placebo	175	613	99	305
P013, qHPV vs adjuvant	2328	2713	2311	2724
P015, qHPV vs adjuvant	4357	6075	4399	6076
P019, qHPV vs adjuvant	756	1908	702	1902
P020, qHPV vs adjuvant	498	2020	463	2029
P001, Gardasil 9 vs qHPV	5096	7099	5069	7105

Study name	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
P018, qHPV vs placebo	0.936	0.841	1.041	-1.222	0.222
P006, Gardasil 9 vs placebo	0.880	0.717	1.079	-1.229	0.219
P013, qHPV vs adjuvant	1.011	0.989	1.034	1.011	0.312
P015, qHPV vs adjuvant	0.991	0.969	1.013	-0.835	0.404
P019, qHPV vs adjuvant	1.074	0.990	1.164	1.722	0.085
P020, qHPV vs adjuvant	1.080	0.967	1.207	1.371	0.170
P001, Gardasil 9 vs qHPV	1.006	0.986	1.027	0.582	0.561
	1.004	0.992	1.016	0.638	0.523



Meta Analysis

Model	Number Studies	Point estimate	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared
Fixed	7	1.004	0.992	1.016	0.638	0.523	9.501	6	0.147	36.847
Random	7	1.005	0.986	1.024	0.523	0.601				

The risk ratio was increased, 1.004 (95% CI 0.992 to 1.016), but the difference was not statistically significant (p = 0.52) according to Merck's reporting. As noted above, this should be considered a false negative finding.

Autoimmune events

Nine of the 14 studies provided data about potential autoimmune events:

	Data source	Page
P006, Gardasil 9 vs placebo	V503 P006 CSR Appendices Section 16 missing	434
P013, qHPV vs adjuvant	V501 P013 CSR_with P013-10 pg 712	356
P015, qHPV vs adjuvant	V501 P015 CSR_protocol P005-10 pg 1917	314
P019, qHPV vs adjuvant	V501 P019 CSR	624
P020, qHPV vs adjuvant	V501 P020 CSR_protocols P020-04 pg 958	351
P122, qHPV vs adjuvant	V501 P122 V01 CSR_Japan	155
P001, Gardasil 9 vs qHPV	V503 P001 CSR	894
P009, Gardasil 9 vs qHPV	V503 P009 CSR	266
P020, Gardasil 9 vs qHPV	V503 P020 CSR	259

There were several issues about how Merck handled these data.

Merck did not split adverse events as usual, into adverse events and new medical history, in two separate sets of tables, but lumped them so that there was only one type of table, e.g. "Subjects With Adverse Events and/or New Medical History Potentially Indicative of an Autoimmune Disorder (During the Entire Study Period - All Vaccinated Subjects)" in study P006.

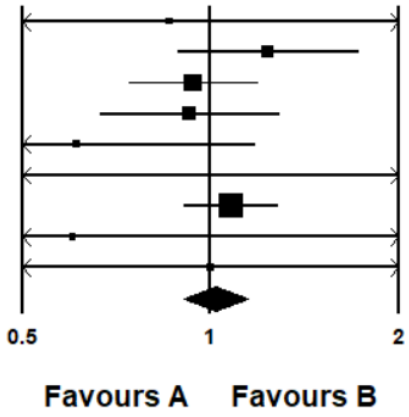
Furthermore, for some studies, Merck operated with three different categories where the reported events became fewer and fewer, as illustrated by the large study P001 that compared Gardasil 9 with Gardasil:

	n Gardasil 9	n Gardasil
Subject With Adverse Events and/or New Medical History Potentially Indicative of an Autoimmune Disorder by System Organ Class (Day 1 Through Visit Cut-off Date, Efficacy Substudy)	254	235
Subject With Adverse Events and/or New Medical History Potentially Indicative of an Autoimmune Disorder by System Organ Class - Events Considered As Autoimmune Conditions by the Reporting Investigator (Day 1 Through Visit Cut-off Date, Efficacy Substudy)	57	44
Subject With Vaccine-Related Adverse Events and/or New Medical History Potentially Indicative of an Autoimmune Disorder by System Organ Class (Day 1 Through Visit Cut-off Date, Efficacy Substudy)	17	20

It is unclear what the differences are between the three ways of reporting events. “Potentially Indicative” “Considered As Autoimmune Conditions by the Reporting Investigator” (57 vs 14) would seem to be rather similar to “Vaccine-Related” “Potentially Indicative of an Autoimmune Disorder” (17 vs 20) but it was not the same. I used the largest numbers for my meta-analysis:

Study name	Group-A Events	Group-A Total N	Group-B Events	Group-B Total N
P006, Gardasil 9 vs placebo	12	608	7	305
P013, qHPV vs adjuvant	74	2713	60	2724
P015, qHPV vs adjuvant	126	6075	134	6076
P019, qHPV vs adjuvant	65	1908	70	1902
P020, qHPV vs adjuvant	14	2020	23	2029
P122, qHPV vs adjuvant	4	554	2	559
P001, Gardasil 9 vs qHPV	254	7106	235	7109
P009, Gardasil 9 vs qHPV	3	299	5	300
P020, Gardasil 9 vs qHPV	2	248	2	248

Study name	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
P006, Gardasil 9 vs placebo	0.860	0.342	2.162	-0.321	0.748
P013, qHPV vs adjuvant	1.238	0.885	1.733	1.246	0.213
P015, qHPV vs adjuvant	0.940	0.739	1.196	-0.500	0.617
P019, qHPV vs adjuvant	0.926	0.664	1.290	-0.457	0.648
P020, qHPV vs adjuvant	0.611	0.316	1.185	-1.458	0.145
P122, qHPV vs adjuvant	2.018	0.371	10.973	0.813	0.416
P001, Gardasil 9 vs qHPV	1.081	0.908	1.287	0.879	0.379
P009, Gardasil 9 vs qHPV	0.602	0.145	2.496	-0.699	0.484
P020, Gardasil 9 vs qHPV	1.000	0.142	7.043	0.000	1.000
	1.019	0.907	1.146	0.320	0.749



Meta Analysis

Model	Number Studies	Point estimate	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared
Fixed	9	1.019	0.907	1.146	0.320	0.749	6.058	8	0.641	0.000
Random	9	1.019	0.907	1.146	0.320	0.749				

The risk ratio was increased, 1.019 (95% CI 0.907 to 1.146), but the difference was not statistically significant (p = 0.75) according to Merck's reporting. Because of the many flaws in the way Merck handled adverse events, this is likely a false negative finding.

Symptoms related to POTS or CRPS

Since the HPV vaccines are suspected of causing POTS (postural orthostatic tachycardia syndrome) and CRPS (complex regional pain syndrome), I examined Merck's studies to find out what they showed.

This proved to be difficult even though a variety of approaches were attempted. As many patients (2.9%) experienced serious adverse events in study P001 that compared Gardasil 9 with Gardasil, I copied the MedDRA terms (MedDRA means the Medical Dictionary for Regulatory Activities) from p827ff in the main trial report (V503 P001 CSR) into a spreadsheet and asked an investigator with expertise in POTS to assess which ones she considered might be associated with POTS and CRPS, in a blinded fashion, i.e. without knowing which of the two groups they came from.

There were 165 MedDRA subterms, grouped under MedDRA headings (e.g. nervous system disorders). The investigator considered that eight and four of these subterms could be associated with POTS or CRPS, respectively (for POTS: vertigo positional, non-cardiac chest pain, headache, migraine, presyncope, syncope, tension headache and dyspnoea; for CRPS: fibromyalgia, myalgia, hypoaesthesia and sensory disturbance). I searched in the study reports using these terms and also "orthostatic," "tilt table test" and "tilt test" (to find occurrences of postural orthostatic tachycardia syndrome), "complex regional pain syndrome," "chronic regional pain syndrome," POTS and CRPS. Lastly, I went through all the study reports again to ensure I had not overlooked anything.

My attempts at finding out if Merck's vaccines might cause POTS or CRPS by examining Merck's deficient clinical trials proved futile. As I have described, a great deal of data were missing, and the data Merck presented were split in so many ways, in many hundreds of tables, that it was impossible to collect them in a way that ensured that the same person was not counted more than once, which is a prerequisite for statistical analyses.

Below I explain some of the problems with Merck's studies that made it impossible to meta-analyse POTS and CRPS.

Future 1 study

In the main report for Future 1 (V501 P013 CSR_with P013-10 pg 712), there was a table of serious clinical adverse experiences (p275), but there were no MedDRA terms. There was no table of systemic adverse experiences, neither in the final report nor in the interim report. I went through the lists of tables (there were 296 tables in total), and I also searched for "by System Organ Class" in the two reports. I found lists of deaths, discontinuations, serious adverse events, pregnancy adverse events, and new medical conditions. MedDRA terms had been used in many places, e.g. in tables of new medical conditions, but there was not a single table of systemic adverse events with MedDRA terms or even one without these terms but showing what was reported.

Such tables existed in the two reports for the substudies P011 and P012 but they were also wanting.

For P011 (V501 P011 CSR), there was a table of systemic adverse events on p217, but under the MedDRA heading "Ear and labyrinth disorders" there were no MedDRA subheadings. We are only told that there were 17 such events but not what they were even though they can be highly relevant. For example, the study report for study P001 mentioned in a table of serious adverse events under this MedDRA heading a case on Gardasil 9 of "vertigo positional," which is a key symptom for POTS (V503 P001 CSR, p827). Also, for "Vascular disorders," there were no MedDRA subheadings; the only information was that there were 14 patients with such disorders.

For P012 (V501 P012), it was even worse. There was a table of systemic adverse events on p176, but under "Ear and labyrinth disorders" we are only told that there were 41 such events in the two main groups plus 2 in the small monovalent vaccine group. For "Eye Disorders" it was the same, 48 events plus 2 in the monovalent vaccine group, but no information about what these events were.

Future 2 study

As for Future 1, a table of serious clinical adverse experiences had no MedDRA terms (V501 P015 CSR_protocol P005-10 pg 1917, p233).

There was no table of systemic adverse experiences for all the patients. An announced listing of "All clinical adverse experiences" in the main report of 5533 pages (p262) did not exist. Another report (V501 P015 V1 CSR) of 2000+ pages is not helpful either, and in a third report (V501 P015 V2 CSR) of 5000+ pages, systemic adverse events were subdivided in many ways, with separate tables for the USA, the UK and "Non-U.S. and Non-U.K. Study Sites," and only showing data for two weeks after each injection, with other tables showing data from day 16 and beyond. It is therefore not possible to avoid double counting of some patients. All in all, there were 270 tables in the reports, many of which add nothing of value.

In the third report, there was a table with "Subjects With Systemic Clinical Adverse Experiences" with MedDRA terms, but it was a subgroup of a subgroup of a subgroup (p303). It was only about events occurring within the first two weeks after each vaccination, only in the United States (only 889 patients (7%) out of the total of 12,050 with data), and only if the incidence was at least 1% in one or more vaccination groups (which means that if 4 patients experienced syncope or positional vertigo on the vaccine, it would not be reported, as there were only 457 patients in the vaccine group). This selective reporting of possible harms is extremely concerning.

Another table, "Clinical Adverse Experience Summary (Days 1 to 15 Following Any Vaccination Visit) — General Safety Cohort (Non-U.S. and Non-U.K. Study Sites)" (p723) looked relevant but it only showed numbers with adverse experiences and was followed by many pages of tables with injection-site reactions in patients from the USA, tables according to whether patients were seronegative on day 1 or not, tables with separate data after each of the three vaccinations, tables from days 1 to 5 and other tables from day 6 and beyond so that double counting cannot be avoided.

On p760, there is a table with MedDRA terms for all systemic clinical adverse experiences but only for the US patients and only for two weeks after each vaccination. It takes another 80 pages before a similar table appears for the 138 patients from the UK on p840. The UK data are seriously insufficient, which Merck acknowledged (no vaccination report card was used). Headache, for example, a key symptom in POTS, occurred in 223 patients (24%) in USA but only in one patient (1%) in the UK.

On p846, there was a table on non-US and non-UK data, still for only the three two-week periods, which showed that only 5 patients (2 on the vaccine and 3 on adjuvant) had any "Ear And Labyrinth Disorders" (1 patient with tinnitus and 4 with vertigo out of 11,002 patients).

As I had serious doubts about the veracity of these data, I compared them with a similar table from trial P001 (Gardasil 9 versus Gardasil), also with systemic adverse events occurring within the three two-week periods (V503 P001 CSR, p1810). The table showed that 106 of 14,149 patients had experienced "Ear And Labyrinth Disorders," and of these, 7 had tinnitus, 26 had vertigo and 1 had positional vertigo. This difference is very unlikely to have occurred by chance. This is seen most clearly if we compare like with like, those patients in both studies that received the qHPV vaccine (Gardasil). There were 2 of 5509 vs 49 of 7078 with "Ear And Labyrinth Disorders," $p = 2 \times 10^{-10}$.

This raises serious concerns. At the very least, such comparisons confirm that what Merck has shown about adverse experiences in its study reports is plainly unreliable.

Future 3 study

As for Future 1 and Future 2, a table of serious clinical adverse experiences had no MedDRA terms (V501 P019 CSR, p577).

As I could not find a list with MedDRA terms in the report, I looked up an earlier report (V501 P019 V1 CSR). As for Future 2, an announced listing of "All adverse experiences" (p508) did not exist. The next line in the text was about "New Medical History," as if this were the same as all adverse experiences.

I went through the index of tables in both reports carefully. There was a total of 399 tables and 7000+ pages. I located a table of all "Systemic Clinical Adverse Experiences," but as usual, only for the three two-week periods after each vaccination (p794). Considering how important this table is, it is remarkable that it

came after a huge amount of irrelevant information, and not in the final report but in an earlier report. This table was number 381 out of the 399 tables and it came on page 6754 out of 7000+ pages.

The table showed that 20 of 1908 patients on qHPV experienced "Ear And Labyrinth Disorders," of which 1 was tinnitus and 14 were vertigo. In the Future 2 study, 2 of 5509 patients experienced "Ear And Labyrinth Disorders;" $p = 2 \times 10^{-10}$, exactly the same as for the difference between Future 2 and the large Gardasil 9 study (see just above).

This also raises serious concerns.

Gardasil 9 vs Gardasil

In contrast to the Future studies, a table of serious adverse events had MedDRA terms (V503 P001 CSR, p827). One patient in the Gardasil 9 group experienced positional vertigo.

As noted above, there was a table of systemic adverse events occurring within the three two-week periods on p1810.

Results of my electronic searches for POTS and CRPS

I did various electronic searches in Merck's study reports to identify cases of POTS or CRPS, in addition to manual searches.

POTS and orthostatic hypotension

I did not find any cases of POTS in Merck's study reports. "Orthostatic hypotension" or orthostatic intolerance was mentioned for 11 patients before they were randomised or prior to the first vaccination:

V501 P012, p2757: 4 patients.
V501 P015 V2 CSR, p588: 1 patient.
V503 P001 CSR, p1642: 1 patient (with orthostatic intolerance).
V503 P001 CSR, p1660: 2 patients.
V503 P006 CSR Appendices Section 16, p265: 3 patients.

During the trials, 13 patients experienced orthostatic hypotension, 11 on Gardasil 9 or Gardasil, and 2 on adjuvant. Nine of the 13 patients were described under the "new medical history" category. Only for one patient could I find any details about the event. In this patient (V503 P020 CSR), the event occurred after the first vaccination with Gardasil 9 and lasted two days (p1809), and it was described as mild (p203).

The 13 patients with orthostatic hypotension:

V501 P013 CSR_with P013-10 pg 712, p658: 1 on qHPV and 1 on adjuvant after day 1, under "New Medical History."
V501 P013 CSR_with P013-10 pg 712, p4311: 1 on adjuvant after month 7, under "New Medical History."
V503 P001 CSR, p1832: 3 patients during first two weeks after each vaccination on qHV.
V503 P001 CSR, p2184: 2 patients on Gardasil 9 and 2 on qHPV after day 1, under "New Medical History."
V503 P020 CSR, p180: 1 patient on Gardasil 9, under "Systemic Adverse Events" during first two weeks after each vaccination.

P007 V503 P007, p261: 2 patients on Gardasil 9, under "Medical History," who also received Repevax (against diphtheria, tetanus, pertussis and polio) concomitantly. No details provided.

The term "orthostatic" appeared once more in my electronic searches:

V503 P001 CSR, p2459: This is a narrative about a serious adverse event (leading to hospitalization) for a patient who felt unwell and dizzy for some minutes before she nearly fainted while exercising, 155 days after the third dose of Gardasil 9, and after having had nausea and vomiting during the previous two weeks. The narrative noted: "orthostatic test normal." This information was repeated on a CIOMS form on p7298.

"Tilt table test" and "tilt test" were mentioned in three study reports. "Tilt table test" was listed for one patient in two trials under Investigations in a list with "New Medical History" (V501 P013 CSR_with P013-10 pg 712, p606, and V503 P001 CSR, p2152). "Tilt test" was mentioned in a narrative for a serious adverse event on Gardasil 9 where a patient experienced syncope and had a positive tilt test (V503 P006 CSR Appendices, p444); the cardiologist did not provide a diagnosis of POTS but of dysautonomia.

Conclusions

My meta-analyses and other analyses demonstrate that Merck underreported potential harms of its vaccines; left out a significant amount of essential data from its study reports even though Merck collected them; and split the data it presented in so many ways that it was often impossible to avoid double counting. This conduct was so pervasive that Merck's trials of its HPV vaccines cannot be used to assess whether the vaccines cause serious, long-lasting harms. Despite all the flaws, in my review of the HPV vaccine trials, I found clear signals of long-lasting, serious, systemic harms, including harms related to dysautonomia.[8] The large trial that compared Gardasil 9 with Gardasil (P001) confirmed this. More patients on Gardasil 9 than on Gardasil experienced nervous system disorders ($p = 0.01$), headache ($p = 0.02$) and dizziness (this difference was not statistically significant, $p = 0.12$, but when events are subdivided, a true signal might not be statistically significant). The number needed to harm for nervous system disorders was only 50. The corresponding table for new medical history also showed that more patients on Gardasil 9 than on Gardasil had nervous system disorders, 515 vs 481.

[8] Jørgensen L, Gøtzsche PC, Jefferson T. Benefits and harms of the human papillomavirus (HPV) vaccines: systematic review with meta-analyses of trial data from clinical study reports. Syst Rev 2020;9:43.

Appendix B

Non-human studies
Review Notes

Contents

Animal and *in vitro* studies

Merck's animal studies cannot be used for a reliable assessment of vaccine toxicity in animals for the following reasons.

Randomisation

I did not find any descriptions of how the animals were selected for the vaccine and control groups. Random allocation is essential for ensuring that the groups are comparable to begin with, before the interventions are applied, and for animal studies, the accepted standard is to use three levels of randomisation: randomisation of animals to intervention and control groups; random housing to prevent behavioural differences between groups introduced through differences in light intensity and temperature; and random outcome assessments to prevent influence on results from diurnal variation.[1]

Blinding

I did not find any descriptions that those who assessed animal behaviour or did the necropsies were blinded, and it must therefore be assumed that they were not, as blinding takes an effort, which would be expected to be mentioned. The lack of blinding is important because some animals received saline injections, which did not have the same visual appearance as vaccine injections. Blinding is essential for avoiding bias in the assessments of the outcomes (apart from objective laboratory results such as antibody titres). Merck acknowledged the importance of blinding in its human studies and it is therefore inconsistent that the company did not blind its animal studies.

Dose of Merck's aluminium adjuvant varied from study to study

For its human studies (see, for example, Appendix C, p59), Merck argued that the dose of the aluminium adjuvant should be the same in the vaccine group as in the control group: "By using placebo that contained a dose of aluminium adjuvant that was identical to the dose included in the qHPV vaccine, it was possible to assess the safety profile attributable to the HPV 6, 11, 16, and 18 L1 VLP components of the vaccine." It therefore makes no sense that Merck did not use the same dose of adjuvant in the control formulation as in the vaccine in its animal studies.

In a large subacute intramuscular toxicity study, Merck's adjuvant (called "aluminium" in a table) was given as 900 µg/mL to 60 control mice and as 788 µg/mL (together with a quadrivalent vaccine) to 60 other mice. There was no explanation why the adjuvant dose was not the same, or why Merck did not use saline or no injection at all for the control animals, which would have been more reasonable choices, particularly considering that the aim of the study was to assess local toxicity: "As indicated in the above table, inflammation was present in the muscle at the injection sites in almost all the animals in the study" (see below). This shows that the adjuvant is harmful. If the control mice had not received any injections with adjuvant, there would not have been inflammatory changes.

[1] Hooijmans CR, Rovers MM, de Vries RBM, et al. SYRCLE's risk of bias tool for animal studies. BMC Med Res Methodol 2014;14:43.

In another large three-month toxicity study in 200 rats (see below), the adjuvant dose was 1.097 mg/mL in the control group misleadingly called placebo whereas it was 0.788 mg/mL in a low-dose vaccine group, 1 mg/ml in a mid-dose group, and 1.097 mg/mL in a high-dose group. The doses of the other four ingredients, sodium borate, sodium chloride, histidine and polysorbate, were exactly the same in the three vaccine groups and the adjuvant group. There was no explanation why the adjuvant doses were not the same.

In contrast, in a study of 90 pregnant rats, the vaccine and the control contained the same amount of aluminium adjuvant, 1000 µg/mL.

In an immunogenicity study in 6 macaques with no control group, the vaccine contained 309.5 µg of aluminium adjuvant per 0.5 mL dose

The excessive precision of the adjuvant dose, while it was not the same in the compared formulations, or from study to study, makes no scientific sense but makes it difficult to compare the various animal studies. Furthermore, it conceals what the harms are to use adjuvant in a control group when studying local toxicity. These are violations of generally accepted research practices and were scientifically inappropriate.

Merck's conclusions contradicted what they found

When Merck found many changes at the injection site and beyond in both the vaccine and the adjuvant groups in the large subacute intramuscular toxicity study (see below), Merck concluded that "None of these changes was treatment related." It is difficult to understand what might have caused these harms if they were not caused by the injections (the treatment).

Merck's statement that, "the overall damage at the injection sites was not more severe in these animals [those receiving the vaccine] as compared to controls [those receiving the adjuvant]" is absurd. If the control mice had not received any injections, there would not have been any changes.

In the three-month toxicity study in 200 rats, Merck stated that there was "progressive resolution of the skeletal muscle changes" at the same time as acknowledging that the residual inflammation was chronic. This is contradictory. Merck admitted that its adjuvant causes harm but argued that since the harms were similar to those caused by the high-dose vaccine, this meant that they had "minimal toxicological significance" (see below). This is a spurious argument. There was also a saline control group, but Merck did not consider the results in this group in its conclusion.

This was scientifically inappropriate for two reasons: It was a violation of generally accepted research practices (improper reporting of results) and conflicting data were omitted (saline does not cause these harms).

Merck concluded that the harms were within acceptable limits for vaccine treatment in rats even though the induced changes had not resolved at the final necropsies. This is an inappropriate conclusion.

Merck's toxicity studies did not go beyond three months although in drug toxicity studies, rats are usually followed until they have all died from natural causes, after a couple of years.

Merck stated that "in general, there were no differences" between the adjuvant control and the saline control groups. This statement is false. According to Merck's summary, the changes in the adjuvant and the high-dose vaccine groups included myofiber degeneration, inflammation, and hyperplasia of the draining iliac and inguinal lymph nodes. When half of the animals were killed for the interim necropsy after

67 days, muscle fiber degeneration in the quadriceps where the injections were given were seen in all 20 rats in the adjuvant group and in all 20 rats in the high-dose vaccine group, but no changes were seen in the saline placebo group. At final necropsy, there were persisting changes in muscle inflammation and lymph nodes in all the 40 rats in the adjuvant and high-dose groups and no changes in the saline group (see below).

Merck's results showed beyond any doubt that the adjuvant causes harm, but Merck claimed the opposite, that the adjuvant has similar effects as saline. This is false.

Missing data or analyses in the largest toxicity study

In the large three-month toxicity study in 200 rats, there were five groups, with 40 animals in each group, but the summary did not mention the results in the placebo group, the phosphate buffered saline group, which is a much more relevant control group than the aluminium adjuvant control group (see below).

This is scientifically inappropriate (selective reporting of findings and omission of conflicting data). Why have a genuine placebo group and then not mention what the results were in this group?

Even though the toxicology report takes up 776 pages, there were also omissions in the main text. Merck argued that because "in general, there were no differences" between the adjuvant control group and the saline placebo control group, they only presented results for the saline and the vaccine groups. As just noted, the argument was false, and in a scientific report, the data should be presented.

At interim necropsy, the low-dose and mid-dose males were not examined, and at final necropsy, the low-dose and mid-dose animals were not examined for either sex. There was no explanation why these data were missing.

The study report mentioned a "damage score," but there were no such scores in the text, and the text did not refer to any tables where they could be found. I went through every page in the report manually and found some information, but this was not called "damage score" but "overall damage." I discovered that the information, which appeared in four tables, was grossly incomplete. One table showed "overall damage" with scores 1 to 4 related to the injection site for female rats at interim autopsy, but only for the three vaccine groups. Another table showed similar scores for males at interim autopsy, but now only for the saline placebo, the adjuvant and the high-dose group. A third table showed scores for females at final necropsy, but only for the saline placebo, adjuvant and the high-dose group. A fourth table showed scores for males at final necropsy for the same three groups out of five.

Merck not only left out essential data from its report but was inconsistent about what they left out.

There were other omissions in the tables, e.g. there were only results for the haematological changes in the three vaccine groups, not in the adjuvant group or in the saline placebo group. I consider it likely that the adjuvant causes changes in some of these variables, as it is a strongly immunogenic substance, compared to a saline placebo, but by omitting the data, Merck has ensured that no one can find out.

The globulins increased in the three vaccine groups, which was expected, because some of these are vaccine induced immune globulins, but yet again, due to missing data, one could not see if the adjuvant also increased globulins. It is scientifically inappropriate to omit these data, which would likely contradict Merck's misleading narrative that its aluminium adjuvant is equally harmless as a saline placebo.

Merck reported that there were statistically significant increases in splenic weights in female rats in the mid- and high-dose groups at interim necropsy compared to the saline placebo and showed the differences to placebo as percentages in a table:

Treatment-Related Organ Weight Changes
(Percent Difference in Mean Values From Concurrent PBS Controls)

	Dose Group							
	Females				Males			
	MAA	V503 Low	V503 Mid	V503 High	MAA	V503 Low	V503 Mid	V503 High
Spleen Weight[a]								
Absolute	-	-	+22*	+24*	-	-	-	-
Relative to body weight	-	-	+19*	+19*	-	-	-	-
Relative to brain weight	-	-	+21*	+21*	-	-	-	-

[a] Statistics performed by trend assessment.
* = p≤0.05.
- = No treatment-related change.
MAA = Merck Aluminum Adjuvant.

Three-Month Intramuscular Toxicity Study in Rats Dosed Once Every 21 Days With a 21-Day Recovery Period.

There were no data for the adjuvant control group or the low-dose vaccine group for female rats, and there were no data at all for male rats for any of the five groups. Instead of data, there was a hyphen and a footnote saying that the hyphen meant "no treatment-related change."

"No change" is a vague and subjective term that should rarely if ever be used in science instead of showing the actual data. It does not exclude the possibility that there *was* an increase in splenic weight in the groups with a hyphen. Some pages further ahead in the study report I found data I could use to resurrect Merck's inappropriate table (mean spleen weight in g; 8-10 animals per group):

	Saline placebo	Adjuvant	Low-dose	Mid-dose	High-dose
Females	0.45	0.46	0.53	0.55	0.56
Males	0.75	0.73	0.79	0.82	0.86

Based on this table, I reconstructed Merck's table, with data in all cells (changes are in per cent, compared to the saline placebo):

Females				Males			
Adjuvant	Low-dose	Mid-dose	High-dose	Adjuvant	Low-dose	Mid-dose	High-dose
2	18	22	24	-3	5	9	15

When the full data set is presented, it appears that there is a dose-response relationship: the higher the dose, the greater the increase in spleen weight.

However, it was not only the content of virus like particles (the antigens) that increased over the three dose levels; the amount of adjuvant increased as well, from 0.788 mg/mL over 1 mg/ml to 1.097 mg/mL, which is 39% more in the high-dose group than in the low-dose group. By increasing the amount of adjuvant, Merck made it difficult to evaluate if the dose-response relationship is solely caused by an increasing number of antigens, or if the adjuvant also contributed to the findings.

This is the largest toxicity study Merck carried out, but Merck ruined it by multiple instances of scientific misconduct.

Suboptimal statistical analyses

In the pivotal three-month toxicity study in 200 rats, Merck analysed the outcomes for females and males separately, which makes it more difficult to detect signals of harm. This is inappropriate also because there is no good reason to expect different reactions in females and males.

Confusing, contradictory and erroneous information

In an immunogenicity study in 25 rats, the aluminium adjuvant injection given to 5 control rats was defined as both L-931224 and as L-931225, on the same page (see below). This information is inconsistent.

There were two control groups. One received the adjuvant and the other a phosphate buffered saline. Merck misleadingly described these groups as "placebo and PBS control groups." The correct description is the opposite: "adjuvant control and PBS placebo groups."

In a three-month toxicity study of 30 rats treated with a 9-valent vaccine and 30 rats treated with saline, the findings were similar to those in the bigger toxicity study of 200 rats described above, but Merck concluded in the summary: "There were no test article-related organ weight changes at scheduled necropsies" (see below). This was not true.

Merck tried to explain away what they found: "At interim necropsy, a few isolated parameters reached statistical significance ($p<0.05$) after adjustment for multiplicity (increase in mean spleen weight when expressed as percent of brain weight and decrease in mean testis weight when expressed as percent of body weight). Owing to the low magnitude of the change and in the absence of any histomorphologic correlate, these were not considered test article-related. At final necropsy, there was a statistically significant decrease in mean adrenal weight when expressed as percent of brain weight. This was not observed at interim necropsy and the difference in mean adrenal weights relative to controls was considered within the expected biological variation and therefore not related to administration of the test article ..."

If one adjusts for multiplicity, one can make any statistical significance disappear if only there are enough tests. This should not be done in a toxicity study where there will usually be many examinations of many organs. Second, it is incorrect to conclude that observed changes are not related to vaccine injections because they are minor and do not have a histomorphologic correlate. An increase in spleen weight is expected and it is well-known that this will *not* be accompanied by histomorphologic changes in the spleen. Third, one cannot argue that a change in organ weight is unrelated to the vaccine because it is "considered within the expected biological variation." This is a vague and elastic concept, and it is Merck's convenient interpretation, not an independent judgment.

Merck wrote several times that the intramuscular injection (which was done in the right and left thighs) "appeared not to have been done in the quadriceps muscles sampled for histopathologic examination" and that local tolerance of the skeletal muscle tissue at the actual injection site could therefore not be assessed. If this is correct, it means that the changes that were observed, "histomorphologic changes noted at the end of the recovery period in the inguinal and/or iliac nodes, sciatic nerves and periarticular tissue from the femoro-tibial joint," which were similar to those found in the large toxicity study of 200 rats, occurred on the side of the body that was not used for the injections, and therefore the changes did not represent local but systemic harms. Merck did not comment on this relevant finding.

The large rat toxicity study was finished five years before this one and it was larger, 200 animals versus 60. An increase in mean spleen weight is expected after vaccination, and the earlier study concluded correctly

that this was caused by the vaccine, in contrast to the current study. Since much of the wording was exactly the same in the two reports, the authors of the most recent report did not produce it independent of the first report. It is scientifically inappropriate to first do a study that shows an effect, and then do another, smaller study and say there is no effect, without quoting the first study.

Other issues

In an in vitro study from 2011 of Chinese hamster ovary cells, the aluminium adjuvant at a dose of 45 pg/mL reduced cell growth to 49% of solvent controls and induced significant increases in chromosomal aberrations compared to the solvent controls (see below). The aberrant findings were intended and expected, to show that the assay system would be sensitive, if there were problems.

These findings show once again that Merck's aluminium adjuvant is not a placebo, which is what Merck misleadingly and consistently called it, but an active substance.

In an immunogenicity study in 6 chimpanzees, the addition of the aluminium adjuvant to a monovalent vaccine produced a stronger immune response than if the vaccine was given without the adjuvant. Yet again, this shows that the adjuvant is not a placebo but an active substance.

The objective of one study was to "demonstrate the general tolerability" of the vaccine. This is unscientific and demonstrates Merck's bias. It implies that Merck already knew the results before the study was carried out. In science, we study *if* something is the case.

Animal studies of monovalent and quadrivalent vaccines

TT 97-2545 & TT 97-2546, acute toxicity in 10 mice and 10 rats

Acute Intramuscular Toxicity Studies in Mice and Rats.

23 May 1997.

P4:

SINGLE DOSE TOXICITY

Study Period (Years): 1997

PRODUCT # L-931,102-004C001 DATE OF

NUMBER OF ANIMALS 5/sex STUDY 19MAR97

SPECIES Mouse STRAIN Crl:CD-1® (ICR) BR SEX M & F

PREPARATION USED: 200 µg of HPV 11, L1 protein/ml suspension with Al(OH)PO_4 (0.4 mg/kg Aluminum/ml) in physiologic saline.

FOOD WITHHELD NA WEIGHT 23.1 to 31.7 g ADMINISTRATION ROUTE Intramuscular

OBSERVATION PERIOD: 14 DAYS

LD_{50} (95% FIDUCIAL LIMITS) = > 100 µl/mouse (not given)

P5:

SINGLE DOSE TOXICITY

Study Period (Years): 1997

PRODUCT # L-931,102-004C001 DATE OF
NUMBER OF ANIMALS 5/sex STUDY 19MAR97
SPECIES Rat STRAIN Crl:CD® (SD) BR SEX M & F
PREPARATION USED: 200 µg of HPV 11, L1 protein/ml with Al(OH)PO_4 (0.4 mg aluminum/ml) in physiologic saline
FOOD WITHHELD NA WEIGHT 132 to 213 g ADMINISTRATION ROUTE Intramuscular
OBSERVATION PERIOD: 14 Days
LD_{50} (95% FIDUCIAL LIMITS) = > 0.2 ml/rat (not given)

Only 10 rats and 10 mice who all survived a single dose. LD50 could therefore not be determined.

Not of interest.

TT 97-2633 & TT 97-2634, acute toxicity in 10 mice and 10 rats

Acute Intramuscular Toxicity Study in Mice and Rats.

Report signed 31 Oct 1997.

P4:

1. SINGLE DOSE TOXICITY

Report Date/Number: TT #97-2634

Study Period (Years): 1997

Product # L-931,135 Number of Animals 10 (5/sex)
Species Rat Strain Crl:CD®(SD) BR Sex M & F Date of Study 05AUG97
Preparation Used 160 µg of HPV 16, LI protein suspended in physiologic saline with AL(OH) PO_4 (0.45 mg aluminum/mL) and thiomersol (50 mcg/mL)
Food Withheld No Weight Range 137 to 205 g Administration Route Intramuscular
Observation Period: (Appl. Day = Day 1) 14 days
LD_{50} (95% Fiducial Limits) = >0.2 mL/rat given at 160 µg/mL

P5:

1. SINGLE DOSE TOXICITY

Report Date/Number: TT #97-2633

Study Period (Years): 1997

Product # L-931,135-003D001 Number of Animals 10 (5/sex)
Species Mouse Strain Crl:CD-1® (ICR) BR Sex M & F Date of Study 05AUG97
Preparation Used 160 µg of HPV 16, LI protein suspended in physiologic saline with Al(OH) PO_4 (0.45 mg aluminum/mL) and thiomersol (50 mcg/mL)
Food Withheld No Weight Range 22.9 to 32.1 g Administration Route Intramuscular
Observation Period: (Appl. Day = Day 1) 14 days
LD_{50} (95% Fiducial Limits) = >100 µl/mouse given at 160 µg/mL

Only 10 rats and 10 mice who all survived a single dose. LD50 could therefore not be determined.

Not of interest.

TT 99-2637 & TT 99-2638, acute toxicity in 10 mice and 10 rats

Acute Intramuscular Toxicity Studies in Mice and Rats.

Report signed 6 Jan 2000.

P4:

SINGLE DOSE TOXICITY Report Date/Number: TT #99-2637

Study Period (Years): 1999

Product # L-931,217-001S (Lot #1) Study Initiation Date (s) 22-Sep-1999

Concentration 160 µg/mL Vehicle Used as submitted Factor NA

Number of Animals 10 (5 F & 5 M) Species Mouse Strain Crl:CD-1®(ICR) BR Sex F & M

Weight Range at Study Initiation 25.2 to 35.2 g Age at Study Initiation Approximately 7 weeks

Route of Administration Intramuscular Food Withheld NA

Observation Period: 14 Days

Approximate Lethal Dose$_{50}$ = >100 µL/mouse

Method of Calculation of ALD$_{50}$ Estimated

P5:

SINGLE DOSE TOXICITY Report Date/Number: TT #99-2638

Study Period (Years): 1999

Product # L-931,217-002U (Lot #1) Study Initiation Date (s) 22-Sep-1999

Concentration 160 µg/mL Vehicle Used as submitted Factor NA

Number of Animals 10 (5 F & 5 M) Species Rat Strain Crl:CD®(SD) IGS BR Sex F & M

Weight Range at Study Initiation 149 to 195 g Age at Study Initiation Approximately 7 weeks

Route of Administration Intramuscular Food Withheld NA

Observation Period: 14 Days

Approximate Lethal Dose$_{50}$ = >200 µL/rat

Method of Calculation of ALD$_{50}$ Estimated

Only 10 rats and 10 mice who all survived a single dose. LD50 could therefore not be determined.

Not of interest.

TT 99-2667 & TT 99-2668, acute toxicity in 10 mice and 10 rats

Acute Intramuscular Toxicity Studies in Mice and Rats.

Report signed 27 Mar 2000.

P5:

SINGLE DOSE TOXICITY Report Date/Number: TT #99-2667

Study Period (Years): 1999

Product # L-931,225-003W (Lot #1) Study Initiation Date 17-Dec-1999

Concentration HPV 6a/11/16/18 at 160/160/80/160 µg/mL Vehicle used as submitted Factor NA

Number of Animals 10 (5 F & 5 M) Species mouse Strain Crl:CD-1® (ICR) BR Sex F & M

Weight Range at Study Initiation 23.1 to 33.6 g Age at Study Initiation approximately 7 weeks

Route of Administration Intramuscular Food Withheld NA

Observation Period: 14 days

Approximate Lethal $Dose_{50}$ = > 100 µL/mouse

Method of Calculation of ALD_{50} Estimated

P6:

SINGLE DOSE TOXICITY Report Date/Number: TT #99-2668

Study Period (Years): 1999

Product # L-931,225-003W (Lot #1) Study Initiation Date 17-Dec-1999

Concentration HPV 6a/11/16/18 at 160/160/80/160 µg/mL Vehicle used as submitted Factor NA

Number of Animals 10 (5 F & 5 M) Species rat Strain Crl:CD® (SD) IGS BR Sex F & M

Weight Range at Study Initiation 152 to 211 g Age at Study Initiation approximately 7 weeks

Route of Administration Intramuscular Food Withheld NA

Observation Period: 14 days

Approximate Lethal $Dose_{50}$ = > 200 µL/rat

Method of Calculation of ALD_{50} Estimated

Only 10 rats and 10 mice who all survived a single dose. LD50 could therefore not be determined.

Not of any interest.

TT 01-0260, ten-week intramuscular toxicity in 60 vs 60 mice

Ten-Week Subacute Intramuscular Toxicity Study in Mice.

Report Audit Dates 02-Aug to 15-Aug-2001.

Index on p8.

P3:
“All animals (30 mice/sex/group) were dosed with either vaccine or placebo.” Thus, there were 60 mice in each group.

P3:

HPV Quadrivalent Vaccine and Placebo Formulations

	L-931225-003W002[b]	L-931224-000F002 (Control)[c]
Ingredient[a]	Concentration (µg/mL)	Concentration (µg/mL)
HPV 6a/11/16/18	160/160/80/160	Not applicable
Aluminum	788	900
NaCl	18,700	18,700
L-Histidine	1560	1550
Polysorbate-80	150	150

[a] Prepared in water for injection USP.
[b] HPV Quadrivalent Vaccine 6a/11/16/18, also referred to as V501-VAI-015-K001.
[c] HPV 2X Alum Placebo, also referred to as V501-VAI-012-A002.

It is unclear why the adjuvant was not given in the same dose to the vaccine group and the control group.

The dose in the control group was a nice round number (900 µg/mL) whereas the dose in the vaccine group was not (788 µg/mL)? In some other animal studies, the doses were identical, e.g. in TT 02-7066 and TT 03-7030 (see below). This is unexplained.

It is unclear why the ingredient was called aluminium when it is not aluminium but Merck's proprietary aluminium adjuvant (which it must be since the vaccine is Merck's qHPV vaccine).

It is unclear why the control substance is called "alum placebo," when it is not a placebo but a strongly immunogenic substance (the adjuvant) plus some additives, in addition to the NaCl. A genuine placebo for injection is usually normal saline without additives.

It is unclear why an active placebo with adjuvant was used instead of normal saline or nothing for the control mice. In Merck's human studies, the explanation is two-fold (see, for example, review of V501 P015 in Appendix B). First, to preserve the blinding, but in a mouse toxicity study this can easily be obtained in other ways, e.g. those who give the injections need not be the same as those who observe the animals for physical signs or do the autopsies. Second, "The safety profile of Merck's aluminum adjuvant is well characterized. On the other hand, the safety profile of the HPV 6, 11, 16, and 18 LI VLPs required further evaluation in humans. By using placebo that contained a dose of aluminum adjuvant that was identical to the dose included in the qHPV vaccine, it was possible to assess the safety profile attributable to the HPV 6, 11, 16, and 18 LI VLP component of the vaccine." This argument is not valid for a mouse toxicity study where one should of course assess the toxicity of the vaccine against a harmless substance, i.e. normal saline, or better: no injection at all. Furthermore, as the dose of the adjuvant was not identical in the vaccine and in the control injection, the argument is invalid also for that reason.

P5:
"Grossly, treatment-related enlargement of the iliac lymph nodes was present at both the interim and final necropsies. As indicated in the above table, inflammation was present in the muscle at the injection sites in almost all the animals in the study. However, the severity of the inflammation was greater in vaccine-injected females at the interim necropsy and in both females and males at the final necropsy than in controls."

Histomorphologic Changes
(Incidence, n=15)

	Females		Males	
	L-931224 (HPV 2X Alum Placebo)	L-931225 (HPV Quadrivalent Vaccine 6a/11/16/18)	L-931224 (HPV 2X Alum Placebo)	L-931225 (HPV Quadrivalent Vaccine 6a/11/16/18)
Iliac lymph nodes				
Hyperplasia				
Interim	1	15[a]	0	14[a]
Final	1	15[a]	0	15[a]
Inguinal lymph nodes				
Hyperplasia				
Interim	2	12[a]	1	9[a]
Final	0	9[a]	0	8[a]
Injection site				
Mixed inflammation				
Interim	15	15[a]	15	13
Final	15	15[a]	15	15[a]

[a] Treatment-related change based on incidence and/or severity.

P6:
"In conclusion, intramuscular administration of 1 or 3 doses (spaced 4 weeks apart) of L-931225 to BALB/c mice was well tolerated over an 8-day (single dose, interim sacrifice) or 64-day (3 doses, terminal sacrifice) study duration."

P7:
“There were no treatment-related organ weight changes.”

P106:
“Despite the slightly increased severity of the cellular infiltration in the muscle in some vaccine-injected animals, the overall damage at the injection sites was not more severe in these animals as compared to controls.”

This comparison is meaningless because the control mice did not receive placebo or no injection but an injection with an active substance, the adjuvant.

P106:
“Several changes were noted both in control animals and in animals receiving the vaccine that were due to the trauma of injection. In some cases, these lesions were an extension of the changes noted in the muscle at the injection site. These changes included inflammation in the dermis and/or subcutis in skin at or adjacent to the injection site, degeneration, regeneration, and/or mineralization in muscle at the injection site, inflammation in synovial tissue or periosteum, periosteal hyperostosis, and inflammation in the adventitia of the sciatic nerve. None of these changes was treatment related.”

Merck finds many changes at the injection site and beyond in both groups but nonetheless concludes that “None of these changes was treatment related.” If the changes were not caused by the injections (the treatment), what then caused them?

P108:
In the tables of organ weights, the control group, called L-931224-000F002, is mentioned first. This is highly unusual and is likely to confuse readers, as they would expect the vaccine group to be mentioned first, which is also what Merck did in its studies in humans.

One would expect spleen weight to be higher in the vaccine group than in the control group and this is also what the tables show:

TABLE B-1. L-931225: TEN-WEEK SUBACUTE INTRAMUSCULAR TOXICITY STUDY IN MICE. TT #01-026-0
INTERIM NECROPSY

AVERAGE ORGAN WEIGHTS (± S.D.)
FEMALE

TREATMENT GROUP	L-931224-000F002	L-931225-003W002
NUMBER OF ANIMALS	30	30
BODY WEIGHT, GRAMS	18.6 ± 1.8	18.5 ± 1.6
BRAIN, GRAMS	0.4382 ± 0.0148	0.4368 ± 0.0143
% B.W.	2.37 ± 0.20	2.38 ± 0.17
SPLEEN, GRAMS	0.0776 ± 0.0101	0.0838 ± 0.0219
% B.W.	0.42 ± 0.03	0.45 ± 0.10
% BR.W.	17.7 ± 2.1	19.2 ± 4.8
HEART, GRAMS	0.1124 ± 0.0086	0.1136 ± 0.0082
% B.W.	0.61 ± 0.04	0.62 ± 0.04
% BR.W.	25.7 ± 1.9	26.0 ± 1.7
KIDNEYS, GRAMS	0.2976 ± 0.0301	0.2935 ± 0.0425
% B.W.	1.60 ± 0.07	1.59 ± 0.19
% BR.W.	68 ± 6	67 ± 9
LIVER, GRAMS	0.9329 ± 0.0821	0.9196 ± 0.0917
% B.W.	5.02 ± 0.21	4.97 ± 0.26
% BR.W.	213 ± 16	210 ± 19

B.W. = BODY WEIGHT
BR.W. = BRAIN WEIGHT

Average spleen weight for female mice is 8% higher in the vaccine group than in the adjuvant control group. In male mice, the spleen weight is 6% higher in the vaccine group (p109).

TT 03-7030, immunogenicitiy and toxicity in 250 female rats with post weaning evaluation

Intramuscular Developmental Toxicity and Immunogenicity Study in Rats With Postweaning Evaluation.

Study Termination Date: 22-Oct-2003
Report signed 30 July 2004.

Index on p2.

260 female rats, 2 or 4 doses given 5 and 2 weeks premating, on gestation day 6, and on lactation day 7. Study length 25 weeks.

Control 1: phosphate buffered saline, control 2: "alum placebo," both given 4 times. 450 µg/mL of adjuvant in both the vaccine and the "placebo."

Dosing volume: 250 µL per quadriceps (500 µL/rat).

	Control 1	Control 2	L-000931225[a]	L-000931225[b]
# test females[c]	65	65	65	65
# females C-sectioned	20	21	22	20
# females delivered	22	22	22	21
# females died or sacrificed	0	0	0	1[d]

[a] Females received 2 doses.
[b] Females received 4 doses.
[c] Each group includes 6 extra females used to obtain 44 mated and 15 for blood sample collections.
[d] Pregnant female sacrificed on GD24 because of failure to deliver offsprings.

P13:
"There were no treatment-related effects observed in the F1 generation, which concluded in an evaluation of fertility and F2 external examination at birth. L-000931225 induced a specific antibody response against HPV Types 6, -11, -16, and -18 in F0 female rats, following one or multiple intramuscular injections."

P29:
The rats were observed twice weekly for physical signs.

P30ff:
"Behavioral Assessments
Tests were performed on one male and one female (previously randomly selected on PND [probably means postnatal day] 0) from each litter when possible. Some animals were tested in more than one behavioral test as indicated below. The following tests were performed:"

Passive avoidance
Auditory Startle Habituation
Open-Field Motor Activity

P35-6:
There were no deaths during the study and no physical changes related to treatment: "The physical signs observed were of the type seen in vehicle-treated rats in this laboratory and were considered unrelated to treatment."

No toxicities were observed.

P38:
F1 generation: “The variations in the numbers of pups that died during the preweaning period were of the type observed in vehicle control rats in this laboratory and are unrelated to treatment with the test article”

P42:
Conclusions: “There were no treatment-related effects in either the primed or naive F0 females, and there were no treatment-related effects observed in their F1 generation, which concluded in an evaluation of fertility and F2 external examination at birth.”

TT 07-7110, immunogenicity and fertility in 100 male rats

Intramuscular Fertility and Immunogenicity Study in Male Rats.

qHPV vaccine.

Report signed 6 Dec 2007.

P8:
The potential effects of V-501 on the fertility of F0 male rats were evaluated following 1 or 3 intramuscular administrations prior to cohabitation. Male Crl:CD(SD) rats were randomized into 4 groups. Male rats in 2 groups of 30 rats each received 1 or 3 dose administrations (3 days prior to cohabitation; or 6 weeks, 3 weeks, and 3 days prior to cohabitation) of V-501. Male rats in 2 groups of 20 rats each received 3 dose administrations (6 weeks, 3 weeks, and 3 days prior to cohabitation) of Phosphate Buffered Saline or Merck Aluminum Adjuvant. The dosing volume was 0.5 ml per animal per dose (administered 0.25 ml per quadriceps). The dose is equivalent to the human clinical dose.

P8:
“There were no unscheduled deaths during the study, and no treatment-related physical signs, changes in mean body weight gain or food observations. There were no treatment-related effects on reproductive performance including fertility, sperm count, and sperm motility. There were no treatment-related gross or histomorphologic changes and no treatment-related effects on testes weights.”

TT 02-7066, immunogenicity in 25 non-pregnant rats

Exploratory Intramuscular Immunogenicity Study in Nonpregnant Female Rats.

Study Termination Date: 02-Jul-2002

25 female rats.

P5:
“Control 1: L-931224 (placebo). Control 2: Phosphate buffered saline.”

	Control 1	Control 2	L-931225
	Females	Females	Females
# test animals	5	5	15[a]
# animals died/sacrificed	0	0	0

[a] Three groups of 5 females each received 2, 3, or 4 doses.

The information is inconsistent. On the same page, Control 1 is defined as both L-931224 and as L-931225. Control 1 is furthermore called placebo, even though it is not placebo but a preparation that contains Merck's adjuvant. This aluminium adjuvant is misleadingly called "aluminium." It was given at a dose of 450 µg/mL to both the vaccine and the "placebo" rats.

P6:
"Intramuscular injections of 2 to 4 doses of L-931225, an HPV Type 6/11/16/18 quadrivalent vaccine, to rats were generally well tolerated over a 25-week duration. There were no deaths or treatment-related physical signs. There was a slight treatment-related decrease in mean body weight gain in females administered 4 doses compared to the placebo and PBS control groups."

P15:
"There was a slight, treatment-related decrease in mean body weight gain in Group 3 (4 doses) females (16% and 13% below Control 1 and Control 2, respectively)."

The animals were not autopsied.

TT 03-7036, immunogenicity in 5 rats

Exploratory Intramuscular Immunogenicity Study in Nonpregnant Female Rats.

Report signed 20 August 2003.

Only 5 rats and no control group.

Objective of Study
To generate positive control serum to be used in the assay to measure anti-HPV antibodies.

All 5 rats were vaccinated.

Not of interest.

TT 99-2639, acute intramuscular irritation in 16 rabbits

Acute Intramuscular Irritation Study in Rabbits.

Report signed 6 Jan 2000.

P5:

Acute Intramuscular Irritation Study Study Period (Years): 1999

Name of Drug: L-931,217-003W (Lot #1)

Species/Strain: Rabbits/New Zealand White

Number of animals: 16 Duration of treatment: Dosed once/site on Day 1

Observation period: 14 days

Administration route: Intramuscular (sacrospinalis muscle)

Treatment of controls: Merck 2X aluminum adjuvant placebo (0.5 mL/left sacrospinalis muscle)

Age at study initiation: 30 weeks Weight range at study initiation: 3.40 to 4.29 kg
Treatment days per week: Once/site on Day 1

Study Group:	(1) L-931,224		(2) L-931,217
Dosage:	Vehicle Control		160 µg/mL
Sex (M/F):	M	F	
Number of test animals:	8[a]	8[a]	
a = Each rabbit received the control article in the left sacrospinalis muscle and L-931,217 in the right sacrospinalis muscle at 0.5 mL/site.			

No treatment-related changes antemortem or post-mortem (apart from a bruise in two rabbits).

Not of interest.

TT 97-2548, fifteen-day intramuscular irritation in 16 rabbits

Fifteen-Day Intramuscular Irritation Study in Rabbits.

Report signed 23 May 1997.

P5:

Fifteen-Day Intramuscular Irritation Study Report Date/Number: TT #97-2548
Study Period (Years): 1997

Name of Drug: Human Papillomavirus vaccine - HPV11,L1 protein with Al(OH)PO_4 (0.4 mg Aluminum) in physiologic saline
Species/Strain: Rabbits/New Zealand White
Number of animals: 16 Duration of treatment: dosed once
Observation period: 15 days
Administration route: Intramuscular (sacrospinalis muscle)

Treatment of controls: 0.9 percent saline Age at start date: 35 to 37 weeks
Body weight at start date: 3.23 to 3.92 kg

Treatment days per week: once

Study Group	Group 1		Group 2		Group 3		Group 4		Group 5	
	0.9% Saline		L-931,106		L-931,102		L-931,102		L-931,102	
Dosage (HPV11,L1 protein)	-		vehicle		20 µg/ml		100 µg/ml		200 µg/ml	
Sex (M/F)	M	F	M	F	M	F	M	F	M	F
Number of test animals:	8*	8*	*	*	*	*	*	*	*	*

*Each rabbit received a single 0.5 ml/site injection of each test agent.

It is not clear from the insert just above that there were only 16 rabbits in total in the whole study. There were no significant findings antemortem or post-mortem.

P20:
“Grossly, at both the Day 5 and 15 necropsies, in occasional injection sites, including saline control sites, there were a few linear pale or red streaks in the muscle but there was no evidence of a treatment-related effect. There were no treatment-related microscopic changes in any of the intramuscular injection sites on Day 5 or Day 15. The overall damage at all sites was graded as none (0) to slight (2). The changes seen in the injection sites included very slight or slight focal histiocytic cell infiltration, hemorrhage, focal necrosis and/or regeneration.”

Not of interest.

TT 97-2632, fifteen-day intramuscular irritation in 16 rabbits

Acute Fifteen-Day Intramuscular Irritation Study in Rabbits.

Report signed 31 October 1997.
P5:

Acute Fifteen-Day Intramuscular Irritation Study Report Date/Number: TT #97-2632

Study Period (Years): 1997

Name of Vaccine: Human Papillomavirus Vaccine-HPV16, L1 protein with A1(OH) PO_4 (0.45 mg/mL) and thimerosal (50 mcg/mL) in physiologic saline.

Species/Strain: Rabbits/New Zealand White breed
Number of animals: 16 Duration of treatment: dosed once
Observation period: 15 days
Administration route: Intramuscular (sacrospinalis muscle)

Treatment of controls: physiologic saline
Age at start date: 27 to 33 weeks

Body weight at start date: 3.24 to 4.11 kg

Treatment days per week: once

Injection Site	A		B		C		D		E	
	0.9% saline		L-931,133		L-931,135		L-931,135		L-931,135	
Dosage (HPV16)			Vehicle		20 µg/mL		80 µg/mL		160 µg/mL	
Sex (M/F)	M	F	M	F	M	F	M	F	M	F
Number of test animals	8*	8*	*	*	*	*	*	*	*	*

*Each rabbit received a single injection of 0.5 mL/site each test agent.

P6:
“Summary of salient findings: L-931,135 at 20, 80 or 160 µg/ml given intramuscularly to rabbits produced very slight to moderate necrosis at the injection site on Day 5, which resolved fully by Day 15.”

Not of interest.

TT 99-2669, fourteen-day intramuscular irritation in 16 rabbits

Acute Intramuscular Irritation Study in Rabbits.

Report signed 24 March 2000.

It is not clear if there were only 16 rabbits in the study or more rabbits, but the text on p8 described only 16 rabbits in total under Methods.

P6:

Acute Intramuscular Irritation Study in Rabbits Study Period (Years): 1999

Name of Test Article: L-931,225-001S; L-931,225-002U; L-931,225-003W; L-931,225-004Y (Lots #1)
Species/Strain: Rabbits/New Zealand White

Number of animals: 16 Duration of treatment: Dosed once/site on Day 1

Observation period: 14 days

Administration route: Intramuscular (sacrospinalis muscle)

Treatment of controls: Merck 2X aluminum adjuvant placebo (0.5 mL/left sacrospinalis muscle)

Age at study initiation: 42 weeks Weight range at study initiation: 3.43 to 4.39 kg
Treatment days per week: Once/site on Day 1

Study Group:	(1) L-931,224		(2) L-931,225-001S	(3) L-931,225-002U	(4) L-931,225-003W	(5) L-931,225-004Y
Dosage: (HPV 6a/11/16/18)	Vehicle Control		40/80/80/ 40 µg/mL	80/80/80/ 80 µg/mL	160/160/80/ 160 µg/mL	160/80/160 80 µg/mL
Sex (M/F):	M	F				
Number of test animals:	8[a]	8[a]				
a = Each rabbit received the control article, L-931,225-002U, and L-931,225-004Y in the left sacrospinalis muscle and L-931,225-001S and L-931,225-003W in the right sacrospinalis muscle at 0.5 mL/site.						

Number of animals died or sacrificed *in extremis*: None

Not of interest.

PD001, immunogenicity in 3 vs 3 rhesus macaques

Monovalent HPV 16 L1 VLP. Immunogenicity in 6 rhesus macaques, three with adjuvant, three without.

Study Termination Date: Sept-2000.

“titers reached and maintained when MAA was present were greatly increased over the titers reached with no adjuvant.”

Not of interest.

PD003, immunogenicity in 4 green monkeys

Monovalent vaccine, HPV 18 L1 VLP, given to 4 African green monkeys.

Termination Date: 2000.

Not of interest.

PD004, immunogenicity in 34 green monkeys, 6-8 animals per group

Monovalent vaccines (HPV 6, HPV 11, HPV 16 or HPV 18) were compared with quadrivalent vaccine in 34 African green monkeys, divided into five groups of 6-8 animals each.

Termination Date: Feb-2001.

Not of interest.

Animal studies of 9-valent vaccine

V503 TT 07-1006_rat study_unsigned, three-month toxicity in 200 rats

Three-Month Intramuscular Toxicity Study in Rats Dosed Once Every 21 Days With a 21-Day Recovery Period. TT #07-1006.

Final Report 24-Jul to 01-Aug-2007.

Index on p3.

Blinding: I could not find any description that those who assessed rat behaviour or did the necropsies were blinded. This is a general problem with all Merck's animal studies.

P15:

Type of Inspection	Inspection Dates	Date Results Reported to Study Director/ Management
Protocol Review	20-Feb-2007	20-Feb-2007
Compound Preparation and Calculation	20-Feb-2007	20-Feb-2007
Compound Administration	20-Feb-2007	20-Feb-2007
Scheduled Sacrifice	27-Apr-2007	27-Apr-2007
	15-May-2007	16-May-2007

This table shows that the interim necropsies took place close to the final necropsies (19 days earlier).

P19:
"Negative Control = Phosphate Buffered Saline (PBS). Placebo Control = Merck Aluminum Adjuvant (MAA)."

This is misleading. It is the PBS that is the placebo control, and there are additional inconsistencies in Merck's terminology, e.g. an "Aluminum Placebo treated Female" (p26).

P10-12:
"Summary
The purpose of this study was to evaluate the potential toxicity and immunogenicity of V503, also known as the 9-valent HPV Vaccine, formulated in Merck Aluminum Adjuvant (MAA) when administered intramuscularly to rats once on each of Study Days 1, 22, 43, and 64 followed by an observation period of 21 days.

Crl:CD(SD) rats were assigned to 5 groups of 20 females and 20 males each that received low-, mid-, and high-dose of V503 formulated in MAA, MAA only, or Phosphate Buffered Saline (PBS) only. Formulations of placebo and vaccine are shown in the table below:"

Formulation of Placebo Control and Test Articles

Ingredient[a]	L-002001047-000B001 (Placebo) Concentration	L-002001044-003G001 (V503 Low Dose) Concentration	L-002001044-001C001 (V503 Mid Dose) Concentration	L-002001044-002E001 (V503 High Dose) Concentration
HPV Type 6 VLP	N/A	40 µg/mL	60 µg/mL	80 µg/mL
HPV Type 11 VLP	N/A	80 µg/mL	80 µg/mL	80 µg/mL
HPV Type 16 VLP	N/A	80 µg/mL	160 µg/mL	160 µg/mL
HPV Type 18 VLP	N/A	40 µg/mL	80 µg/mL	160 µg/mL
HPV Type 31 VLP	N/A	40 µg/mL	40 µg/mL	60 µg/mL
HPV Type 33 VLP	N/A	40 µg/mL	40 µg/mL	60 µg/mL
HPV Type 45 VLP	N/A	40 µg/mL	40 µg/mL	60 µg/mL
HPV Type 52 VLP	N/A	40 µg/mL	40 µg/mL	60 µg/mL
HPV Type 58 VLP	N/A	40 µg/mL	40 µg/mL	60 µg/mL
Aluminum[b]	1.097 mg/mL	0.788 mg/mL	1 mg/mL	1.097 mg/mL
Sodium borate	35 µg/dose	35 µg/dose	35 µg/dose	35 µg/dose
Sodium chloride	0.32M	0.32M	0.32M	0.32M
Histidine	10 mM	10 mM	10 mM	10 mM
Polysorbate 80	0.01%	0.01%	0.01%	0.01%
pH	6.2	6.2	6.2	6.2

[a] Prepared in water for injection.
[b] As aluminum hydroxyphosphate sulfate.
HPV = Human papillomavirus.
VLP = Virus-Like Particle.

It is unclear why the doses of the adjuvant vary from study to study and why there were two of the three doses applied in this study given with excessive accuracy, three decimals, and the third one without decimals. The composition of the adjuvant is known to vary from batch to batch and even within the same batch, according to a Merck patent application from 2013:[2] "During the course of a batch precipitation, the composition of the reacting mixture can change dramatically, leading to the production of adjuvant that is somewhat different from the start of the batch to the end of the batch. The result can be a heterogeneous mixture with some kind of "average" of properties."

One of the adjuvant doses was 1.097 mg/mL; why not 1 mg/ml, which would have been the obvious dose to use? The other dose was 0.788 mg/mL; why not 1 mg/mL, which is not much different? The doses of the other four ingredients, sodium borate, sodium chloride, histidine and polysorbate, were exactly the same in the three vaccine groups and the adjuvant group.

Merck describes five groups: Three doses of the vaccine, the adjuvant and Phosphate Buffered Saline (PBS). Why was the genuine placebo group, PBS, not listed in the above table?

PBS is an isotonic buffer frequently used in biological applications, such as washing cells, transportation of tissues, and dilutions. PBS closely mimics the pH, osmolarity, and ion concentrations of the human body. Since it is nontoxic to cells, it is extensively used for cell container rinsing and other preparations that might leave a residue. It is simple to prepare and has good shelf life but will precipitate in the presence of zinc ions.

Again, Merck inappropriately called the adjuvant group a placebo group in the table heading when this is not correct and when there actually was a placebo group in the study.

Table 1. Required components

Component	Amount	Concentration
NaCl (mw: 58.4 g/mol)	8 g	0.137 M
KCl (mw: 74.551 g/mol)	200 mg	0.0027 M
Na_2HPO_4 (mw: 141.96 g/mol)	1.44 g	0.01 M
KH_2PO_4 (mw: 136.086 g/mol)	240 mg	0.0018 M

[2] https://patents.google.com/patent/WO2013078102A1/en

P11-12, summary:

"… Treatment-related antemortem findings were limited to very slight to moderate changes in hematological parameters (increases in leukocytes, neutrophil, eosinophil, and monocyte counts on Study Day 67 only) and serum biochemical parameters (decreases in albumin values and increases in globulin, resulting in decreases in A/G ratio), as anticipated immunological responses, which were recovered or at least partially recovered by the end of the 21-day recovery period.

At interim necropsy (3 days after the last dose) but not at final necropsy (after a 21-day recovery period), statistically significant increases in splenic weights, with no gross or histomorphologic correlate, were observed in female rats injected with the mid- and high-dose of V503. The increase in splenic weights was considered secondary to the stimulation of the immune system by vaccination.

Treatment-related gross and histomorphologic findings at the interim and final necropsies in MAA control rats and V503 high-dose rats were observed only at the injection site and in the draining lymph nodes. Red to tan colored foci observed during interim necropsy at the injection site, correlated with the inflammation and muscle fiber degeneration observed in the quadriceps muscle. At the final necropsy, there was no myofiber degeneration observed in the quadriceps muscle, and the residual inflammation was less severe, and more chronic in nature as compared to interim necropsy, indicating progressive resolution of the skeletal muscle changes. At both interim and final necropsy, the incidence and severity of the histomorphologic changes at the injection sites were similar between MAA control rats and V503 high-dose rats. Therefore, resolution of the changes at the injection site was similar in the MAA control rats and V503 high-dose rats.

Hyperplasia of the draining iliac and inguinal lymph nodes, of similar incidence and severity, was observed histomorphologically in MAA control rats and V503 high-dose rats, at interim and final necropsy. This correlated with the increased size of lymph nodes observed grossly. The change observed in the draining lymph nodes was considered secondary to stimulation of the immune system by MAA and V503. Since the character and severity of histomorphologic changes were similar between the MAA control rats and V503 high-dose rats, the changes at the injection site and the draining iliac and inguinal lymph nodes were considered to be of minimal toxicological significance and within acceptable limits for vaccine treatment in rats ..."

This summary is scientifically inappropriate, for several reasons. There were five groups of rats, with 40 animals in each group, but the summary does not mention the results in the placebo group, the phosphate buffered saline group. Furthermore, the data do not warrant the conclusions. One cannot claim "progressive resolution of the skeletal muscle changes" at the same time as acknowledging that the residual inflammation was chronic. The fact that an adjuvant causes similar harms as a high-dose vaccine group cannot be used to argue that this has "minimal toxicological significance." It only shows that the adjuvant is a potent substance.

How can it be concluded that the harms were of minimal toxicological significance and within acceptable limits for vaccine treatment in rats when they had not resolved at the final necropsies? This is a subjective and scientifically invalid conclusion.

It is unclear why Merck did not do any toxicology study that followed the rats until they had all died from natural causes, after a couple of years, which is how toxicology studies in rats are normally performed. The total study length was only three months, after which all the rats were killed.

P29:
"Changes Related to Treatment
In general, there were no differences between the MAA and PBS control groups, therefore, the comparison of the V503 treatment groups to the PBS group are presented below."

It is unclear on what basis Merck concluded that there were no differences between the adjuvant and the placebo group. As stated in the summary, the adjuvant group caused similar changes in the rats as the high-dose vaccine group, including myofiber degeneration, inflammation, and hyperplasia of the draining iliac and inguinal lymph nodes. According to Merck's own definition of what a placebo is, a placebo does not cause such harms (see also below).[3]

P29:
"Treatment-related hematology findings consisting of very slight to moderate changes in white cell parameters were observed in females and males at all doses, as indicated in the table below. There were very slight increases in leukocytes, and moderate increases in neutrophil, eosinophil, and monocyte counts on Study Day 67. These changes were likely attributed to non-specific immune responses. Recovery from these changes was observed by Study Day 81. The majority of these changes were also statistically significant by Dunnet's test ($p<0.05$)."

Merck did not show the results for the adjuvant group and the placebo group in the table just below.

It is thus unclear what the results were for the adjuvant group and the placebo group.

It is unclear what the results were of statistical testing of the influence of the adjuvant on these variables compared to the placebo. Since a genuine placebo group would not display such differences in haematology findings related to immune responses, a statistical test comparing adjuvant versus placebo is highly likely to be significant for neutrophils, eosinophils and monocytes.

Treatment-Related Hematological Changes
(Percent Difference in Mean Values From PBS Concurrent Controls)

		V503					
	Study	Females			Males		
Parameter	Day	Low	Mid	High	Low	Mid	High
Leukocytes	4	-	-	-	-	-	-
	67	+46	+35	+42	-	+19	+22
	81	-	-	-	-	-	-
Neutrophils	4	-	-	-	-	-	-
	67	+120	+147	+136	+99	+122	+120
	81	-	-	-	-	-	-
Eosinophils	4	-	-	-	-	-	-
	67	+110	+100	+70	+100	+136	+91
	81	-	-	-	-	-	-
Monocytes	4	-	-	-	-	-	-
	67	+200	+200	+173	+121	+171	+179
	81	-	-	-	-	-	-

- = No treatment-related change.

[3] Merck: Placebos. https://www.merckmanuals.com/home/drugs/overview-of-drugs/placebos.

P30:

Treatment-Related Serum Biochemical Changes
(Percent Difference in Mean Values From PBS Concurrent Controls)

Parameter	Study Day	V503					
		Females			Males		
		Low	Mid	High	Low	Mid	High
Albumin	4	-	-	-	-	-	-
	67	-10	-18	-15	-11	-11	-11
	81	-	-	-	-	-	-
Globulin	4	-	-	-	-	-	-
	67	+22	+26	+22	+22	+22	+22
	81	+17	+17	+17	+6	+6	+6
A/G Ratio	4	-	-	-	-	-	-
	67	-24	-29	-29	-31	-31	-31
	81	-12	-18	-12	-10	-15	-15

- = No treatment-related change.

There were increased globulin concentrations, which are an expression of induction of immunity (p31) that means that antibodies (immune globulins) have increased.

P49:

Continued
Table A-3. V503: Three-Month Intramuscular Toxicity Study in Rats Dosed Once Every 21 Days with a 21-Day Recovery Period.
TT #07-1006

Average Hematology Values for Female Rats

Parameter	Units	Interval	Stat	C1	T1	T2	T3
Neutrophils	10[3]/mm[3]	Study Day 4	Mean	0.89	0.81	1.07	1.09
			S. E.	0.15	0.08	0.17	0.18
			N	10	9	10	9
Neutrophils	10[3]/mm[3]	Study Day 67	Mean	0.86	1.89*	2.12*	2.03*
			S. E.	0.16	0.32	0.26	0.26
			N	10	8	10	10
Neutrophils	10[3]/mm[3]	Study Day 81	Mean	1.13	0.68	0.78	0.92
			S. E.	0.37	0.13	0.15	0.22
			N	9	10	10	9

C1 = PBS Control T1 = Low Dose in MAA T2 = Medium Dose in MAA T3 = High Dose in MAA
Dunnett's Multiple Comparisons with the Reference Group
N = Group Size
S. E. = Standard Error of the Mean
* = P-value ≤ .05

It is unclear why Merck analysed females and males separately when it is considered substandard research to split the data in harms studies, as it reduces the power to detect signals of harm.

Merck did not show the full dataset, i.e. also the data for the adjuvant group.

Even with the reduced power, the changes compared to placebo (called CI in the tables) were significant, both for females and males for several of the haematology outcomes.

P584:
The rats were said to be "euthanized by exsanguination."

P588:
"At interim necropsy, statistically significant increases in splenic weights were observed in female rats in the V503 Mid- and High-Dose groups, as summarized in the following table. There were no gross or histomorphologic changes in the spleen that correlated with the increased splenic weights. Splenic weights were within normal limits at the final necropsy following a 21-day recovery period. The increase in splenic weights post-vaccination is considered secondary to the stimulation of the immune system by the mid and high dose of V503."

Treatment-Related Organ Weight Changes
(Percent Difference in Mean Values From Concurrent PBS Controls)

	Dose Group							
	Females				Males			
	MAA	V503 Low	V503 Mid	V503 High	MAA	V503 Low	V503 Mid	V503 High
Spleen Weight[a]								
Absolute	-	-	+22*	+24*	-	-	-	-
Relative to body weight	-	-	+19*	+19*	-	-	-	-
Relative to brain weight	-	-	+21*	+21*	-	-	-	-

[a] Statistics performed by trend assessment.
* = $p \leq 0.05$.
- = No treatment-related change.
MAA = Merck Aluminum Adjuvant.

Three-Month Intramuscular Toxicity Study in Rats Dosed Once Every 21 Days With a 21-Day Recovery Period.

Merck did not show the full dataset but used a hyphen, e.g. for the adjuvant group, stating in a footnote that the hyphen means "no treatment-related change."

"No change" is a vague term that does not exclude the possibility that there was an increase in splenic weight in the adjuvant group, which is expected, at the lymph nodes were enlarged in the adjuvant group. It is even worse to say, "no treatment-related change," which suggest that there was a change that Merck subjectively decided to label "not treatment related."

This is extremely poor science, and it is incredible that this can happen in a major drug company. I constructed a relevant table based on data listings I found on p596 and p598 (mean spleen weight in g; 8-10 animals per group):

	PBS placebo	Adjuvant	Low-dose	Mid-dose	High-dose
Females	0.45	0.46	0.53	0.55	0.56
Males	0.75	0.73	0.79	0.82	0.86

Based on this table, I re-constructed Merck's table, with data in all cells:

Females				Males			
Adjuvant	Low-dose	Mid-dose	High-dose	Adjuvant	Low-dose	Mid-dose	High-dose
2	18	22	24	-3	5	9	15

Of these 8 values, the only ones offered in the main text in Merck's report were 22 and 24 in the mid- and high-dose groups, respectively, and only in females. When the full data set is presented, it appears there is a dose-response relationship: the higher the dose, the greater the increase in spleen weight.

P590:

Interim Necropsy: Treatment-Related Histomorphologic Changes
(Incidence, n=10)

	Females					Males				
	Controls		V503-Treated			Controls		V503-Treated		
	G1	G2	G3[a]	G4[a]	G5	G1	G2	G3	G4	G5
Injection Site								NE	NE	
Muscle fiber, Degeneration	-	10	1	-	10	-	10			10
Muscle, Inflammation	3	10	1	1	10	3	10			10
Lymph Node								NE	NE	
Iliac, Hyperplasia	-	9	1	1	9	-	10			10
Inguinal, Hyperplasia	-	1	-	-	2	-	2			2

G1 = PBS Control.
G2 = Aluminum Adjuvant Placebo Control (MAA).
G3 = V503 Low Dose.
G4 = V503 Mid Dose.
G5 = V503 High Dose.
[a] n=1, one rat examined due to its early termination.
- = Change not observed.
NE = Group not examined.

For the interim necropsy after 67 days, half of the 40 rats in each group, or 10 for each sex, were killed (p22). Muscle fiber degeneration in the quadriceps where the injections were given were seen in all 20 rats in the adjuvant group and in all 20 rats in the high-dose vaccine group, but not in any of the 20 rats in the PBS genuine placebo group.

It is unclear on what basis did Merck concluded that there were no differences between the adjuvant and the placebo group (see question 9 above) when this clearly was not the case.

"Grossly, red or tan colored foci were observed in the quadriceps muscle of rats in the MAA control group and V503 treated groups. The incidence of these foci was comparable between the MAA control group and V503 treated groups. These foci from both MAA control group and V503 high dose group correlated with the histomorphologically observed slight to moderate inflammation and very slight to slight muscle fiber degeneration in the quadriceps muscle. Inflammation in the quadriceps muscle was characterized by central areas of degenerate neutrophils and eosinophilic debris surrounded by neutrophils, lymphocytes, macrophages and occasional plasma cells. The macrophages were large with abundant amphophilic to slightly basophilic granular cytoplasm. These areas of inflammation were associated with degeneration of muscle fibers characterized by myofiber swelling and fragmentation of the sarcoplasm. The severity of the inflammation and degeneration was similar between the MAA control group and the V503 high dose group. Occasionally, in both the MAA control group and V503 high dose group, the inflammation extended to the perineural tissue around the sciatic nerve, skin overlying the injection site, periosteum of the underlying femur bone and/or the adjacent femorotibial joint. The incidence and severity of these changes in the tissues adjacent to the injection site were similar between MAA control group and V503 high dose group. The inflammation in these adjacent tissues were likely related to the inadvertent injection into these tissues and/or extension of the MAA or V503 material from the muscle into these tissues due to the relatively large volume of the material injected into comparatively small quadriceps muscle of rats.

The quadriceps muscle of PBS control rats showed very slight inflammation characterized by focal, linear infiltration of very few mononuclear cells between myofibers. The changes were consistent with needle trauma associated with intramuscular injections.

Overall damage scores were determined based on the severity of histomorphologic changes at the injection site. The overall damage scores were comparable between the MAA control group and V503 high dose group. The overall damage for PBS control rats was minimal and therefore was not scored."

Again, it is unclear on what basis Merck concluded that there were no differences between the adjuvant and the placebo group (see question 9 above) when this clearly was not the case.

Merck's results show without question that the adjuvant causes harm.

P592:

Final Necropsy: Treatment-Related Histomorphologic Changes
(Incidence, n=10)

	Females					Males				
	Control		V503-Treated			Control		V503-Treated		
	G1	G2	G3	G4	G5	G1	G2	G3	G4	G5
Injection Site			NE	NE				NE	NE	
Muscle, Inflammation	-	10			10	-	10			10
Lymph Node			NE	NE				NE	NE	
Iliac, Hyperplasia	-	9			9	-	9			7
Inguinal, Hyperplasia	-	1			2	-	2			2

G1 = PBS Control.
G2 = Aluminum Adjuvant Placebo Control (MAA).
G3 = V503 Low Dose.
G4 = V503 Mid Dose.
G5 = V503 High Dose.
- = Change not observed.
NE = Group not examined.

Once again, it is unclear on what basis Merck concluded there were no differences between the adjuvant and the placebo group when this clearly was not the case (see the table just above).

At final necropsy, there were persisting changes in muscle inflammation and lymph nodes in the adjuvant and high-dose group.

It is unclear why Merck did not show the results for the low- and mid-dose groups. According to the text, they were not examined for muscular toxicity. Why not? Why did Merck include five groups of mice and then only examined some of them?

P592-3:
"Overall damage scores were similar between MAA control rats and V503 high dose rats. The absence of muscle fiber degeneration and the decrease in overall damage score after 21 days of recovery demonstrates the ongoing resolution of the changes at the injection site. In addition, there were small numbers of MAA control rats and V503 high dose rats with very slight inflammation of the tissues (skin, periosteum and femorotibial joint) adjacent to the injection site. The intramuscular injection sites in the quadriceps muscle from the PBS injected rats were not remarkable."

It is unclear what Merck meant when it stated, "not remarkable."

The text describes similar inflammatory changes at the final autopsy as at the interim necropsy, and they were seen in all the animals in the adjuvant group and the high-dose group.

The text speaks about "damage score" on pages 591 and 592, but there were no such scores anywhere in the text. Furthermore, the text did not refer to any tables where such scores could be found. I went through every page in the report manually and found some information, but this was not called "damage score" but "overall damage." This information appeared in four tables and it was incomplete:

On p674, a table shows "overall damage" with scores 1 to 4 related to the injection site for female rats at interim autopsy, but only for the three vaccine groups.

On p676, there are similar scores for males at interim autopsy, but only for the PBS placebo, the adjuvant and the high-dose group.

On p753, there are scores for females at final necropsy, but only for PBS placebo, adjuvant and the high-dose group.

On p755, there are scores for males at final necropsy for the same three groups out of five.

Merck did not provide all the data and reported in such a way that made it difficult to find even the incomplete data.

V503 TT 12-6017_rat study, three-month toxicity in 60 rats

Toxicity study in rats.

Index on p2.

Blinding: I could not find any description that those who assessed rat behaviour or did the necropsies were blinded.

Final Report 01-Oct-2012
Interim Necropsy Date: 25-May-2012 (study day 68)
Final Necropsy Date: 19-Jun-2012

P7, summary:
60 rats (30 were females) received a 9-valent vaccine or PBS (saline) placebo every 3 weeks, four times, followed by a 4-week treatment-free period.

"The first 10 rats/sex/group were designated for interim necropsy (4 days after the fourth dose) and the last 5 rats/sex/group were designated for final necropsy in Study Week 14 after a 4-week treatment-free period."

"Test article-related antemortemen findings were limited to very slight changes in hematological (increases in white blood cells, neutrophils, eosinophils, monocytes, and/or platelets in both sexes) and serum biochemical parameters (increases in globulin with decreases in albumin/globulin ratio in females only) generally consistent with the anticipated immune response. Following the 4-week treatment-free period, the hematological changes were fully reversible while the serum biochemical changes were still present.

There were no test article-related organ weight changes at scheduled necropsies. Test article-related histomorphologic findings were present at interim and final necropsies in the iliac and inguinal lymph nodes draining the hindlimbs, and around the sciatic nerves and the femoro-tibial joint.

There was hyperplasia in the iliac and inguinal nodes at scheduled necropsies, often associated with increased size of these lymph nodes grossly at interim necropsy.

Hyperplasia noted at the end of the recovery period in the iliac and inguinal nodes was usually less severe than that observed at interim necropsy. The changes noted in the draining iliac and inguinal lymph nodes were within the normal limits for vaccine treatment in rats and were considered of minimal toxicological significance.

Focal cellular infiltration was noted occasionally around the sciatic nerve of animals from the L-005128981-treated [vaccine] group at both scheduled necropsies.

Focal inflammation was noted at both scheduled necropsies in the periarticular tissue from the femoro-tibial joint. The microscopic changes noted around the sciatic nerve and the periarticular tissue were likely related to inadvertent injection into these tissues and/or extension of L-005128981 material from the injected muscle into these tissues.

The decreased severity and/or incidence of the histomorphologic changes noted at the end of the recovery period in the inguinal and/or iliac nodes, sciatic nerves and periarticular tissue from the femoro-tibial joint are indicative of the progressive recovery from intramuscular administration of the test article. Since the intramuscular injection appeared not to have been done in the quadriceps muscles sampled for histopathologic examination, local tolerance of the skeletal muscle tissue at the actual injection site could not be assessed in this study."

These findings are similar to those in the other rat toxicity study, but what is new is that the harms caused by the vaccine in the quadriceps appeared to be present in the muscle that was not used for the injections. This information is repeated on p47:

"local tolerance of the skeletal muscle tissue at the actual injection site could not be assessed in this study since the injection appeared not to have been done in the quadriceps muscles sampled for histopathologic examination."

And again, on p48:

"Since the intramuscular injection appeared not to have been done in the quadriceps muscles sampled for histopathologic examination, local tolerance of the skeletal muscle tissue at the actual injection site could not be assessed in this study."

P20:

PBS Formulation

Ingredients	Quantity
Potassium chloride	200 mg/L
Potassium phosphate monobasic anhydrous	200 mg/L
Sodium chloride	8000 mg/L
Sodium phosphate dibasic anhydrous	1150 mg/L

This formulation is a little different to the one I found when reviewing the other three- month tox study:

Table 1. Required components

Component	**Amount**	**Concentration**
NaCl (mw: 58.4 g/mol)	8 g	0.137 M
KCl (mw: 74.551 g/mol)	200 mg	0.0027 M
Na_2HPO_4 (mw: 141.96 g/mol)	1.44 g	0.01 M
KH_2PO_4 (mw: 136.086 g/mol)	240 mg	0.0018 M

P26:
"The Dunnett's multiple comparisons test was conducted to determine statistically significant differences ($p<0.05$) between the individual dose groups and the control (reference) group."

This is scientifically inappropriate. Dunnett's test is used to compare each of a number of treatments with a single control but as there was only one treatment group, Merck should have used a two-sample test instead, e.g. the two-sample t-test.

P44:
"Organ weights
There were no test article-related organ weight changes at scheduled necropsies. At interim necropsy, a few isolated parameters reached statistical significance ($p<0.05$) after adjustment for multiplicity (increase in mean spleen weight when expressed as percent of brain weight and decrease in mean testis weight when expressed as percent of body weight). Owing to the low magnitude of the change and in the absence of any histomorphologic correlate, these were not considered test article-related.

At final necropsy, there was a statistically significant decrease in mean adrenal weight when expressed as

percent of brain weight. This was not observed at interim necropsy and the difference in mean adrenal weights relative to controls was considered within the expected biological variation and therefore not related to administration of the test article ..."

This information contradicts the information in the summary: "There were no test article-related organ weight changes at scheduled necropsies."

The other rat toxicity study was finished five years before this one and it was bigger, 200 animals versus 60. An increase in mean spleen weight is expected after vaccination, and the earlier study concluded correctly that this was caused by the vaccine, in contrast to the current study. Since much of the wording is exactly the same in the two reports, the authors of this most recent report did not produce it independent of the first report. It is scientifically inappropriate to first do a study that shows an effect, and next, to do another, smaller study and then say there is no effect, without quoting the first study.

P47-8:
The conclusions are very similar to those for the other toxicity study and are therefore similarly misleading.

V503 TT 07-7400, pregnancy, 90 rats

Intramuscular Developmental Toxicity and Immunogenicity Study in Rats With Prenatal Evaluation.

Index on p3.

Compound Preparation and 22-Oct-2007
Compound Administration 22-Oct-2007
Scheduled Sacrifice - 27-Nov-2007

This is a report on the toxicity of 9-valent HPV vaccine in relation to pregnancy in 90 rats. Nothing interesting was found (see Summary on p7). Both the vaccine and the adjuvant control contained 1000 µg/mL of aluminium adjuvant (pp14 and 15). There was also a PBS placebo group.

P16:

	Number of Females Per Group
Control 1 (PBS)	25[a]
Control 2 (MAA)	25[a]
V503	40[b]

[a] Includes 5 extra females to obtain 20 females with identified matings for cesarean section.
[b] Includes 12 females used only for blood sample collections and 8 extra females to obtain 20 identified matings for cesarean section and at least 10 pregnant females for immunogenicity.

V503 TT 09-7320_rat study, offspring, 50 female rats

Rat study of offspring.

Index on p2.

50 female rates received 9-valent HPV vaccine or the adjuvant before mating. Not of interest.

V503 PD001, immunogenicity in 6 rhesus macaques

Nine-Valent Human Papillomavirus [Types 6,11,16,18,31,33,45,52, 58] Recombinant Vaccine (V503): Immunogenicity in Rhesus Macaques.

Study Initiation Date: 18-Aug-2006
Termination Date: 02-Mar-2007

However, the report is dated January 30, 2012.

"The objective of this study was to demonstrate the immunogenicity of a nine-valent recombinant HPV LI VLP vaccine candidate produced in yeast and formulated with a proprietary amorphous aluminum hydroxyphosphate sulfate adjuvant (AAHS)."

"Conducted at New Iberia Research Center (NIRC), New Iberia, Louisiana, U.S.A., as a non-GLP study in accordance with Standard Operating Procedures."

It is unclear why this was not a Good Laboratory Practice study.

Six rhesus macaques.

Formulation.
9 valent HPV vaccine: The vaccine contained 2, 4, 4, and 2 mcg of HPV 6, 11, 16 and 18 VLPs per 0.5 mL dose. The vaccine also contained HPV types 31, 33, 45, 52 and 58 VLPs at 2 mcg each per 0.5 mL dose. In addition, the vaccine contained 309.5 mcg AAHS per 0.5 mL dose.

The amounts of virus like particles (the antigens) were very small. It is unclear why such an odd number of mcg of the adjuvant were used, with excessive precision, and why was the amount differed to that used in Merck's other animal studies.

The vaccine was administered on Day 0, Week 8 and Week 24.

Each animal was observed daily for any abnormal clinical signs, signs of illness or distress as per standard NIRC care. Behavioral sciences personnel also performed daily observations for evidence of behavioral stereopathies, or distress for duration of the study.

Mortality
All six animals were sacrificed at Week 28 for exsanguination.

Merck purportedly killed the monkeys by bleeding them to death and called it a sacrifice. It makes no sense to kill the monkeys as no autopsies were performed.

Physical Examinations
There were no adverse physical signs observed during the study.

"well tolerated. There were no vaccine associated deaths, adverse physical signs, or adverse effects on body weight gain."

It is not quite correct to state that there were "no vaccine associated deaths" given Merck would not have killed the monkeys if the monkeys had not been vaccinated.

Animal or in vitro studies, adjuvant versus control

PD002_adjuvant studies, immunogenicity in 6 chimpanzees

PD002: Monovalent HPV 16 LI VLP Immunogenicity Study in Chimpanzees: Merck Aluminum Adjuvant (MAA) versus no adjuvant.

Study Initiation Date: 1997
Termination Date: 1998

Section A. Antemortem Report
Section B. Immunoassay Report

P3:
"Objective of Study
Evaluate the optimal way to formulate the HPV 16 LI VLP vaccine in order to produce a strong immunological response in Chimpanzees, large non-human primates. The study will demonstrate the general tolerability and immune response to HPV 16 LI VLPs formulated with no adjuvant or formulated with Merck Aluminum Adjuvant."

It is unscientific to state that a study will demonstrate the general tolerability of a vaccine or drug. It implies that Merck already knew the results before the study was carried out.

6 Chimpanzees, approximately 9-11 years old.

P4ff
"Formulation
HPV 16 LI VLPs 20 mcg/mL plus or minus 1 X MAA"

Two groups, the first immunized with HPV 16 LI VLP + MAA (4 Chimps) and the second group immunized with HPV 16 LI VLPs without adjuvant (2 Chimps).

The vaccine was administered on Day 0, week, 8 and week 24. Dosing Volume 0.5 mL per injection / dose.

Blood samples were collected into appropriate sized non-additive serum separator Vacutainer-type tubes (SST) from all animals at Day 0, and Weeks 4, 8, 12, 16, 21, 24, 28, 32, 36, 40, 44, 48, and 52.

No adverse physical signs were observed.

a. **Results** * indicates week of vaccination, performed after serum collection

Group	Weeks / Animal ID	0*	4	8*	12	16	21	24*
16+MAA	86A005	<10	188	170	9000	3033	598	408
	88A005	<10	11	<10	1300	592	353	296
	88A002	<10	<10	26	640	<10	21	80
	A055B	<10	<10	14	88	284	28	17
16 no Adj.	87A003	<6	6	14	93	68	32	nd
	88A001	<6	<6	nd	<6	<6	<6	nd

Group	Weeks / Animal ID	28	32	36	40	44	48	52
16+MAA	86A005	3068	2607	1332	561	902	1078	1161
	88A005	1784	1279	1186	1016	530	612	471
	88A002	399	293	168	158	148	529	96
	A055B	201	70	34	30	36	14	9
16 no Adj.	87A003	233	82	120	85	46	48	51
	88A001	<6	<6	6	<6	<6	<6	<6

The adjuvant produced a stronger immune response, but one animal responded quite poorly, perhaps because the vaccine dose was low (my interpretation).

TT 11-8051, mutagenesis in bacteria

Microbial Mutagenesis Assay.

Summary: L-000931224: Microbial Mutagenesis Assay. TT #11-8051

L-000931224 (2X Aluminum Hydroxyphosphate Sulfate) was evaluated for mutagenic potential in a microbial mutagenesis test system using mutant strains of *Salmonella typhimurium* (TA1535, TA97a, TA98, and TA100) and *Escherichia coli* (WP2 uvrA pKM101). In this test system, mutation was measured as reversion to histidine prototrophy of *Salmonella* test strains which are histidine auxotrophs and as reversion to tryptophan prototrophy of an *E. coli* test strain which is a tryptophan auxotroph. The test article was tested with and without a liver microsomal enzyme activation system (S-9) prepared from rats treated with phenobarbital and beta-naphthoflavone. The test article was tested using triplicate plates with and/or without metabolic activation for each strain tested. This study was conducted at Merck Research Laboratories, West Point, Pennsylvania, U.S.A., from 18-Apr-2011 to 20-Apr-2011, in accordance with Standard Operating Procedures.

L-000931224, an aluminum adjuvant formulation consisting of 900 µg/mL aluminum (present as an amorphous aluminum hydroxyphosphate sulfate adjuvant) was used as a suspension in a Diluent Buffer (140 µg/mL Sodium Borate and 9 mg/mL Sodium Chloride) The final concentrations tested were 5.5, 11, 22.5, 45 and 90 µg/plate with and without S-9 metabolic activation. The high dose for these studies, 90 µg/plate aluminum, was the maximum feasible concentration (MFC), based on the concentration of test article in the formulation (900 µg/mL aluminum). A range-finding assay was not considered necessary, since a maximum feasible concentration was used.

The results of the Microbial Mutagenesis Assay indicated that L-000931224 did not produce any 2-fold or greater increases in revertants relative to control. The positive control and diagnostic mutagens showed appropriate S-9- and strain-dependent increases in revertants. No precipitate was seen on the plates at any concentration tested. No inhibition of bacterial lawn or revertant growth was noted.

L-000931224 (2X Aluminum Hydroxyphosphate Sulfate) did not induce 2-fold or greater dose-related increases in revertants relative to the solvent control in any of the test strains, and thus is not mutagenic in the Microbial Mutagenesis Assay when using a high dose at the maximum feasible concentration (90 µg/plate aluminum). There was no indication of any increase in mutation or toxicity that indicated a need to repeat the mutation assay.

In conclusion, L-000931224 was negative in the Microbial Mutagenesis Assay.

Not of interest.

T 11-8635 & TT 11-8639, chromosomal aberrations in hamster cells

Assay for Chromosomal Aberrations In Vitro, in Chinese Hamster Ovary Cells.

“Summary: L-000931224: Assay for Chromosomal Aberrations In Vitro, in Chinese Hamster Ovary Cells. TT #11-8635 and TT #11-8639

L-000931224 (2X Aluminum Hydroxyphosphate Sulfate adjuvant) was evaluated for its potential to cause chromosomal aberrations in Chinese hamster ovary (CHO) cells (subclone WBL).

L-000931224, an aluminum adjuvant formulation consisting of 900 pg/mL aluminum (present as an amorphous aluminum hydroxyphosphate sulfate adjuvant) in a Diluent Buffer (140 pg/mL Sodium Borate and 9 mg/mL Sodium Chloride) was tested with and without a metabolic activation system (S-9) prepared from the livers of rats treated with beta-naphthoflavone and phenobarbital. Cytotoxicity was assessed as reductions in cell growth or monolayer confluence. The aberration assays involved 3 treatment conditions; 3-hour treatments with or without S-9 and a continuous treatment without S-9 for about 20 hours (TT #11-8635). In the repeat study (TT #11-8639) cultures were treated for 17 hours, washed and harvested 3 hours later. The concurrent solvent control cells were treated with 5% v/v Diluent Buffer. Positive controls (cyclophosphamide with S-9 activation or mitomycin C without S-9) were included. The cells were fixed for analysis of chromosome aberrations about 20 hours from the beginning of treatment (about 1.5 normal cell cycle lengths).

The high dose for these studies, 45 pg/mL aluminum, was the maximum feasible concentration (MFC), based on the concentration of test article in the formulation (900 pg/mL aluminum) and the maximum dosing volume for cultures (5% v/v). L-000931224 was tested as a suspension in cultures.

In the chromosomal aberration assays, TT #1 1-8635 and TT #11-8639, the top dose of L-000931224 scored for aberrations was the MFC. In the first assay, TT #11-8635, the treatment levels of L-000931224 scored for aberrations were 5, 20, and 45 pg/mL after the 3-hour treatments with and without S-9. Suspended and adhering test article was evident after all treatments and cell growth at 20 hours at 45 pg/mL was about 90% of concurrent solvent controls. Cell growth at 45 pg/mL after the 20-hour treatment was reduced to 76% of concurrent solvent controls. The assays after the 3-hour treatments with and without S-9 were negative. Slides from the 20-hour treatment could not be scored because test article precipitate interfered with scoring the slides and the series was repeated with a wash included before harvest, to reduce the amount of test material present at the time of scoring the slides.

In the repeat test (TT #11-8639) cultures were treated for 17 hours without S-9 activation, washed and allowed to recover for 3 hours in the presence of colcemid. The treatment levels of L-000931224 scored for aberrations were 2.5, 30, and 45 pg/mL and cell growth at the top dose was 49% of solvent controls. The assay after a 17-hour treatment without S-9 was negative.

In both assays, the high-dose positive controls induced significant increases in aberrations over the concurrent solvent controls. There was no increase in structural chromosome aberrations in cultures treated with L-000931224, so that the assay was negative. In summary, L-000931224, 2X Aluminum Hydroxyphosphate Sulfate adjuvant, did not cause chromosomal aberrations in Chinese Hamster Ovary cells when using a high dose at the Maximum Feasible Concentration (45 pg/niL aluminum).”

“the high dose, 45 pg/mL aluminum, was the maximum feasible concentration (MFC), based on the concentration of test article in the formulation (900 pg/mL aluminum) and the maximum dosing volume for cultures (5% v/v).”

“Treatment concentrations for cytotoxic test articles are generally selected to include a dose giving a growth reduction not greatly exceeding 50% of concurrent solvent controls. Generally, 200 cells per dose

are scored under code from a minimum of 3 doses of test article and from negative and/or solvent controls. Positive controls are also used, treated with mitomycin C (without metabolic activation) or cyclophosphamide (with metabolic activation)."

This study was carried out in 2011, report dated 17 May 2011. The aberrant findings were intended and expected, to show that the assay system would be sensitive, if there were problems. No problems were described. No blinding of readings was described.

TT 11-8636 & TT 11-8637, micronucleus induction in rat bone marrow

Assay for Micronucleus Induction in Rat Bone Marrow.

Summary: L-000931224: Assay for Micronucleus Induction in Rat Bone Marrow.

L-000931224, (2X Aluminum Hydroxphosphate Sulfate adjuvant) was evaluated for its potential to induce micronuclei in bone marrow polychromatic erythrocytes of male (TT #11-8636) and female (TT #11-8637) rats. A total of 40 male and 40 female Crl:CD(SD) rats, approximately 7-8 weeks old, and weighing 231 to 270 g (males) or157 to 185 g (females) at study start were used.

Two groups of 10 rats per sex each received 225 or 450 pg/rat of L-000931224 as a single intramuscular dose to each quadriceps. The vehicle controls (10 rats per sex) received a single intramuscular dose to each quadriceps of the Diluent Buffer (140 pg/mL Sodium Borate and 9 mg/mL Sodium Chloride). The dosing volume for all these animals was 0.25 mL per quadriceps (0.50 mL per rat). The high dose for these studies, 450 pg/rat aluminum, was the maximum feasible dose, based on the concentration of test article (900 pg/mL aluminum) and the maximum intramuscular dosing volume per animal.

For the vehicle control and L-000931224 treated groups, 5 per group per sex were sacrificed for harvest of bone marrow cells 24 hours and 48 hours after dosing. Male and female rats from the positive control groups (mitomycin C) were sacrificed 24 hours after dosing.

Rats were examined for clinical signs of toxicity after drug administration and at each sacrifice interval. All animals appeared normal throughout these studies and there were no deaths.

Slides were prepared from bone marrow cells that were harvested at sacrifice and stained with acridine orange. Two thousand to 4 thousand polychromatic erythrocytes (PCE) per rat were scored for micronuclei (MN-PCE) from coded slides. The frequencies of PCE and of mature, normochromatic erythrocytes (NCE) were also recorded among 1000 to 2000 erythrocytes per rat. Micronuclei were scored from each of 5 rats per sex per group at each time point.

The study was negative in males and females. The high-dose positive control, mitomycin C, induced marked increases in micronuclei. There was no apparent effect of L-000931224 on the proportions of bone marrow PCE among total erythrocytes.

Not of interest.

Appendix C

Monovalent and quadrivalent HPV vaccine Clinical Trials

Review Notes

Contents

“Placebo-controlled” study of quadrivalent HPV vaccine

V501 P018 V1 CSR

Study Initiation Date (FPI): 08-0ct-2003
Study Completion Date (LPO): 19-Jan-2005
Clinical Study Report Date: 08-Aug-2005

P364: list of appendices, starting with publications.
P372: another index, e.g. with protocol amendments.
Synopsis on p27.

P27:
“OBJECTIVE(S): Primary Safety Objective: To demonstrate that a 3-dose regimen of quadrivalent Human Papillomavirus (HPV) (Types 6, 11, 16, 18) L1 VLP vaccine is generally well tolerated in adolescents and preadolescents. Secondary Objectives: (1) To demonstrate that the 4-week Postdose 3 anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 responses induced by a 3-dose regimen of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine in preadolescent and adolescent boys are noninferior to the responses observed in preadolescent and adolescent girls. (2) To describe the persistence of immune response to the quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine, when given in a 3-dose regimen.”

Thus, the primary focus in the study was clearly safety. Immune responses were secondary.

“Vaccination at Day 1, Month 2, and Month 6 plus 14 calendar days of clinical follow-up after administration of each dose. All subjects will be followed for persistence of antibody response and safety evaluation through Month 18.” Both girls and boys were included; 1781 children were vaccinated (p28):

	Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Vaccine	Non-Alum Placebo	Total
SCREENING FAILURES:			20
RANDOMIZED:	1184	597	1781
Female (age range – years)	617 (9 to 15)	322 (9 to 15)	939
Male (age range – years)	567 (9 to 16)	275 (9 to 15)	842
VACCINATED AT:			
Dose 1	1179	596	1775
Dose 2	1149	573	1722
Dose 3	1123	562	1685
VACCINATION PERIOD (Day 1 Through Month 7)			
ENTERED	1179	596	1775
COMPLETED	1120	560	1680
CONTINUING†	1	0	1
DISCONTINUED	58	36	94
With Long-Term Follow-Up	7	4	11
Clinical Adverse Experience	2	0	2
Other	5	4	9
Without Long-Term Follow-Up	51	32	83
Clinical Adverse Experience	1	0	1
Lost to Follow-up	17	7	24
Moved	4	1	5
Other Reasons	1	2	3
Parent withdrew consent	9	8	17
Withdrew consent	19	14	33

† Subject did not complete Month 7 visit prior to the Month 7 visit date cutoff of 19-Jan-2005.
HPV = Human papillomavirus; VLP = Virus-like particles.

A non-aluminum-containing placebo was chosen for the study at the request of a regulatory agency (p63). The placebo was described as “carrier solution” (on p28 and p61), but nowhere in the report could I find the composition of this carrier solution. If it had been saline, Merck presumably would have written that.

Merck did not explain what it put in the carrier solution. According to the index, this information should be on p60 in the report but there was none, instead, Merck stated: “To provide a control for the quadrivalent

F1PV (Types 6, 11, 16, 18) L1 VLP vaccine, the placebo used in this study contained identical components to those in the vaccine, with the exception of FIPV L1 VLPs and aluminum adjuvant." Not even in the original protocol for the study was there any information, instead, Merck stated: "To provide an appropriate control for the Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Vaccine, the placebo used in this study will contain the exact ingredients as in the vaccine except HPV L1 VLPs and aluminum adjuvant" (p1383).

My research group has done extensive work on this issue previously and found out that, according to the FDA: "Each 0.5-mL dose of the vaccine contains approximately 225 mcg of aluminum (as Amorphous Aluminum Hydroxyphosphate Sulfate adjuvant), 9.56 mg of sodium chloride, 0.78 mg of L-histidine, 50 mcg of polysorbate 80, 35 mcg of sodium borate, <7 mcg yeast protein/dose, and water for injection."[1]

The substances in the carrier solution are not placebos. Polysorbate 80 is used to stabilize aqueous formulations of medications for parenteral administration. It is used as an excipient in some European and Canadian influenza vaccines. Influenza vaccines contain 2.5 µg of polysorbate 80 per dose. Another article explains, with references:[2] "Polysorbate 80, like some other surfactants, is not an inert compound … In drug formulations, polysorbate 80 has been implicated in a number of systemic reactions (e.g., hypersensitivity, nonallergic anaphylaxis, rash) and injection- and infusion-site adverse events (ISAEs; e.g., pain, erythema, thrombophlebitis)."

According to a safety datasheet for sodium borate,[3] this substance: may be harmful if inhaled; may cause respiratory tract irritation; may be harmful if swallowed; may be harmful if absorbed through skin; may cause skin irritation; and may cause eye irritation. "High dose animal feeding studies in rat, mouse and dog have demonstrated effects on fertility and testes. Studies with boric acid have demonstrated developmental effects on the foetus including foetal weight loss and minor skeletal variations. The doses administered were many times in excess of those to which humans would normally be exposed. Human epidemiological studies show no increase in pulmonary disease or fertility effects in populations with chronic exposure to boric acid or sodium borate dust." Sodium borate is used in the treatment of diaper rash, insect bites and stings, and sunburn, and in the prevention of otitis externa.

About yeast proteins in vaccines,[4] the WHO announced on 7 January 2005: "There is a theoretical risk of contamination of vaccines with yeast antigens with resultant mimicry between peptides of yeast and human myelin proteins. T-cells might be activated, with a resultant cross-reaction with myelin proteins."

Thus, at least two of the four substances in the carrier solution, polysorbate 80 and yeast proteins could be immunogenic. At any rate, it was not appropriate for Merck to call its carrier solution a placebo, which would normally mean saline when dealing with injections. Merck itself defines a placebo as: "A placebo is made to look exactly like a real drug but is made of an inactive substance, such as a starch or sugar."[5]

Gardasil was approved by the FDA on 8 June 2006,[6] which was 10 months after the date of the clinical study report.

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[1] https://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm111263.pdf
[2] Schwartzberg LS, Navari RM. Safety of Polysorbate 80 in the Oncology Setting. Adv Ther 2018;35:754–67.
[3] https://www.abcam.com/index.html?pageconfig=resource&rid=13171
[4] https://www.who.int/vaccine_safety/committee/topics/yeast/jan_2005/en/
[5] Merck: Placebos. https://www.merckmanuals.com/home/drugs/overview-of-drugs/placebos.
[6] https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/gardasil-vaccine-safety

There is no public trial identifier in the study report even though the trial was submitted to a trial register, clinicaltrials.gov, where its number is NCT00092547. The trial register shows that the main and first publication of this trial is: Reisinger KS, Block SL, Lazcano-Ponce E, Samakoses R, Esser MT, Erick J, Puchalski D, Giacoletti KE, Sings HL, Lukac S, Alvarez FB, Barr E. Safety and persistent immunogenicity of a quadrivalent human papillomavirus types 6, 11, 16, 18 L1 virus-like particle vaccine in preadolescents and adolescents: a randomized controlled trial. Pediatr Infect Dis J. 2007 Mar;26(3):201-9.

Even though 6 of the publication's 12 authors are Merck employees, the abstract states: "Methods: In this randomized, double-blind trial, 1781 sexually naive children were assigned (2:1) to quadrivalent HPV-6/11/16/18 vaccine or saline placebo administered at day 1 and months 2 and 6."

People thus erroneously believe a saline placebo was used – even drug regulators, e.g. the director of the Danish Board of Health stated at a meeting of the Danish Medical Association on 15 August 2017 about the HPV vaccines[7] – that it was a placebo controlled.

P29:
"Safety: The primary objective of this study related to the safety of the vaccine. The primary hypothesis stated that a 3-dose regimen of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine will be generally well tolerated in adolescents and preadolescents. In order to address this objective, the study called for a detailed tolerability analysis, with emphasis on the following prespecified adverse experiences: vaccine-related adverse experiences, vaccination report card (VRC)-prompted injection-site adverse experiences (swelling/redness and pain/tenderness/soreness), VRC-prompted systemic adverse experiences (muscle/joint pain, headaches, hives, rashes, diarrhea), severe adverse experiences, and fever."

Similar information is given in the section on statistical methods on p80-1.

P75:
""The important variables of interest for safety/tolerability were the occurrence of severe injection-site adverse experiences and the incidence of any vaccine related serious adverse experiences."

Merck raised the bar considerably for reporting adverse events, compared to the text on p29.

P30:
"… risk differences and associated 95% confidence intervals were computed comparing the vaccine and placebo groups across all vaccination visits with respect to adverse experiences with ≥ 1% incidence in either vaccination group and elevated temperatures. p-Values were computed only for those adverse experiences that were prompted for on the VRC (elevated temperatures, injection-site pain, injection-site swelling, injection-site redness, muscle/joint pain, headaches, hives, rashes, diarrhea) ..."

This is poor and biased research. First, there were 1179 patients in the vaccine group, so if 11 patients (0.9%) experienced an important harm versus none of the 594 patients in the placebo group, this would be ignored with a 1% incidence as the limit for reporting, even though p = 0.02 for this difference (Fisher's exact test).

Second, the emphasis was on "prespecified adverse experiences: vaccine-related adverse experiences …" Since a placebo-controlled trial had never been carried out before, no one could know which adverse events the vaccine might cause, and it was therefore inappropriate to prespecify these. Both the 1% limit and the prespecifications mean that unanticipated harms, e.g. symptoms suggesting the occurrence of POTS

[7] Gøtzsche PC. Vaccines: truth, lies, and controversy. New York: Skyhorse; 2021.

(postural orthostatic tachycardia syndrome), CRPS (complex regional pain syndrome) or autoimmune diseases, would very likely be missed.

Third, it is inadequate for a study with a primary focus on safety that a drug regulator requested be carried out using a genuine placebo control to only collect and test possible harms in a fourteen-day period after each vaccination.

Fourth, it is inadequate to only focus on adverse events that were prompted for on the vaccination report card and to only compute p-values for these.

P30:
"In order to eliminate the impact of aluminum-containing non-study vaccinations received during the course of this study on the assessment of the quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine and the non-aluminum-containing placebo groups in terms of the incidence of adverse experiences, summaries of incidence rates of overall adverse experiences, specific adverse experiences that occur in ≥ 1% of subjects in either vaccination group, and elevated temperatures were also provided, by vaccination group, excluding those subjects who received any aluminum-containing non-study vaccinations during this study. These summaries were provided across all vaccination visits. No formal comparisons were performed in this subset of subjects."

P48:
"Vaccine and placebo were visually distinguishable and therefore required the use of unblinded study personnel to prepare and administer injections. For details regarding the role of the unblinded site personnel, see Section II.5.4.5.1.1."

P60:
The placebo used in this study contained identical components to those in the vaccine, with the exception of FIPV L1 VLPs and aluminum adjuvant ... Because vaccine and placebo were not visually indistinguishable, an unblinded staff member at each study site was designated to administer injections.

P63:
"One study investigator, identified as the Coordinating Investigator, was responsible for reviewing the CSR [clinical study report] for this study. During the review, the Coordinating Investigator would have become partially unblinded to the individual subject vaccination allocations. At the time of this review the study was still ongoing, thus the Coordinating Investigator was required to recuse himself from further active involvement in the study (i.e., conducting study visits, review of clinical data, adverse experience assessment or other study-related activities)."

These procedures are not acceptable for Merck's only supposedly placebo-controlled trial that specifically focussed on safety, at a drug regulator's request.

To have both blinded and non-blinded personnel in a study at the same study sites creates a huge risk of unblinding also the investigators, which has been documented to occur in other trials.

P64:
"The main analyses of immunogenicity and safety presented in this CSR are based on data collected up to 1 month Postdose 3 (i.e., the Month 7 visit). No interim analyses were planned. In order to conduct the Month 7 analysis, inhouse Merck personnel were unblinded to treatment group after the Month 7 data were reviewed and the database was frozen."

P62:
“Merck’s hepatitis B vaccine is manufactured by a technology that is similar to that used to manufacture the HPV vaccine (i.e., generation of recombinant proteins made in the yeast Saccharomyces cerevisiae).”

P75:
“The important variables of interest for safety/tolerability were the occurrence of severe injection-site adverse experiences and the incidence of any vaccine related serious adverse experiences.”

It is inappropriate to only focus on severe injection-site adverse experiences and vaccine related serious adverse experiences. Local and systemic adverse experiences of moderate or severe intensity are also important. Merck defines the severity categories this way, in all its trials (p78):

— Mild: awareness of sign or symptom, but easily tolerated
— Moderate: discomfort enough to cause interference with usual activities
— Severe: incapacitating with inability to work or do usual activity

Merck’s definition of a serious adverse experience is (p78):

“A serious adverse experience is any adverse experience occurring at any dose that:

‡ Results in death; or
‡ ls life threatening (places the subject, in the view of the investigator, at immediate risk of death from the experience as it occurred [Note: This does not include an adverse experience that, had it occurred in a more severe form, might have caused death.]); or
‡ Results in a persistent or significant disability/incapacity (substantial disruption of one’s ability to conduct normal life functions); or
‡ Results in or prolongs an existing inpatient hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation) (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse experience); or
‡ ls a congenital anomaly/birth defect (in offspring of subject taking the product regardless of time to diagnosis); or

ALSO :
Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the (‡) outcomes listed above.

In addition, Merck requires the collection of the following:
cancer, or
overdose (whether accidental or intentional) (Note: Overdose in this study was defined as a subject receiving >3 doses (0.5-mL) of vaccine or placebo throughout the study or receiving >0.75 mL of vaccine or placebo in any 1 dose).”

Merck’s information about which safety variables are important, is contradictory. The text on p29 speaks about a detailed tolerability analysis that is not limited in the way specified on p75 (see just above):

“Safety: The primary objective of this study related to the safety of the vaccine ... In order to address this objective, the study called for a detailed tolerability analysis, with emphasis on the following prespecified

adverse experiences: vaccine-related adverse experiences, vaccination report card (VRC)-prompted injection-site adverse experiences (swelling/redness and pain/tenderness/soreness), VRC-prompted systemic adverse experiences (muscle/joint pain, headaches, hives, rashes, diarrhea), severe adverse experiences, and fever."

The study's shortcomings inevitably resulted in not finding out if the vaccine causes systemic adverse experiences, compared to placebo.

P76:

> placebo. Follow-up at Month 2, Month 6, Month 7, Month 12, and Month 18 included an interview to assess general safety. The interview consisted of a review of the VRC, which solicited for specific adverse experiences and for any severe adverse experiences that the subject may have encountered. The subject's parent/legal guardian was instructed to notify the study physician immediately if any unexpected or severe adverse experience occurred. At the Month 12 visit, which will consist of a telephone interview, the parent/legal guardian will be solicited for any new medical conditions as specified by the protocol or severe adverse experiences that the subject may have encountered.

This is inadequate. The patients were interviewed but there was no information about how these interviews should be done, neither in this report, nor in any other of Merck's study reports, other than: "The interview consisted of a review of the VRC [vaccination report card], which solicited for specific adverse experiences and for any severe adverse experiences that the subject may have encountered."

As the investigators were not instructed about how they should elicit nonspecific or unexpected (not "prespecified") adverse events, this gave the impression that such events were not of interest. Furthermore, important harms can be overlooked if the investigators do not use an open question such as "Have you noticed anything unusual since your last visit?"

"At the Month 12 visit, which will consist of a telephone interview, the parent/legal guardian will be solicited for any new medical conditions as specified by the protocol or severe adverse experiences that the subject may have encountered."

This is inadequate.

First, systemic adverse experiences of moderate intensity were not solicited.

Second, the trial subjects were not asked about their experiences (see below). By not asking the trial subjects, some vaccine harms likely were missed.

Third, it is not clear in this trial or in any of Merck's trials how investigators should distinguish between adverse experiences and "new medical conditions." A new medical condition can be virtually everything, including the common cold. In contrast, Merck was highly specific when it came to injection-site adverse events, which were explored in great detail in this trial and in all of Merck's other trials even though they are short-lived and far less important than systemic adverse events.

Fourth, nowhere in the protocol could I find any definition of what a new medical condition is, which is concerning given the text on p76 mentioned "any new medical conditions as specified by the protocol" but these were not specified in the protocol.

P78:

5.5.3.4 Serious Clinical Adverse Experiences

Investigators were instructed to report any serious adverse experience, including death due to any cause, occurring in any subject from the time the consent was signed through 14 days following the first vaccination and from the time of any subsequent vaccinations through 14 days thereafter, whether or not related to the investigational product.

In addition, if a death due to any cause, or a serious adverse experience that was considered by the investigator to be possibly, probably, or definitely vaccine related occurred at any time during the study, it was to be immediately reported to the Sponsor. Furthermore, a serious adverse experience that was considered by the investigator to be possibly, probably, or definitely related to a study procedure was to be immediately reported to the Sponsor. Serious adverse experiences were to be reported within 24 hours to MRL.

To collect only serious adverse events of interest that only occur shortly after the vaccinations is inadequate and signals a lack of interest in finding out if the vaccine causes important systemic adverse experiences.

P88:
"Amendment 018-02 [3.3.3] was a partial amendment to include VAQTA™3 (hepatitis A vaccine, inactivated) as an optional provision to subjects in Spain. All Spanish subjects are eligible to receive VAQTA1M. VAQTA1M will be offered to all Spanish subjects at the Month 18 study visit after all study procedures for that visit have been completed and at an additional Month 24 study visit."

P90:
"5.8.2 Changes in the Statistical Analyses
The statistical analyses performed for this study differed from those stated in the Protocol [3.3] or in the informational amendment contained in a letter sent to the U.S. FDA CBER [3.15] as follows … Data collected after Month 7 will not be included in this CSR, but will be summarized separately, as the data become available."

P91:
"6. Study Subjects and Data Sets Analyzed
6.1 Accounting for Subjects in the Study
... This CSR will cover the period between Day 1 and Month 7 (inclusive). Separate reports will summarize the findings for the period after Month 7 and through Month 18."

I searched for safety data between month 7 and month 18 to see why Merck did not report these data when Merck had them. I did not find these data in any of Merck's reports, including its 10-year follow-up of these patients (see below, V501 P018 LTFU CSR_ w protocols P018-05, -06, -10 and -11).

I looked at the protocol appendices for an explanation. They ran over 466 pages and were called Protocol 018-00, Protocol Amendment 018-01, 018-02, 018-03 and 018-04.

Protocol 018-00 was dated 24 July 2003. As the study initiation date was 8 0ctober 2003, this presumably was the original protocol:

P1363:
"OBJECTIVES:
Primary: To demonstrate that a 3-dose regimen of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine is generally well tolerated in adolescents and preadolescents.

Secondary: Secondary: (1) To demonstrate that the quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine, when given in a 3-dose regimen, induces acceptable anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 responses 4 weeks Postdose 3 in adolescents and preadolescents; and (2) To describe the persistence of immune response to the quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine, when given in a 3-dose regimen."

The objectives as described in the clinical study report were:

P27:
"OBJECTIVE(S): Primary Safety Objective: To demonstrate that a 3-dose regimen of quadrivalent Human Papillomavirus (HPV) (Types 6, 11, 16, 18) L1 VLP vaccine is generally well tolerated in adolescents and preadolescents. Secondary Objectives: (1) To demonstrate that the 4-week Postdose 3 anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 responses induced by a 3-dose regimen of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine in preadolescent and adolescent boys are noninferior to the responses observed in preadolescent and adolescent girls. (2) To describe the persistence of immune response to the quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine, when given in a 3-dose regimen."

The original protocol had no objective about comparing the immune response in boys and girls, but the safety objective was the same in the study report as in the original protocol.

P1363-5:
"For each subject enrolled, the duration of the study will be approximately 1.5 years ... All subjects will be followed up for Adverse Experience (AE) events. All adverse experiences will be collected on the subject's Vaccination Report Card (VRC) daily for 15 days after each vaccination. At Month 2, Month 6, Month 7, Month 12 and Month 18, subjects will be evaluated for any new medical condition or health concerns ... All subjects enrolled will receive full-dose vaccine or placebo and will be included in the safety data analysis … A physical exam and final assessment will be performed at the Month 18 visit."

P1368:
A study flow-chart clearly states that non-serious adverse experiences (NSAEv) also were to be collected at the visits at month 12 and month 18:

STUDY FLOW CHART

			PERIOD:							
Compound No: V501 **Protocol No:** 018			**TIME FRAME** ***(Day, Week, Month)*:**	Day 1	Month 2	Month 6	Month 7	Month 12†	Month 18	UNS
			VISIT:	**1**	**2**	**3**	**4**	**5**	**6**	**U**
Procedure	**Pick Option Number**	**Module ID**	**Worksheet ID**							
Informational brochure/prescreening		None	Brochure	x						
Informed consent/assent		None	Worksheet	x						
Inclusion criteria		50980	INCL	x						
Exclusion criteria		51020	EXCL	x						
Demographics	2/4	34997	D	x						
Telephone contact log		None	Worksheet					x		
Subject telephone contact		51040	STC					x		
Temperature (pediatric)		17177	TEMPp		x	x	x			x
Adverse experience	3/7	34977	NSAEv/SAEv/ AEOS		x	x	x	x	x	x

P1375-6:
Under Background and Rationale, Merck mentions that the incidence of systemic adverse experiences in Merck's previous trials were comparable among those who received a vaccine and those who received placebo. But again, none of the patients in the control group received placebo; they all received the aluminium adjuvant. "Further information can be obtained in the 'Quadrivalent HPV Vaccine Confidential Investigator Brochure'."

P1377-8:
"this study will provide important tolerability information, including (a) comparison to a non-aluminum-containing placebo; (b) safety follow-up for 12 months postvaccination [i.e. till month 18], and (c) active surveillance for common systemic AEs. The protocol is focused on a detailed tolerability analysis ... All subjects will be included in the evaluation of vaccine tolerability."

P1405:
"An addendum to the primary Clinical Study Report will include safety data through Month 18."

P1410:
"8. Interim Analysis
The main analysis of immunogenicity and safety for this study will be based on data collected up to 6 months Postdose 3 (i.e., the Month 12 visit); safety and immunogenicity measurements obtained following Month 12 will be included in a separate analysis."

P1414-5:
"Workbooklets/worksheets will be provided by the SPONSOR to record data in the clinic. Data on workbooklets/worksheets may be handwritten ... After preliminary review of these worksheets by the Investigator/study staff, the worksheets are entered into a database by SPONSOR personnel ... As a result of the SPONSOR data review process, corrections or changes to data may be required. Discrepancies or questions concerning the data will be sent to the Investigator. The discrepancy reports should be resolved by the Investigator/study staff, signed and dated, and a copy returned to the SPONSOR. The original discrepancy report must be retained in the subject binder as a record of changes or acknowledgment of the receipt of queries on the data."

P1416:
"Telephone interview will be conducted at Month 12 with all participating subjects. Any new medical condition, health concern, or vaccine-related adverse experience will be reviewed."

All of the above is text from the original trial protocol, which states that possible vaccine harms will be collected during the whole trial period, till month 18. I compared this with what the parents and potential trial participants were told before they signed the informed consent forms.

On p1823-48, there are copies of three informed consent forms: Two that parents were asked to read and sign before accepting their child's participation in the trial (one for USA, 12 pages, and one for other countries, 12 pages), and one that children aged 9 to 15 were asked to read and sign (2 pages).

P1823:
"each subject will be followed for 12 months after the last vaccine injection to check for medical problems."

P1827:

Sixth Visit

The sixth visit will be 6 months after the fifth visit (18 months after starting the study). A physical exam and final assessment will be performed on all subjects. A blood specimen (up to a maximum of 2-3 teaspoons) will also be taken to test for the presence of HPV antibodies.

You will be asked about your child's medical history. Your child's vital signs will be taken, including temperature, weight, blood pressure, pulse rate and breathing rate.

Thus, the parents were informed (albeit not directly, "check for medical problems") that possible adverse effects of the vaccine would be collected up to 18 months after the first vaccination.

P1825:
"Your child will receive a dose of the quadrivalent HPV vaccine or a vaccine with no active ingredient called a placebo."

The parents were misinformed, as Merck's carrier solution was not a placebo, not even according to Merck's own definition of what a placebo is: "A placebo is made to look exactly like a real drug but is made of an inactive substance, such as a starch or sugar."[8]

P1827-9:
"Has this vaccine been given to people before?
Approximately 25,300 subjects have been enrolled in 10 HPV vaccine clinical studies conducted by Merck & Co., Inc. Approximately 13,400 subjects have received at least one dose of an HPV vaccine. These subjects have received vaccines that contained either one or all components (types 6, 11, 16, 18) of the vaccine that your child will receive in this study.
1. Findings in women who received an HPV vaccine containing only one component of the HPV vaccine that your child will receive."

This information is misleading. It conveys the message that it has been tested in 10 trials where ca. 13,400 subjects received the vaccine and ca. 11,900 subjects did not. It gives the impression that the 11,900 controls were not vaccinated or received a placebo. No one would know the controls received a highly active adjuvant, and the parents would not know previous trials were inadequate for an assessment of the safety of the vaccine.

1. Findings in women who received an HPV vaccine containing only one component of the HPV vaccine that your child will receive

In two clinical studies, 112 subjects have received a research vaccine that contains virus-like particles for HPV type 11 alone and 82 subjects received a research vaccine that contains virus-like particles for HPV type 16 alone. Both research formulations were found to be generally well-tolerated. The most common clinical complaints were headache or pain at the site where the shot was given. No serious adverse (bad) effects related to the vaccine were reported.

In two other studies, 1,626 subjects have received another formulation of the vaccine that contains virus-like particles for HPV type 16 alone. This vaccine was made in a process more similar to the process that was used to make the HPV vaccine that your child will receive in this study. So far, no serious adverse effects related to the vaccine have been reported in these studies.

In another study, 27 subjects received a formulation of a vaccine that contains virus-like particles for HPV type 18 alone. No serious adverse effects related to the vaccine were reported and the vaccine was generally well-tolerated.

[8] Merck: Placebos. https://www.merckmanuals.com/home/drugs/overview-of-drugs/placebos.

In clinical practice, doctors are obliged to tell their patients not only about possible serious harms of a drug but also about common harms that are not serious. In clinical research, these demands are higher of course, not lower, and when previous trials have been carried out, the sponsor is obliged to tell what they showed. But Merck only mentioned serious adverse effects and states that the vaccine was "generally well-tolerated," which is a meaningless statement, particularly considering that it was not derived from placebo-controlled trials.

2. Findings in women who received an HPV vaccine similar to the HPV vaccine that your child will receive in this study (a vaccine that contains virus-like particles for HPV types 6, 11, 16, and 18)

In a study of the HPV vaccine that contains virus-like particles for HPV types 6, 11, 16, and 18 all together, 1155 subjects were enrolled. Of these subjects, 864 subjects received at least one injection of active HPV vaccine. The doses that they received were at least as high (and in some cases more than 2 times as high) as those of the full-dose vaccine that is being tested in this study. In the study, 286 subjects received at least 1 dose of the HPV vaccine similar to the full-dose vaccine that will be used in this study (20/40/40/20 µg/dose). The vaccine was generally well-tolerated. There were no serious adverse reactions attributable to the vaccine reported during the course of the clinical trial.

In another two studies of the HPV vaccine that contains virus-like particles for HPV types 6, 11, 16, and 18 all together, as well as vaccine that contains virus-like particles for HPV 16 alone, approximately 5,800 subjects have been enrolled. Of these, approximately 2,740 received at least one injection of the quadrivalent HPV vaccine and approximately 320 subjects received a vaccine that contains virus-like particles for HPV 16 alone. The studies are ongoing, so we only have early information. Overall, the vaccine was generally well-tolerated. There was one serious adverse experience that occurred in a placebo recipient. This subject fainted and had a seizure immediately after vaccination. The study doctors believe that this event occurred as a result of an unusually strong reaction to the pain of the injection of placebo. There was one serious adverse reaction that the study doctors thought may have been related to the vaccine. A woman developed wheezing and asthma after she received a vaccination. She had to get emergency room care and she had to receive medications to take for the following few weeks. We do not know if the subject received active vaccine or placebo.

In another study of the HPV vaccine that contains virus-like particles for HPV types 6, 11, 16, and 18 all together, approximately 12,200 subjects have been enrolled. Of these, approximately 6,100 received at least one injection of the quadrivalent HPV vaccine. The study is ongoing, so we only have early information. Overall, the vaccine was generally well tolerated. There were two serious adverse reactions that the study doctors thought may have been related to the vaccine. In one case, a woman developed a lot of pain in her arm that caused her to have difficulty using her arm for several days. She eventually recovered. We do not know if the subject received active vaccine or placebo. The other case was a woman that had a fever, headache, swollen face and eye redness that occurred approximately two hours after vaccination. She recovered two days later. We do not know if the subject received active vaccine or placebo.

Another study has enrolled approximately 1,250 women, 1,250 girls aged 10 to 15 years, and 500 boys aged 10 to 15 years. Of these, 625 women, 625 girls, and 500 boys received the full dose formulation of the HPV vaccine that contains virus-like particles for HPV types 6, 11, 16, and 18 all together, and the remainder received lower dose formulations of the HPV vaccine that contains virus-like particles for HPV types 6, 11, 16, and 18 all together. The study is ongoing, so we only have early information. Overall, the vaccine was generally well tolerated and there were no serious adverse reactions that the study doctor thought may have been related to the vaccine.

About the first trial, of 1155 subjects, parents are told, as for the other trials, that the "vaccine was generally well-tolerated" and that "there were no serious adverse reactions attributable to the vaccine reported during the course of the clinical trial." They are not told that it is impossible to determine if serious adverse reactions (or other adverse reactions, which Merck says nothing about) are attributable to the vaccine when the control group received active substances, the aluminium adjuvant plus the various additives I have described above, some of which can produce similar harms as the vaccine.

P1829-30:

What adverse (bad) effects can happen to my child by participating in the study?

The following adverse effects have been reported by people taking either HPV vaccine or HPV vaccine placebo in previous quadrivalent HPV studies or have been seen in animal experiments:

- Headache
- Fever
- Upper respiratory infection
- Abdominal pain
- Nausea
- Fatigue
- Influenza
- Allergic reactions
- Soreness, tenderness, itching, redness, bruising or swelling at the injection site.

The HPV vaccine placebo contains no active vaccine. If the quadrivalent vaccine is found to be protective against the HPV types it contains and your child received placebo, your child will not be protected. Adverse effects for the HPV vaccine placebo may also include those listed for HPV vaccine.

There are other less common adverse effects that the study doctor can identify for you. The study doctor or staff will discuss these with you. There can be other adverse effects that are not presently known about HPV vaccine.

There may be some discomfort from the procedures including bruising and/or tenderness at the site where the blood is taken, and fainting or feeling faint.

Merck mentions that "Adverse effects for the HPV vaccine placebo may also include those listed for HPV vaccine."

This is misleading, as it conveys the message that vaccine harms are at placebo level, even though placebo had not been used in Merck's trials, with one exception. Since many patients experience pain of moderate or severe intensity at the injection site, and it is the most common injection-site reaction, which Merck knew when it planned this trial, it is inaccurate to not mention pain as a possible harm, but only soreness and tenderness, which are not the same but milder.

The consent form for parents from non-US countries is very similar to that for the USA, but the consent form for the trial participants is different in relation to possible harms even though it only takes up two pages (p1847-8). This is the information about possible harms:

"What bad effects can happen to me by being in the study?
After I receive the study vaccine, I might feel sick.

I may have one or more of the following:

• Infection in my chest caused by a virus or bacteria

• Headache
• Pain in my stomach
• Influenza, a virus that can cause fever, muscle pain, headache and cough
• Fever
• Allergic reactions
• Feel sick to my stomach
• Feeling tired
• Pain, tenderness, redness, swelling, itching, warmth, or bruising at the site where the shot is given

I may experience bruising and/or tenderness in my arm where the blood is taken from. I may feel light headed or pass out while blood is being taken from my arm.

I may feel other effects not mentioned here. I will tell my parents and study doctor if I feel sick.

On the vaccination report card or diary, some of the questions may be hard for me to answer and I may not enjoy trying to answer them."

P1455:
Protocol/Amendment No.: 018-01.
Dated 6 Nov 2003.

"The purpose of this amendment is to include VAQTA™ (Hepatitis A Vaccine, Inactivated) and MENJUGATE™ (Meningococcal Group C-CRM197 Conjugate Vaccine) as optional provisions to subjects in Canada … A separate summary of the incidences of SAEs [serious adverse experiences] will be provided by treatment group (Quadrivalent HPV Vaccine or Placebo) at the 14-day post Month 18 and 14-day post Month 24 time points for those subjects in Canada who received VAQTA™ and/or MENJUGATE™ at Month 18 and Month 24."

I have not seen any such safety data.

P1579:
Protocol/Amendment No.: 018-02.
Dated 8 Jan 2004.

"Include VAQTA™ [Hepatitis A Vaccine, Inactivated] as an optional provision to subjects in Spain ... A separate summary of the incidences of SAEs will be provided by treatment group (Quadrivalent HPV Vaccine or Placebo) at the 14-day post Month 18 and 14-day post Month 24 time points for those subjects in Spain who received VAQTA™ at Month 18 and Month 24."

I have not seen any such safety data.

P1614:
Protocol/Amendment No.: 018-03.
Dated 7 Sept 2004.

There was a summary over three pages describing the changes to the protocol. Most important changes:

1 "The immunogenicity objective was changed to a comparison between genders."

2 “After the study is completed, subjects who received placebo will be offered vaccination with the marketed HPV vaccine, if and when the vaccine becomes commercially available for the indication to be used in the subjects’ population in the country where the subject was enrolled.”

3 “The placebo used in this study does not contain aluminum that may be present in nonstudy vaccines as alum adjuvant. Therefore, it is recommended that the administration of nonstudy vaccines be deferred until the end of the study. If this is not feasible, the information of vaccination with nonstudy vaccines should be recorded on previous and/or concomitant nonstudy vaccination worksheets for every subject enrolled in the study and a summary of nonstudy vaccines should be generated” (p1642).

4 “In this study, an overdose is defined as a subject receiving >3 doses (0.5 mL) of vaccine throughout the study or receiving >0.75 mL of vaccine in any one dose” (p1654).

On p96 in the study report, Merck writes: “To ensure that subjects in the comparator (placebo) group for the quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine were not exposed to aluminum during the study vaccination period, the study protocol prohibited the use of non-study aluminum-adjuvanted vaccines during the period of Day 1 to Month 7, inclusive. Despite this prohibition, 30 subjects in the quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine group and 16 subjects in the non-aluminum placebo group received such vaccines. The primary safety summaries presented in this CSR include these subjects. Sensitivity analyses excluding these subjects are also provided.”

It is not correct that the study protocol prohibited the use of non-study aluminum-adjuvanted vaccines from day 1 to month 7. The original protocol states (p1384):

“c. Prior and Concomitant Medicationts)/Treatment(s)
To reduce their potential interference with the evaluation of the immunologic response and reactogenicity of the study vaccine, nonstudy inactivated vaccines must not be received within the 14 days before or 14 days after any dose of study vaccine. Nonstudy live virus vaccines must not be received within the 21 days prior to or 14 days after any dose of study vaccine.”

It is also incorrect to write that the study protocol “<u>prohibited</u>” the use of non-study aluminum-adjuvanted vaccines (which are non-live vaccines). It only did this during four weeks around each vaccination in the original protocol and after the amendment, it was only a <u>recommendation</u> that the administration of non-study vaccines be deferred until the end of the study. Since the amendment came 11 months into the study, which was completed after another 11 months, it is misleading not to mention this in the study report, which puts the blame for the use of non-study vaccines on the patients, parents and investigators, with a strong wording, “Despite this prohibition,” 46 subjects received other vaccines, in a section called “6.2 Protocol Deviations.” It <u>was not</u> a protocol deviation to give other vaccines outside the five-week interval during the first half of the study.

P1711:
Protocol/Amendment No.: 018-04.
Dated 8 Sept 2004.

This amendment came only one day after the previous one. I compared it with the previous ones. The only difference I could find was that the word “Post-vaccination” had been changed to “Postvaccination:”

A. Background and Rationale Table 1.	• **Deleted Days 0 to 14 Following Any Vaccination and added Day 1 through 15 Postvaccination.**

A. Background and Rationale Table 1.	• **Deleted Days 0 to 14 Following Any Vaccination and added Day 1 through 15 Post-vaccination.**

P1365:
"Ten milliliters (10 mL) of blood samples for HPV 6, 11, 16, and 18 antibody assays will be obtained at Day 1 and Months 7 and 18 from all study subjects. An additional 1.5 mL of serum, at the same time points as above, is to be stored at the investigative site as retention serum."

There is a considerable public health interest in finding out if patients who have developed POTS, CRPS, autoimmune diseases and some other diseases after vaccination did this because the vaccine caused the production of destructive autoantibodies. If the HPV vaccine causes dysautonomia, for example, we would expect to find autoantibodies against the autonomic nervous system more often in those patients than in other patients. In one study, such autoantibodies were found in most of 17 patients with POTS, whereas 7 patients with vasovagal syncope and 11 healthy controls did not have them.[9] Another, larger study was carried out at the Danish Syncope Centre. It showed that, after vaccination, autoantibodies were identified in most girls with POTS combined with other symptoms of dysautonomia but only in a minority of those vaccinated girls who were healthy, and in even fewer healthy controls.[10] There are additional such studies.[11] *Given Merck collected and stored blood samples from baseline and after 7 and 18 months, Merck should provide serum samples for selected patients from all trials for independent evaluation.*

After this discussion of the protocol amendments and the informed consent forms, I shall now return to the main text in the clinical study report.

P140:
This page provides a summary of the clinical adverse experiences, but only includes data from the first two weeks after each vaccination.

[9] Fedorowski A, Li H, Yu X, et al. Antiadrenergic autoimmunity in postural tachycardia syndrome. Europace 2016; Oct 4. doi:10.1093/europace/euw154.
[10] Mehlsen J, Brinth L, Pors K, et al. Autoimmunity in patients reporting long-term complications after exposure to human papilloma virus vaccination. J Autoimmun 2022;133:102921.
[11] Chandler RE. Modernising vaccine surveillance systems to improve detection of rare or poorly defined adverse events. BMJ 2019;365:l2268.

Clinical Adverse Experience Summary
(Days 1 to 15 Following Any Vaccination Visit)

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=1179)		Non-Alum Placebo (N=594)		Protocol Non-Compliant Vaccination Regimen† (M=2)			
					Following Injection of HPV (Types 6, 11, 16, 18) L1 VLP Vaccine		Following Injection of Non-Alum Placebo	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in analysis population	1179		594		2		2	
Subjects without follow-up	14		10		0		0	
Subjects with follow-up	1165		584		2		2	
Number (%) of subjects								
with no adverse experience	202	(17.3)	192	(32.9)	0	(0.0)	0	(0.0)
with one or more adverse experiences	963	(82.7)	392	(67.1)	2	(100)	2	(100)
injection-site adverse experiences	877	(75.3)	292	(50.0)	2	(100)	1	(50)
systemic adverse experiences	541	(46.4)	260	(44.5)	1	(50)	2	(100)
with vaccine-related‡ adverse experiences	913	(78.4)	339	(58.0)	2	(100)	1	(50)
injection-site adverse experiences	877	(75.3)	292	(50.0)	2	(100)	1	(50)
systemic adverse experiences	274	(23.5)	134	(22.9)	0	(0.0)	0	(0.0)
with serious adverse experiences	5	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
with serious vaccine-related adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

P142:

- The proportions of subjects reporting a moderate or severe injection-site adverse experience were higher in the quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine group compared with the non-aluminum-containing placebo group.
- There were 3 adverse experiences reported per vaccine recipient and 2 adverse experiences reported per placebo recipient.

Here, Merck mentions subjects with adverse experiences of moderate or severe intensity whereas in some other trials, e.g. in P004 and P019 (Future 3), it was mild or moderate intensities that were lumped. This is inconsistent.

P143:

Table 8-2

Number (%) of Subjects Who Reported Any Clinical Adverse Experience
by Maximum Intensity Rating
(Days 1 to 15 Following Any Vaccination Visit)

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=1179)	Non-Alum Placebo (N=594)
	n (%)	n (%)
Number of subjects with follow-up	1165	584
Number of subjects without adverse experiences	202	192
Number (%) of subjects with adverse experiences	963 (82.7)	392 (67.1)
Number (%) of subjects by maximum intensity rating of adverse experience		
Mild	452 (38.8)	208 (35.6)
Moderate	379 (32.5)	138 (23.6)
Severe	123 (10.6)	40 (6.8)
Unknown	9 (0.8)	6 (1.0)

Percentages are calculated as 100*(n/number of subjects with follow-up).
N = Number of subjects who received only the clinical material in the given column.
n = Number of subjects with the indicated characteristic.
HPV = Human papillomavirus; VLP = Virus-like particles.

Data Source: [4.2.1]

Table 8-3

Frequency of Intensity Ratings of All Clinical Adverse Experiences
(Days 1 to 15 Following Any Vaccination Visit)

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=1179)	Non-Alum Placebo (N=594)
	n (%)	n (%)
Number of adverse experiences reported	3664	1297
Number of adverse experiences reported by intensity rating		
Mild	2568 (70.1)	925 (71.3)
Moderate	901 (24.6)	319 (24.6)
Severe	184 (5.0)	46 (3.5)
Unknown	11 (0.3)	7 (0.5)

Percentages are calculated as 100*(n/number of adverse experiences reported).
N = Number of subjects who received only the clinical material in the given column.
n = Number of subjects with the indicated characteristic.
HPV = Human papillomavirus; VLP = Virus-like particles.

Data Source: [4.2.1]

There were 3 vs 2 adverse events per patient.

P144-54:
Injection site adverse events are described in great detail over 11 pages: “the most common injection-site adverse experience was pain.” This is very clear in a table:

Table 8-4

Number (%) of Subjects With Injection-Site Adverse Experiences (Incidence ≥1% in One or More Vaccination Groups)
(Days 1 to 5 Following Any Vaccination Visit)

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=1179)				Non-Alum Placebo (N=594)			
	All Adverse Experiences		VR		All Adverse Experiences		VR	
	n	(%)	n	(%)	n	(%)	n	(%)
Number of subjects	1179				594			
Subjects without follow-up	14				10			
Subjects with follow-up	1165				584			
Number (%) of subjects with one or more injection-site adverse experiences	877	(75.3)			289	(49.5)		
Injection Site Erythema	237	(20.3)	237	(20.3)	77	(13.2)	77	(13.2)
Injection Site Haemorrhage	27	(2.3)	27	(2.3)	15	(2.6)	15	(2.6)
Injection Site Pain	853	(73.2)	853	(73.2)	265	(45.4)	265	(45.4)
Injection Site Paraesthesia	17	(1.5)	17	(1.5)	10	(1.7)	10	(1.7)
Injection Site Pruritus	13	(1.1)	13	(1.1)	5	(0.9)	5	(0.9)
Injection Site Reaction	13	(1.1)	13	(1.1)	4	(0.7)	4	(0.7)
Injection Site Swelling	241	(20.7)	241	(20.7)	45	(7.7)	45	(7.7)

Percentages are calculated based on the number of subjects with follow-up.
Although a subject may have had 2 or more adverse experiences, the subject is counted only once in the overall total.
Adverse experience terms are from MedDRA Version 7.1.
n = Number of subjects with the indicated characteristic.
N = Number of subjects who received only the clinical material in the given column.
VR = Vaccine related. Entries in this column refer to the number (%) of subjects with injection-site adverse experiences that were determined by the investigator to be possibly, probably, or definitely related to the vaccine.
HPV = Human papillomavirus; VLP = Virus-like particles.

Data Source: [4.2.1]

The risk difference is 27.8% ($p < 0.001$, p148), which means that for every four subjects treated with the vaccine instead of the placebo, one subject will experience pain that would not have experienced pain on placebo. The number needed to harm (NNH) is therefore four.

The pain was severe in 2.5% vs 0.5% and moderate or severe in 23.0% vs 6.2% (p152).

P151:

Number (%) of Subjects Who Reported Injection-Site Clinical Adverse Experiences
by Maximum Intensity Rating
(Days 1 to 5 Following Any Vaccination Visit)

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=1179)	Non-Alum Placebo (N=594)
	n (%)	n (%)
Number of subjects with follow-up	1165	584
Number of subjects without injection-site adverse experiences	288	295
Number (%) of subjects with injection-site adverse experiences	877 (75.3)	289 (49.5)
Number (%) of subjects by maximum intensity rating of injection-site adverse experience		
Mild	570 (48.9)	244 (41.8)
Moderate	247 (21.2)	41 (7.0)
Severe	60 (5.2)	4 (0.7)

Percentages are calculated as 100*(n/number of subjects with follow-up).
n = Number of subjects with the indicated characteristic.
N = Number of subjects who received only the clinical material in the given column.
HPV = Human papillomavirus; VLP = Virus-like particles.

Data Source: [4.2.1]

There was a large difference in vaccination site AEs, which was even bigger when all events were tabulated (pain was the dominant symptom):

Table 8-7

Frequency of Intensity Ratings of All Injection-Site Clinical Adverse Experiences
(Days 1 to 5 Following Any Vaccination Visit)

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=1179)	Non-Alum Placebo (N=594)
	n (%)	n (%)
Number of injection-site adverse experiences reported	2455	641
Number of injection-site adverse experiences reported by intensity rating		
Mild	1929 (78.6)	581 (90.6)
Moderate	446 (18.2)	56 (8.7)
Severe	80 (3.3)	4 (0.6)

Percentages are calculated as 100*(n/number of injection-site adverse experiences reported).
n = Number of subjects with the indicated characteristic.
N = Number of subjects who received only the clinical material in the given column.
HPV = Human papillomavirus; VLP = Virus-like particles.

Data Source: [4.2.1]

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P154:

S.2.2.2 Systemic Clinical Adverse Experiences

A summary, by vaccination group, of the number and percentage of subjects who reported systemic clinical adverse experiences Days 1 to 15 following any vaccination visit (with an incidence ≥ 1% in one or more vaccination groups) is provided in Table 8-11. A summary of the number and percentage of subjects who reported systemic clinical adverse experiences Days 1 to 15 following any vaccination visit, regardless of incidence, is provided in Table 11-55 (Section II. 11.3). The most common adverse experiences reported were headache, pyrexia (fever), and pharyngolaryngeal pain (sore throat).

… Table 8-13 provides risk differences, 95% confidence intervals, and p-values for the systemic clinical adverse experiences prompted for on the Vaccine Report Card (VRC) (muscle/joint pain, headaches, rashes, hives, and diarrhea).

Corresponding comparisons of the percentages of subjects who reported specific systemic clinical adverse experiences Days 1 to 15 following any vaccination visit (with an incidence ≥ 1% in one or more vaccination groups), including risk differences and associated 95% confidence intervals, are included in Table 8-12.
In addition, Table 8-13 provides risk differences, 95% confidence intervals, and p-values for the systemic clinical adverse experiences prompted for on the VRC (muscle/joint pain, headaches, rashes, hives, and diarrhea)[2]. (Footnote 2: Each adverse experience included in Table 8-13 corresponds to several MedDRA

terms (which are used to identify specific adverse experiences in Table 8-11 and Table 8-12). Table 11-56 (Section II.11.3) provides an accounting of the correspondence between the MedDRA terms and the terms used on the VRC.)

… Summaries of the number and percentage of subjects who reported systemic clinical adverse experiences prompted for on the VRC (categorized separately as adverse experiences of muscle/joint pain, headaches, rashes/hives, and diarrhea) and an overall summary of all VRC-prompted systemic clinical adverse experiences is in [4.4.3; 4.4.4; 4.4.5; 4.4.6; 4.4.7]. All confidence intervals on risk differences between the quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine group and the non-aluminum placebo group with respect to the percentages of subjects who reported any specific systemic clinical adverse experience Days 1 to 15 following any vaccination visit contained 0 with the exception of influenza which was higher in the placebo group compared to the vaccine group.

As noted above, this approach to detecting, analysing and reporting possible harms in a safety study is scientifically inappropriate. MedDRA means Medical Dictionary for Regulatory Activities.

P157: rather similar systemic AEs in the two groups.

P161: Prompted for on vaccination card.

P162:
Table 8-17 displays a frequency summary, by intensity rating, of all VRC prompted systemic clinical adverse experiences (muscle/joint pain, headaches, rashes/hives, and diarrhea) reported Days 1 to 15 following any vaccination visit. There were somewhat higher percentages of patients with severe headache and muscle/joint pain in the vaccine group than in the placebo group.

P163:

Table 8-14

Number (%) of Subjects Who Reported Systemic Clinical Adverse Experiences
by Maximum Intensity Rating
(Days 1 to 15 Following Any Vaccination Visit)

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=1179)	Non-Alum Placebo (N=594)
	n (%)	n (%)
Number of subjects with follow-up	1165	584
Number of subjects without systemic adverse experiences	624	324
Number (%) of subjects with systemic adverse experiences	541 (46.4)	260 (44.5)
Number (%) of subjects by maximum intensity rating of systemic adverse experience		
Mild	228 (19.6)	100 (17.1)
Moderate	234 (20.1)	117 (20.0)
Severe	69 (5.9)	37 (6.3)
Unknown	10 (0.9)	6 (1.0)

Percentages are calculated as 100*(n/number of subjects with follow-up).
n = Number of subjects with the indicated characteristic.
N = Number of subjects who received only the clinical material in the given column.
HPV = Human papillomavirus; VLP = Virus-like particles.

Data Source: [4.2.1]

There should have been 11 more patients with systemic adverse experiences in the placebo group to match the incidence in the vaccine group. There were slightly fewer severe events in the vaccine group, 5.9% vs 6.3%, but when all events were tabulated (some patients had more than one), there were more severe events in the vaccine group, 8.6% vs 6.4%:

Table 8-15

Frequency of Intensity Ratings of All Systemic Clinical Adverse Experiences
(Days 1 to 15 Following Any Vaccination Visit)

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=1179)	Non-Alum Placebo (N=594)
	n (%)	n (%)
Number of systemic adverse experiences reported	1205	652
Number of systemic adverse experiences reported by intensity rating		
Mild	636 (52.8)	341 (52.3)
Moderate	454 (37.7)	262 (40.2)
Severe	104 (8.6)	42 (6.4)
Unknown	11 (0.9)	7 (1.1)

Percentages are calculated as 100*(n/number of systemic adverse experiences reported).
n = Number of subjects with the indicated characteristic.
N = Number of subjects who received only the clinical material in the given column.
HPV = Human papillomavirus; VLP = Virus-like particles.

Data Source: [4.2.1]

P164-5:
Number (%) of Subjects With Systemic Clinical Adverse Experiences by Maximum Intensity (Incidence ≥ 1% in One or More Vaccination Groups) by System Organ Class (Days 1 to 15 Following Any Vaccination Visit).

There are two separate tables; one for the vaccine group and another for the placebo group (see next page). These two tables are incomplete. Influenza, upper respiratory tract infection, dysmenorrhoea, rhinorrhoea and rash are missing in the first table, of severity in the vaccine group, whereas they appear in the second table, of severity in the placebo group. Since the two tables are kept separate and appear on two different pages, these omissions can easily be overlooked.. There were no conspicuous differences, apart from severe headache where p = 0.15 (more severe headaches in the vaccine group; Fisher's exact test, my calculation).

Table 8-16

Number (%) of Subjects With Systemic Clinical Adverse Experiences by Maximum Intensity (Incidence ≥1% in One or More Vaccination Groups) by System Organ Class
(Days 1 to 15 Following Any Vaccination Visit)

Vaccination Group: Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine	Maximum Intensity									
Subjects in analysis population: 1179	Unknown		Mild		Moderate		Severe		Total	
Number of Subjects With Follow-up: 1165	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Ear And Labyrinth Disorders									**19**	**(1.6)**
Gastrointestinal Disorders									**150**	**(12.9)**
Abdominal pain	0	(0.0)	8	(0.7)	8	(0.7)	3	(0.3)	19	(1.6)
Abdominal pain upper	0	(0.0)	19	(1.6)	17	(1.5)	2	(0.2)	38	(3.3)
Diarrhoea	0	(0.0)	25	(2.1)	14	(1.2)	4	(0.3)	43	(3.7)
Nausea	0	(0.0)	16	(1.4)	22	(1.9)	0	(0.0)	38	(3.3)
Vomiting	0	(0.0)	11	(0.9)	11	(0.9)	4	(0.3)	26	(2.2)

P171:
There were no deaths, but five serious systemic adverse events occurred, all in the vaccine group:
1) Heavy menstrual bleeding. Was taken to the emergency room 11 days after receiving the second dose where she reported she was also light-headed and dizzy.
2) Appendicitis.
3) Right finger fracture.
4) Experienced insulin dependent diabetes mellitus incipient and high urine glucose 2 days after receiving the first dose.
5) Infected toe.

The patient with the finger fracture subsequently developed acute renal failure:

AN 71340, a 15-year-old Hispanic male who received HPV (Type 6, 11, 16, 18) L1 VLP vaccine experienced a right finger fracture requiring outpatient surgery 5 days after receiving Dose 1. External Finger Fixation surgery was performed and the subject received sufentanil (Sufentanil, Abbott Laboratories) citrate, lidocaine, tetanus toxoid, bupivacaine hydrochloride + lidocaine ketorolac and dipyrone. The subject developed vomiting and dizziness and was taken to a pediatrician the day following surgery and 6 days after receiving Dose 1. The pediatrician suspected hepatitis and laboratory tests were performed. Nine (9) days after receiving Dose 1, results of the laboratory tests (serum blood urea 64.2 mg.d [abnormal], serum blood urea nitrogen 30 mg/dl [abnormal], serum creatinine 3.17 mg/dL [abnormal], and diagnostic urinalysis test 300 mg/dL [abnormal]) suggested acute renal failure. The subject was treated with furosemide (Lasix™, Aventis) (dose unknown) and metoclopramide (dose unknown). Medications administered during outpatient surgery, sufentanil citrate (Sufentanil, Abbott Laboratories), lidocaine, tetanus toxoid, bupivacaine hydroxhloride (+) lidocaine, ketorolac and dipyrone are considered the second suspect therapy of acute renal failure. Laboratory tests performed 21 days after receiving Dose 1 were normal and the subject recovered. The reporting investigator determined that acute renal failure was not related to study vaccine/placebo. No further study vaccine/placebo was administered and the subject was discontinued from the study [3.13].

Dipyrone is now banned because of its harms. Both this drug and ketorolac can cause kidney problems.

In a 10-year follow-up of this trial (see below), Merck was only interested in serious adverse events, but nonetheless planned to report to www.clinicaltrials.gov a non-serious adverse event, a scrotal cyst in a boy. Since I could not understand why Merck wanted to report something as banal as this, as there must have been many other non-serious adverse events, I looked up the trial in the register.[12]

The last update in the register by Merck was from 20 February 2018. There were not 5 vs 0 serious adverse events in the register but 6 vs 0, and they were partly different from the 5 events in the study report:

1) Haemorrhagic anaemia
2) Colitis ulcerative
3) Appendicitis
4) Localised infection
5) Type 1 diabetes mellitus
6) Pain in extremity

All six events were stated to have been "collected by non-systematic assessment" and the terms used were from MedDRA 11.0. The five events in the study report were:

1) Heavy menstrual bleeding (also diagnosed with haemorrhagic anaemia)
2) Appendicitis
3) Right finger fracture (and acute renal failure)
4) Insulin dependent diabetes mellitus
5) Infected toe (with pain).

Three patients appeared to be the same, those with haemorrhagic anaemia, appendicitis and diabetes. Assuming that the patient with localised infection is the same as the one with an infected toe, leaves three

[12] https://clinicaltrials.gov/ct2/show/NCT00092547

additional patients that do not appear to be the same: colitis ulcerative, pain in extremity, finger fracture and renal failure. In total 7 vs 0 patients with serious adverse events. This discrepancy is unexplained. I did not find the boy with a scrotal cyst either in the register.

P180:
The most common new medical conditions reported were headache and upper respiratory infections.

P291:

Table 11-55

Number (%) of Subjects With Systemic Clinical Adverse Experiences
(Incidence >0% in One or More Vaccination Groups) by System Organ Class
(Days 1 to 15 Following Any Vaccination Visit)

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=1179)				Non-Alum Placebo (N=594)			
	All Adverse Experiences		VR		All Adverse Experiences		VR	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in analysis population	1179				594			
Subjects without follow-up	14				10			
Subjects with follow-up	1165				584			
Number (%) of subjects with one or more systemic adverse experiences	541	(46.4)			260	(44.5)		
Number (%) of subjects with no systemic adverse experience	624	(53.6)			324	(55.5)		
Blood and Lymphatic System Disorders	**6**	**(0.5)**	**4**	**(0.3)**	**1**	**(0.2)**		
Anaemia	1	(0.1)			0	(0.0)		
Lymphadenitis	1	(0.1)	1	(0.1)	0	(0.0)		
Lymphadenopathy	4	(0.3)	3	(0.3)	1	(0.2)		

In this table, there was no lower limit for incidence to qualify for getting into the table. Taking account of the fact that there were double as many patients in the vaccine group than in the placebo group, there were 7 more cases of dizziness in vaccine group as expected, based on the placebo occurrence, 25 vs 9, whereas the occurrence of headache was similar, 221 vs 110.

P354:

Table 11-79

Number (%) of Subjects With New Medical Conditions
(Incidence >0% in One or More Vaccination Groups) by System Organ Class
(Vaccination Period, Day 1 Through Month 7)

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=1179)		Non-Alum Placebo (N=594)	
	n	(%)	n	(%)
Subjects in analysis population	1179		594	
Subjects with one or more new medical conditions	520	(44.1)	280	(47.1)
Subjects with no new medical conditions	659	(55.9)	314	(52.9)
Blood and Lymphatic System Disorders	**6**	**(0.5)**	**3**	**(0.5)**
Iron Deficiency Anaemia	1	(0.1)	0	(0.0)
Lymphadenitis	2	(0.2)	2	(0.3)
Lymphadenopathy	3	(0.3)	1	(0.2)

Only one patient had “dizziness, postural,” syncope or orthostatic hypotension, in the placebo group. We cannot know if it was the same patient for all three symptoms.

P1177: synopses of other trials: studies 4,6,2,1,5,7 and 16 in that order.

P1240: HPV Vaccine Protocol 005 Preliminary Primary Analysis Report. This is study V501 P005 that I describe below.

P1849-1912
Blank case report forms, very similar to those used in other Merck trials.

P2276-2280:
Number (%) of Subjects With Systemic Clinical Adverse Experiences (Incidence >0% in One or More Vaccination Groups) by System Organ Class (Days 1 to 15 Following Any Vaccination Visit) Systemic VRC Report.

Number (%) of Subjects With Systemic Clinical Adverse Experiences (Incidence >0% in One or More Vaccination Groups) by System Organ Class
(Days 1 to 15 Following Any Vaccination Visit) Systemic VRC Report

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=1179)				Placebo (Alum-Free) (N=594)			
	All Adverse Experiences		VR		All Adverse Experiences		VR	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in analysis population	1179				594			
Subjects without follow-up	14				10			
Subjects with follow-up	1165				584			
Number (%) of Subjects with one or more systemic adverse experiences	321	(27.6)			157	(26.9)		
Number (%) of Subjects with no systemic adverse experience	844	(72.4)			427	(73.1)		
Gastrointestinal Disorders	**44**	**(3.8)**	**11**	**(0.9)**	**22**	**(3.8)**	**3**	**(0.5)**
Diarrhoea	43	(3.7)	11	(0.9)	21	(3.6)	3	(0.5)
Enteritis	0	(0.0)			1	(0.2)		
Irritable bowel syndrome	1	(0.1)			0	(0.0)		

This table is similar to the one on p291 which, however, is far more extensive, although it is described with similar words: "Number (%) of Subjects With Systemic Clinical Adverse Experiences (Incidence >0% in One or More Vaccination Groups) by System Organ Class (Days 1 to 15 Following Any Vaccination Visit)." It is unclear why the entries and numbers are not the same in the two tables. Since adverse experiences were registered on the vaccination report cards for both tables, they should be the same. The numbers are indeed exactly the same for the three only gastrointestinal events listed in the table on p2276 but there were 25 such events on p291-2. The number of patients with one or more systematic adverse experiences are not the same in the two tables, 541 vs 260 on p291 and only 321 vs 157 on p2276.

The table on p2276 is not listed in the index for the report on p3 but in an additional index about data on p374. The table on p2276 is listed under a subheading 4.4, "Data Displays Mentioned in CSR Text But Not Included in CSR Text." It is not clear why this table was not included in the text of the report (which it actually was, but very late). After tables of "Baseline Characteristics of Non-Randomized Subjects," "Summary of Subjects Not Randomized Into Study," "Number (%) of Subjects With Specific Systemic Clinical Adverse Experiences (Incidence >0% in One or More Vaccination Groups) by System Organ Class (Days 1 to 15 Following Any Vaccination Visit) Diarrhea," and similar tables for headache, muscle/joint pain and rashes/hives, comes the mention of the table on p2276, which is the last one in the additional index.

I went through the whole report again and found this description on p155: "Summaries of the number and percentage of subjects who reported systemic clinical adverse experiences prompted for on the VRC (categorized separately as adverse experiences of muscle/joint pain, headaches, rashes/hives, and diarrhea) and an overall summary of all VRC-prompted systemic clinical adverse experiences is in [4.4.3; 4.4.4; 4.4.5; 4.4.6; 4.4.7]."

However, this is also confusing. First, it seems that only diarrhoea is prompted for on the VCR, but there were two additional gastrointestinal events that were also prompted for. Both statements cannot be correct.

There is a copy of the VCR on p1905-12. Of gastrointestinal events, it is only diarrhoea that is prompted for. Merck's information about the overall summary of all VRC-prompted events is therefore false and it is incorrect to list also enteritis and irritable bowel syndrome in the table as if these were also prompted for.

V501 P018 LTFU CSR_ w protocols P018-05, -06, -10 and -11

Long-term follow-up study (about 10 years) of the placebo-controlled study P018.

Trial Initiation Date First Subject First Visit: 30-JUL-2007
Trial Completion Date Last Subject Last Visit: 01-JUN-2015
Report Date 06-NOV-2015

Index on p15.
Index of appendices on p173.

This report is considerably longer than the clinical study report (2000+ pages), even though the opposite would have been more adequate and relevant. Furthermore, despite its length, a lot of data have been left out.

P2:
"No study vaccinations were provided within the context of this long-term follow-up study. Subjects in early vaccination group (EVG) were vaccinated at 9 to 15 years of age in base study (V501-018-00), and subjects in the catch up vaccination group (CVG) were vaccinated at 11 to 18 years of age in the first extension study (V501-018-05/-06) ... Planned duration of extension phase: 126 months after enrollment in the base study."

P4:
In addition to measuring antibodies, these endpoints were defined:

• Serious Adverse Experiences (as defined in the protocol) judged by the study investigator to be possibly, probably, or definitely related to prior administration of qHPV vaccine.
• Serious Adverse Experiences (as defined in the protocol) judged by the study investigator to be possibly, probably, or definitely related to a study procedure.
• Death of a study subject.
• Pregnancy information and infant information.

The synopsis ends on p14, and safety results were not mentioned with one word. This is unacceptable, particularly considering that the primary objective of the placebo-controlled study was safety and that such a study had been requested by a drug regulator.

It is also unacceptable to have as endpoints only those serious adverse experiences judged by the study investigator to be possibly, probably, or definitely related to prior administration of the vaccine, which Merck's trial that compared Gardasil 9 with qHPV in 14,215 subjects clearly illustrates. In Merck's publication of this trial in New England Journal of Medicine,[13] there were 416 serious adverse events, but

[13] Joura EA, Giuliano AR, Iversen OE, et al. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in

only 4 of these (1%) were judged to be vaccine related by the trial authors, many of whom had conflicts of interest with Merck and other vaccine manufacturers. Further, since both groups received an active vaccine, it would be difficult to judge with any acceptable certainty whether a serious adverse event was vaccine related. Placebo-controlled trials are needed to make such a judgment.

In contrast to the main study P018, adverse experiences were not divided into mild, moderate and severe; they were not even collected or reported unless they were serious and judged vaccine related. Merck squandered the opportunity to find out if its vaccine caused important harms that took longer to develop or to get diagnosed than the little time window in the trial, 14 days after each vaccination and only 7 months in total (Merck failed to report safety results for the full trial period, 18 months, even though the company promised to do this in the study report, see above).

The influenza vaccine Pandemrix provides an example of a vaccine harm that takes a long time to develop and to get diagnosed. It caused narcolepsy in over 1300 people, a life-long, seriously debilitating condition with poor treatment options where people suddenly fall asleep, with an onset from about two months after vaccination and up to at least two years later.[14] [15] Its manufacturer, GlaxoSmithKline, has acknowledged the causal link,[16] and the likely mechanism is an autoimmune cross-reaction in people with a particular tissue type between the active component of the vaccine and receptors on brain cells controlling the day rhythm.

It is unclear why Merck, in the only "placebo-controlled" study ever performed with qHPV, only considered adverse experiences that were serious (e.g. led to hospital admission or death) and that were judged by the study investigator to be possibly, probably, or definitely related to prior administration of the vaccine of interest in this 10-year follow-up study. It is also unclear why Merck did not ask the investigators to collect also adverse events that were of severe intensity, which, according to Merck's definition means "incapacitating with inability to work or do usual activity," and those of moderate intensity ("discomfort enough to cause interference with usual activities").

P152:
12.2.4.1 Serious Adverse Events

"A listing of subjects who reported new or updated serious adverse experiences during the LTFU [long-term follow-up] period are displayed in Table 12-1. Narratives for subjects with serious adverse events reported as occurring or updated since Month 37 (relative to base study Day 1) are in Section 14.4. Subject narratives were summarized using data from the safety database CIOMS reports in [16.2.7] and the case report tabulations in [16.4], both of which were independently maintained and may have minor differences in content that do not impact the key narrative information.

Three SAEs including: a fatal road traffic accident, 1 case of tonic-clonic movements, and 1 case of VII nerve paralysis were reported as occurring or updated in the LTFU study. Of note, one of these SAE (VIII nerve paralysis) was considered possibly vaccine-related by the investigator. This SAE was reported prior to Month 37 but was updated in the LTFU study (event term for this previously reported SAE was changed from facial palsy to VII Nerve Paralysis). This represents a single report occurring more than 5 years prior to completion of the LTFU study."

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women. N Engl J Med 2015;372:711–23.

[14] Institutet för Hälsa och Välfärd. Förhöjd narkolepsirisk i två år efter Pandemrix-vaccinationen. 2014; June.

[15] Nohynek H, Jokinen J, Partinen M, et al. AS03 adjuvanted AH1N1 vaccine associated with an abrupt increase in the incidence of childhood narcolepsy in Finland. PLoS One 2012;7:e33536.

[16] Vogel G. Why a pandemic flu shot caused narcolepsy. Science 2015; July 1.

A serious nerve paralysis considered possibly vaccine related was reported prior to month 37 and updated in the LTFU study (where there is a narrative, AN 70721, see below).

Short narratives for each subject follow:

Allocation number (AN) 70721, an Asian male, 13 years old at the time of enrollment, with a medical history of myalgia, was randomized to receive placebo and was administered 3 doses of placebo (blinded therapy) on 08-Feb-2004, 18-Apr-2004 and 01-Aug-2004 respectively. At age 16, as part of the extension, the subject received open-label qHPV vaccine on 15-Jul-2006, 14-0ct-2006 and 04-Feb-2007. On approximately 14-Jun-2007, 131 days Postdose 3 of qHPV vaccination, the subject developed numbness on the left side of his face. On 15-Jun-2007 he had left facial palsy with difficulty on mastication and a decreased sense of taste. A neurologist diagnosed peripheral neuritis. He was given prednisolone, vitamin Bl-6-12 and omeprazole. He recovered completely on 02-Jul-2007. The reporting investigator considered the facial palsy to be possibly related to study therapy. During the reporting period the SAE term was updated to VII Nerve Paralysis.

AN 70132, a white male, 13 years old at time of enrollment was randomized to receive qHPV vaccine and was administered 3 doses of qHPV vaccine on 12-Dec-2003, 09-Feb-2004 and **redacted** 2004 respectively. On **redacted** -2009, 1718 days Postdose 3 of qHPV vaccination, the subject experienced a fatal road traffic accident. The reporting investigator considered the road traffic accident as not related to study therapy.

AN 71251, a white female 15 years old at time of enrollment, with a medical history of seasonal allergy, myopia, acne, headache, skin papilloma and dysmenorrhea, was randomized to receive qHPV vaccine and was administered 3 doses of qHPV vaccine on 02-Feb-2004, 12-Apr-2004, and 09-Aug-2004. The subject experienced non-serious adverse experiences of vaccine related injection site pain on two occasions, 24-Feb-2004 and 12-Apr-2004, both of resolved the same day. The subject also experienced non-serious adverse experience of fatigue on 13-Apr-2004 which resolved the same day. On 05-July-2011, 2522 days Postdose 3 of qHPV vaccination, the subject experienced tonic clonic movements that lasted 3 minutes. The tonic clonic movement resolved and the investigator considered the tonic clonic movements as not related to study therapy.

P156:
“12.2.4.2 Deaths
One subject died in the long term follow-up study. The subject was in the EVG and died as a result of a fatal car accident approximately 4 and a half years after dose 3.”

“12.2.6 Adverse Events of Special Interest
There were no adverse events of special interest for this trial.”

“12.2.7 Listing of All Adverse Events by Subject
Subject listings of adverse events by subject are in [16.4]”

P169:
“14.3 Safety Data
14.4 Listings of Deaths, Other Serious and Significant Adverse Events
Not Applicable the subject death and SAEs are listed in Table 12-1 in Section 12.2.4.1,
14.4.1 Narratives of Deaths, Other Serious and Significant Adverse Events
Narratives for Serious Adverse Event Reports are in [16.2.7], Additionally short narratives for SAEs, derived from data in the safety database are in Section 12.1. For the complete subject data, see the data tabulations from the clinical database.”

P3414:
“16.2.1 Discontinued Subjects
See 16.2 Table of ICH Subject Data Listings.”

The table that follows is another table:

“16.2.2 Protocol Deviations
(16.2.2 V501-018 PD list)”

P3447:
“16.2.7 Adverse Event Data
See 16.2 Table of ICH Subject Data Listings”

As I was unable to find this table, I looked up the index again, on p176-7:

Several of these entries of potential interest for an assessment of safety were empty: 16.2.1 Discontinued Subjects and 16.2.7 Adverse Event Data both referred to the missing ICH Subject Data Listings, but there were some CIOMS reports.

16.2.7.2 Subjects With Non-serious Adverse Events, to be Reported to www.clinicaltrials.gov was a table about events with an “(Incidence > 0% in One or More Treatment Groups) Cases Reported Since Month 37 through Month 126 (Entire LTFU Period).” There was only one event, a scrotal cyst.

On p3414 there is this information:

16.2 Subject Data Reports/Listings

Table of ICH Subject Data Listings
(available upon request or linked as applicable)

Appendix	File Name
16.2.1	discontinued-patients-dl-a.pdf
16.2.2	protocol-deviations.pdf
16.2.3	patients-excluded-from-efficacy-analysis.pdf
16.2.4	demographic-data-dl-a.pdf
16.2.5	Not Applicable (No vaccine administered)
16.2.6	individual-efficacy-response-data-dl-a.pdf
16.2.7	adverse-event-data-dl-a.pdf
16.2.8	listing-individual-laboratory-measurements-by-patient-dl-a.pdf

The references to tables in the report appear to be circular. First, readers are referred to a table that does not exist, table of ICH subject data listings. Next, when this table is mentioned again, as a header, then, instead of the table, there is another table with entries, some of which are empty.

Going through the whole report again, I found out that on p37 there is this information:

"10 TRIAL SUBJECTS AND DATA SETS ANALYZED
Individual subject level data listings [16.2.1], [16.2.4], [16.2.6], [16.2.7], and [16.2.8] are available upon request or linked as appropriate."

P151 says:
"Additional tables specifically designed for disclosure of clinical trial results on publicly accessible databases displaying all SAEs occurring with an incidence >0% in at least one vaccination group is provided in Section 16.2.7. A similar table for non-serious adverse events is provided in Section 16.2.7. A listing of all subjects' adverse experiences during the LTFU can be found in [16.4]."

This is simply not true. There is no listing of "all subjects' adverse experiences" during the 10-year follow-up in 16.4. The only information under 16.4, which is the last page in the report, is this:

"16.4 Individual Subject Data Listings
The Data Definition File page contains a list of the individual case report tabulation."

Dose-response studies of monovalent vaccine

V501 P001 CSR, monovalent HPV 11 L1 VLP vaccine

Randomized, double-blind, placebo-controlled, sequential dose-escalating study of 10-, 20-, 50-, and 100-mcg doses of HPV 11 L1 VLP vaccine.

Study Initiation Date (FPI): 22-Sep-1997
Study Completion Date (LPO): 07-Aug-2001
Clinical Study Report Date 03-Mar-2004

Index on p3.
List of appendices on p307.

P26:
“DURATION OF TREATMENT: Vaccination at Day 0, Month 2, and Month 6 plus 14 calendar days of clinical follow-up after the administration of each dose. A subset of subjects (approximately one-half of the subjects in each dose group, except the 10-mcg dose group) received a fourth dose of vaccine/placebo at Month 12. Subjects receiving the fourth dose of clinical material were also followed for 14 calendar days after the injection. All subjects were followed to assess persistence of anti-HPV 11 responses through Month 36.

PRIMARY OBJECTIVE(S): (1) To determine that the administration of 3 or 4 doses of research lot HPV type 11 L1 VLP vaccine is generally safe and well tolerated. (2) To evaluate the anti-HPV 11 responses, as measured by serum-RIA, of initially PCR-negative for HPV type 6 and 11, HPV 6/11-seronegative subjects after 3 doses of research lot HPV type 11 L1 VLP vaccine at several vaccine dose levels. (3) To evaluate, in the same subjects, the percentage achieving neutralizing antibody after the third dose.

STUDY DESIGN: This was a randomized, double-blind (all subjects, investigators [and their staff], and laboratory personnel who analyzed the clinical samples were blinded to treatment group), multicenter, sequential dose-escalating, placebo-controlled trial.

P27:

SUBJECT ACCOUNTING:

		HPV 11 L1 VLP vaccine				
	Placebo	10 mcg/ 0.5 mL	20 mcg/ 0.5 mL	50 mcg/ 0.5 mL	100 mcg/ 0.5 mL	Total
ENTERED: Total	28	28	28	28	28	140

All females. Three-year study.

P28:
“Serious adverse experiences that occurred any time through Month 7 of the study (and between Month 12 and Month 13 for fourth-dose recipients), whether or not related to the investigational product, were reported. In addition, any serious adverse experience that occurred outside the time period previously specified was reported to the Sponsor if the event was a death that resulted in subject discontinuation from the study or an event that was determined by the investigator to be possibly, probably, or definitely vaccine related.”

Similar problems as in other trials.

P29:
Lowest dose fails to meet acceptability criteria for antibodies.

P31:

Clinical Adverse Experience Summary
(Days 0 to 14 Following Any Vaccination Visit [Doses 1 Through 3 Only])
(0-, 2-, 6-Month) Vaccination Regimen

	Treatment Group				
		HPV 11 L1 VLP Vaccine			
	Placebo	10 mcg	20 mcg	50 mcg	100 mcg
	(N=28) n (%)	(N=28) n (%)	(N=28) n (%)	(N=28) n (%)	(N=28) n (%)
Number of subjects	28	28	28	28	28
Subjects without follow-up	0	0	0	0	0
Subjects with follow-up	28	28	28	28	28
Number (%) of subjects:					
with no adverse experience (AE)	8 (28.6)	9 (32.1)	5 (17.9)	2 (7.1)	4 (14.3)
with one or more AEs	20 (71.4)	19 (67.9)	23 (82.1)	26 (92.9)	24 (85.7)
injection-site AEs	11 (39.3)	10 (35.7)	17 (60.7)	20 (71.4)	17 (60.7)
systemic AEs	16 (57.1)	18 (64.3)	16 (57.1)	21 (75.0)	20 (71.4)
with vaccine-related AEs †	14 (50.0)	10 (35.7)	18 (64.3)	22 (78.6)	19 (67.9)
injection-site AEs	11 (39.3)	10 (35.7)	17 (60.7)	20 (71.4)	17 (60.7)
systemic AEs	5 (17.9)	0 (0.0)	4 (14.3)	8 (28.6)	11 (39.3)
with serious AEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
with serious vaccine-related AEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
who died	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
discontinued ‡ due to an AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
discontinued due to a vaccine-related AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
discontinued due to a serious AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
discontinued due to a serious vaccine-related AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

† Determined by the investigator to be possibly, probably, or definitely related to the vaccine.
‡ Did not complete vaccination phase, including receipt of 3 doses of HPV 11 L1 VLP vaccine and a blood draw 4 weeks after the third dose.
Does not include adverse experiences following the fourth dose, for those subjects who received 4 vaccinations.
Percentages are calculated based on the number of subjects with follow-up after any visit.
HPV = Human papillomavirus; VLP = Virus-like particles.

P48:
"Each 0.5-mL dose of vaccine contained 10, 20, 50, or 100 micrograms of HPV 11 L1 VLP. In addition, each dose contained 225 mcg of aluminum as amorphous aluminum hydroxyphosphate sulfate (AAHS) and thimerosal (1:20,000) as preservative. Placebo was standard Merck aluminum adjuvant (AAHS). Aluminum placebo was chosen as the appropriate control for the study for the following reasons: (1) use of aluminum allowed placebo and vaccine to be visually indistinguishable in appearance, and (2) the safety profile of Merck aluminum adjuvant is well described; however, the safety profile of HPV 11 L1 VLP vaccine was not known. By using aluminum-placebo, it was possible to assess the adverse experience profile attributable to HPV 11 L1VLPs."

There is no mention of what is in the placebo until the Discussion section of the report. It appears Merck was not interested in safety but in antibody responses to the different doses of the vaccine. It makes no sense to put the adjuvants into the placebo, as antibody levels are objective and are not influenced by any lack of blindness.

P57:
"The HPV 11 L1 VLP vaccine and placebo were visually indistinguishable ... This study was double-blind, but was not conducted under in-house blinding procedures. Both the subject and the investigator (and their staff) were blinded to who received vaccine and who received placebo but not to the dosage level of the active group at the given stage."

It makes no sense to blind the vials and then let the investigators know which doses of the vaccine are being administered. It is also not clear why they had four separate placebos when they all four had the same content (p52):

Table 2

Treatment Plan

Group	Dosage Level (mcg)	Sample Size		
		HPV 11 L1 VLP vaccine	Placebo†	Total
A	10	28	7	35
B	20	28	7	35
C	50	28	7	35
D	100	28	7	35
Total				140

† The placebo was identical for all groups.
HPV = Human papilloma virus; VLP = Virus-like particle.

Data Source: [3.3.8]

P76:
"Follow-up at Months 1, 2, 3, 6, and 7 after the first injection included an interview to assess general safety ... The interview solicited broadly for any gynecologic health concerns and any serious adverse experiences that the subject may have experienced."

P82-3:
"Safety: The primary safety hypothesis addressed adverse experiences. No formal hypothesis tests were performed, and therefore no power calculations were performed ... Dose Response: Another secondary hypothesis stated that a dose-response relationship exists with respect to antibody titer (as measured by anti-HPV 11 serum RIA or HPV 11 Cervicovaginal Lavage-Capture-ELISA) after the third dose of vaccine. This hypothesis was tested using the NOSTASOT procedure [1.2.23] ($\alpha = 0.05$), a step-down test for trend to identify the lowest vaccine dose level with evidence of immunogenicity."

P87:
"Adverse experiences and elevated temperatures (> 100°F, oral) reported following any vaccination were compared between each vaccine dose level and placebo (pooled across vaccine dose stages), using risk differences and associated 95% confidence intervals. The pooling of placebo groups corresponding to each vaccine dose level had the potential to introduce a confounding effect if the characteristics of the participants changed over time ... Incidence rates were compared observationally between vaccine dose levels, but no formal comparisons were made."

This method of eliciting adverse events is inadequate. Merck tested dose-response for efficacy but not for safety.

Merck fails to note that there is batch-to-batch variation in the composition of the adjuvant. This is likely the reason they prepared a separate placebo for each comparison with a vaccine. I can see no other plausible reason. Possible confounding because "the characteristics of the participants changed over time" is a nonsense argument because the patients were randomised to placebo and a dose of the vaccine. Therefore, there cannot be any confounding due to "the characteristics of the participants changing over time."

P182:
"There was a dose-dependent increase in the percentages of subjects reporting a clinical adverse experience (82.1, 92.9, and 85.7% for the 20-, 50-, and 100-mcg HPV 11 L1 VLP vaccine groups, respectively, compared with 71.4% and 67.9% for the placebo and 10-mcg HPV 11 L1 VLP vaccine groups, respectively) (Table 44). This dose-dependent increase in clinical adverse experiences was due to modest dose-dependent increases in the incidence of injection-site adverse experiences."

P186:
""There was a dose-dependent increase in the percentages of subjects reporting a clinical adverse experience (82.1, 92.9, and 85.7% for the 20-, 50-, and 100-mcg HPV 11 L1 VLP vaccine groups, respectively, compared with 71.4% and 67.9% for the placebo and 10-mcg HPV 11 L1 VLP vaccine groups, respectively)... The most common injection-site adverse experience reported in all treatment groups was pain/tenderness/soreness, with incidence rates ranging from 35.7% in the 10-mcg group to 71.4% in the 50-mcg group."

P188:
"More subjects in the 100-mcg group reported injection-site adverse experiences of moderate intensity (28.6%) compared with the placebo group (7.1%) or other vaccine dose level groups (7.1, 17.9, and 14.3%, for the 10-, 20-, and 50-mcg groups, respectively).

P192:
"The overall incidences of systemic clinical adverse experiences were higher in the 50-mcg and 100-mcg groups compared with the placebo and 10-mcg and 20-mcg groups. The most common clinical adverse experience was headache, followed by upper respiratory infection, nausea and asthenia/fatigue."

P198:
"The percentage of subjects who reported systemic clinical adverse experiences that were severe was higher in the 50-mcg and 100-mcg groups (14.3% in each) compared with the placebo group (3.6%) and the 10-mcg and 20-mcg groups (0% and 7.1%, respectively)."

P200:
"5 subjects (all in the vaccine groups) reported fever as an adverse experience during the 14 days of clinical follow-up following any of the first 3 vaccinations."

P237:
"Compared with the subjects who received placebo, there were numerical increases in the overall incidence of adverse experiences in women receiving the HPV 11 L1 VLP vaccine. A similar trend was observed for both injection-site adverse experiences and systemic adverse experiences."

P238:
"a higher proportion of systemic adverse experiences were judged by the subjects to be severe in intensity in the HPV 11 L1 VLP vaccine 20-, 50-, and 100-mcg groups (7.7, 12.3, and 5.7%, respectively) than in the HPV 11 L1 VLP vaccine 10-mcg and placebo groups (0% and 1.3%, respectively). The most common systemic adverse experience was headache."

Just below the latest of all these admissions come these conclusions:

P238-9:
"Overall, the HPV L1 VLP vaccine was generally well tolerated in young women 18 to 26 years of age... Overall Immunogenicity, Efficacy, and Safety Conclusions … The HPV 11 L1 VLP vaccine is generally well tolerated based on safety data in the population studied."

There is nothing about all this in the synopsis that merely states: "The HPV 11 L1 VLP vaccine is generally well tolerated based on safety data in the population studied" (p32). However, it seems that the more virus like particles that are put in the vaccine, for the same amount of adjuvant, the worse its harms. This was also found in the large trial comparing Gardasil 9 with Gardasil 4 (there was more adjuvant in Gardasil 9).

P183:

Serious Clinical Adverse Experiences

One subject (AN 0348) reported a serious clinical adverse experience (hospitalization for anxiety/depression) during the study follow-up. The subject was in the 100-mcg HPV 11 L1 VLP vaccine treatment group.

This serious adverse experience was reported more than 14 days following vaccination, and is therefore not included in Table 49 (Section II.8.2.2.2).

P189:

Table 46

Frequency of Intensity Ratings† for Injection-Site Adverse Experiences by Treatment Group (Days 0 to 14 Following Any Vaccination Visit [Doses 1 Through 3 Only]) (0-, 2-, 6-Month) Vaccination Regimen

	Number of Reported Injection-Site Adverse Experiences With Intensity Rating†				
		HPV 11 L1 VLP Vaccine			
	Placebo	10 mcg	20 mcg	50 mcg	100 mcg
Intensity Rating†	n (%)	n (%)	n (%)	n (%)	n (%)
Mild	24 (88.9)	20 (83.3)	36 (81.8)	45 (88.2)	47 (83.9)
Moderate	3 (11.1)	2 (8.3)	8 (18.2)	6 (11.8)	9 (16.1)
Severe	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)
Total	27 (100)	24 (100)	44 (100)	51 (100)	56 (100)

† During the first 5 days of follow-up after each vaccination, subjects were asked to record on the vaccine report card the size of any injection-site redness or swelling they experienced; these adverse experiences were then reported by the same intensity ratings as all other adverse experiences for the remainder of the follow-up period. For reporting purposes, the size categories of "<1 inch," "1-2 inches," and "more than 2 inches" correspond to the intensity categories of "mild," "moderate," and "severe," respectively.
HPV = Human papillomavirus.
VLP = Virus-like particle.
n = Number of reported adverse experiences with given intensity rating.

Data Source: [4.2.1]

In this table, one patient could contribute with more than one adverse event.

P190:

Table 47

Frequency of Subjects Reporting Injection-Site Adverse Experiences With Maximum Intensity Ratings†‡ by Treatment Group (Days 0 to 14 Following Any Vaccination Visit [Doses 1 Through 3 Only]) (0-, 2-, 6-Month) Vaccination Regimen

	Number of Subjects Reporting a Maximum Intensity Rating†‡ for Injection-Site Adverse Experiences in the Given Intensity Category				
		HPV 11 L1 VLP Vaccine			
Maximum Adverse Experience Intensity Rating †‡	Placebo (N=28)	10 mcg (N=28)	20 mcg (N=28)	50 mcg (N=28)	100 mcg (N=28)
	n (%)	n (%)	n (%)	n (%)	n (%)
No adverse experiences	16 (57.1)	14 (50.0)	10 (35.7)	8 (28.6)	11 (39.3)
Mild	9 (32.1)	7 (25.0)	12 (42.9)	16 (57.1)	9 (32.1)
Moderate	2 (7.1)	2 (7.1)	5 (17.9)	4 (14.3)	8 (28.6)
Severe	0 (0.0)	1 (3.6)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	1 (3.6)	4 (14.3)	1 (3.6)	0 (0.0)	0 (0.0)

P198:

Frequency of Intensity Ratings for Systemic Clinical Adverse Experiences by Treatment Group (Days 0 to 14 Following Any Vaccination Visit [Doses 1 Through 3 Only]) (0-, 2-, 6-Month) Vaccination Regimen

	Number of Reported Systemic Adverse Experiences With Intensity Rating				
		HPV 11 L1 VLP Vaccine			
	Placebo	10 mcg	20 mcg	50 mcg	100 mcg
Intensity Rating	n (%)	n (%)	n (%)	n (%)	n (%)
Mild	51 (67.1)	37 (78.7)	32 (82.1)	36 (55.4)	45 (64.3)
Moderate	24 (31.6)	10 (21.3)	4 (10.3)	21 (32.3)	21 (30.0)
Severe	1 (1.3)	0 (0.0)	3 (7.7)	8 (12.3)	4 (5.7)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	76 (100)	47 (100)	39 (100)	65 (100)	70 (100)

HPV = Human papillomavirus.
VLP = Virus-like particle.
n = Number of reported adverse experiences with given intensity rating.

Data Source: [4.2.1]

In this table, one patient could obviously contribute with more than one adverse event.

P199:

Frequency of Subjects Reporting Systemic Clinical Adverse Experiences
With Maximum Intensity Ratings by Treatment Group
(Days 0 to 14 Following Any Vaccination Visit [Doses 1 Through 3 Only])
(0-, 2-, 6-Month) Vaccination Regimen

Maximum Adverse Experience Intensity Rating†	Number of Subjects Reporting a Maximum Intensity Rating for Systemic Adverse Experiences in the Given Intensity Category				
		HPV 11 L1 VLP Vaccine			
	Placebo (N=28)	10 mcg (N=28)	20 mcg (N=28)	50 mcg (N=28)	100 mcg (N=28)
	n (%)	n (%)	n (%)	n (%)	n (%)
No adverse experiences	11 (39.3)	9 (32.1)	11 (39.3)	7 (25.0)	8 (28.6)
Mild	8 (28.6)	13 (46.4)	12 (42.9)	12 (42.9)	6 (21.4)
Moderate	7 (25.0)	5 (17.9)	2 (7.1)	5 (17.9)	10 (35.7)
Severe	1 (3.6)	0 (0.0)	2 (7.1)	4 (14.3)	4 (14.3)
Unknown	1 (3.6)	1 (3.6)	1 (3.6)	0 (0.0)	0 (0.0)

V501 P002 CSR, monovalent HPV 16 L1 VLP vaccine

Double-blind, placebo-controlled, single-center, sequential dose-escalating study.

Study Initiation Date (FPI): 05-Jan-1998
Study Completion Date (LPO): 31-Oct-2001
Clinical Study Report Date 02-Sep-2004

Index on p3. Listing of appendices on p266.

P22:
“DURATION OF TREATMENT: Vaccination at Day 0, Month 2, and Month 6 plus 14 calendar days of clinical follow-up after the administration of each dose. All subjects were followed to assess persistence of anti-human papillomavirus (HPV) 16 responses through Month 36.

PRIMARY OBJECTIVE(S): (1) To determine that the administration of 3 doses of research lot HPV type 16 L1 VLP vaccine was generally safe and well tolerated. (2) To evaluate the antibody responses, as measured by serum radioimmunoassay (RIA), of initially HPV 16 polymerase chain reaction (PCR)-negative and HPV 16-seronegative subjects after 3 doses of research lot HPV type 16 L1 VLP vaccine at several vaccine dose levels.

STUDY DESIGN: This was a randomized, double-blind (all subjects, investigators [and their staff], and laboratory personnel that analyzed the clinical samples were blinded to treatment group), single-center, sequential dose-escalating, placebo-controlled trial.”

Exactly like in study 001. And done at the same time. Design the same. Described as the first such trial even though it started four months later than study 001.

All were females.

SUBJECT ACCOUNTING:

	Placebo	HPV 16 L1 VLP vaccine			Total
		10/40 mcg/ 0.5 mL†	40 mcg/ 0.5 mL†	80 mcg/ 0.5 mL	
ENTERED: Total	27	13	45	24	109

P29:
The study is very messy: “Originally, subjects were to be randomized 3:1 to panels consisting of sequentially higher doses of HPV 16 L1 VLP vaccine or placebo, respectively. However, early in the study, the 10-mcg dose showed decreased immunogenicity in mice; subjects already randomized to the 10-mcg dose group

were subsequently given the 40-mcg dose. Of the 13 subjects originally assigned to the 10-mcg dose panel, 2 received 2 doses of 10-mcg HPV 16 L1 VLP vaccine and 1 dose of 40-mcg vaccine, while the other 11 subjects received 1 dose of 10-mcg vaccine and 2 doses of 40-mcg vaccine. The 40-mcg dose panel was also expanded to more thoroughly evaluate this vaccine dose."

P27:

Clinical Adverse Experience Summary
(Days 0 to 14 Following Any Vaccination Visit)

	Placebo (N=27)		HPV 16 L1 VLP Vaccine 10/40 mcg† (N=13)		40 mcg (N=45)		80 mcg (N=24)	
	n	(%)	n	(%)	n	(%)	n	(%)
Number of subjects	27		13		45		24	
Subjects without follow-up	0		0		0		0	
Subjects with follow-up	27		13		45		24	
Number (%) of subjects:								
with no adverse experience (AE)	1	(3.7)	0	(0.0)	2	(4.4)	0	(0.0)
with one or more AEs	26	(96.3)	13	(100)	43	(95.6)	24	(100)
injection-site AEs	17	(63.0)	6	(46.2)	35	(77.8)	17	(70.8)
systemic AEs	26	(96.3)	12	(92.3)	37	(82.2)	22	(91.7)
with vaccine-related‡ AEs	22	(81.5)	7	(53.8)	41	(91.1)	22	(91.7)
injection-site AEs	17	(63.0)	6	(46.2)	35	(77.8)	17	(70.8)
systemic AEs	15	(55.6)	5	(38.5)	23	(51.1)	15	(62.5)
with serious AEs	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
with serious vaccine-related AEs	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to an AE	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a vaccine-related AE	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious AE	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious vaccine-related AE	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

P28:
CONCLUSIONS … The HPV 16 L1 VLP vaccine is generally well tolerated."

P48:

Treatment Plan

Group	Dosage Level (mcg)	Sample Size: HPV 16 L1 VLP vaccine	Placebo†	Total
A	10/40	13	4	17
B	40	45	15	60
C	80	24	8	32
Total				109

† The placebo was identical for all groups.
HPV = Human papillomavirus; VLP = Virus-like particle.

Data Source: [3.3.6]

See above, about using several placebos.

"The HPV 16 L1 VLP vaccine and placebo for the study were supplied in identical vials. The active vaccine and placebo material were visually indistinguishable. The clinical materials were provided by Merck & Co., Inc., West Point, PA, U.S.A. in single-dose vials containing a volume of 0.8 mL. Vaccine and placebo were used as supplied; no dilution was necessary. The protocol-defined dose of vaccine/placebo was 0.5 mL. Each 0.5-mL dose of vaccine used in this study contained 10, 40, or 80 meg of HPV 16 L1 VLP, 225 mcg of aluminum as aluminum hydroxyphosphate, and thimerosal (1:20,000) as a preservative. For placebo used in this study, a 0.5-mL dose contained 225 mcg of aluminum as aluminum hydroxyphosphate in physiologic saline."

P51:
“The main goal of the Phase I clinical studies was to define the safety/tolerability and dose-response profiles of varying doses of research lot monovalent HPV 16 and HPV 11 L1 VLP vaccines in a 3-dose regimen given at 0, 2, and 6 months. Because this study represented the first introduction of the HPV 16 L1 VLP vaccine in humans, the study utilized a conservative dose-escalation format. This study evaluated vaccine formulations containing 10, 40, and 80 meg HPV 16 L1 VLP based on anticipated immune responses and manufacturing considerations.”

P82:
“adverse experience incidences of different dose-level groups were compared with one another and with pooled placebo recipients to investigate any trends in the frequency of post-injection local and systemic adverse experiences. Any existing trend was identified by observation only.”

In contrast to study 001, Merck states here that dose-response of safety is a main goal of the study. But no statistical testing, in contrast to dose-response for antibody levels (p80 and p139).

P53:
Same issues with lack of blinding as in study 001:

“This study was double-blind, but was not conducted under in-house blinding procedures. Both the subject and the investigator (and their study personnel) were blinded to the subject’s treatment allocation. However, the investigator (and study personnel) were not blinded to the dosage level of the active group at the given stage.”

P69:
“Follow-up at Months 2, 3, 6, and 7 after the first injection included an interview to assess general safety. The interview solicited broadly for any gynecologic health concerns and any serious adverse experiences that the subject may have experienced.”

Same issue as in study 001.

P73:
“The primary safety objective of the study was to determine that the administration of 2 priming doses plus a booster dose of research lot HPV type 16 vaccine is generally safe and well tolerated. The primary endpoints for safety are the incidences of serious vaccine-related adverse experiences and severe injection-site reactions. Point estimates of the incidences and the corresponding 95% confidence intervals were provided.”

This is an inappropriate way of collecting and analysing possible harms of the vaccine.

P75, P80, P81:
Dose-response was examined. Same issues as for study 001, also about the nonsense argument of participants confounding the study.

P157:
“Serious adverse experiences that occurred any time through Month 7 of the study, whether or not related to the investigational product, were reported.”

This is unacceptable. Antibodies were followed till month 36 but serious adverse events only to month 7 even though it can take much longer than 7 months before these become detected.

P165:
“Vaccine recipients tended to report a larger percentage of injection-site adverse experiences as being moderate in intensity. Thus, 4.2%, 7.1%, 12.6%, and 13.6% of injection-site adverse experiences reported in the placebo, and HPV 16 L1 VLP vaccine 10/40-, 40-, and 80-mcg groups, respectively, were reported to be moderate in intensity.”

Frequency of Intensity Ratings for Injection-Site Adverse Experiences
by Treatment Group
(Days 0 to 14 Following Any Vaccination Visit)

Intensity Rating	Number (%) of Reported Injection-Site Adverse Experiences With Intensity Rating			
		HPV 16 L1 VLP Vaccine		
	Placebo	10/40 mcg†	40 mcg	80 mcg
	n (%)	n (%)	n (%)	n (%)
Mild	22 (91.7)	13 (92.9)	97 (87.4)	38 (86.4)
Moderate	1 (4.2)	1 (7.1)	14 (12.6)	6 (13.6)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)
Total	24 (100)	14 (100)	111 (100)	44 (100)

† Because the 10-mcg dose showed decreased immunogenicity in mice early in the study, subjects originally assigned to the 10-mcg dose panel were subsequently given the 40-mcg dose. Of the 13 subjects originally assigned to the 10-mcg dose panel, 2 received 2 doses of 10-mcg HPV 16 L1 VLP vaccine and 1 dose of 40-mcg vaccine, while the other 11 subjects received 1 dose of 10-mcg vaccine and 2 doses of 40-mcg vaccine.
n = Number of reported adverse experiences with given intensity rating.
Note: The same adverse experience may be counted more than once within visit follow-up or across visit follow-ups.
HPV = Human papillomavirus.
VLP = Virus-like particle.
Data Source: [4.2.1]

In this table, one patient could contribute with more than one adverse event.

P166:
“More subjects reported the maximum injection-site adverse experience intensity as moderate in the 40-mcg (22.2%) and the 80-mcg (20.8%) dose groups, compared with the placebo group (3.7%) and the 10/40-mcg dose group (7.7%).”

Frequency of Subjects Reporting Injection-Site Adverse Experiences
With Maximum Intensity Ratings
by Treatment Group
(Days 0 to 14 Following Any Vaccination Visit)

Maximum Intensity Rating†	Number (%) of Subjects Reporting a Maximum Intensity Rating for Injection-Site Adverse Experiences in the Given Intensity Category			
		HPV 16 L1 VLP Vaccine		
	Placebo (N = 27)	10/40 mcg‡ (N = 13)	40 mcg (N = 45)	80 mcg (N = 24)
	n (%)	n (%)	n (%)	n (%)
No adverse experiences	10 (37.0)	7 (53.8)	10 (22.2)	7 (29.2)
Mild	15 (55.6)	5 (38.5)	25 (55.6)	12 (50.0)
Moderate	1 (3.7)	1 (7.7)	10 (22.2)	5 (20.8)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)

P174:

Frequency of Intensity Ratings for Systemic Clinical Adverse Experiences
by Treatment Group
(Days 0 to 14 Following Any Vaccination Visit)

Intensity Rating	Number (%) of Reported Systemic Clinical Adverse Experiences With Intensity Rating			
		HPV 16 L1 VLP Vaccine		
	Placebo	10/40 mcg‡	40 mcg	80 mcg
	n (%)	n (%)	n (%)	n (%)
Mild	37 (35.9)	11 (31.4)	74 (39.4)	31 (52.5)
Moderate	54 (52.4)	19 (54.3)	83 (44.1)	21 (35.6)
Severe	12 (11.7)	5 (14.3)	31 (16.5)	7 (11.9)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	103 (100.0)	35 (100.0)	188 (100.0)	59 (100.0)

† Because the 10-mcg dose showed decreased immunogenicity in mice early in the study, subjects originally assigned to the 10-mcg dose panel were subsequently given the 40-mcg dose. Of the 13 subjects originally assigned to the 10-mcg dose panel, 2 received 2 doses of 10-mcg HPV 16 L1 VLP vaccine and 1 dose of 40-mcg vaccine, while the other 11 subjects received 1 dose of 10-mcg vaccine and 2 doses of 40-mcg vaccine.
n = Number of reported adverse experiences with given intensity rating.
Note: The same adverse experience may be counted more than once within visit follow-up or across visit follow-ups.
HPV = Human papillomavirus.
VLP = Virus-like particle.
Data Source: [4.2.1]

P175:

Frequency of Subjects Reporting Systemic Clinical Adverse Experiences
With Maximum Intensity Ratings by Treatment Group
(Days 0 to 14 Following Any Vaccination Visit)

	Number (%) of Subjects Reporting a Maximum Intensity Rating for Systemic Adverse Experiences in the Given Intensity Category			
		HPV 16 L1 VLP Vaccine		
Maximum Intensity Rating†	Placebo (N = 27) n (%)	10/40 mcg‡ (N = 13) n (%)	40 mcg (N = 45) n (%)	80 mcg (N = 24) n (%)
No adverse experiences	1 (3.7)	1 (7.7)	8 (17.8)	2 (8.3)
Mild	4 (14.8)	3 (23.1)	2 (4.4)	7 (29.2)
Moderate	13 (48.1)	6 (46.2)	18 (40.0)	9 (37.5)
Severe	9 (33.3)	3 (23.1)	17 (37.8)	6 (25.0)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

P178:
“There was a general trend of increased rates of injection-site adverse experiences in vaccine recipients compared with placebo recipients, especially in the 40-mcg and 80-mcg vaccine groups.”

V501 P004 CSR, monovalent HPV 16 L1 VLP vaccine

Double-Blind, Placebo-Controlled, Dose-Ranging Study of HPV 16 L1 VLP Vaccine (10-, 20-, 40-, 80-mcg Dose) Over 2 Years.

Study Initiation Date (FPI): 12-Oct-1998
Study Completion Date (LPO): 30-Sep-2001
Clinical Study Report Date: 27-Sep-2004

Index on p3. List of appendices on p367.

P26:
“DURATION OF TREATMENT: Vaccination at Day 0, Month 2, and Month 6 plus 14 calendar days of clinical follow-up after administration of each dose. All subjects were followed for persistence through Month 24.

PRIMARY OBJECTIVE(S): (1) To determine that the administration of 3 doses of pilot manufacturing material of HPV 16 L1 VLP vaccine is generally safe and well tolerated in subjects who are either HPV 16 seronegative at Day 0 or subjects who tested positive for HPV 16 by serum cRIA or serum Capture ELISA at Day 0. (2) To evaluate antibody responses as measured by anti-HPV 16 serum cRIA levels across 4 active dose levels (10, 20, 40, and 80 meg) and placebo at Week 4 after the third dose in subjects who were HPV 16 seronegative at Day 0.

STUDY DESIGN: This was a randomized, double-blind (subject, investigators [and their staff], and the laboratory personnel who analyzed clinical samples were blinded to vaccination group), placebo-controlled, multicenter study.”

Females, very similar to study 001 and 002.

SUBJECT DISPOSITION:

	Vaccination Group					
		HPV 16 L1 VLP Vaccine				
	Placebo	10 mcg	20 mcg	40 mcg	80 mcg	Total
RANDOMIZED:	52	112	105	104	107	480

P27:
“The primary endpoints for safety were the incidences of serious vaccine-related adverse experiences and severe injection site adverse experiences.”

P41:
“Primary Objectives

1. To determine that the administration of 3 doses of pilot manufacturing material of HPV 16 L1 VLP vaccine is generally safe and well tolerated …

2. To evaluate antibody responses as measured by anti-HPV 16 serum cRIA levels across 4 active dose levels (10, 20, 40, and 80 mcg) and placebo at Week 4 after the third dose in subjects who are HPV 16 seronegative at Day 0.”

P63:
“The primary variables of interest for safety/tolerability were the occurrence, if any, of severe, local injection-site reactions and the incidence of any serious vaccine-related adverse experiences.”

P152:
“For those specific injection-site adverse experiences, which subjects were prompted to report on the VRC, the two-sided p-values for tests of the null hypothesis that the risk difference (active dose placebo) equals 0 are also provided ... A statistically significantly higher proportion of subjects in the 20-mcg vaccine group (34.0%) reported erythema than in the placebo group (18.0%) (p=0.041).”

On p153ff and pp170ff, each individual vaccine dose group is being compared with the same placebo group, which is therefore the control multiple times.

Given the primary endpoints, primary objectives and primary variables of interest, this is inadequate for a study with a focus on safety. There is no statistical test for trend and results for individual vaccine groups are compared with placebo, which is also inappropriate and misleading. If one does not do a trend test, the combined vaccine groups should be compared with placebo, not each one of them separately. This is poor research.

P28, P67 and P118:
Dose-response analyses for antibodies but not for safety.

P31:

Clinical Adverse Experience Summary
(Days 0 to 14 Following Any Vaccination Visit)

	Vaccination Group									
		HPV 16 L1 VLP Vaccine								
	Placebo (N=52)		10 mcg (N=112)		20 mcg (N=105)		40 mcg (N=104)		80 mcg (N=107)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Number of subjects	52		112		105		104		107	
Subjects without follow-up	2		5		2		6		3	
Subjects with follow-up	50		107		103		98		104	
Number (%) of subjects:										
with no adverse experience	3	(6.0)	9	(8.4)	8	(7.8)	8	(8.2)	9	(8.7)
with one or more adverse experience	47	(94.0)	98	(91.6)	95	(92.2)	90	(91.8)	95	(91.3)
injection-site adverse experiences	44	(88.0)	87	(81.3)	85	(82.5)	87	(88.8)	88	(84.6)
systemic adverse experiences	35	(70.0)	84	(78.5)	74	(71.8)	67	(68.4)	71	(68.3)
with vaccine-related† adverse experiences	44	(88.0)	94	(87.9)	92	(89.3)	88	(89.8)	93	(89.4)
injection-site adverse experiences	44	(88.0)	87	(81.3)	85	(82.5)	87	(88.8)	88	(84.6)
systemic adverse experiences	22	(44.0)	48	(44.9)	45	(43.7)	46	(46.9)	44	(42.3)
with serious adverse experiences	0	(0.0)	1	(0.9)	0	(0.0)	0	(0.0)	0	(0.0)
with serious vaccine-related adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

CSR Synopsis_V501_004_P004_VERSION 2.1 APPROVED 01-Oct-2004

P45:
Same as other studies, “Placebo used in this study consisted of 225 mcg of aluminum as AAHS.”

P53:
“This study was double-blind, but was not conducted under in-house blinding Procedures ... Sponsor clinical, statistical, and data management personnel were not blinded.”

P136:
“The incidences of both injection-site and systemic clinical adverse experiences were comparable across the 5 groups ... In all vaccination groups, the majority of adverse experiences were reported as mild or moderate. The distributions of the adverse experience intensity grades were generally comparable among vaccination groups.”

This result is so much at variance with Merck’s other studies, it is suspect.

P147:

Frequency of Intensity Ratings for Injection-Site Adverse Experiences
by Vaccination Group
(Days 0 to 14 Following Any Vaccination Visit)

	Number (%) of Reported Injection-Site Adverse Experiences by Intensity Rating				
	Vaccination Group				
		HPV 16 L1 VLP Vaccine			
	Placebo (N=52)	10 mcg (N=112)	20 mcg (N=105)	40 mcg (N=104)	80 mcg (N=107)
Intensity Rating	n (%)	n (%)	n (%)	n (%)	n (%)
Mild	106 (90.6)	222 (83.1)	209 (76.8)	226 (86.9)	230 (87.5)
Moderate	11 (9.4)	41 (15.4)	59 (21.7)	31 (11.9)	30 (11.4)
Severe	0 (0.0)	3 (1.1)	4 (1.5)	3 (1.2)	3 (1.1)
Unknown	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Total	117 (100)	267 (100)	272 (100)	260 (100)	263 (100)

HPV = Human papillomavirus.
VLP = Virus-like particle.
N = Number of subjects vaccinated.
n = Number of reported adverse experiences with given intensity rating.

Data Source: [4.2.1]

In this table, one patient could contribute with more than one adverse event.

P148:

Frequency of Subjects Reporting Injection-Site Adverse Experiences
With Maximum Intensity Ratings by Vaccination Group
(Days 0 to 14 Following Any Vaccination Visit)

	Number (%) of Subjects Reporting a Maximum Intensity Rating for Injection-Site Adverse Experiences in the Given Intensity Category				
	Vaccination Group				
		HPV 16 L1 VLP Vaccine			
	Placebo (N=52)	10 mcg (N=112)	20 mcg (N=105)	40 mcg (N=104)	80 mcg (N=107)
Maximum Intensity Rating†	n (%)	n (%)	n (%)	n (%)	n (%)
No AEs	6 (11.5)	17 (15.2)	17 (16.2)	10 (9.6)	15 (14.0)
Mild	37 (71.2)	61 (54.5)	48 (45.7)	67 (64.4)	68 (63.6)
Moderate	7 (13.5)	22 (19.6)	35 (33.3)	17 (16.3)	18 (16.8)
Severe	0 (0.0)	3 (2.7)	2 (1.9)	3 (2.9)	2 (1.9)
Unknown	2 (3.8)	9 (8.0)	3 (2.9)	7 (6.7)	4 (3.7)

† Maximum intensity rating of all injection- site adverse experiences (AEs) reported by the subject. A subject is counted as having “no AEs” only if she reported having no injection-site AEs at all visits. If the subject had missing data for at least 1 visit and reported no injection-site AEs at the other visits, then the maximum intensity was recorded as “unknown.”
HPV = Human Papillomavirus; VLP = Virus-like particle.
N = Number of subjects vaccinated.
n = Number of subjects with a maximum intensity rating for a reported injection-site adverse experiences in the given intensity category.

Data Source: [4.2.1]

P165:

Frequency of Intensity Ratings for Systemic Clinical Adverse Experiences
by Vaccination Group
(Days 0 to 14 Following Any Vaccination Visit)

	Number (%) of Reported Systemic Clinical Adverse Experiences by Intensity Rating				
	Vaccination Group				
		HPV 16 L1 VLP Vaccine			
	Placebo (N=52)	10 mcg (N=112)	20 mcg (N=105)	40 mcg (N=104)	80 mcg (N=107)
Intensity Rating	n (%)	n (%)	n (%)	n (%)	n (%)
Mild	52 (49.1)	115 (42.9)	84 (36.5)	109 (44.9)	109 (46.0)
Moderate	45 (42.5)	113 (42.2)	117 (50.9)	119 (49.0)	107 (45.1)
Severe	6 (5.7)	32 (11.9)	25 (10.9)	12 (4.9)	18 (7.6)
Unknown	3 (2.8)	8 (3.0)	4 (1.7)	3 (1.2)	3 (1.3)
Total	106 (100)	268 (100)	230 (100)	243 (100)	237 (100)

HPV = Human papillomavirus; VLP = Virus-like particle.
N = Number of subjects vaccinated.
n = Number of reported adverse experiences with given intensity rating.

Data Source: [4.2.1]

In this table, one patient could contribute with more than one adverse event.

P166:

Frequency of Subjects Reporting Systemic Clinical Adverse Experiences
With Maximum Intensity Ratings by Vaccination Group
(Days 0 to 14 Following Any Vaccination Visit)

	Number (%) of Subjects Reporting a Maximum Intensity Rating for Systemic Clinical Adverse Experiences in the Given Intensity Category				
	Vaccination Group				
		HPV 16 L1 VLP Vaccine			
	Placebo (N=52)	10 mcg (N=112)	20 mcg (N=105)	40 mcg (N=104)	80 mcg (N=107)
Maximum Intensity Rating†	n (%)	n (%)	n (%)	n (%)	n (%)
No AEs	15 (28.8)	22 (19.6)	27 (25.7)	29 (27.9)	30 (28.0)
Mild	13 (25.0)	24 (21.4)	18 (17.1)	21 (20.2)	22 (20.6)
Moderate	17 (32.7)	40 (35.7)	40 (38.1)	38 (36.5)	37 (34.6)
Severe	5 (9.6)	19 (17.0)	16 (15.2)	8 (7.7)	11 (10.3)
Unknown	2 (3.8)	7 (6.3)	4 (3.8)	8 (7.7)	7 (6.5)

Other comparisons of monovalent vaccine with adjuvant

V501 P005 CSR, monovalent HPV 16 L1 VLP vaccine

Study Initiation Date (FPI): 22-Oct-1998
Study Completion Date (LPO): 31-Mar-2004
Clinical Study Report Date: 08-Mar-2005

Index on p3.

P37:
Vaccination at Day 1. Month 2, and Month 6 plus 14 calendar days of clinical follow-up after administration of each dose. All subjects were followed for persistence of antibody response and efficacy evaluation through Month 48.

This study was double-blind (with in-house blinding).

P38:

	HPV 16 L1 VLP Vaccine 40 mcg	Placebo	Total
RANDOMIZED:	1204	1205	2409
Female (age range)	16 to 25 years	16 to 23 years	16 to 25 years

Active HPV 16 L1 VLP vaccine contained 40 mcg of HPV 16 L1 VLP along with 225 mcg of amorphous aluminum hydroxyphosphate sulfate (AAHS) adjuvant in a 0.5 mL dose. Placebo contained 225 mcg of AAHS adjuvant in a 0.5 mL dose.

P39:
Safety assessed like in other Merck trials.

Findings as reported in the synopsis quite similar to other trials. The vaccine was monovalent, so I did not review entire report.

V501 P026_Clinical Report

Extension of trial P005 of monovalent vaccine against "placebo" (aluminium adjuvant).

P6:
"The objectives of this study were to provide data on efficacy approximately eight years after administration of a prophylactic HPV-16 L1 VLP vaccine. Between March 2006 and May 2008, 290 women (148 vaccine recipients and 142 placebo recipients) who had participated in a phase IIb Randomized Clinical Trial (RCT) of this vaccine (also known as Merck & Co., Inc., HPV Protocol 005) in Seattle (November 1998 - January 2004) were enrolled in an extended follow-up study."

"Participants were followed for serious adverse experiences, new medical conditions, and pregnancy data."

There were no serious adverse events. As this is one of the few trials that has any long-term follow-up (range between 86.5 and 114.2 months, or up to 9.5 years), I show the table of new medical conditions:

Table 1.6. Onset of new medical conditions and history of pregnancy

	Vaccine Group	Placebo Group
	n = 148	n = 142
Severe or frequent headaches, n (%)	31 (20.9)	22 (15.5)
Visual or hearing disorders, n (%)	9 (6.1)	16 (11.3)
Thyroid disorders, n (%)	4 (2.7)	5 (3.5)
Diabetes, n (%)	0 (0)	3 (2.1)
Lung disorders, n (%)	15 (10.1)	12 (8.5)
High cholesterol, n (%)	1 (0.7)	1 (0.7)
High blood pressure, n (%)	5 (3.4)	4 (2.8)
Stroke, n (%)	0 (0)	0 (0)
Thrombophlebitis, blood clots, n (%)	1 (0.7)	0 (0)
Heart disease, n (%)	0 (0)	0 (0)

Breast lumps, pain, or nipple discharge, n (%)	7 (4.7)	12 (8.5)
Breast cancer, n (%)	0 (0)	0 (0)
Polycystic ovarian syndrome, n (%)	0 (0)	5 (3.5)
Cervical, uterine, or ovarian cancer, n (%)	0 (0)	0 (0)
Other cancer, n (%)	0 (0)	1 (0.7)
Liver disorders, n (%)	4 (2.7)	0 (0)
Gallbladder disease, n (%)	0 (0)	2 (1.4)
Gastrointestinal disorders, n (%)	8 (5.4)	10 (7.0)
Urinary disorders, n (%)	22 (14.9)	19 (13.4)
Muscle, joint, or bone disorders, n (%)	18 (12.2)	26 (18.3)
Skin disorders, n (%)	39 (26.3)	32 (22.5)
Seizure, neurological disorders, n (%)	0 (0)	6 (4.2)
Eating disorders, n (%)	3 (2.0)	0 (0)
Depression, bipolar, psychiatric disorders, n (%)	25 (16.9)	20 (14.1)
Drug addiction, n (%)	0 (0)	3 (2.1)
Immune system disorders, n (%)	3 (2.0)	4 (2.8)
Number of pregnancies with known fetus outcome	92	69
Live birth, n (%)*	43 (46.7)	29 (42.0)
Termination, n (%)*	36 (39.1)	30 (43.5)
Miscarriage, n (%)*	13 (14.1)	10 (14.5)

* Percentage is calculated based on the number of pregnancies with known fetus outcome

It is difficult to make much use of this table. There were more headaches in those women who had received the vaccine (31 vs 22), which is a key symptom in POTS.

V501 P006 CSR, monovalent HPV 18 L1 VLP vaccine

Study Initiation Date (FPI): 02-Mar-2000
Study Completion Date (LPO): 25-Jan-2001
Clinical Study Report Date 06-May-2003

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P16:
Vaccination at Day 0, Month 2, and Month 6 plus 14 calendar days of clinical follow-up after the administration of each dose.

Only 27 versus 13 subjects.

P36:
Each 0.5-mL dose of vaccine used in this study contained 80 mcg of a final development process (FDP) lot of HPV 18 L1 VLP vaccine and 450 mcg of AAHS adjuvant. For placebo used in this study, a 0.5-mL dose contained 450 mcg of AAHS adjuvant.

The "placebo" was consistently called a placebo, and with similar explanations why an adjuvant was used as in other Merck trials (p31). As only 40 people participated, and as the vaccine was monovalent, which is not used, I did not review the whole report.

Dose-response studies of Gardasil

V501 P007 CSR_protocol amendments_pg 2047

Study Initiation Date (FPI): 26-May-2000
Study Completion Date (LPO): 10-May-2004
Clinical Study Report Date: 25-Feb-2005

Index on p3.

P44:
Vaccination at Day 1, Month 2, and Month 6 plus 14 calendar days of clinical follow-up after administration of each dose. All subjects were followed for persistence of antibody response and efficacy evaluation through Month 36.

This study was conducted in 2 parts. Part A was a randomized, double-blind, placebo-controlled, multicenter, sequential dose-escalating evaluation. Part B was a randomized, double-blind (operating under in-house blinding procedures), placebo-controlled, multicenter, dose ranging study.

P45:

	Placebo (mcg) (Aluminum Adjuvant)		Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Vaccine (mcg)			
	225	450	20/40/40/20	40/40/40/40	80/80/40/80	Total
RANDOMIZED:	135	140	277	274	280	1106
Female (age range)	16 to 23	13 to 23	16 to 23	15 to 24	16 to 23	13 to 24

P46:
"The primary endpoint for safety was the proportion of subjects with serious vaccine-related adverse experiences."

This is a far too limited focus on safety, and the problems are the same as for Merck's other safety trials. Statistical testing was also limited: "p-Values were computed only for those adverse experiences that were prompted for on the vaccination report card (VRC), including elevated temperatures, and injection-site pain, swelling and redness" (p47).

P47:
"Due to differing concentrations of aluminum in the various vaccine and placebo treatment groups, subjects who received quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine 20/40/40/20-mcg and 40/40/40/40-mcg doses were primarily compared with subjects who received placebo with 225 mcg aluminum per dose. Subjects who received quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine 80/80/40/80 mcg dose were compared with subjects who received placebo with 450 mcg aluminum per dose."

Merck seems to acknowledge that the adjuvant can cause harm; otherwise, there would be no reason to divide the analyses this way.

P54:
"Safety: … (1) the proportion of subjects who reported any injection-site adverse experience was slightly increased among the quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine groups compared with the matched placebo groups; (2) the proportions of subjects who reported one or more systemic adverse experiences were generally comparable among the 5 vaccination groups; (3) among the active vaccination groups, there was a slight dose response with regard to the proportions of subjects who reported any adverse experience, which was mainly caused by the injection-site adverse experiences … One subject in the quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine group died of pancreatic cancer during the study. Her death is not included in these tables as a serious adverse experience because the death occurred outside the 15 day period following any vaccination visit."

To exclude a death from the tables just because it occurred outside an arbitrary time window of only two weeks after each vaccination is inappropriate.

P55

Clinical Adverse Experience Summary
(Days 1 to 15 Following Any Vaccination Visit)
Dose-Ranging Phase

	Placebo (Aluminum Adjuvant) 225 mcg (N=135)		Placebo (Aluminum Adjuvant) 450 mcg (N=140)		Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Vaccine 20/40/40/20 mcg (N=275)†		Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Vaccine 40/40/40/40 mcg (N=272)		Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Vaccine 80/80/40/80 mcg (N=280)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Number of subjects	135		140		275		272		280	
Subjects without follow-up	1		0		3		3		3	
Subjects with follow-up	134		140		272		269		277	
Number (%) of subjects:										
with no adverse experience (AE)	18	(13.4)	14	(10.0)	22	(8.1)	18	(6.7)	12	(4.3)
with one or more adverse experiences	116	(86.6)	126	(90.0)	250	(91.9)	251	(93.3)	265	(95.7)
injection-site adverse experiences	100	(74.6)	112	(80.0)	234	(86.0)	240	(89.2)	255	(92.1)
systemic adverse experiences	95	(70.9)	95	(67.9)	187	(68.8)	186	(69.1)	192	(69.3)
with vaccine-related‡ adverse experiences	108	(80.6)	117	(83.6)	243	(89.3)	245	(91.1)	262	(94.6)
injection-site adverse experiences	100	(74.6)	112	(80.0)	234	(86.0)	240	(89.2)	255	(92.1)
systemic adverse experiences	49	(36.6)	41	(29.3)	104	(38.2)	92	(34.2)	107	(38.6)
with serious adverse experiences	0	(0.0)	2	(1.4)	2	(0.7)	0	(0.0)	2	(0.7)
with serious vaccine-related AEs	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued§ due to an adverse experience	0	(0.0)	1	(0.7)	0	(0.0)	2	(0.7)	0	(0.0)
discontinued due to a vaccine-related AE	0	(0.0)	1	(0.7)	0	(0.0)	2	(0.7)	0	(0.0)
discontinued due to a serious AE	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious vaccine-related AE	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

P94:
"Each 0.5-mL dose of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine used in this study contained 20/40/40/20 mcg, 40/40/40/40 mcg, or 80/80/40/80 mcg of HPV 6, 11, 16,18 L1 VLPs, respectively, and 225 mcg (in the 2 lower dose groups) or 395 mcg (in the highest dose group) of aluminum as AAHS. Placebo used in this study consisted of 225 mcg or 450 mcg of aluminum as AAHS."

What was the rationale for not using the same dose of adjuvant in the high-dose vaccine group (395 mcg) as in the high-dose "placebo" group (450 mcg)? It makes no sense, particularly not when Merck divided its analyses according to dose, both for the antigens and the adjuvant.

P295:
"The placebo containing 450 mcg of aluminum adjuvant represents the proper comparator for the quadrivalent HPV (Types 6, 11, 16, 18) L 1 VLP vaccine 80/80/40/80-mcg dose."

Why did Merck not explain anywhere in its 3000+ page report how the high-dose "placebo" group could be a "proper comparator" for the high-dose vaccine group when the "placebo" contained more adjuvant than the vaccine?

P301:

Number (%) of Subjects Who Reported Adverse Experiences by Maximum Intensity Rating
(Days 1 to 15 Following Any Vaccination Visit)
Dose-Ranging Phase

	Placebo (Aluminum Adjuvant)		Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Vaccine		
	225 mcg (N=135)	450 mcg (N=140)	20/40/40/20 mcg (N=275) †	40/40/40/40 mcg (N=272)	80/80/40/80 mcg (N=280)
Number of Subjects With Follow-Up	134	140	272	269	277
Number (%) of Subjects With No Adverse Experiences	18 (13.4)	14 (10.0)	22 (8.1)	18 (6.7)	12 (4.3)
Number (%) of Subjects by Maximum Intensity Rating of Adverse Experience					
Mild	30 (22.4)	43 (30.7)	78 (28.7)	72 (26.8)	81 (29.2)
Moderate	64 (47.8)	54 (38.6)	120 (44.1)	116 (43.1)	130 (46.9)
Severe	22 (16.4)	29 (20.7)	52 (19.1)	61 (22.7)	54 (19.5)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)

More patients reported moderate or severe adverse experiences on the vaccine than on the adjuvant, 64.4% vs 61.4%.

P302:

Frequency of Intensity Ratings of All Adverse Experiences Reported
(Days 1 to 15 Following Any Vaccination Visit)
Dose-Ranging Phase

	Placebo (Aluminum Adjuvant)		Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Vaccine		
	225 mcg (N=135)	450 mcg (N=140)	20/40/40/20 mcg (N=275)†	40/40/40/40 mcg (N=272)	80/80/40/80 mcg (N=280)
Number of Subjects With Follow-Up	134	140	272	269	277
Number (%) of Adverse Experiences Reported	640	655	1462	1439	1599
Number (%) of Adverse Experiences Reported by Intensity Rating					
Mild	420 (65.6)	425 (64.9)	933 (63.8)	895 (62.2)	990 (61.9)
Moderate	185 (28.9)	183 (27.9)	438 (30.0)	443 (30.8)	518 (32.4)
Severe	35 (5.5)	47 (7.2)	90 (6.2)	99 (6.9)	91 (5.7)
Unknown	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.1)	0 (0.0)

The differences are similar when adverse events instead of patients with one or more events are counted.

P303:
"Among the active vaccine groups, there was a modest dose response with regard to the proportion of subjects reporting any injection-site adverse experience."

P311:
"Within each injection-site adverse experience category, slightly higher percentages of subjects in the 3 active vaccine groups had injection site adverse experiences with maximum intensity rating of moderate or severe compared with subjects in the corresponding placebo groups."

Merck sometimes combines moderate with severe.

P313:

Number (%) of Subjects Who Reported Injection-Site Adverse Experiences by Maximum Intensity Rating
(Days 1 to 5 Following Any Vaccination Visit)
Dose-Ranging Phase

	Placebo (Aluminum Adjuvant)		Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Vaccine		
	225 mcg (N=135)	450 mcg (N=140)	20/40/40/20 mcg (N=275)†	40/40/40/40 mcg (N=272)	80/80/40/80 mcg (N=280)
Number of Subjects with follow-up	134	140	272	269	277
Number (%) of Subjects with no Adverse Experiences	34 (25.4%)	28 (20.0%)	38 (14.0%)	30 (11.2%)	23 (8.3%)
Number (%) of Subjects by Maximum Intensity Rating of Adverse Experience					
Mild	64 (47.8%)	76 (54.3%)	131 (48.2%)	134 (49.8%)	135 (48.7%)
Moderate	34 (25.4%)	33 (23.6%)	95 (34.9%)	89 (33.1%)	105 (37.9%)
Severe	2 (1.5%)	3 (2.1%)	8 (2.9%)	16 (5.9%)	14 (5.1%)
Unknown	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

P314:

Frequency of Intensity Ratings of All Injection-Site Adverse Experiences Reported
(Days 1 to 5 Following Any Vaccination Visit)
Dose-Ranging Phase

	Placebo (Aluminum Adjuvant)		Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Vaccine		
	225 mcg (N=135)	450 mcg (N=140)	20/40/40/20 mcg (N=275)†	40/40/40/40 mcg (N=272)	80/80/40/80 mcg (N=280)
Number of Subjects With Follow-Up	134	140	272	269	277
Number (%) of Adverse Experiences Reported	304	336	792	821	921
Number (%) of Adverse Experiences Reported by Intensity Rating					
Mild	253 (83.2%)	278 (82.7%)	619 (78.2%)	637 (77.6%)	703 (76.3%)
Moderate	47 (15.5%)	53 (15.8%)	158 (19.9%)	163 (19.9%)	201 (21.8%)
Severe	4 (1.3%)	5 (1.5%)	15 (1.9%)	21 (2.6%)	17 (1.8%)
Unknown	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Differences were more pronounced when all events were counted.

P369:

Number (%) of Subjects Who Reported Systemic Clinical Adverse Experiences by Maximum Intensity Rating
(Days 1 to 15 Following Any Vaccination Visit)
Dose-Ranging Phase

	Placebo (Aluminum Adjuvant)		Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Vaccine		
	225 mcg (N=135)	450 mcg (N=140)	20/40/40/20 mcg (N=275)†	40/40/40/40 mcg (N=272)	80/80/40/80 mcg (N=280)
Number of Subjects With Follow-Up	134	140	272	269	277
Number (%) of Subjects with No Systemic Adverse Experiences	39 (29.1%)	45 (32.1%)	85 (31.3%)	83 (30.9%)	85 (30.7%)
Number (%) of Subjects by Maximum Intensity Rating of Systemic Adverse Experience					
Mild	25 (18.7%)	25 (17.9%)	48 (17.6%)	48 (17.8%)	46 (16.6%)
Moderate	50 (37.3%)	43 (30.7%)	92 (33.8%)	90 (33.5%)	102 (36.8%)
Severe	20 (14.9%)	27 (19.3%)	47 (17.3%)	46 (17.1%)	44 (15.9%)
Unknown	0 (0%)	0 (0%)	0 (0%)	2 (0.7%)	0 (0%)

P370:

Frequency of Intensity Ratings of All Systemic Clinical Adverse Experiences Reported
(Days 1 to 15 Following Any Vaccination Visit)
Dose-Ranging Phase

	Placebo (Aluminum Adjuvant)		Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Vaccine		
	225 mcg (N=135)	450 mcg (N=140)	20/40/40/20 mcg (N=275)†	40/40/40/40 mcg (N=272)	80/80/40/80 mcg (N=280)
Number of Subjects With Follow-Up	134	140	272	269	277
Number (%) of Systemic Adverse Experiences Reported	334 (100%)	319 (100%)	666 (100%)	612 (100%)	668 (100%)
Number (%) of Systemic Adverse Experiences Reported by Intensity Rating					
Mild	166 (49.7%)	147 (46.1%)	312 (46.8%)	254 (41.5%)	279 (41.8%)
Moderate	138 (41.3%)	130 (40.8%)	278 (41.7%)	279 (45.6%)	315 (47.2%)
Severe	30 (9.0%)	42 (13.2%)	75 (11.3%)	77 (12.6%)	74 (11.1%)
Unknown	0 (0%)	0 (0%)	1 (0.2%)	2 (0.3%)	0 (0%)

P371:

“The percentages of subjects who reported a maximum temperature of 38.9°C or greater or abnormal was somewhat higher among 2 of the 3 active vaccine groups (20/40/40/20-mcg and 40/40/40/40-mcg) compared with the relevant placebo recipients.”

P373:

Number (%) of Subjects With Elevated Temperature by Vaccination Group
(Days 1 to 5 Following Any Vaccination Visit)
Dose-Ranging Phase

	Placebo (Aluminum Adjuvant)				Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Vaccine					
	225 mcg (N=135)		450 mcg (N=140)		20/40/40/20 mcg (N=275)[†]		40/40/40/40 mcg (N=272)		80/80/40/80 mcg (N=280)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Number of subjects	135		140		275		272		280	
Subjects without follow-up	1		1		4		4		3	
Subjects with follow-up	134		139		271		268		277	
Maximum Temperature (Oral Equivalent):										
< 37.8°C (<100 °F) or normal[‡]	126	(94.0)	123	(88.5)	245	(90.4)	235	(87.7)	244	(88.1)
≥37.8°C (≥100 °F) and < 38.9°C (<102°F) or abnormal[§]	8	(6.0)	14	(10.1)	25	(9.2)	30	(11.2)	26	(9.4)
≥ 38.9°C (≥102 °F) and < 39.9°C (<103.8°F)	0	(0.0)	2	(1.4)	1	(0.4)	3	(1.1)	5	(1.8)
≥ 39.9°C (≥103.8 °F) and < 40.9°C (<105.6°F)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.7)
≥ 40.9°C (≥105.6 °F)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

P378:
Short narratives of six nonfatal serious clinical adverse experiences.

P381:
“Three (3) subjects discontinued from the study due to nonserious clinical adverse experiences. A listing of subjects who discontinued due to a clinical adverse experience in the dose-ranging phase is provided in Table 8-19. No subjects discontinued due to a clinical adverse experience in the dose-escalation phase.

AN 7027, a 19-year-old Hispanic female who received aluminum adjuvant placebo 450 mcg, discontinued from the study due to numbness in extremities (hypoaesthesia) of mild intensity following Dose 1. Other adverse experiences noted Postdose 1 included nausea, stomach cramps, palms of hands sweating, and pain/tenderness at the injection site. The adverse experience of numbness in extremities (hypoaesthesia) caused no further vaccine doses to be given and was determined by the investigator to be probably related to the test vaccine/placebo.

AN 7149, a 19-year-old White female who received quadrivalent HPV (Types 6,11, 16, 18) L1 VLP vaccine 40/40/40/40-mcg dose, discontinued from the study due to swelling at the injection site with a maximum size of 4 (inches) following Dose 1. Other adverse experiences noted Postdose 1 included influenza, common cold, redness at the injection site, and pain/tenderness at the injection site. The adverse experience of swelling at the injection site caused no further vaccine doses to be given and was determined by the investigator to be definitely related to the test vaccine/placebo.

AN 7412, an 18-year-old Black female who received quadrivalent HPV (Types 6,11, 16, 18) L1 VLP vaccine 40/40/40/40-mcg dose, discontinued from the study due to redness (erythema) at the injection site with a maximum size of 2 (inches)and pain/tenderness at the injection site of severe intensity following Dose 2. The subject reported no additional adverse experiences following Dose 2, and reported only pain/tenderness at the injection site of mild intensity following Dose 1. The redness (erythema) and pain/tenderness at the injection site caused no further vaccine doses to be given and were determined by the investigator to be definitely related to the test vaccine/placebo.

P394:
New Medical History.

V501 P016 V1 CSR

Study Initiation Date (FPI): 07-Dec-2002
Study Completion Date (LPO): 20-Sep-2004
Clinical Study Report Date: 17-Jun-2005

Index on p3.

P30:
“Vaccination at Day 1, Month 2, and Month 6 plus 14 calendar days of clinical follow-up after administration of each dose. All subjects were followed to assess anti-human papillomavirus (HPV) types 6, 11, 16, and 18 responses through Month 7. After approval of Amendment 016-01, subjects in the 10- to 15-year-old age groups were followed for health status evaluation at Month 12 … This CSR focusses on the Adolescent Immunogenicity substudy. The End-Expiry substudy is addressed in a separate CSR ... All subjects were to receive a 3-dose regimen of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine 20/40/40/20 mcg.”

P31:

SUBJECT/PATIENT DISPOSITION:	Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine			
	10- to 15-Year-Old Females	10- to 15-Year-Old Males	16- to 23-Year-Old Females	Total
SCREENING FAILURES				55
RANDOMIZED	506	510	513	1529

DOSAGE/FORMULATION NOS.: All subjects in this substudy received the 100% dose formulation of the quadrivalent HPV VLP vaccine at Day 1, Month 2, and Month 6.

There is no hint that people were randomised to different doses of the same vaccine in the main study until much later in the report.

P33, in the Synopsis:
“In response to a request from a regulatory agency received after the study was initiated, the study protocol was amended to extend follow-up for safety (new medical conditions, vaccine-related serious adverse experiences) for the 10-to 15-year-old subjects through Month 12 (6 months following administration of the vaccine dose 3). However, some of these subjects had already completed the study at Month 7 before the protocol amendment was approved at their sites. Therefore, only 44% of subjects in the 10- to 15-year-old groups underwent the Month 12 safety follow-up visit.”

There are similar problems with assessing safety as in other Merck studies.

P59:
“5.1 Overall Study Design and Plan: Description
Protocol 016 was a multicenter immunogenicity and safety study in approximately (~) 3000 subjects. Of the ~3000 subjects, ~1250 were females aged 16 to 23 years, ~1250 were females aged 10 to 15 years, and ~500 were males aged 10 to 15 years (See Table 1-1 in Section II.1.7). The females (N = ~2500) were randomized in a 1:1:1:2 ratio to receive 20, 40, 60, or 100% dose quadrivalent vaccine within each of the 2 age strata (Table 1-1). In addition, ~500 males 10 to 15 years of age were given full-dose quadrivalent vaccine. The study was randomized and double-blinded (operating under in-house blinding procedures) with respect to the comparisons among the various vaccine doses. However, with respect to the comparison of the adults to the adolescents, the study was not blinded or randomized. Only Group I contributed to the Adolescent Immunogenicity Substudy, which is described in this CSR. Only female subjects contributed to the End-Expiry Substudy, which is described in a separate CSR.”

Much fewer females were listed on p31 in the report (see just above), and on this page, no males were listed.

P74:
“Participants received a total of 3 intramuscular injections of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine at Day 1, Month 2 (±3 weeks), and Month 6 (±4 weeks). Approximately 1500 subjects were to be randomized to receive the full-dose formulation (HPV 6— 20 µg, HPV 11—40 µg, HPV 16—40 µg, and HPV 18—20 µg). Three groups of approximately 500 subjects (250 adult women and 250 girls) were to receive formulations of 20% (HPV 6— 4 µg, HPV 11— 8 µg, HPV 16—8 µg, and HPV 18—4 µg), 40% (HPV 6—8 µg, HPV 11— 16 µg,HPV 16— 16 µg, and HPV 18 8 µg), and 60% (HPV 6— 12 µg, HPV 11— 2 4 µg, HPV 16—24 µg, and HPV 18— 12 µg) dose of the quadrivalent HPV vaccine (total of ~1500 subjects receiving partial-dose formulations). Each subject received 1 injection at each vaccination visit (Day 1, Month 2, and Month 6). All vaccine formulations (full-dose and partial-dose) contained 225 µg of aluminum adjuvant per dose ... For the Adolescent Immunogenicity Substudy, each 0.5-mL dose of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine contained HPV 6—20 µg, HPV 11—40 µg, HPV 16— 40 µg, and HPV 18—20 µg.”

P75:
“Following the determination that all entry criteria were met, each eligible subject received an [allocation number], and female subjects were randomized among the 4 vaccination (dose formulation) groups. All male subjects were assigned to the 100% dose formulation [3.8.1; 3.8.2; 3.8.3].”

P76:
“The 20/40/40/20-mcg dose of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine was chosen for evaluation in Phase III clinical studies based on a planned interim analysis of Protocol 007, the first study of Merck’s quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine. The interim analysis was complete in Jun-2001 [2.1.7].”

V501 P016 V2 CSR

Study Initiation Date (FPI): 07-Dec-2002
Study Completion Date (LPO): 20-Sep-2004
Clinical Study Report Date: 04-Aug-2005

The first two dates are the same as for the V1 report just above; the study report date is seven weeks after the first report.

Index on p3; a list of appendices on p467.

P23:

SUBJECT DISPOSITION:

	Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Vaccine				
	20% Formulation	40% Formulation	60% Formulation	100% Formulation	Total
SCREENING FAILURES					49
RANDOMIZED	504	514	508	1019	2545
COMPLETED VACCINATION AND COMPLETED STUDY	465	489	471	947	2372
Completed study at Month 7 †	353	367	346	707	1773
Completed study at Month 12 ‡	112	122	125	240	599

P23, in the Synopsis:
“In response to a request from a regulatory agency received after the study was initiated, the study protocol was amended to extend follow-up for safety (new medical conditions, vaccine-related serious adverse experiences) for the 10- to 15-year-old subjects through Month 12 (6 months Postdose 3).

However, some of these subjects had already completed the study at Month 7 before the protocol amendment (016-01) was approved at their study sites. Therefore, only approximately 25% of subjects in the 10- to 15-year-old age stratum underwent the Month 12 safety follow-up visit."

This information contrasts with the information given in V1 on p33 (see above): "… Therefore, only 44% of subjects in the 10- to 15-year-old groups underwent the Month 12 safety follow-up visit."

P24:

Product	Formulation Number	Dosage	Route of Administration
Quadrivalent HPV L1 VLP vaccine (100%)	V501VAI020I004	20/40/40/20 mcg plus 225 mcg aluminum adjuvant/0.5 mL	Intramuscular Injection
Quadrivalent HPV L1 VLP vaccine (60%)	V501VAI022Q001	12/24/24/12 mcg plus 225 mcg aluminum adjuvant /0.5 mL	Intramuscular Injection
Quadrivalent HPV L1 VLP vaccine (40%)	V501VAI023R001	8/16/16/8 mcg plus 225 mcg aluminum adjuvant /0.5 mL	Intramuscular Injection
Quadrivalent HPV L1 VLP vaccine (20%)	V501VAI024S001	4/8/8/4 mcg plus 225 mcg aluminum adjuvant /0.5 mL	Intramuscular Injection
HPV = Human papillomavirus; VLP = Virus-like particles.			

Thus, all four groups got the same dose of the adjuvant, 225 mcg, which is confirmed on p60.

P26:
"No statistical comparisons of safety profiles among the 4 vaccination groups were made for this substudy."

This is unacceptable. Merck did a dose-response study comparing 20%, 40%, 60% and 100% of its vaccine and it is expected that the more antigens people receive, the greater the harms, but Merck did not look for a dose-response relation of vaccine harms whereas the company compared the various doses' ability to produce antibodies against HPV.

P30:
Merck concluded about safety:
"Safety
The table that follows displays a summary of clinical adverse experiences reported from Day 1 through Day 15 following any vaccination visit by vaccination group. The following observations can be made:
- The overall proportions of subjects with at least 1 clinical adverse experience reported within 15 days of any vaccination visit were generally comparable among the 4 vaccination groups.
- The proportions of subjects with at least 1 injection-site adverse experience and the proportions of subjects with at least 1 systemic adverse experience were generally comparable among the 4 vaccination groups.
- Five (5) subjects experienced a serious adverse experience within 15 days of any vaccination visit. None of these was judged by the investigator to be related to study vaccine.
- Four (4) subjects discontinued study participation within 15 days of any vaccination visit due to an adverse experience.
- No subjects died days 1 to 15 following any vaccination visit."

This, and a table, also about these 15 days is all. This is unacceptable and violates accepted scientific principles. The protocol was amended in response to a request from a regulatory agency to include safety follow-up data after 12 months. There is nothing about these data in the synopsis.

P31:

Clinical Adverse Experience Summary
(Days 1 to 15 Following Any Vaccination Visit)

	Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Vaccine							
	20% Formulation (N=503)		40% Formulation (N=514)		60% Formulation (N=507)		100% Formulation (N=1015)	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in analysis population	503		514		507		1015	
Subjects without follow-up	7		5		7		17	
Subjects with follow-up	496		509		500		998	
Number (%) of subjects:								
with no adverse experience	52	(10.5)	66	(13.0)	59	(11.8)	87	(8.7)
with one or more adverse experiences	444	(89.5)	443	(87.0)	441	(88.2)	911	(91.3)
injection-site adverse experiences	408	(82.3)	406	(79.8)	402	(80.4)	840	(84.2)
systemic adverse experiences	291	(58.7)	294	(57.8)	304	(60.8)	591	(59.2)
with vaccine-related† adverse experiences	429	(86.5)	422	(82.9)	424	(84.8)	867	(86.9)
injection-site adverse experiences	408	(82.3)	406	(79.8)	402	(80.4)	840	(84.2)
systemic adverse experiences	171	(34.5)	165	(32.4)	168	(33.6)	314	(31.5)
with serious adverse experiences	3	(0.6)	0	(0.0)	1	(0.2)	1	(0.1)
with serious vaccine-related adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued‡ due to an adverse experience	2	(0.4)	0	(0.0)	1	(0.2)	1	(0.1)
discontinued due to a vaccine-related adverse experience	1	(0.2)	0	(0.0)	1	(0.2)	1	(0.1)
discontinued due to a serious adverse experience	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious vaccine-related adverse experience	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

P71:
"The full- and partial-dose formulations of the quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine were supplied in identical vials and were visually indistinguishable."

P87:
"The important variables of interest for safety/tolerability were the occurrence of severe injection-site adverse experiences and the incidence of any vaccine-related serious adverse experiences ... The interview solicited broadly for any serious adverse experiences that the subject may have encountered."

As noted for other studies, this is inappropriate, particularly for a safety study requested by a drug regulator and for an intervention that is to be used in healthy people.

P174:
A table showing number of subjects with systemic clinical adverse experiences in the four dose groups.

P177:
A table showing temperatures in the four dose groups.

P184:
A narrative of a 17-year-old female who experienced a seizure and was admitted to the emergency room. In my view, the seizure was likely caused by the psychiatric drugs she received.

P197:
A table of new medical conditions up to month 7.

As in other studies, injection-site adverse events and systemic adverse events were divided into mild, moderate and severe (p89), but even though there were numerous tables of adverse events in the 2706-page report, there wasn't any for the severity of the events.

Comparisons of quadrivalent vaccine with adjuvant and other studies

Future 1, study P013

V501 P013 CSR_with P013-10 pg 712

Study Initiation Date (FPI): 28-Dec-2001
Study Completion Date (LPO): 31-Jul-2007
Clinical Study Report Date: 09-Nov-2007
Interim CSRs for the same Protocol: 20-Mar-2007, 04-Jan-2006

Index on p16 (but only till page 669). List of tables on p26.

P4:
"DURATION OF TREATMENT: Vaccination at Day 1, Month 2, and Month 6 with 14 calendar days of clinical follow-up after administration of each dose. All subjects were to be followed for efficacy evaluation and persistence of antibody response through Month 48."

P363:
"This report is the final report for Future 1."

P9:
"The primary safety objective was to demonstrate that the qHPV vaccine was generally well tolerated. The 2 substudies, Protocol 011 and Protocol 012, evaluated the tolerability of the qHPV vaccine and its matching placebo during the vaccination phase of the study (i.e., through 4 weeks Postdose 3). Separate CSRs [clinical study reports] were written to summarize the findings of these substudies."

It is scientifically inappropriate to have a research objective that is to demonstrate that an intervention is well tolerated. This suggests that the result is already known before the research is carried out. In research, we say "to investigate if the intervention is well tolerated."

P6:

SUBJECT/PATIENT DISPOSITION:

	qHPV Vaccine	HPV 16 L1 VLP Vaccine	Placebo	Total
SCREENING FAILURES:				1008
RANDOMIZED:	2723	304	2732	5759

This was a pretty large, and therefore important, study that randomised 5455 subjects to qHPV vaccine or to vaccine adjuvant, erroneously called placebo. I have not paid attention to the 304 subjects randomised to monovalent vaccine, as this vaccine has not been marketed.

The study report is messy, and there are many errors. There are 117 tables. The first table that presents the "Number (%) of Subjects With New Medical History" by system organ class after day 1 is table 12-9 on p350 is, but it only includes events with an "Incidence ≥ 5% in One or More Vaccination Groups," which is not useful. The next table is about such events occurring after month 7. Next, follows 47 tables about other issues, e.g. about efficacy results, about which regions in the world the trial subjects came from, and secondary efficacy analyses, before there are any tables of all patients (incidence > 0%) with new medical

history. There are two tables about this, but they are in reverse order, with data after month 7 on p473, before the most relevant table with data after day 1 finally appears on p559, 209 pages after the first table about this that arbitrarily listed only conditions with an incidence of at least 5%.

I found errors in the index. For example, this entry in the index:

contrasts with the list of tables:

I searched on 12.2.7 in the report, which led to this text on p306:

"12.2.7 Listing of All Adverse Experiences by Subject/Patient
All clinical adverse experiences reported are listed in Section 14.4."

Next, I searched on 14.4, which turned out to be (p660):

"14.4 Narratives of Serious Adverse Experiences Reported in Infants of Vaccinated Subjects Who Were Potentially Exposed to Test Product."

This has very little to do with the "Listing of all adverse experiences by subject/patient" I was looking for. Infants are a subgroup of a subgroup, those females who became pregnant.

The design was very similar to that of other Merck studies. Vaccination at day 1, month 2, and month 6 with 14 calendar days of clinical follow-up after administration of each dose. All subjects were to be followed for efficacy evaluation and persistence of antibody response through month 48. However, after the primary analysis results became available, the Data and Safety Monitoring Board requested an acceleration of month 48 study visits to allow for vaccination of "placebo" subjects.

P5, 9 and 10 about safety:
"Subjects completed a vaccination report card (VRC) after each vaccination. Subjects were asked regarding new medical conditions at each visit … The primary safety objective was to demonstrate that the qHPV vaccine was generally well tolerated … This CSR [clinical study report] summarizes all serious clinical adverse experiences, including any deaths or any serious adverse experience determined by the study coordinator to be related to the study vaccine or a study procedure. In addition to reporting all serious adverse experiences, this CSR summarizes (1) new clinical adverse experiences reported after the Month 7 visit; (2) new medical conditions that occurred after the Month 7 visit … STATISTICAL PLANNING AND ANALYSIS … Safety: Listings of all serious clinical adverse experiences, including any deaths or any serious adverse experience determined to be related to the study vaccine or a study procedure were provided ... The table that follows presents a summary of clinical adverse experiences reported at any time during the study by vaccination group. All subjects who received an injection and had safety follow-up were included in the summary."

It seems that only deaths or serious adverse events that were "determined by the study coordinator to be related to the study vaccine or a study procedure" were reported, but we are also informed about "reporting all serious adverse experiences." All subjects who received an injection and had safety follow-up [my emphasis] were included in the summary" All serious adverse events must be followed up as per legislation. It is unclear whether Merck adhered to this principle. The text also seems to contradict the text on P82: "All subjects who received at least one dose of vaccine or placebo were followed for safety."

P10:
"The table that follows presents a summary of clinical adverse experiences reported at any time during the study by vaccination group."

It did not. The table that followed this text was about the benefits of the vaccine, as it defined the per-protocol efficacy population. The clinical adverse events summary came on p13:

Clinical Adverse Experience Summary
(Days 1 to 9999 Following Any Vaccination Visit)

	qHPV (N=2713)		HPV 16 L1 VLP Vaccine (N=304)		Placebo (N=2724)	
	n	(%)	n	(%)	n	(%)
Subjects in analysis population	2713		304		2724	
Subjects without follow-up	40		5		52	
Subjects with follow-up	2673		299		2672	
Number (%) of subjects:						
with no adverse experience	176	(6.6)	21	(7.0)	267	(10.0)
with one or more adverse experiences	2497	(93.4)	278	(93.0)	2405	(90.0)
injection-site adverse experiences	2353	(88.0)	250	(83.6)	2133	(79.8)
systemic adverse experiences	1746	(65.3)	211	(70.6)	1701	(63.7)
with vaccine-related† adverse experiences	2434	(91.1)	262	(87.6)	2286	(85.6)
injection-site adverse experiences	2353	(88.0)	250	(83.6)	2132	(79.8)
systemic adverse experiences	1162	(43.5)	140	(46.8)	1087	(40.7)

Subjects who were also enrolled in Protocol 011 received, in addition, a hepatitis B vaccine (recombinant) or "placebo" at day 1, month 2, and month 6. Those who got "placebo" were eligible to receive active hepatitis B vaccine at months 18, 19, and 24.

There is no explanation of why Merck did not use the same amount of adjuvant in the "placebo" group as in the vaccine group (420 µg vs 500 µg, see the table just below).

P7:
Hepatitis B Vaccine (Recombinant) or Placebo – Protocol 011

Clinical Material	Control Number	Formulation Number	Dosage	Package
Hepatitis B vaccine (Recombinant)	WP-K523	CV501 VAI002A001	10 mcg HBsAg with 500 mcg aluminum adjuvant/1.0 mL	1.2-mL single-dose vial
Placebo	WP-K523	PV501 VAI003P001	420 mcg aluminum adjuvant/1.0 mL	1.2-mL single-dose vial

P8:
Some of the patients also participated in protocol 012 comparing two lots:

Clinical Material	Control Number	Formulation Number	Dosage	Package
qHPV Vaccine (Lot 1)	WP-K085	V501 VAI020I001	20/40/40/20 mcg HPV 6/11/16/18 VLP with 225 mcg aluminum adjuvant/0.5 mL	0.75-mL single-dose vial
qHPV Vaccine (Lot 2)	WP-K085	V501 VAI020I002	20/40/40/20 mcg HPV 6/11/16/18 VLP with 225 mcg aluminum adjuvant/0.5 mL	0.75-mL single-dose vial
Placebo	WP-K085	PV501 VAI019A001	225 mcg aluminum adjuvant/0.5 mL	0.75-mL single-dose vial

Clinical Material	Control Number	Formulation Number	Dosage	Package
HPV 16 L1 VLP Vaccine	WP-K085	V501 VAI021C001	40 mcg HPV 16 with 225 mcg aluminum adjuvant/0.5 mL	0.75-mL single-dose vial

P15, conclusion:
"Administration of a 3-dose regimen of qHPV vaccine is generally well tolerated."

The wording is exactly the same as under objectives: "The primary safety objective was to demonstrate that the qHPV vaccine was generally well tolerated."

Merck's predefined conclusion about safety is not correct. According to the clinical adverse events summary (see just above), there were 75 more patients in the vaccine group than in control group with systemic vaccine-related adverse experiences, according to the investigator (P = 0.03, Fisher's exact test, my calculation). Merck's reports, also the published ones, emphasised whether the investigators consider the events vaccine related.

With a difference of 2.8% in systemic vaccine-related adverse experiences, the number needed to harm is only 36. This means that for every 36 subjects treated with the vaccine instead of the adjuvant, one subject will experience a systemic adverse event that would not have experienced an event on the adjuvant.

It is inappropriate to conclude that a vaccine is well tolerated, against the presented evidence, and not to inform the readers about a significant difference in systemic adverse events for a vaccine that is to be used in healthy people. Merck did not even test this difference statistically.

P88 exclusion criteria:
"Individuals with history of splenectomy, known immune disorders (e.g., systemic lupus erythematosus, rheumatoid arthritis), or receiving immunosuppressives …"

Why were females with known autoimmune disorders not allowed to participate in Merck's vaccine trials?

P95:
"Aluminum adjuvant was chosen as the appropriate control for the qHPV vaccine for the following reasons:

1. The inclusion of aluminum adjuvant in both vaccines and placebos preserved the blinding of the study because it allowed the vaccine and placebo to be visually indistinguishable; and

2. The safety profile of the Sponsor's aluminum adjuvant is well characterized. On the other hand, the safety profile of the HPV 6, 11, 16, and 18 L1 VLPs required further evaluation in humans. By using placebo that contained a dose of aluminum adjuvant that was identical to the dose included in the qHPV vaccine, it was possible to assess the safety profile attributable to the HPV 6, 11, 16, and 18 L1 VLP components of the vaccine."

These explanations, which appear also in Merck's other study reports, are unsupported, for at least five reasons.

First, the argument that the adjuvant was needed to preserve the blinding is false. The vaccine and the placebo could have been made visually indistinguishable in other ways that did not involve the unnecessary addition of a harmful substance to the placebo formulation. Furthermore, there are other ways to blind studies than to make the fluid in the injections look identical, e.g. by wrapping something around the syringe. Finally, blinding when reading pathology reports to establish whether there were cancerous lesions could have been obtained without adding adjuvant to the placebo; in fact, blinding could have been assured even without giving any injection to the control group.

Second, Merck's argument that, for blinding reasons, the so-called placebo "contained a dose of aluminum adjuvant that was identical to the dose included in the qHPV vaccine" is also spurious, as Merck did not adhere to this principle when it blinded its hepatitis B vaccine where the amount of adjuvant was 420 µg vs 500 µg, respectively (see above).

Third, my research group has investigated whether the safety of Merck's adjuvant, amorphous aluminium hydroxyphosphate sulfate ($AlHO_9PS^{-3}$or just AAHS), has ever been tested in comparison with an inert substance in humans. We have been unable to find any evidence of this. Merck's adjuvant has a confidential formula; its properties are variable from batch to batch and even within batches.[17] [18] *The harms caused by the adjuvant therefore likely to vary.*

Fourth, it is untrue that "The safety profile of Merck's aluminum adjuvant is well characterized." Since the adjuvant varies from batch to batch, it is impossible to support this claim. Tom Jefferson from my research group pointed this out in a letter to the European Ombudsman on 21 November 2016 where he complained that the batch numbers had been redacted in the clinical study reports we had received from the European Medicines Agency (EMA) for our research on the HPV vaccines. It makes no sense to redact the batch numbers unless Merck has something to hide. In his letter, Jefferson explains:

"The vaccines use a variety of adjuvants, substances which are added to the antigens to stimulate immunity. Adjuvants are not regulated and the stand alone properties of some of them are at present unclear to us. The manufacturers report in their patent applications that the properties could vary from batch to batch and within batch (see quote in footnote). This may mean that effects of the vaccines on humans vary accordingly. Effects of specific vaccine batches are sometimes investigated (for example by Lareb in Holland (http://databankws.lareb.nl/Downloads/Lareb_rapport_HPV_dec15_03.pdf - see pdf page 14) or even withdrawn following a serious adverse event: (http://www.sehd.scot.nhs.uk/publications/DC20090930hpv3.pdf,

[17] Jørgensen L, Gøtzsche PC, Jefferson T. The Cochrane HPV vaccine review was incomplete and ignored important evidence of bias: Response to the Cochrane editors. 2018; 17 September. https://ebm.bmj.com/content/early/2018/07/27/bmjebm-2018-111012.responses#the-cochrane-hpvvaccine-review-was-incomplete-and-ignored-important-evidence-of-bias-response-to-the-cochraneeditors.

[18] Thiriot DS, Ahl PL, Cannon J, et al. Method for preparation of aluminium hydroxyphosphate adjuvant. Patent WO2013078102A1. 2013; 30 May. https://patents.google.com/patent/WO2013078102A1/en.

http://www.gardasilhpv.com/2009/09/schoolgirls-death-aftercervarix-hpv.html). WHO recognises that "batch information is of crucial importance" (http://www.who.int/vaccine_safety/initiative/tools/CIOMS_report_WG_vaccine.pdf) (pdf page 34) specifically for these reasons. It is also mandatory for vaccinators to record batch used in the immunisation. In the absence of batch identifiers, effects cannot be assessed."

Fifth, adjuvants are not "safe," and they cannot possibly be safe, as they are strongly immunogenic substances. In its literature searches, the European Medicines Agency (EMA) revealed that "POTS [postural orthostatic tachycardia syndrome] … frequently start after viral illness" and that one study had found that "up to 50% of cases have antecedent of viral illness."[19] EMA's literature searches also showed that chronic fatigue syndrome has been linked to other vaccines and vaccine adjuvants; that some of the POTS patients might have small-fibre neuropathy; and that there were case reports of CRPS (complex regional pain syndrome) after other vaccines.[20] Since adjuvants are strongly immunogenic, an otherwise benign viral illness could lead to serious harm in people with certain tissue types if they have received an injection with an adjuvant in a "placebo" group.

A patent application shows that Merck's adjuvant has a similar harm profile as the vaccine,[21] and Merck's own trials also show that its adjuvant is not safe, e.g. when Merck compared Gardasil 9 with Gardasil in 14,215 females, there were far more serious local reactions with the 9-valent vaccine (e.g. 272 vs 109 cases of swelling).[22] A supplementary appendix in the trial publication revealed that there were also more serious systemic adverse events in females receiving the 9-valent vaccine than in those receiving the 4-valent vaccine (3.3% vs. 2.6%, p = 0.01). Thus, the number needed to harm was only 141 (= 1/(3.3%-2.6%)), and it would have been even smaller if the control group had not received Gardasil or adjuvant, but saline or nothing at all. Gardasil 9 contains 500 µg of the adjuvant whereas Gardasil 4 contains only 225 µg. As it also contains four more antigens, this could also contribute to the increased level of vaccine harms.

P96:
"The clinical, data management and statistics personnel at the Sponsor remained blinded to individual vaccination allocation through the completion of data review for this fixed case analysis."

What happens in clinical trials are far from ideal and there are always many ambiguities, uncertainties and unclear uses of language in the case report forms. Errors are also made. It is therefore essential that data review is blinded, which Merck stated it was. However, such blinding needs to extend far beyond the data review process. In 1996, I argued in the membership journal of the US Society for Clinical Trials – using examples from my own randomised trials - why it is essential that that data analysis and the writing of reports are also blinded.[23]I gave a talk about this at the Society's annual meeting in Houston in 1994 for a large audience that included many industry representatives. As ambiguities also arise after the initial data review, additional blinding is needed to protect against biased decisions. In none of Merck's HPV vaccine reports are there any descriptions of such precautions.

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[19] Benarroch EE. Postural tachycardia syndrome: a heterogeneous and multifactorial disorder. Mayo Clin Proc 2012;87:1214-25.
[20] Gøtzsche PC. Vaccines: truth, lies, and controversy. New York: Skyhorse; 2021.
[21] Thiriot DS, Ahl PL, Cannon J, et al. Method for preparation of aluminium hydroxyphosphate adjuvant. Patent WO2013078102A1. 2013; 30 May.
https://patents.google.com/patent/WO2013078102A1/en.
[22] Joura EA, Giuliano AR, Iversen OE, et al. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. N Engl J Med 2015;372:711–23.
[23] Gøtzsche PC. Blinding during data analysis and writing of manuscripts. Controlled Clin Trials 1996;17:285-90.

When my research group examined a cohort of 44 industry-initiated trials, we found out that, according to the protocols, the sponsor had access to accumulating data during 16 trials, e.g. through interim analyses and participation in data and safety monitoring committees.[24] Such access was disclosed in only one corresponding trial article. These 44 trials were approved in 1994-1995 by Danish research ethics committees and were typical for industry trials, as 43 (98%) had multinational pharmaceutical firms as sponsors.

P127:
"Primary Safety and Tolerability Parameters. The important variables of interest for safety/tolerability were the occurrence of severe injection-site adverse experiences and the incidence of any vaccine-related serious adverse experiences."

It is scientifically inappropriate that the important safety measure is vaccine-related serious adverse experiences.

First, it is subjective to decide if an adverse experience is vaccine related.

Second, it is difficult to make this decision when there is no placebo and when the adjuvant in the control group can cause similar harms as the vaccine.

Third, those making these decisions may have conflicts of interest with Merck and other vaccine manufacturers.[25] This may influence their judgments, as suggested by Merck's trial that compared Gardasil 9 with Gardasil in 14,215 subjects. In Merck's publication of this trial in New England Journal of Medicine,[26] there were 416 serious adverse events, but only 4 of these (1%) were judged to be vaccine related by the trial authors.

Fourth, for a drug to be given prophylactically to healthy girls at a certain age of whom only a tiny minority will benefit as it is rare to develop cervical cancer and as screening is highly effective in preventing this, not only serious adverse events (e.g. those leading to death or hospital admission, see definition of this concept on p9 above), but all adverse events are important.

P128:
... Follow-up at Months 2, 3, 6, and 7 after the first injection included an interview to assess general safety. The interview solicited broadly for any serious adverse experiences that the subject may have encountered."

This means that serious adverse experiences were collected up to month 7 but apparently not to month 48. But we do not know if all such experiences are in the report because the study coordinators could veto them. This is made explicit in the study report for the Future 2 trial where such people are mentioned (see p8 in that report which states):

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[24] Gøtzsche PC, Hróbjartsson A, Johansen HK, Haahr MT, Altman DG, Chan A-W. Constraints on publication rights in industry-initiated clinical trials. JAMA 2006;295:1645-6.
[25] Topol EJ. Failing the public health - rofecoxib, Merck, and the FDA. N Engl J Med 2004;351:1707-9; Testimony of David J. Graham, MD, MPH, November 18, 2004, accessible at https://www.finance.senate.gov/imo/media/doc/111804dgtest.pdf; Kesselheim AS, Avorn J. The role of litigation in defining drug risks. JAMA 2007;297:308-11.
[26] Joura EA, Giuliano AR, Iversen OE, et al. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. N Engl J Med 2015;372:711–23.

"This CSR [clinical study report] focuses on summarizing all serious clinical adverse experiences, including any deaths or any serious adverse experience determined by the study coordinator to be related to the study vaccine or a study procedure."

The use of unclear language, "focuses on summarizing" and that, furthermore, the serious adverse events needed to be "determined by the study coordinator to be related to the study vaccine," and, in addition, having a main focus on only the three two-week periods after each vaccination, leaves the door wide open to biased reporting.

The interviews at months 2, 3, 6, and 7 to assess general safety "solicited broadly for any serious adverse experiences that the subject may have encountered" (p128). I have not seen any instructions for these interviews, either for this trial, nor for any other of Merck's trials. This is a serious limitation of Merck's trials. What gets detected is highly dependent on how such an interview is done. Important harms can be overlooked if the investigators do not use an open question such as, "Have you noticed anything unusual since your last visit?"

p275-296:
Table 12-2. Listing of Subjects With Serious Clinical Adverse Experiences (Entire Study Period):

Study Number	AN	Gender	Race	Age at First Vaccination	Relative Day from Start of Trial	Dose Number (Vaccine Given)	Relative Day of Onset Postdose	Adverse Experience	Duration of Adverse Experience	Intensity /Size [+]	Vaccine Relationship	Action Taken	Outcome
qHPV													
011001	24046	F	Hispa	19 yr	1	1 (HPV rL1 6 11 16 18 VLP vaccine (yeast))	1	Overdose	1 day	mild	def not	none	recovered
					1	1 (placebo (concomitant-vaccine matched))	1						
011013	20512	F	black	19 yr	295	1 (HPV rL1 6 11 16 18 VLP vaccine (yeast))	295	Hypotension	2 hr	mod	prob not	none	recovered
					295	1 (hepatitis B virus vaccine (unspecified))	295						
	25212	F	white	19 yr	555	3 (HPV rL1 6 11 16 18 VLP vaccine (yeast))	373	Head injury	1 day	severe	def not	discont follow-up only	fatal
					555	3 (hepatitis B virus vaccine (unspecified))	373						

P297:
"12.2.4.2 Deaths
A total of 5 deaths have been reported in Protocol 013 as of 31-Jul-2007. A total of 2 deaths have been reported in the group that received qHPV vaccine and 3 deaths have been reported in the group that received placebo. There were no new deaths reported in Protocol 013 since the submission of the First Supplemental Clinical Report. None of the deaths were considered by the investigator to be vaccine related. A listing of the subjects who died can be found in Table 12-3."

This is not correct. Only 4 deaths are shown in the table; one on placebo is missing.

P349:
"New medical conditions were not considered adverse experiences when their onset occurred outside the safety follow-up period (15 days following any study vaccination) and/or were not considered by the study investigators to be vaccine/placebo related."

Clinical trials that adverse experiences that could be harms of drugs are not considered adverse events but "new medical conditions" if they do not occur within an arbitrary very short time frame defined by the sponsor or if the study investigators do not consider them drug related is concerning. This means that even if they occurred within the much too narrow interval of two weeks for collection of safety data after each vaccination, they might be called new medical conditions if the investigators so pleased.

Merck's messages and instructions are inconsistent.

Even though symptoms of POTS may appear early, it can take years before the diagnosis is objectively established by a tilt test.[27]

According to an expert assessment report for Gardasil 9 written on behalf of the European Medicines Agency (EMA)[28] *the rapporteurs were concerned that Sanofi (Merck) had avoided identifying possible cases of serious harms of the vaccine. Their concerns were shared by EMA's own trial inspectors*[29] *who criticised that adverse events were only reported for 14 days after each vaccination; that any new symptoms at other times were reported as "new medical events" without medical assessments or final outcomes being recorded; and that the reporting of serious adverse events was not required during the full course of the trial even though systemic side effects could appear long after the vaccinations were given (see Dunder in the footnote). The inspectors also criticised that three people had been diagnosed with POTS in the clinical safety database after receipt of Gardasil 9 but that these were not reported as adverse events; that a case of POTS after Gardasil was called "new medical history" instead of an adverse event; that hospitalisation for severe dizziness was not reported as a serious adverse event (which is against the rules); and that for another person the term "dysautonomia" was not included on the list of events.*

In 2014, the Danish drug regulator instructed Sanofi Pasteur MSD on how to search on specific symptoms in its database including dizziness, palpitations, rapid heart rate, tremor, fatigue and fainting. Despite these clear instructions, Sanofi only searched on postural dizziness, orthostatic intolerance and palpitations <u>and</u> dizziness. The Danish authorities discovered this because only 3 of 26 registered Danish reports of POTS showed up in Sanofi's searches.[30]

P473-558:
Table 14-43. Number (%) of Subjects With New Medical History (Incidence >0% in One or More Vaccination Groups) by System Organ Class (>Month 7).

These 86 pages of tables are not particularly useful, as it is obscure and arbitrary when an event is an adverse event or "new medical history," and as it is a subgroup of all "medical history" events.

P559-659:
Table 14-44. Number (%) of Subjects With New Medical History (Incidence >0% in One or More Vaccination Groups) by System Organ Class (>Day 1).
There were 101 pages.

The events that occurred first, after day 1 (the full dataset), are reported last, after those that occurred after month 7.

[27] Blitshteyn S, Brinth L, Hendrickson JE, Martinez-Lavin M. Autonomic dysfunction and HPV immunization: an overview. Immunol Res 2018;66:744-54.
[28] Dunder K, Mueller-Berghaus J. Rapporteurs' Day 150 Joint Response Assessment Report. Gardasil 9. 2014; 23 Nov.
[29] Joelving F. What the Gardasil testing may have missed. Slate 2017; 17 Dec.

[30] Weber C, Andersen S. Firma bag HPV-vaccinen underdrev omfanget af alvorlige bivirkninger. Berlingske 2015; 26 Oct.

P617:
There were somewhat more patients with nervous system disorders in the vaccine group than in the control group, 363 vs 310. All types of headaches: 292 vs 271, and all syncopes incl. presyncope: 26 vs 12 (but one patient could appear in more than one category).

P356:
Number of subjects with new medical history (incidence >0% in one or more vaccination groups) by system organ class (>day 1) potentially consistent with autoimmune phenomena: 74 vs 60.

Table 12-11

Number (%) of Subjects With New Medical History
(Incidence >0% in One or More Vaccination Groups) by System Organ Class
(>Day 1) Potentially Consistent With Autoimmune Phenomena

	qHPV (N= 2713)		HPV 16 L1 VLP Vaccine (N= 304)		Placebo (N= 2724)	
	n	(%)	n	(%)	n	(%)
Subjects in analysis population	2713		304		2724	
Subjects with one or more new Medical History	74	(2.7)	12	(3.9)	60	(2.2)
Subjects with no new secondary diagnosis	2639	(97.3)	292	(96.1)	2664	(97.8)
Blood And Lymphatic System Disorders	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.0)**
Idiopathic Thrombocytopenic Purpura	0	(0.0)	0	(0.0)	1	(0.0)

P694:
Protocol amendments are listed in an index but as for Future 2, only 1-5 and 10. Amendments 6-9 are not in this list, and there is no explanation why not:

P709:

NA = Not Applicable.

V501 P013 V1 CSR

Clinical Study Report Date: 04-Nov-2005. Two years earlier than the final report.

Index on p3. List of tables on p18, list of appendices on p778.

P3318ff:
Same set of ambiguous and very short forms for registering serious and non-serious adverse events as for the Future 2 trial (see p831-2 below, under this trial).

V501 P011 CSR

Study report date: 22 September 2005, two years earlier than the final report.

Index on p3 for first few hundred pages. Index on p457 for appendices, incl. three protocol amendments (p467).

There is a table of systemic adverse events on p217.

P31:
The objectives of substudy 011 were:
"Primary Immunogenicity Objective: To demonstrate that the concomitant administration of quadrivalent HPV (Types 6,11,16,18) L1 VLP vaccine and hepatitis B vaccine (recombinant) does not interfere with the immune response to either vaccine. Primary Safety Objective: To demonstrate that quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine is generally well tolerated when administered alone or concomitantly with hepatitis B vaccine (recombinant)."

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine +		Placebo (HPV Vaccine Matched)		
	Hepatitis B Vaccine (Recombinant)	Placebo (Hepatitis B Vaccine Matched)	Hepatitis B Vaccine (Recombinant)	Placebo (Hepatitis B Vaccine Matched)	Total
SCREENING FAILURES:					649
RANDOMIZED:	468	471	467	471	1877

This report is not particularly interesting because the patients are included in the main report. As noted above (under P7:), it is odd and unexplained why the amount of adjuvant was not the same in active hepatitis B vaccine as in the control. In the main report, these doses were 420 µg vs 500 µg, whereas they are now 402 µg vs 500 µg, which is probably a typing error:

Clinical Material	Control Number	Formulation Number	Dosage	Package
Hepatitis B Vaccine (Recombinant)	WP-K523	CV501 VAI002A001	10 mcg HBsAg with 500 mcg aluminum adjuvant/1.0 mL	1.2-mL single dose vial
Placebo	WP-K523	PV501 VAI003P001	402 mcg aluminum adjuvant/1.0 mL	1.2-mL single dose vial

P194:
"The proportion of subjects who reported injection-site adverse experiences appeared to be lower in the 2 quadrivalent HPV vaccine matched placebo groups than in the 2 quadrivalent HPV (Types 6,11,16,18) L1 VLP vaccine groups."

The tables have several errors in them:

P195:

Clinical Adverse Experience Summary
(Days 1 to 15 Following Any Vaccination Visit)

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine + Hepatitis B Vaccine (Recombinant) (N=466)		Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine + Placebo (Hepatitis B Vaccine Matched) (N=468)		Placebo (HPV Vaccine Matched) + Hepatitis B Vaccine (Recombinant) (N=467)		Placebo (HPV Vaccine Matched) + Placebo (Hepatitis B Vaccine Matched) (N=468)	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in analysis population	466		468		467		468	
Subjects without follow-up	8		5		9		4	
Subjects with follow-up	458		463		458		464	
Number (%) of subjects:								
with no adverse experience	31	(6.8)	40	(8.6)	52	(11.4)	45	(9.7)
with one or more adverse experiences	427	(93.2)	423	(91.4)	406	(88.6)	419	(90.3)
injection-site adverse experiences	411	(89.7)	401	(86.6)	376	(82.1)	381	(82.1)
systemic adverse experiences	257	(56.1)	282	(60.9)	279	(60.9)	269	(58.0)
with vaccine-related‡ adverse experiences	424	(92.6)	415	(89.6)	389	(84.9)	405	(87.3)
injection-site adverse experiences	411	(89.7)	401	(86.6)	376	(82.1)	381	(82.1)
systemic adverse experiences	184	(40.2)	201	(43.4)	176	(38.4)	176	(37.9)

This table agrees with the text on p270: "When combining the 2 groups receiving active quadrivalent HPV (Types 6,11,16 18) L1 VLP vaccine and comparing with the placebo group, quadrivalent HPV (Types 6,11,16,18) L1 VLP vaccine recipients experienced a higher rate of injection-site adverse experiences compared with placebo recipients" (812 vs 757).

However, the text on p271 says that, "There was a statistically significant increase in the incidence of severe injection-site adverse experiences among quadrivalent HPV (Types 6,11,16,18) L1 VLP vaccine recipients compared with placebo recipients." This is not what the table on p212 shows:

Number (%) of Subjects Who Reported Injection-Site Adverse Experiences by Maximum Intensity Rating
(Days 1 to 5 Following Any Vaccination Visit)

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine Injection Site		Hepatitis B Vaccine (Recombinant) Injection Site	
	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine + Hepatitis B Vaccine (Recombinant) (N=466)	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine + Placebo (Hepatitis B Vaccine Matched) (N=468)	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine + Hepatitis B Vaccine (Recombinant) (N=466)	Placebo (HPV Vaccine Matched) + Hepatitis B Vaccine (Recombinant) (N=467)
	n (%)	n (%)	n (%)	n (%)
Number of subjects with follow-up	458	463	458	458
Number of subjects without injection-site adverse experiences	63	78	83	99
Number (%) of subjects with injection-site adverse experiences	395 (86.2)	385 (83.2)	375 (81.9)	359 (78.4)
Number (%) of subjects by maximum intensity rating of injection-site adverse experience				
Mild	228 (49.8)	204 (44.1)	243 (53.1)	233 (50.9)
Moderate	143 (31.2)	153 (33.0)	115 (25.1)	106 (23.1)
Severe	4 (5.2)	27 (5.8)	17 (3.7)	20 (4.4)
Unknown	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)

It seems that at least two column headings are wrong, as there cannot be three groups with active HPV vaccine and only one group with a "placebo" hepatitis B vaccine. The number 4 in the first column is also wrong, as 5.2% of 466 is 24, not 4. Thus, there seems to be 51 vs 37 with severe injection site reactions.

On p209, there is another table, which shows statistically significant differences, but not for active HPV vaccine against “placebo” HPV vaccine. This is when all three groups that contain one or both active vaccines (against HPV and hepatitis) are compared with a double “placebo” group:

Comparison of Vaccination Groups With Respect to the Number (%) of Subjects Who Reported Specific Injection-Site Adverse Experiences With ≥1% Incidence in One or More Vaccination Groups (Days 1 to 5 Following Any Vaccination Visit) (Quadrivalent HPV [Types 6,11,16,18] L1 VLP Vaccine Group Versus Placebo [HPV Vaccine Matched] Group)

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine + Hepatitis B Vaccine (Recombinant) and Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine + Placebo (Hepatitis B Vaccine Matched) (N=934)		Placebo (HPV Vaccine Matched) + Placebo (Hepatitis B Vaccine Matched) (N=468)		Risk Difference (Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine - Placebo)	95% Confidence Interval	p-Value †
	n	(%)	n	(%)			
Number of subjects without follow-up	13		4				
Number (%) of subjects with follow-up	921		464				
Number(%) of subjects with one or more injection-site adverse experiences	780	(84.7)	350	(75.4)	9.3	(4.8 , 13.9)	
Injection Site Bruising	8	(0.9)	4	(0.9)	0.0	(-1.4 , 1.0)	
Injection Site Burning	11	(1.2)	0	(0.0)	1.2	(0.4 , 2.1)	
Injection Site Discomfort	14	(1.5)	5	(1.1)	0.4	(-1.1 , 1.7)	
Injection Site Erythema	164	(17.8)	52	(11.2)	6.6	(2.7 , 10.3)	0.001*
Injection Site Haemorrhage	13	(1.4)	3	(0.6)	0.8	(-0.6 , 1.9)	
Injection Site Pain	768	(83.4)	349	(75.2)	8.2	(3.7 , 12.9)	<0.001*
Injection Site Pruritus	48	(5.2)	16	(3.4)	1.8	(-0.7 , 3.9)	
Injection Site Swelling	212	(23.0)	82	(17.7)	5.3	(0.8 , 9.7)	0.022*

V501 P012

Study report was from 27 September 2005, two years before the final report.

Index on p3 for first few hundred pages. Index on p373 for appendices, incl. three protocol amendments (p381).

There is a table of systemic adverse events on p176.

P27:
The objectives of substudy 012 were:
“Primary Immunogenicity Objective: To demonstrate that the Final Manufacturing Process (FMP) results in quadrivalent HPV (Types 6,11,16,18) L1 VLP vaccine that, when given in a 3-dose regimen, induces similar anti-HPV 16 responses to those induced by the Pilot Manufacturing Material (PMM) HPV 16 L1 VLP vaccine 4 weeks Postdose 3 (immunogenicity bridge to Protocol 005: Study of Pilot Manufacturing Lot of HPV 16 Virus-Like Particle (VLP) Vaccine in the Prevention of HPV 16 Infection in 16- to 23-year-old Females). Primary Safety Objective: To demonstrate that quadrivalent HPV (Types 6,11,16,18) L1 VLP vaccine is generally well tolerated.”

	FMP Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine	PMM Monovalent HPV 16 L1 VLP Vaccine	Placebo	Total
SCREENING FAILURES				359
RANDOMIZED:	1784	304	1794	3882

This report is not particularly interesting because the patients are included in the main report.

There were two different lots, and in this case, the amount of adjuvant was the same in all the groups:

FMP Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine or Placebo

Clinical Material	Control Number	Formulation Number	Dosage	Package
Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (Lot 1)	WP-K085	V501 VAI020I001	20/40/40/20 mcg HPV 6/11/16/18 VLP with 225 mcg aluminum adjuvant/ 0.5 mL	0.75-mL single dose vial
Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (Lot 2)	WP-K085	V501 VAI020I002	20/40/40/20 mcg HPV 6/11/16/18 VLP with 225 mcg aluminum adjuvant/ 0.5 mL	0.75-mL single dose vial
Placebo	WP-K085	PV501 VAI019A001	225 mcg aluminum adjuvant/0.5 mL	0.75-mL single dose vial

PMM Monovalent HPV 16 L1 VLP vaccine

Clinical Material	Control Number	Formulation Number	Dosage	Package
HPV 16 L1 VLP Vaccine	WP-K085	V501 VAI021C001	40 mcg HPV 16 VLP with 225 mcg aluminum adjuvant/0.5 mL	0.75-mL single dose vial

P171:

Number (%) of Subjects Who Reported Injection-Site Adverse Experiences by Maximum Intensity Rating (Days 1 to 5 Following Any Vaccination Visit)

	FMP Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=1779)		PMM Monovalent HPV 16 L1 VLP Vaccine (N=304)		Placebo (N=1789)	
	n	(%)	n	(%)	n	(%)
Number of subjects with follow-up	1752		299		1750	
Number of subjects without injection-site adverse experiences	213		49		375	
Number (%) of subjects with injection-site adverse experiences	1539	(87.8)	250	(83.6)	1375	(78.6)
Number (%) of subjects by maximum intensity rating of injection-site adverse experience						
Mild	966	(55.1)	164	(54.8)	1015	(58.0)
Moderate	488	(27.9)	72	(24.1)	321	(18.3)
Severe	85	(4.9)	13	(4.3)	37	(2.1)
Unknown	0	(0.0)	1	(0.3)	2	(0.1)

This substudy confirmed that there are more moderate or severe injection site adverse events in the vaccine group than in the control group: “Most of the maximum intensity ratings were mild or moderate. The proportions of subjects with severe and moderate injection-site adverse experiences were smaller in the placebo group than in the 2 HPV vaccine groups” (p170).

As these differences were not tested statistically, I did that: 573/1779 vs 358/1789 ($p = 2 \times 10^{-16}$, Fisher’s exact test, my calculation). This is an extremely small p-value.

P186:

Number (%) of Subjects Who Reported Systemic Clinical Adverse Experiences by Maximum Intensity Rating (Days 1 to 15 Following Any Vaccination Visit)

	FMP Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=1779)		PMM Monovalent HPV 16 L1 VLP Vaccine (N=304)		Placebo (N=1789)	
	n	(%)	n	(%)	n	(%)
Number of subjects with follow-up	1752		299		1750	
Number of subjects without systemic adverse experiences	558		88		611	
Number (%) of subjects with systemic adverse experiences	1194	(68.2)	211	(70.6)	1139	(65.1)
Number (%) of subjects by maximum intensity rating of systemic adverse experience						
Mild	336	(19.2)	73	(24.4)	366	(20.9)
Moderate	577	(32.9)	88	(29.4)	503	(28.7)
Severe	251	(14.3)	45	(15.1)	246	(14.1)
Unknown	30	(1.7)	5	(1.7)	24	(1.4)

The text on p185 stated that, “Most of the maximum intensity ratings were mild or moderate. Approximately 14% of subjects experienced severe systemic adverse experiences. The proportion of subjects with each maximum systemic clinical adverse experience intensity rating appeared to be comparable among the 3 vaccination groups.”

This is incorrect. There were many more patients with moderate or severe systemic adverse events in the vaccine group than in the control group: 828/1779 vs 749/1789 (p = 0.005, my calculation).

Future 2, study P015

With 12,167 patients, this trial is the biggest one of Gardasil. The study started six months after Future 1. Future 2 and Future 3 were designed in the same way as Future 1. The science and its reporting were problematic; there were unexplained inconsistencies; and some statements were contradicted elsewhere in the reports.

V501 P015 CSR_protocol P005-10 pg 1917

Study Initiation Date (FPI): 24-Jun-2002
Study Completion Date (LPO): 31-Jul-2007
Clinical Study Report Date: 13-Nov-2007
Interim CSRs for the same Protocol: 27-Sep-2005, 01-Nov-2005, 29-Mar-2007.

Even though it is the final report, it is incomplete, which means that earlier reports must be read as well. There are very few patient narratives of serious adverse events; the majority are to be found in an earlier report. This makes it difficult and laborious for drug agencies and others to find out what the harms are of the vaccine.

P4:
“DURATION OF TREATMENT: Vaccination at Day 1, Month 2, and Month 6 with 14 calendar days of clinical follow-up after administration of each dose. All subjects were followed for efficacy evaluation through Month 48.”

P3902:
“Vaccination of Placebo Subjects. When each subject completes all study visits, she is eligible to receive a full course of GARDASIL™ if she was randomized to the placebo group at enrollment.”

It is not clear what is meant by all study visits, but other text shows that this vaccination took place not after month 6, but after month 48.

P227:
“A summary of safety data collected for Day 1 through Month 7 vaccination periods was presented in the CSR for Protocol 015 submitted with the Original Application. Subsequent safety data was collected from the CSR through 15-Jun-06 and was summarized in the First Supplemental BLA Clinical Report. This report includes complete summaries for all new fatal and nonfatal serious adverse experiences and discontinuations due to an adverse experience not reported in the Protocol 015 CSR and First Supplemental BLA Clinical Report for safety data and new medical history collected through 31-Jul-2007. In addition, the complete summaries for pregnancies and lactation outcomes are provided in this section.”

P80:
“Aluminum adjuvant was chosen as the appropriate control for the qHPV vaccine for the following reasons:
1. The inclusion of aluminum adjuvant in both vaccine and placebo preserved the blinding of the study because it allowed the vaccine and placebo to be visually indistinguishable; and
2. The safety profile of Merck’s aluminum adjuvant is well characterized. On the other hand, the safety profile of the HPV 6, 11, 16, and 18 L1 VLPs required further evaluation in humans. By using placebo that contained a dose of aluminum adjuvant that was identical to the dose included in the qHPV vaccine, it was possible to assess the safety profile attributable to the HPV 6, 11, 16, and 18 L1 VLP component of the vaccine.”

Same text as for Future 1. See under Future 1 above, why Merck’s explanations are incorrect, for at least five reasons.

P732-3:
“The vaccine is provided by the SPONSOR in single-dose vials containing a volume of 0.75 mL. The vaccine will be administered as a 0.5-mL dose. Each 0.5-mL dose contains 225 µg of aluminum as amorphous aluminum hydroxyphosphate sulfate (Merck Aluminum Adjuvant) ... To provide an appropriate control for the Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Vaccine, the placebo used in this study will be Merck standard aluminum diluent (225 µg alum) in normal saline, USP (NaCl 0.9%).”

There are similar descriptions in the final reports for Future 1 (p1845 in the main report) and Future 3 (p4 in V501 P019 V1 CSR) that explains that what Merck calls placebo is Merck’s standard aluminum diluent that is also used in the HPV vaccine.

The fact that Merck calls a strongly immunogenic adjuvant placebo is misleading. Furthermore, by giving readers the impression that the “placebo” just contained a “diluent,” Merck created a false impression that the vaccine has adverse effects similar to a placebo.

Merck's misleading communications on this issue are apparent both in Merck's clinical study reports, its informed consent forms and in corresponding journal publications,[31] [32] [33] which used the term placebo although, even in Merck's own documents, the definition of placebo is: "A placebo is made to look exactly like a real drug but is made of an inactive substance, such as a starch or sugar."[34]

The Cochrane review of the HPV vaccines also erroneously claimed placebo had been used based on Merck's misrepresentations.[35]

EMA also claimed that Merck's trials of Gardasil were placebo-controlled.[36] My research group complained to the European Ombudsman in October 2016 about EMA's handling of the issue of suspected serious harms of the HPV vaccines and in the ensuing correspondence, EMA Executive Director Guido Rasi explained to the Ombudsman that, "all studies submitted for the marketing authorisation application for Gardasil were placebo controlled."[37] EMA's official report also gave this impression and mentions "placebo cohorts" for the Gardasil trials.[38]

The WHO has stated that using adjuvant or another vaccine as comparator instead of placebo makes it difficult to assess the harms of a vaccine, and that placebo can be used in trials of vaccines against diseases for which there are no existing vaccines.[39] The HPV vaccines and their adjuvants[40] have similar harm profiles, the manufacturers – and GlaxoSmithKline also used other vaccines as comparators in their Cervarix trials and not a placebo. To say they are safe based on this methodology is like saying that cigarettes and cigars must be safe because they have similar harm profiles.

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[31] Jørgensen L, Gøtzsche PC, Jefferson T. Benefits and harms of the human papillomavirus (HPV) vaccines: systematic review with meta-analyses of trial data from clinical study reports. Syst Rev 2020;9:43.

[32] FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med 2007;356:1915-27.

[33] Garland SM, Hernandez-Avila M, Wheeler CM, et al. Quadrivalent Vaccine against Human Papillomavirus to Prevent Anogenital Diseases. N Engl J Med 2007;356:1928-43.

[34] Merck: Placebos. https://www.merckmanuals.com/home/drugs/overview-of-drugs/placebos.

[35] Jørgensen L, Gøtzsche PC, Jefferson T. The Cochrane HPV vaccine review was incomplete and ignored important evidence of bias: Response to the Cochrane editors. 2018; 17 September. https://ebm.bmj.com/content/early/2018/07/27/bmjebm-2018-111012.responses#the-cochrane-hpvvaccine-review-was-incomplete-and-ignored-important-evidence-of-bias-response-to-the-cochraneeditors.

[36] Gøtzsche PC. Vaccines: truth, lies, and controversy. New York: Skyhorse; 2021.

[37] Gøtzsche PC, Jørgensen KJ, Jefferson T, et al. Our comment on the decision by the European Ombudsman about our complaint over maladministration at the European Medicines Agency related to safety of the HPV vaccines. 2017; 2 Nov. http://www.deadlymedicines.dk/wp-content/uploads/2019/02/1.-2017-11-02-Our-assessment-on-the-Ombudsmans-decision.pdf.

[38] European Medicines Agency. Assessment report. Review under Article 20 of Regulation (EC) No 726/2004. Human papilloma virus (HPV) vaccines. 2015; 11 Nov. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/HPV_vaccines_20/Opinion_provided_by_Committee_for_Medicinal_Products_for_Human_Use/WC500197129.pdf.

[39] Expert consultation on the use of placebos in vaccine trials. WHO 2013. https://apps.who.int/iris/bitstream/handle/10665/94056/9789241506250_eng.pdf?sequence=1.

[40] Thiriot DS, Ahl PL, Cannon J, et al. Method for preparation of aluminium hydroxyphosphate adjuvant. Patent WO2013078102A1. 2013; 30 May. https://patents.google.com/patent/WO2013078102A1/en.

Problematic methods for collecting and reporting adverse events

P8:
"Safety: The primary safety objective was to demonstrate that the qHPV vaccine was generally well tolerated."

*This is not an appropriate research objective; it is the same in the Future 1 and 3 trials. In research, the objective should be "to **investigate if** the vaccine is well tolerated."*

I have studied a total of 43,211 pages describing the three Future trials, which corresponds to about 200 medium-sized books.

The role of study coordinators

P8:
"This CSR [clinical study report] focuses on summarizing all serious clinical adverse experiences, including any deaths or any serious adverse experience determined by the study coordinator to be related to the study vaccine or a study procedure."

This is the same text as in the Future 1 trial report (see above where I explain in detail what is wrong with this).

It is unacceptable to report only those serious events that a study coordinator decides are vaccine related, and it leaves the door wide open to biased reporting. There is the additional problem that the instructions to investigators and study coordinators are contradictory. The Future 1 trial has the same information on p106 in the study report as this:

P88: "All investigators were instructed to report any serious adverse experience, including death due to any cause, occurring in any subject from the time the consent form was signed through 14 days following the first vaccination and from the time of any subsequent vaccinations through 14 days thereafter, whether or not related to the investigational product."

Investigators were obliged to report all serious adverse experiences, occurring within 14 days of each vaccination, whether or not deemed related to the vaccine, whereas only events determined by the study coordinator to be related to the vaccine or a study procedure were reported in the clinical study report (see previous page). I do not recall ever seeing such a procedure in a company sponsored trial before.

In the Future trials, serious adverse events, incl. deaths, were not supposed to be reported if they occurred outside the two-week intervals, but such events are in the tables, so this is also inconsistent.

P88:
"In addition, at any time during the study, if the event was a death that resulted in discontinuation of the subject from the study, or a serious adverse experience that was considered by the investigator to be possibly, probably, or definitely vaccine related, it was to be immediately reported to the Sponsor."

This information is also inconsistent with other information.

When the investigator was obliged to report immediately to Merck, then why was there an added filter in the form of a study coordinator? Why did Merck allow the study coordinator to decide whether such events should be described in the study report? P8 in the study report states: "This CSR [clinical study report]

focuses on summarizing all serious clinical adverse experiences, including any deaths or any serious adverse experience determined by the study coordinator to be related to the study vaccine or a study procedure."

P107:
"Primary Safety and Tolerability Parameters. The important variables of interest for safety/tolerability were the occurrence of severe injection-site adverse experiences and the incidence of any vaccine-related serious adverse experiences."

"For all subjects, follow-up at Months 2, 6, and 7 after the first injection included a general assessment of safety, soliciting broadly for any serious adverse experiences that the subject may have encountered. Participants were instructed to notify the study physician immediately if any unexpected or severe adverse experience occurred."

As already noted for the Future 1 trial (above), it is not appropriate to focus on serious adverse events and for "soliciting broadly for any serious adverse experiences" at follow-up visits for a drug to be given prophylactically to healthy girls at a certain age of whom only a minority will benefit as it is rare to develop cervical cancer and as screening is highly effective in preventing this. Furthermore, we do not even know whether all serious or severe adverse experiences are in the study report because the study coordinators could veto them (see just above).

P108:
Participants from the US and UK "were evaluated for all adverse experiences (nonserious and serious) during the 14-day period after each dose."

P109:
"The remaining subjects in Protocol 015 were solicited only for serious adverse experiences that occurred during the 14 days after each vaccination. This occurred at 2 months following the first vaccination, 4 months following the second, and 1 month following the third vaccination. Solicitation occurred via general questioning and all the information obtained was reported to the Sponsor. The reporting of non-serious adverse experiences while not formally solicited from subjects in this population could be reported based on investigator discretion. Adverse experience reports received from these investigators were only captured if they occurred during the 14 days following each vaccination similar to the US and UK subjects."

P110:
"For all subjects, investigators were instructed to report any serious adverse experience, including death due to any cause, occurring in any subject from the time the consent was signed through 14 days following the first vaccination and from the time of any subsequent vaccinations through 14 days thereafter, whether or not related to the investigational product."

P119:
"All subjects who received at least 1 injection and had follow-up data were included in the safety summaries and listings. Subjects were grouped according to the clinical material they received."

Merck's collecting and reporting adverse events, even lethal ones, which, according to p110 in the report, should only be reported if the deaths occurred within 14 days after each vaccination (which is inappropriate) is confusing and contradicted elsewhere.

It is unacceptable to tell doctors that, "The reporting of non-serious adverse experiences while not formally solicited from subjects in this population could be reported based on investigator discretion." This effectively told investigators that there is no need to report anything unless the patient dies, experiences a life-

threatening adverse event, goes to hospital or experiences a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (see the FDA definition just below).

It is remarkable that drug regulators accepted Merck's contradictory, biased and misleading reports based on trials that were already flawed by design (using adjuvant as "placebo" and using many manoeuvres that avoided reporting possible harms of the vaccine).

P775:
"All subjects will be followed for the reporting of serious adverse experiences from the time the consent is signed through 14 days following the first vaccination and from the time of any subsequent vaccination(s) through 14 days thereafter, and such events will be recorded at each examination on the Adverse Experience Case Report Forms. Additionally, any serious adverse experience brought to the attention of the investigator at any time outside the 14 day reporting period must be reported if the event is either a death which resulted in the subject discontinuing the study, a SAE that is considered to be vaccine related, or a SAE that is considered to be related to a study procedure. Serious adverse experiences will be collected as described in Section I.G.4.a."

This Section I.G.4.a comes some pages down:

P780:
"Serious Adverse Experiences
ANY SERIOUS ADVERSE EXPERIENCE, INCLUDING DEATH DUE TO ANY CAUSE, WHICH OCCURS TO ANY SUBJECT FROM THE TIME THE CONSENT IS SIGNED THROUGH 14 DAYS FOLLOWING THE FIRST VACCINATION(S) AND FROM THE TIME OF ANY SUBSEQUENT VACCINATION(S) THROUGH 14 DAYS THEREAFTER, WHETHER OR NOT RELATED TO THE INVESTIGATIONAL PRODUCT, MUST BE REPORTED WITHIN 24 HOURS TO ONE OF THE INDIVIDU AL(S) LISTED ON THE SPONSOR CONTACT INFORMATION PAGE.

ADDITIONALLY, ANY SERIOUS ADVERSE EXPERIENCE BROUGHT TO THE ATTENTION OF THE INVESTIGATOR AT ANY TIME OUTSIDE OF THE TIME PERIOD SPECIFIED IN THE PREVIOUS PARAGRAPH ALSO MUST BE REPORTED IMMEDIATELY TO ONE OF THE INDIVIDUALS LISTED ON THE SPONSOR CONTACT INFORMATION PAGE IF THE EVENT IS EITHER:

1. A DEATH WHICH RESULTED IN THE SUBJECT DISCONTINUING THE STUDY
OR
2. A SERIOUS ADVERSE EXPERIENCE THAT IS CONSIDERED BYTHE INVESTIGATOR TO BE POSSIBLY, PROBABLY, OR DEFINITELY VACCINE RELATED
OR
3. A SERIOUS ADVERSE EXPERIENCE THAT IS CONSIDERED BY THE INVESTIGATOR TO BE POSSIBLY, PROBABLY, OR DEFINITELY RELATED TO A STUDY PROCEDURE.

ALL SUBJECTS WITH SERIOUS ADVERSE EXPERIENCES MUST BE FOLLOWED UP FOR OUTCOME."

In 2012, according to the FDA, a serious adverse event is an event, which, "in the view of either the investigator or sponsor … results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this

definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse."[41]

As already noted, Merck defines serious adverse events this way, including an overdose of the vaccine:

P777:
"A serious adverse experience is any adverse experience occurring at any dose
that:
— ǂ Results in death; or
— ǂ Is life threatening (places the subject, in the view of the investigator, at immediate risk of death from the experience as it occurred [Note: This does not include an adverse experience that, had it occurred in a more severe form, might have caused death.]); or
— ǂ Results in a persistent or significant disability/incapacity (substantial disruption of one's ability to conduct normal life functions); or
— ǂ Results in or prolongs an existing inpatient hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation) (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse experience.); or
— ǂ Is a congenital anomaly/birth defect (in offspring of subject taking the product regardless of time to diagnosis); or
— Is a cancer; or
— Is the result of an overdose (whether accidental or intentional)

ALSO :
Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a ǂ)."

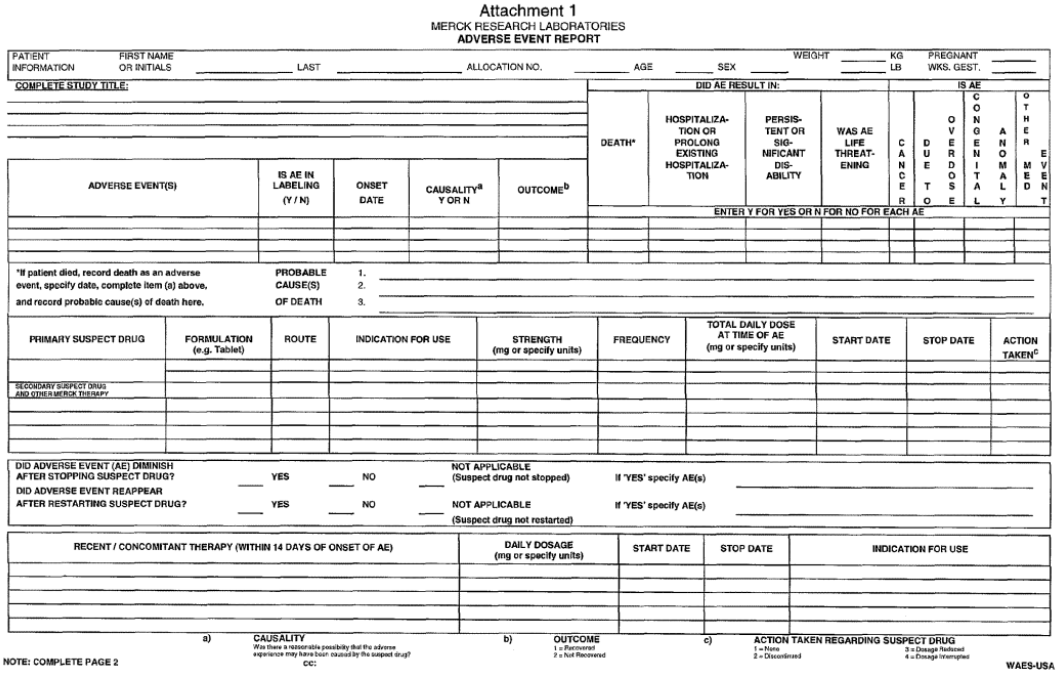
P776:
"Evaluating and Recording Adverse Experiences. An adverse experience is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the SPONSOR'S product, whether or not considered related to the use of the product.
— Mild is awareness of sign or symptom, but easily tolerated;
— Moderate is discomfort enough to cause interference with usual activity;
— Severe is incapacitating with inability to work or do usual activity."

P831-2:
"Attachment 1 - Adverse Event Report Form."

Apparently, as there are no specifications in the study report and as there are entries for the types of seriousness, including death, this form is to be used for both serious and non-serious events. It takes up two pages but only one-third of a page is for the narrative, which is far too little for many serious events. It is not clear whether these forms were filled out by hand or on a computer, but they are constructed in such a way that it seems handwriting was used. There are additional forms, but no instructions about when to use which one (see just below).

[41] https://www.fda.gov/files/drugs/published/Safety-Reporting-Requirements-for-INDs-%28Investigational-New-Drug-Applications%29-and-BA-BE-%28Bioavailability-Bioequivalence%29-Studies.pdf.

First page:



Attachment 1
MERCK RESEARCH LABORATORIES
ADVERSE EVENT REPORT

PATIENT INFORMATION — FIRST NAME OR INITIALS _____ LAST _____ ALLOCATION NO. _____ AGE _____ SEX _____ WEIGHT _____ KG _____ LB PREGNANT _____ WKS. GEST. _____

COMPLETE STUDY TITLE:

ADVERSE EVENT(S)	IS AE IN LABELING (Y / N)	ONSET DATE	CAUSALITY[a] Y OR N	OUTCOME[b]	DID AE RESULT IN: DEATH*	HOSPITALIZATION OR PROLONG EXISTING HOSPITALIZATION	PERSISTENT OR SIGNIFICANT DISABILITY	WAS AE LIFE THREATENING	IS AE: CANCER	DUE TO OVERDOSE	CONGENITAL	ANOMALY	OTHER MED EVENT
					ENTER Y FOR YES OR N FOR NO FOR EACH AE								

*If patient died, record death as an adverse event, specify date, complete item (a) above, and record probable cause(s) of death here.

PROBABLE CAUSE(S) OF DEATH
1.
2.
3.

PRIMARY SUSPECT DRUG	FORMULATION (e.g. Tablet)	ROUTE	INDICATION FOR USE	STRENGTH (mg or specify units)	FREQUENCY	TOTAL DAILY DOSE AT TIME OF AE (mg or specify units)	START DATE	STOP DATE	ACTION TAKEN[c]
SECONDARY SUSPECT DRUG AND OTHER MERCK THERAPY									

DID ADVERSE EVENT (AE) DIMINISH AFTER STOPPING SUSPECT DRUG? ____ YES ____ NO ____ NOT APPLICABLE (Suspect drug not stopped) If 'YES' specify AE(s) _____

DID ADVERSE EVENT REAPPEAR AFTER RESTARTING SUSPECT DRUG? ____ YES ____ NO ____ NOT APPLICABLE (Suspect drug not restarted) If 'YES' specify AE(s) _____

RECENT / CONCOMITANT THERAPY (WITHIN 14 DAYS OF ONSET OF AE)	DAILY DOSAGE (mg or specify units)	START DATE	STOP DATE	INDICATION FOR USE

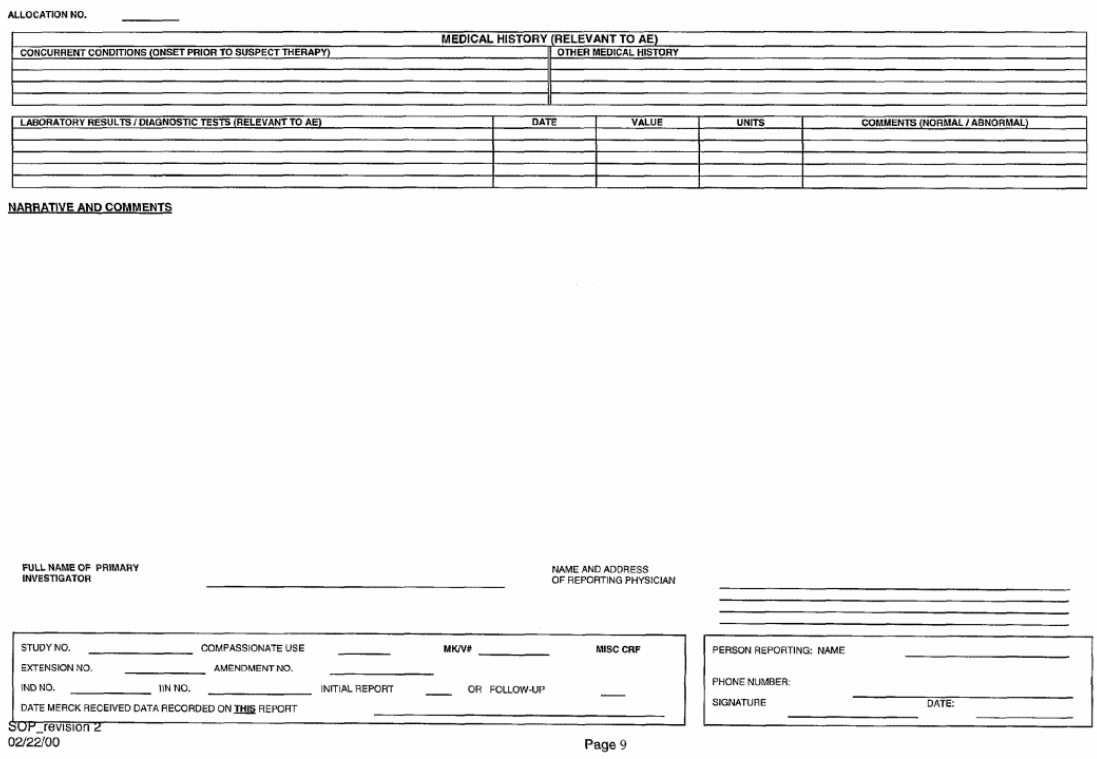
a) CAUSALITY — Was there a reasonable possibility that the adverse experience may have been caused by the suspect drug?
b) OUTCOME — 1 = Recovered; 2 = Not Recovered
c) ACTION TAKEN REGARDING SUSPECT DRUG — 1 = None; 2 = Discontinued; 3 = Dosage Reduced; 4 = Dosage Interrupted

cc:

NOTE: COMPLETE PAGE 2

WAES-USA

Second page:



ALLOCATION NO. _____

MEDICAL HISTORY (RELEVANT TO AE)

CONCURRENT CONDITIONS (ONSET PRIOR TO SUSPECT THERAPY)	OTHER MEDICAL HISTORY

LABORATORY RESULTS / DIAGNOSTIC TESTS (RELEVANT TO AE)	DATE	VALUE	UNITS	COMMENTS (NORMAL / ABNORMAL)

NARRATIVE AND COMMENTS

FULL NAME OF PRIMARY INVESTIGATOR _____

NAME AND ADDRESS OF REPORTING PHYSICIAN _____

STUDY NO. _____ COMPASSIONATE USE ____ MK/V# _____ MISC CRF

EXTENSION NO. _____ AMENDMENT NO. _____

IND NO. _____ IIN NO. _____ INITIAL REPORT ____ OR FOLLOW-UP ____

DATE MERCK RECEIVED DATA RECORDED ON THIS REPORT _____

PERSON REPORTING: NAME _____

PHONE NUMBER: _____

SIGNATURE _____ DATE: _____

SOP_revision 2
02/22/00

Page 9

P2232:
This is another form, to be used for non-serious adverse experiences:

GENERAL INSTRUCTIONS FOR COMPLETING
NON-SERIOUS ADVERSE EXPERIENCE (**NSAEv**) REPORT FORM – ***ADULT***

If AE resulted in Death, Hospitalization, Prolongation of Existing Inpatient Hospitalization, or Persistent or Significant Disability/Incapacity, or if AE is immediately Life-Threatening, Cancer, Congenital Anomaly/Birth Defect, Due to Overdose, or Other Important Medical Event, enter event on the SAE form. If, at the end of the study, no NSAE has occurred, submit the NSAE Report Form with the other workbooklets/worksheets.

P2234:

Did any **nonserious AEs** occur during the protocol specified clinical follow-up period?
None ☐ *or complete form below*

Type of AE	Systemic ☐ Injection Site ☐ Laboratory ☐ Other ☐	Systemic ☐ Injection Site ☐ Laboratory ☐ Other ☐	Systemic ☐ Injection Site ☐ Laboratory ☐ Other ☐
AE Term *(For Lab AE use the term "Increased" or "Decreased")*			
Did Primary Test Product cause NSAE? *(Refer to Guidelines for Causality then enter classification)*	Definitely not ☐ Probably not ☐ Possibly ☐ Probably ☐ Definitely ☐ DD-Mon-YYYY	Definitely not ☐ Probably not ☐ Possibly ☐ Probably ☐ Definitely ☐ DD-Mon-YYYY	Definitely not ☐ Probably not ☐ Possibly ☐ Probably ☐ Definitely ☐ DD-Mon-YYYY

Brief description of AE (if necessary):

Very little information could be gathered on this form, and the tiny space at the bottom for the narrative could even be for three different events. Moreover, it was only to be used "if necessary."

There was yet another form on p2237 for serious adverse events, which was similarly brief, only one page. Here is the whole form (there are GENERAL INSTRUCTIONS FOR COMPLETING SERIOUS ADVERSE EXPERIENCE (SAEv) REPORT FORM on p2235, but still no instructions about when to use which form):

Unscheduled **SAEv**

Compound	Protocol	Study Site	IIN	VISIT	Baseline Number	Allocation Number
V501	015-00			U		

SERIOUS ADVERSE EXPERIENCE 34976

Use this form if AE resulted in Death, if AE is immediately Life-Threatening, results in Persistent or Significant Disability/Incapacity, results in Hospitalization or Prolongs an Existing Hospitalization, is a Congenital Anomaly/Birth Defect, a Cancer, the result of an Overdose, or Other Important Medical Event.
INFORM MERCK OF SERIOUS ADVERSE EXPERIENCE WITHIN 24 HOURS.

THIS PAGE IS TO BE REVIEWED/COMPLETED AT EACH VISIT.

Did any **serious AEs** occur during the protocol specified clinical follow-up period?
None ☐ *or complete form below*

Type of AE	Systemic ☐ Injection Site ☐ Laboratory ☐ Other ☐	Systemic ☐ Injection Site ☐ Laboratory ☐ Other ☐
AE Term (SAE)		
Check if **Worsening of Preexisting Condition**	☐	☐
Onset Date *(Lab date if Lab SAE)*	DD-Mon-YYYY:	DD-Mon-YYYY:
Stop Date or check box if **continuing** *(Not applicable for Lab or Other)*	DD-Mon-YYYY: Continuing ☐	DD-Mon-YYYY: Continuing ☐
Duration – if less than 24 hours *(Not applicable for Lab or Other)*	Hour ☐ Minute ☐ Second ☐	Hour ☐ Minute ☐ Second ☐
Intensity *(Not applicable for Lab or Other)*	Mild ☐ Moderate ☐ Severe ☐	Mild ☐ Moderate ☐ Severe ☐
Maximum size *(1-8) (Injection site SAEs only)*		
Injection site *(Injection site SAEs only)*	Right Arm ☐ Left Arm ☐ Right Thigh ☐ Left Thigh ☐ Other *(specify)*: _____	Right Arm ☐ Left Arm ☐ Right Thigh ☐ Left Thigh ☐ Other *(specify)*: _____
Did the SAE Result in:		
Persistent or Significant Disability/Incapacity?	No ☐ Yes ☐	No ☐ Yes ☐
Hospitalization or Prolongation?	No ☐ Yes ☐	No ☐ Yes ☐
Death? *(Provide death date)*	No ☐ Yes ☐	No ☐ Yes ☐
Death Date:	DD-Mon-YYYY:	DD-Mon-YYYY:

Is the SAE:		
Immediately Life-threatening?	No ☐ Yes ☐	No ☐ Yes ☐
Cancer?	No ☐ Yes ☐	No ☐ Yes ☐
Due to Overdose?	No ☐ Yes ☐	No ☐ Yes ☐
Congenital Anomaly/Birth Defect?	No ☐ Yes ☐	No ☐ Yes ☐
Other Important Medical Event?	No ☐ Yes ☐	No ☐ Yes ☐
Action Taken on Primary Test Product Due to SAE:	None ☐ No further test vaccinations given ☐ Discontinued from follow-up only ☐	None ☐ No further test vaccinations given ☐ Discontinued from follow-up only ☐
Did SAE diminish after stopping test product? *(Dechallenge)*	No ☐ Yes ☐ NA ☐	No ☐ Yes ☐ NA ☐
Did SAE reappear after restarting test product? *(Rechallenge)*	No ☐ Yes ☐ NA ☐	No ☐ Yes ☐ NA ☐
Did Primary Test Product cause SAE? *(Refer to Guidelines for Causality then enter classification)*	Definitely not ☐ Probably ☐ Probably not ☐ Definitely ☐ Possibly ☐ Inv. Initial's DD-Mon-YYYY	Definitely not ☐ Probably ☐ Probably not ☐ Definitely ☐ Possibly ☐ Inv. Initial's DD-Mon-YYYY
Brief description of SAE (if necessary):		

Investigator's name: If this worksheet is **used as a source document**, it must be **initialed** and **dated** by the individual making the observation/recording →

060201 **Restricted Confidential - Merck & Co., Inc.**, Whitehouse Station, New Jersey, USA Printed in USA

Even serious adverse events are only supposed to be recorded within two weeks after each vaccination. There is virtually no space for a serious adverse event narrative and that the text is: "Brief description of SAE (if necessary)." It is ALWAYS necessary and required to describe serious adverse events. Furthermore, two serious AEs can be reported on just one page.

Next, comes another one-page form (p2239):

Unscheduled **SFUQ**

Compound	Protocol	Study Site	IIN	VISIT	Baseline Number	Allocation Number
V501	015-00			U		

SAFETY FOLLOWUP QUESTION 17235

NOTE: • ***This questionnaire is applicable if any safety information was received during clinical follow-up.***

• ***Refer to protocol to determine if subject completed safety follow-up for the required number of days.***

Last date of safety follow-up: _____ DD-Mon-YYYY

Investigator's name: If this worksheet is **used as a source document**, it must be **initialed** and **dated** by the individual making the observation/recording →

060201 **Restricted Confidential - Merck & Co., Inc.**, Whitehouse Station, New Jersey, USA Printed in USA

On the form is written “Safety followup question. Note: This questionnaire is applicable if any safety information was received during clinical follow-up.”

Investigators are not encouraged to ask questions, and there was no guide as to how they should ask if they insisted on asking. The fourth form should only be filled out “If any safety information was received.” This is like saying: “Merck does not want you to report anything but if you are desperate to do so, here is your opportunity.”

New medical conditions/history

P308:
“New medical conditions were not considered adverse experiences when they occurred outside the safety follow-up period (Day 1 through Month 7) and/or were not considered by the study investigators to be vaccine/placebo related.”

This is more inclusive than for Future 1 where the safety follow-up period was only the “15 days following any study vaccination” (see above).

I do not recall ever seeing clinical trial adverse experiences that could be harms of drugs not being called adverse events but “new medical conditions” if they do not occur within an arbitrary time frame defined by the sponsor or if the study investigators do not consider them drug related. Whether the safety follow-up period is now 7 months rather than two weeks after each vaccination is not clear.

This is particularly problematic for the suspected harms of the HPV vaccines. For POTS, it can take years before the diagnosis is objectively established by a tilt test. [42]

P736:
“The investigator or study coordinator must notify the SPONSOR immediately when a subject has been discontinued/withdrawn due to an adverse experience (telephone or FAX).” This information is repeated 8 times in the document.

P2498, from a CV of one of the investigators:
“Medical Study Coordinator of V501 - protocol 015 IBCC / Merck &Co., Inc. (Since jan/2003) … Medical Principal Investigator Study of V501 - protocol 015 Hospital do Cancer / Merck & Co., Inc. (Since jan/2003).”

There are 175 pages of CVs in the report. Most of them take up only 2-3 pages. But only one mentions a role as study coordinator, even though there likely is one at each trial site:

P2841, about patients moving address:
“Attached to this letter is a checklist for the study coordinator’s reference. The study coordinator should complete this checklist and keep a copy in the subject’s study file.”

P3900:
“All study sites were also instructed to provide detailed reports on the following events occurring after the Month 7 visit:
- any serious adverse experience that was judged by the study investigator to be possibly, probably, or

[42] Blitshteyn S, Brinth L, Hendrickson JE, Martinez-Lavin M. Autonomic dysfunction and HPV immunization: an overview. Immunol Res 2018;66:744-54.

definitely vaccine-related;
- any serious adverse experience that was judged by the study coordinator to be possibly, probably, or definitely related to a procedure specified in the protocol;"

It is not clear what was meant to be done if the study coordinator and the investigator disagreed about whether a serious adverse experience was judged to be possibly, probably, or definitely related to a procedure specified in the protocol. Although the study coordinators clearly played a key role, the study coordinator should not be allowed to overrule the investigators.

It appears the Data and Safety Monitoring Board for the Future 2 trial considered the blurred distinction between adverse events and "new medical history" a problem. This question was raised at a board meeting (p3347):

"When a subject indicates that they are no longer interested in participating, you are often not informed of their reason for withdrawing consent. E. Barr [Merck's HPV Vaccine Program Project Leader, p3445] indicated that sites are instructed to ask if it was due to an adverse event or a new medical problem. If due to an AE, the reason would change categorically to discontinued due to an AE. The problem is that subjects often say that they do not want to continue and the reason is never learned. For this reason, we review these categories as well as the 'withdrawn consent' category by treatment group, obviously when unblinded, to see if there is an imbalance which would be an indication of a potential hidden AE issue. We also look at the previously reported AE as well as the AE profiles of women who withdrew consent to determine if it deviates from the general AE profile of the Program."

Thus, Merck's own Data and Safety Monitoring Board recognized the arbitrary and artificial split between adverse events and "new medical history."

P262 in the study report states: "12.3 Clinical Evaluation of Laboratory Safety Tests. No routine laboratory safety tests were conducted within the context of the study." None of the 102 tables in the report are about laboratory values, and p67 has a table that indicates that no laboratory measurements were made:

Table 9-5

Schedule of Clinical Observations and Laboratory Measurements

Event/Test	Random-ization Day 1	Months 2	6	7	12	24	36	48
Obtain informed consent	+							
Complete gynecologic/medical history	+			+	+	+	+	+
Physical examination	+							
Gynecologic examination of external genitalia	+			+	+	+	+	+
Specimen collection/laboratory measurements (in serial order):								
Pregnancy test	+	+	+					
Urine for gonorrhea PCR or LCR or SDA	+					+		+
Urine for chlamydia PCR or LCR or SDA	+				+	+	+	+
Serum for HPV (6, 11, 16, 18) anti-HPV 6, 11, 16, and 18 cLIA antibody measurements	+							
Labial/vulvar/perineal/and perianal swabs for HPV PCR[‖]	+			+				
Endo/ectocervical swab for HPV 16 and 18 PCR[‖]	+			+		(+)	(+)	(+)
Pap test (ThinPrep™) for cytology	+			+	+	+	+	+
Bimanual exam of uterus and adnexa	+			+	+	+	+	+
Colposcopy and cervical biopsy for histology and HPV detection LEEP procedure								
Vaccination	+	+	+					
Clinical follow-up for safety	+	+	+					
Clinical contact visit documentation[‖‖]	+	+	+	+	+	+	+	+
Study Close-Out Visit (Month 48)								

I did not find values for any laboratory measurements in any of Merck's human studies, only in some of its animal studies (see Appendix B). In the important, large three-month toxicity study in 200 rats (V503 TT 07-1006_rat study_unsigned), the globulins increased in the three vaccine groups, which was expected, because some of these are vaccine induced immune globulins, but Merck left out the data for the adjuvant control group. Due to this failure, one cannot see if the immunogenic adjuvant also increases globulins.

It is curious that Merck did nothing to find out if its vaccine or its adjuvant cause harm that is detectable in laboratory analyses when it is a fact that no one knows what the harms are of Merck's adjuvant because it has never been tested against an inert placebo or nothing. Merck randomised tens of thousands of healthy people to an HPV vaccine or to the adjuvant but did not use this opportunity to elucidate the harms of its adjuvant.

P67:
"Table 9-5. Schedule of Clinical Observations and Laboratory Measurements."

See this table on the previous page. Physical examination was only done on day 1, and it appears that blood pressure and pulse were not measured. On p2192, there is a case report form for day 1 that seems to indicate that it was not obligatory to measure blood pressure and pulse: "Was exam performed?" If they were measured, it was in the sitting position, and no tilt test was performed:

VITAL SIGNS 4074

Was exam performed? **No** ☐ *If **yes**, complete form below.*

Exam performed on visit date ☐ **or** specify date: _____ (DD-Mon-YYYY)

VITAL SIGNS	RESULT	*AE? No	Yes
Weight kg ☐ lb ☐		☐	☐
Temperature °C ☐ °F ☐ *Method:* oral		☐	☐
Blood pressure (mmHg) *Position:* sitting	Systolic / Diastolic	☐	☐
Pulse rate (beats/min) *Position:* sitting		☐	☐
Respiratory rate (breaths/min)		☐	☐

If any "YES" box is checked, complete the appropriate ADVERSE EXPERIENCE (NSAE/SAE) form.

The question on the form, "Was exam performed?", contradicts information on p58: "A general physical examination was performed at Day 1. The documented physical examination included height, weight, sitting blood pressure, sitting pulse, respirations, and an oral temperature."

After the day 1 forms, the same forms reappear, starting on p2210, but now under the heading "Unscheduled," which is confusing as subsequent vaccination visits after day 1 had been scheduled. The form does not say that it should be completed at every visit, in contrast to the adverse event form on p2232 onwards. Yet again, it seems optional whether to measure blood pressure and pulse (p2214).

I find it odd that Merck did not require investigators to measure blood pressure and pulse at the vaccination visits when its vaccine was an experimental drug, when the harms of its adjuvant used in the control group were unknown, and when it was well known that vaccinations can lead to changes in blood pressure and pulse, and to fainting and near-fainting.

P2232:
GENERAL INSTRUCTIONS FOR COMPLETING NON-SERIOUS ADVERSE EXPERIENCE (NSAEv) REPORT FORM

Although looking similar to one of the forms above, it is a new one. Not much information was to be collected; there was very little room for a narrative; and the tiny space at the bottom could even be for three different events. Furthermore, the "Brief description of AE" was only to be filled out "if necessary":

THIS PAGE IS TO BE REVIEWED/COMPLETED AT EACH VISIT.			
Did any **nonserious AEs** occur during the protocol specified clinical follow-up period? **None** ☐ *or complete form below*			
Type of AE	Systemic ☐ Injection Site ☐ Laboratory ☐ Other ☐	Systemic ☐ Injection Site ☐ Laboratory ☐ Other ☐	Systemic ☐ Injection Site ☐ Laboratory ☐ Other ☐
AE Term *(For Lab AE use the term "Increased" or "Decreased")*			

Brief description of AE (if necessary):

Data and Safety Monitoring Board meetings. Although safety is the primary concern for such a board, and the DSMB meeting on 2-3 October 2002 was followed by a joint meeting with the Steering Committee for the trial for the next two days, and many slides were presented, not a single slide showed any safety monitoring results, they were all about efficacy and principles (p3215). And although a review of the safety data was an objective at the DSMB meeting on 30 April 2003, there were only slides about some selected adverse events - no systematically collected data on serious adverse events (a few concrete patients with such events were presented), and very little detail (p3270).

P3315:
2 Oct 2003, teleconference for the DSMB.

There were slides on serious adverse events, but as they were not divided per treatment group, it must have been close to impossible for the board to discuss them in any meaningful way. Here is an example (p3328; the 127 deaths include abortions):

Summary of SAEs – Phase III

Number of Subjects with:	Total
Any Serious Adverse Experience (SAE)	223
Protocol-specified SAE†	75
SAE associated with a pregnancy	137
SAE in Infants of Lactating Mothers	14
Vaccine-related SAEs	5
Discontinuations due to SAEs	1
Deaths‡	127

† Protocol-specified = Any SAE occurring within 14 days of vaccination, or any procedure-related SAE, or a death, or any SAE judged by the investigator to be possibly, probably, or definitely vaccine-related regardless of time of onset

‡ Deaths – in accordance with FDA guidelines, all spontaneous or elective abortions are reported as an SAE resulting in death

Source – WAES Database

It appears that some board members suspected the vaccine could cause syncope, convulsions and deaths:

"*Question (T. Cox & F. Langmark)*: For the 19-year-old Czech woman who died in the MVA [motor vehicle accident], was there any one else in the car? Did she have a syncopal episode or seizure event that made her lose control of the car? What was the timeframe from vaccination to death? Dr, Sattler will inquire with the Czech Republic subsidiary" (p3320).

"*Question (V. Odlind)*: Isn't it strange that two traffic accidents occurred on the day of the vaccination? Dr. L. Koutsky pointed out that there could have been other motor accidents we are not aware of which occurred in between visits when subjects are not in contact with the sites. Dr. V. Odlind asked whether we would know if someone had died. *Answer*: Yes, we are informed of all deaths unless they are in between visits. It was noted that at this time, the majority of subjects are in between visits" (p3321).

Given that the Data and Safety Monitoring Board already in 2003, a year after the trial started, were concerned about syncope, also if it occurred in the intervals between the vaccinations (and therefore not the

result of the needle prick), in my opinion Merck should have changed its procedures to detect such possible, serious harms of its vaccine.

Merck apparently did not get information about deaths if they occurred between visits but yet again, the information is not consistent. On p88, we are told that deaths need only to be reported immediately to the sponsor if considered by the investigator to be possibly, probably, or definitely vaccine related, but on p780 we are told that, whether or not related to the investigational product, deaths must be reported within 24 hours to one of the individual(s) listed on the sponsor contact information page.

POTS was also much more commonly reported from Denmark compared to the rest of world after the females had received active HPV vaccine. The Danish Syncope Unit identified POTS in 60% of a cohort of 53 patients[43] and found that 87% and 90% of the patients fulfilled the official criteria for chronic fatigue syndrome (CFS) and myalgic encephalomyelitis (ME), respectively.[44]

These data suggest that serious harms of the vaccines were underreported in Merck's trials.

P3465, DSMB 9 April 2007:
Deaths in trial 020 were discussed (p3512).

P3585:
"For all nonserious adverse experience summaries, verbatim terms (i.e. terms used by subjects to report their adverse experiences) are automatically encoded using a logic algorithm to an international standardized dictionary. At this time, none of the auto-encoded terms in the clinical database have been compared with the verbatim terms."

I have not seen the verbatim terms for the adverse events, not even for the serious ones, from the investigators, study coordinators or patients themselves. I have only reviewed narratives for serious adverse events written by Merck employees. I have been informed that the clinical trials databases that would contain this information (i.e., the raw data) have been decommissioned and are no longer accessible to cross-check Merck's representations. See Fred Marchev Declaration dated January 31, 2020. This is very serious.

"[R]aw data from clinical trials most closely reflect the study observations. The analyzable data set, by contrast, is the result of many decisions made by clinical trialists … If there are errors, flaws, or biases in the processing of raw data, such problems will not necessarily be identified in the analyzable data set. Examples of the value of raw data include the detection of serious errors or biases as well as fraud uncovered by detailed and intense audits of raw data conducted by central statistical centers when inconsistencies or anomalies have been noted in analyzable data sets (Fisher et al. 1995; Soran et al., 2006; Temple and Pledger, 1980." The Committee on Strategies for Responsible Sharing of Clinical Trial Data, Board on Health Sciences Policy; Institute of Medicine, Sharing Clinical Trial Data: Maximizing Benefits, Minimizing Risk (2015).

[43] Brinth LS, Pors K, Theibel AC, et al. Orthostatic intolerance and postural tachycardia syndrome as suspected adverse effects of vaccination against human papilloma virus. Vaccine 2015;33:2602-5.
[44] Brinth L, Pors K, Hoppe AAG, et al. Is chronic fatigue syndrome/myalgic encephalomyelitis a relevant diagnosis in patients with suspected side effects to human papilloma virus vaccine? Int J Vaccines Vaccin 2015;1:00003.

P710:
“Safety Substudy (NSAE) [non-serious adverse experiences]. At preselected sites, a subset of subjects (n=1150) will be followed for all adverse experiences from Day 1 to Day 14 after each dose of vaccine/placebo. Temperature will be recorded for 5 days following each injection (4 hours after injection, and daily for the next 4 days). All adverse experiences (AEs) will be collected on the subject’s Vaccination Report Card [VRC] daily for 14 days after each vaccination.”

P775:
“For Subjects Participating in the NSAE Substudy … All comments are to be reviewed by the study personnel and discussed with the participant for clarification if necessary. The information on the VRC should be generated only by the subject and is to be signed and dated by the subject to confirm the accuracy of the recorded information. Original information recorded by the participant should never be altered by study personnel. Any information gained by phone contact with the subject should be clearly documented, initialed, and dated on the subject workbooklet or source documentation, other than the VRC.”

Events were similar in the two groups.

P2184:
Case report forms for inclusion of patients.

P2198:
“INSTRUCTIONS FOR REPORTING MEDICAL HISTORY.”

This is not about new medical history but the history when patients are enrolled in the trial. There are various forms for this.

P3985:
Narratives of three deaths. For many of the serious adverse events, incl. deaths, there were no narratives in this final report, only in interim reports, which is peculiar. Narratives of nine more deaths only exist in an earlier report.

V501 P015 V1 CSR

27 Sept 2005, interim report, dated two years earlier than the final report.

Repetitive, many synopses, and many protocol amendments, no narratives of adverse events.

P179: Index for the rest of the report (List of appendices only).

V501 P015 V2 CSR

Index on p3.

16 Oct 2005 report, but it is called 1 Nov 2005 at the bottom of the pages. Dated two years earlier than the final report.

P1035-48:
Narratives of events not related to pregnancy.

P203-5:
"Table 6-19 summarizes, by drug category, the number and percentage of subjects in the United States with specific concomitant therapies with an incidence of ≥1% in at least one vaccination group from Days 1 to 15 following any vaccination visit. Concomitant drugs listed and compared."

These data are from the NSAE (non-serious adverse events) substudy. There were only 458 vs 455 patients in the analysis population; Future 2 included a total of 12,050 females with follow-up data.

P291:

Clinical Adverse Experience Summary
(Days 1 to 15 Following Any Vaccination Visit)—
Detailed Safety Cohort (United States)

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=457)		Placebo (N=454)	
	n	(%)	n	(%)
Subjects in analysis population	457		454	
Subjects without follow-up	9		7	
Subjects with follow-up	448		447	
Number (%) of subjects:				
with no adverse experience	39	(8.7)	52	(11.6)
with one or more adverse experiences	409	(91.3)	395	(88.4)
injection-site adverse experiences	379	(84.6)	349	(78.1)
systemic adverse experiences	271	(60.5)	266	(59.5)

P291-2:
"A higher proportion of subjects in the quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine group reported any adverse experiences and injection-site adverse experiences after vaccination Visit 2 and Visit 3 than in the placebo group. The proportions of subjects with systemic adverse experiences were higher in both vaccination groups following vaccination Visit 1 than following vaccination Visit 2 or Visit 3."

So, both "any adverse experiences" and "injection-site adverse experiences" were more common with the vaccine than with the adjuvant after vaccination visits 2 and 3. The table does not show data for the separate visits but only the total for all visits.

P293:

Number (%) of Subjects Who Reported Any Clinical Adverse Experience
by Maximum Intensity Rating
(Days 1 to 15 Following Any Vaccination Visit)—
Detailed Safety Cohort (United States)

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N = 457) n (%)	Placebo (N = 454) n (%)
Number of Subjects with follow-up	448	447
Number of subjects without adverse experiences	39	52
Number (%) of subjects with adverse experiences[†]	409 (91.3)	395 (88.4)
Number (%) of subjects by maximum intensity rating of adverse experience		
Mild	174 (38.8)	169 (37.8)
Moderate	175 (39.1)	167 (37.4)
Severe	59 (13.2)	58 (13.0)
Unknown	1 (0.2)	1 (0.2)

[†] Number of subjects with adverse experiences Days 1 to 15 following any vaccination visit.
Percentages are calculated as 100*(n/number of subjects with follow-up).
N = Number of subjects who received only the clinical material indicated in the given column.
HPV = Human papillomavirus; VLP = Virus-like particles.

Number of people with moderate or severe clinical adverse experiences in the United States was similar in the two groups, 234 vs 225.

P299:

Table 8-8

Number (%) of Subjects Who Reported Injection-Site Adverse Experiences
by Maximum Intensity Rating
(Days 1 to 5 Following Any Vaccination Visit)—
Detailed Safety Cohort (United States)

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N = 457) n (%)	Placebo (N = 454) n (%)
Number of Subjects with follow-up	448	447
Number of subjects without Injection-Site adverse experiences	70	99
Number (%) of subjects with Injection-Site adverse experiences[†]	378 (84.4)	348 (77.9)
Number (%) of subjects by maximum intensity rating of Injection-Site adverse experience		
Mild	259 (57.8)	273 (61.1)
Moderate	109 (24.3)	71 (15.9)
Severe	10 (2.2)	4 (0.9)

[†] Number of subjects with adverse experiences Days 1 to 5 following any vaccination visit.
Percentages are calculated as 100*(n/number of subjects with follow-up).
N = Number of subjects who received only the clinical material indicated in the given column.
HPV = Human papillomavirus; VLP = Virus-like particles.

Data Source: [4.2.1]

More patients had moderate or severe injection-site adverse events in the vaccine group: 119 vs 75 patients (p = 0.0005, Fisher's exact test, my calculation; Merck did not do a significance test on these severity data). Thus, despite the fact that there was adjuvant in the "placebo," injection site experiences in this US substudy that focused on adverse experiences were clearly worse with the vaccine, and significantly so, despite the small number of patients.

P315:

Table 8-13

Number (%) of Subjects Who Reported Systemic Clinical Adverse Experiences
by Maximum Intensity Rating
(Days 1 to 15 Following Any Vaccination Visit)—
Detailed Safety Cohort (United States)

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N = 457) n (%)	Placebo (N = 454) n (%)
Number of Subjects with follow-up	448	447
Number of subjects without Systemic adverse experiences	177	181
Number (%) of subjects with Systemic adverse experiences[†]	271 (60.5)	266 (59.5)
Number (%) of subjects by maximum intensity rating of Systemic adverse experience		
Mild	92 (20.5)	72 (16.1)
Moderate	127 (28.3)	136 (30.4)
Severe	51 (11.4)	57 (12.8)
Unknown	1 (0.2)	1 (0.2)

[†] Number of subjects with adverse experiences Days 1 to 15 following any vaccination visit.
Percentages are calculated as 100*(n/number of subjects with follow-up).
N = Number of subjects who received only the clinical material indicated in the given column.
HPV = Human papillomavirus; VLP = Virus-like particles.

Data Source: [4.2.1]

Moderate or severe adverse experiences were 234 vs 225 for clinical adverse experiences; 119 vs 75 for injection-site adverse experiences; and 178 vs 193 for systemic clinical adverse experiences. Clinical adverse events must therefore include both systemic and injection-site events and some people must have had

events in both subgroups, since the addition of them gives 297 vs 268. There were no definitions in the protocol of these three types of events:

"Systemic Clinical Adverse Experiences" were mentioned in the protocol on p135 but were not defined. In HPV vaccine trials, and in other trials, "systemic" is used to distinguish these experiences from "local" experiences, which occur when people are vaccinated or treated with a cream, for example.

On page 287, the term "Clinical Adverse Experiences" is used as a heading, but it is not explained, or if it could be something else than "Systemic Clinical Adverse Experiences." The text mentions that, "Each study participant in the Detailed Safety Cohort (United States) recorded her oral temperature 4 hours after each injection and daily for the next 4 days (Days 1 to 5) on a VRC [vaccination report card]. Any systemic adverse experience or injection-site adverse experience, which occurred on Day 1 or within the 14 calendar days thereafter, was also recorded on the VRC. This procedure was repeated for each injection of study material. Information from the VRC was transcribed onto worksheets and submitted to Merck Research Laboratories."

Based on this information, one would assume that "Clinical Adverse Experiences" covers both systemic adverse experiences and injection-site adverse experiences, also because the latter are just as clinical as systemic experiences, e.g. a rise in blood pressure or body temperature, and because it is common to distinguish between clinical adverse experiences and laboratory adverse experiences, e.g. a rise in creatinine.

This interpretation agrees with the text on p302: "A summary of the number and percent of subjects who reported systemic clinical adverse experiences by system organ class (incidence ≥1%) within 15 days following any vaccination visit is provided in Table 8-11."

P294-5:
The UK substudy: "Because these subjects did not use the VRC [Vaccination Report Card], there was substantial reduction in the reporting of adverse experiences."

Clinical Adverse Experience Summary
(Days 1 to 15 Following Any Vaccination Visit)—
General Safety Cohort (United Kingdom)

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=109)		Placebo (N=129)	
	n	(%)	n	(%)
Subjects in analysis population	109		129	
Subjects without follow-up	5		1	
Subjects with follow-up	104		128	
Number (%) of subjects:				
with no adverse experience	85	(81.7)	111	(86.7)
with one or more adverse experiences	19	(18.3)	17	(13.3)
injection-site adverse experiences	3	(2.9)	3	(2.3)
systemic adverse experiences	17	(16.3)	15	(11.7)
with vaccine-related† adverse experiences	6	(5.8)	6	(4.7)
injection-site adverse experiences	3	(2.9)	3	(2.3)
systemic adverse experiences	4	(3.8)	3	(2.3)
with serious adverse experiences	0	(0.0)	1	(0.8)
with serious vaccine-related adverse experiences	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)
discontinued‡ due to an adverse experience	1	(1.0)	0	(0.0)
discontinued due to a vaccine-related adverse experience	1	(1.0)	0	(0.0)
discontinued due to a serious adverse experience	0	(0.0)	0	(0.0)
discontinued due to a serious vaccine-related adverse experience	0	(0.0)	0	(0.0)

In the US substudy, 91% vs 88% had one or more adverse experiences. In the UK substudy, only 18% vs 13% had this. Since there were only 3 vs 3 patients with injection-site adverse experiences, it would not be

possible to see in the UK data if such experiences were more severe with the vaccine than with the placebo, and there is no table that shows the severity of the 36 adverse experiences, as for the US data.

In the US data, although the percentages of patients with systemic adverse experiences were about the same (60.5% vs 59.5%, p315), there were 39.7% vs 43.2% where the events were moderate or severe. This 3.5% difference could be a chance finding, but one would expect a vaccine plus adjuvant to be more harmful than the adjuvant, not less harmful. I therefore looked up "new medical history" to see if some events that should have been included under systemic adverse experiences in the Gardasil group had ended up there instead:

P353:
"Number (%) of Subjects With New Medical History (Incidence ≥1% in One or More Vaccination Groups) by System Organ Class (Vaccination Period, Day 1 Through Month 7). Detailed Safety Cohort (United States)."

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=457)		Placebo (N=454)	
	n	(%)	n	(%)
Subjects in analysis population	457		454	
Subjects with one or more new Medical History	261	(57.1)	241	(53.1)
Subjects with no new secondary diagnosis	196	(42.9)	213	(46.9)

The percentages of patients with a new medical history were 57.1% vs 53.1%. These are not divided into mild, moderate or severe anywhere in the reports but the difference of 4% is very similar to the difference of 3.5% in the other direction just above for moderate and severe intensity. Whether these are chance findings, I cannot know, but my findings emphasize once again that it is arbitrary and scientifically questionable to distinguish between adverse experiences and new medical history, and it gives the sponsor an opportunity to conceal important adverse events.

P1068:
The text in the narrative is incorrect. Pt. 40212, who experienced pyrexia for six days and withdrew from the trial, is listed under placebo in the main text but is described as having been vaccinated in the narrative: "was vaccinated with her first dose of quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine 20/40/40/20-mcg dose on 05-Sep-2002." On p3680, one can see the randomisation list; this patient got placebo.

P2163:
Synopsis of a substudy where three different lots were compared.

"Primary Objective: To demonstrate that the Final Manufacturing Process (FMP) results in quadrivalent HPV (Types 6,11,16,18) L1 VLP vaccine that, when given in a 3-dose regimen, induces consistent serum anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 responses 4 weeks Postdose 3."

This objective is not an appropriate research hypothesis. To demonstrate that is a foregone conclusion. It should have been to investigate if different vaccine lots give similar results for antibodies.

There were 500, 510 and 504 patients in the three groups. There was selective reporting of the safety data:

"Safety: The primary safety objective of this study was to demonstrate that a 3-dose regimen of quadrivalent HPV (Types 6,11,16,18) L1 VLP vaccine is generally well tolerated. The primary hypothesis stated that the quadrivalent HPV (Types 6,11,16,18) L1 VLP vaccine will be generally well tolerated in 16- to

23-year-old female subjects. Detailed safety summaries and analyses will appear in the CIN 2/3 Efficacy CSR. However, summaries of clinical adverse experiences, injection-site adverse experiences, systemic clinical adverse experiences and elevated temperatures by consistency lot for the subset of subjects in both the Consistency Lot substudy and the nonserious adverse experience (NSAE) substudy are provided in this CSR."

It is not clear where one might find the full safety data for the three lots comparison substudy. When I searched electronically for "CIN 2/3 Efficacy CSR" in the pdf of the final report for study 015, I found similar descriptions for overall safety on p3862: "Detailed safety summaries and analyses will appear in the CIN 2/3 Efficacy CSR." My electronic search did not yield any other returns than page 3862. After handsearching, I found out that "CIN 2/3 Efficacy CSR" is the main report of Future 2. This term was used at the top of the title page, which was page 2 in the report (and also on page 3; I found it nowhere else, apart from page 3862):

V501 Prot. No. 015
CIN 2/3 Efficacy Trial in Women

1. Title Page

Reference 015
Reports of Efficacy and Safety Studies
Study Report of Controlled Clinical Studies Pertinent to Indication

The first page of the main study report did not reveal that the "the CIN 2/3 Efficacy CSR" was the main study report:

Reference P015

A Randomized Worldwide, Placebo-Controlled, Double-Blind Study to Investigate the Safety, Immunogenicity, and Efficacy on the Incidence of HPV 16-/18-Related CIN 2/3 or Worse of the Quadrivalent HPV (Types 6, 11, 16, 18] L1 Virus-Like Particle (VLP) Vaccine in 16- to 23-Year-Old Women - The FUTURE II Study (Females United to Unilaterally Reduce Endo/Ectocervical Disease)

This is another example of how Merck's reports are not well organized. To write in a 5533-page main study report that "Detailed safety summaries and analyses will appear in the CIN 2/3 Efficacy CSR" suggests to the readers that this information is not in the main report but somewhere else, and where that exactly is remains obscure and will remain obscure for all readers but the most tenacious.

For safety, there were only data from the United States and Puerto Rico (p2169), with very few patients:

Clinical Adverse Experience Summary
(Days 1 to 15 Following Any Vaccination Visit)
Consistency Lot Substudy Population in the United States or Puerto Rico

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine					
	Consistency Lot 1 (N=67)		Consistency Lot 2 (N=69)		Consistency Lot 3 (N=71)	
	n	(%)	n	(%)	n	(%)
Subjects in analysis population	67		69		71	
Subjects without follow-up	1		1		2	
Subjects with follow-up	66		68		69	
Number (%) of subjects:						
with no adverse experience	4	(6.1)	8	(11.8)	6	(8.7)
with one or more adverse experiences	62	(93.9)	60	(88.2)	63	(91.3)

Merck only reported on 207 patients even though there were 1514 patients in the study:

SUBJECT/PATIENT DISPOSITION:	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine			
	Consistency Lot 1	Consistency Lot 2	Consistency Lot 3	Total
SCREENING FAILURES:				540
RANDOMIZED:	500	510	504	1514

V501 P015-20 CSR

This report is from 13 Nov 2018. This is a long-term follow-up based on registers in four countries: Denmark, Sweden, Norway, and Iceland; 2750 vs 2097 patients.

First Participant, First Visit	Last Participant, Last Visit	Database Lock Date
14-JUN-2002	31-MAR-2017	06-AUG-2018

"Cohort 1: Subjects who received qHPV vaccine in the base study with approximately 14 years of follow-up postvaccination (ie, 4 years within the base study and 10 years within the LTFU study).

Cohort 2: Subjects who received placebo in the base study and qHPV vaccine after completion of the base study and prior to entry into the LTFU. This cohort provided approximately 10 years of follow-up postvaccination."

"Following completion of the base study, subjects who received placebo were offered vaccination with qHPV vaccine."

There are many reasons why adverse experiences cannot be compared in an unbiased way in such follow-up studies. Only people who tolerated three vaccinations with active vaccine and have remained in the study were followed up, and "placebo" patients were told that they would now receive an active vaccine (see later, about a similar follow-up study from Colombia in Future 3), which would likely have biased their assessments of adverse experiences, also because there were more harms with the first vaccination than subsequent ones (see p103 above). The advantage of the randomisation is lost, and it is a selected subgroup of those in the "placebo" group who were vaccinated. The two groups are therefore no longer of similar size, but 2448 vs only 1888 (p168):

Table 14.3-1
Subject New Medical History Conditions
(Incidence >0% in One or More Vaccination Groups)
During the Long-term Follow-up
(All Subjects as Treated)

	Cohort 1		Cohort 2	
	n	(%)	n	(%)
Subjects in population	2,448		1,888	
With one or more new medical conditions	2,085	(85.2)	1,578	(83.6)

This report is not helpful in assessing the harms of the HPV vaccine. Merck does not try to distinguish between adverse experiences and "new medical history" but equates safety data with New Medical Conditions:

14.3 Safety Data

14.3.1 New Medical Conditions

Table 14.3-1
Subject New Medical History Conditions
(Incidence >0% in One or More Vaccination Groups)
During the Long-term Follow-up
(All Subjects as Treated)

There is no table on adverse experiences, only a long one (30 pages) about "new medical history."

V501 P015-21_Report #4

Interim report of long-term follow-up study (LTFU) from 22 Nov 2016.

P113:
"Overall, there was no specific pattern of new medical conditions within or between the 2 cohorts. In the base study, there were 4 subjects who had multiple sclerosis (MS). Two of the subjects had prevalent MS at enrollment and were subsequently vaccinated with qHPV vaccine, and 2 subjects developed MS during the study. Both of the latter subjects were diagnosed with MS during the base study, had received placebo, and did not receive qHPV vaccine subsequently. During the first reporting period of the LTFU there was 1 subject who had a new medical history condition of MS. In each of the second, third, and fourth reporting intervals there were 2 subjects who had a new medical history condition of MS. This brings the total number of subjects in the LTFU study with a new medical condition of MS to 7. These observed cases of MS are within the expected incidence for subjects of this age."

The final report from 2018 (P015-20 just above) lists 9 vs 5 cases of multiple sclerosis (p183). It also lists 13 vs 0 cases of concussion (p175), which the current report also does (p120).

Future 3, study P019

V501 P019 CSR

Study Initiation Date (FPI): 18-Jun-2004

Study Completion Date (LPLV): 30-Apr-2009
The final report is dated 17 November 2009.

The design is the same as for Future 1 and Future 2, with four years of follow-up, till month 48. The primary safety endpoint was also the same (vaccine-related serious adverse events), and the study is unreliable for the same reasons as Future 1 and Future 2.

P203:
"The primary safety endpoint was the proportion of subjects with vaccine-related SAE. The proportion of subjects with severe injection-site adverse experiences was also of special interest."

P4765:
"This CSR [clinical study report] focuses on summarizing all serious clinical adverse experiences, including any deaths or any serious adverse experience determined by the study coordinator to be related to the study vaccine or a study procedure."

P8:
"Safety: Administration of the qHPV vaccine was generally well tolerated. The proportions of subjects who reported serious adverse experiences were comparable among the qHPV vaccine group and the placebo group. Few subjects discontinued study participation due to an adverse experience."

P566:
"Table 12.1. Clinical Adverse Experience Summary (Vaccination and Follow-up Periods, Days 1 to 9999) (All Vaccinated Subjects)."

	qHPV (N=1908)		Placebo (N=1902)	
	n	(%)	n	(%)
Subjects in analysis population	1908		1902	
Subjects without follow-up	18		14	
Subjects with follow-up	1890		1888	
Number (%) of subjects:				
with no adverse experience	245	(13.0)	353	(18.7)
with one or more adverse experiences	1645	(87.0)	1535	(81.3)
injection-site adverse experiences	1450	(76.7)	1213	(64.2)
systemic adverse experiences	1121	(59.3)	1135	(60.1)
with vaccine-related† adverse experiences	1565	(82.8)	1391	(73.7)
injection-site adverse experiences	1449	(76.7)	1213	(64.2)
systemic adverse experiences	746	(39.5)	697	(36.9)
with serious adverse experiences	14	(0.7)	16	(0.8)
with serious vaccine-related adverse experiences	0	(0.0)	0	(0.0)
who died	7	(0.4)	1	(0.1)
discontinued‡ due to an adverse experience	7	(0.4)	2	(0.1)
discontinued due to a vaccine-related adverse experience	5	(0.3)	2	(0.1)
discontinued due to a serious adverse experience	2	(0.1)	0	(0.0)
discontinued due to a serious vaccine-related adverse experience	0	(0.0)	0	(0.0)

† Determined by the investigator to be possibly, probably, or definitely related to the vaccine.
‡ Discontinued = Subject discontinued from therapy.
Percentages are calculated based on the number of subjects with follow-up.

There is no list of individual MedDRA terms, only this overall summary. More people had serious vaccine-related injection site and systemic adverse experiences in the vaccine group than in the "placebo" group.

No listing of numbers of patients experiencing adverse events according to MedDRA terms, which other Merck reports have, and does not show this table.

P575:
"One new subject in the qHPV group (AN 80655) and one new subject in the placebo group (AN 82000) with nonfatal serious clinical adverse experiences were mistakenly not incorporated into the Clinical Trials Systems (CTS) database but were reported in the worldwide adverse experience system (WAES) database. These adverse experiences will be added into the database. These 2 SAEs are not noted in Table 12-1 or in Table 12-3."

I did not see an explanation in the more than 100,000 pages I read about Merck's trials what Merck's procedures were for including serious adverse experiences in its databases and why there were two possibilities when Merck conducted its trials.

Even though this is the final report for Future 3, two serious adverse events are missing from the tables. Table 12.1 is the summary table just above. Table 12.3 (p577) is a "Listing of Subjects With Serious Clinical Adverse Experiences (Entire Study Period) (All Vaccinated Subjects)."

There are narratives for these two serious adverse events on p575-6, plus a third one.

According to table 12-1 and the text on p575, there should be narratives of 15 events on the vaccine and 17 on "placebo," but they appeared in several places in the report, and some of them were not included, even though it was the final report but were supposed to be in an earlier report. Below are my comments (A means the final report: V501 P019 CSR and B the interim report: V501 P019 V1 CSR).

PA575:
"12.2.4.2 Nonfatal Serious Adverse Experiences
In addition to the 8 fatalities described in Section 12.2.4.1, 24 subjects (9 in the qHPV group and 15 in the placebo group) experienced nonfatal serious clinical adverse experiences during the entire study period. A listing of subjects with serious clinical adverse experiences (fatal and nonfatal) can be found in Table 12-3. Non-fatal serious clinical adverse experiences reported since the endpoint-driven CSR are noted in bold type."

It is not correct that Table 12-3 on pA577 lists subjects with serious clinical adverse experiences (fatal and nonfatal). Two cases are missing in this table, AN 80655 on qHPV and AN 82000 on adjuvant, for which there are narratives on pA575 (both nonfatal). There is a third narrative in the text, for AN 84451 on adjuvant (nonfatal), which <u>is</u> listed in table 12-3. It therefore appears that the report writer forgot to list two of these three events in the summary table, which describes 14 patients on qHPV (7 fatalities) and 16 on adjuvant (1 fatality).

Two of the 8 patients who died, AN 81322 and AN 81654, are also listed in "Table 12-4. Listing of Subjects Discontinued Due to Clinical Adverse Experiences (Entire Study Period) (All Vaccinated Subjects)" (pA586). It is not clear why only 2 of the 8 patients who died are listed in this table. AN 81654, which is listed, developed various symptoms on Day 203 (03-Mar-2006) Postdose 3, and "died on 05-Mar-2005" (pB463), presumably a typing error, as the patient died one year before she developed her symptoms. Another patient, AN 81011, who was diagnosed with breast cancer on "approximately Day 250 (22-Feb-2006) Post

dose 3" (pA568), is not listed. In both cases, the events occurred after the stipulated 7-months follow-up period, so it is not obvious why only one of them was listed.

PB468:
"In addition to the 5 fatalities described in Section 12.2.4.1, 26 subjects (11 in the qHPV group and 15 in the placebo group) experienced nonfatal serious clinical adverse experiences during the entire study period. A listing of all subjects with serious clinical adverse experiences (fatal and nonfatal) can be found in Table 12-19. Individual subject narratives of the serious clinical adverse experiences can be found in Section 14.5.2."

This is not correct. In section 14.5.2 (pB1079), there are only 14 narratives (4 for qHPV, 10 for adjuvant) and not 31 as the text stipulates.

Concerning narratives for nonfatal serious adverse experiences for 7 patients: 80058, 80619 and 83827 on qHPV, and 80212, 81687, 82043 and 84815 on adjuvant, I searched these numbers in the text in report B and found narratives for 6 of them. However, they were not in section 14.5.2 as stipulated, but in "14.5.3 Serious Clinical Adverse Experiences Reported During Subject Pregnancies."

As to a narrative for patient 82043, I also searched report A, and found one, on p5535. This narrative was different to the others. It was not part of the text but was a WAES adverse experience report that contained a narrative:

WAES ADVERSE EXPERIENCE REPORT

WAESNUM: **0702COL00011 v 3**
placebo (unspecified)
Initial Report Date : 27-Feb-2007

Protocol # 019 Extension # 0 Amendment # 2 Site # 0041 Allocation # 82043

Action Taken: None

AE/Lowest Level Term/Reported	Onset	Ser	Assn	CCA	Died	Hos	Dis	LT	CA	Cong	OD	OM	CC	End	Outcome
Ectopic pregnancy	[redacted]2005	Y	N		N	Y	N	N	N	N	N	N	N	N	1
Ectopic pregnancy ectopic pregnant															
Drug exposure during pre	[redacted]2005	N	N		N	N	N	N	N	N	N	N	N	N	1
Vaccine exposure during pregnanc viral vaccine exposure during preg															

Cause of Death:

Primary Therapy	Lot No.	Total Daily Dose / Rte	Start	Stop	Duration
INJ placebo (unspecified)		1 IM	20-Apr-2005		
INJ placebo (unspecified)		1 IM	22-Jun-2005		
INJ placebo (unspecified)		1 IM	10-Oct-2005		

Secondary Therapy	Lot No.	Total Daily Dose / Rte	Start	Stop	Duration

Concomitant	Lot No.	Total Daily Dose / Rte	Start	Stop	Duration

I found that there are narratives not for 14 patients, or 30 patients, or 31 patients, or 32 patients (all these options were mentioned), but for 33. There is also a narrative for patient AN 80560 who first received two injections with the adjuvant and then one with the vaccine, in violation of the trial protocol (pB1082).

P615:
"Table 12-9. Number (%) of Subjects With New Medical History (Incidence ≥1% in One or More Vaccination Groups) by System Organ Class (Vaccination Period) (All Vaccinated Subjects)."

It is not clear what "vaccination period" means but it seems to be day 1 to month 7:

P614:
"12.6 New Medical History
Table 12-9 displays the number and percentage of subjects who reported new medical conditions with an incidence >1% in either treatment group during the vaccination period. The most common new medical conditions reported during the Day 1 to Month 7 period were …"

However, safety data are collected in the same time period, as stated on p564 and also on p227 in the main study report for Future 2: "A summary of safety data collected for Day 1 through Month 7 vaccination periods was presented."

P618:
Table 12-10. Number (%) of Subjects With New Medical History (Incidence ≥1% in One or More Vaccination Groups) by System Organ Class (Follow-Up Period) (All Vaccinated Subjects).

Merck omitted rare events (1% occurrence or less). All events should have been included (which can be found in a later table). As there were a little over 1900 patients in each group, Merck's selective reporting effectively left out all events that occurred in 19 or fewer patients. This is not right.

P624:
There were a large number of tables, 186 in total. We do not see a table of all events before suddenly a table of all events (Incidence >0%) (After Day 1) that were "Potentially Consistent with Autoimmune Phenomena" appears (Table 12-11). There were 65 vs 70 such events:

Table 12-11

Number (%) of Subjects With New Medical History
(Incidence >0% in One or More Vaccination Groups) by System Organ Class
(After Day 1) (All Vaccinated Subjects) Potentially Consistent with Autoimmune Phenomena

	qHPV (N= 1908)		Placebo (N= 1902)	
	n	(%)	n	(%)
Subjects in analysis population	1908		1902	
Subjects with one or more new Medical History	65	(3.4)	70	(3.7)
Subjects with no new secondary diagnosis	1843	(96.6)	1832	(96.3)
Endocrine Disorders	**22**	**(1.2)**	**31**	**(1.6)**
Basedow's Disease	2	(0.1)	1	(0.1)
Goitre	1	(0.1)	4	(0.2)
Hyperthyroidism	2	(0.1)	2	(0.1)
Hypothyroidism	15	(0.8)	24	(1.3)
Thyroiditis	1	(0.1)	0	(0.0)
Toxic Nodular Goitre	1	(0.1)	0	(0.0)

Why Merck focused on autoimmune disorders in its HPV vaccine trials is unexplained. Merck also excluded females with known autoimmune disorders from participating in its vaccine trials.

P627:
"13. Discussion and Conclusions."

We still haven't seen a table of <u>all</u> new medical events before the findings are being discussed. To only show events with an incidence ≥1% will miss many events, as illustrated by, for example, this section of the table on p616:

Musculoskeletal And Connective Tissue Disorders	**81**	**(4.2)**	**80**	**(4.2)**
Back Pain	19	(1.0)	20	(1.1)

Back pain is the only MedDRA term mentioned but this event only constitutes 24% (39/161) of the total musculoskeletal and connective tissue disorder events. We don't know what the other events were.

P638:
"13.1.8.1 Overall Safety Findings.
Administration of the qHPV vaccine was generally well tolerated. The proportions of subjects who reported a serious adverse experience Day 1 to 15 following any vaccination visit were comparable among the qHPV vaccine group and the placebo group. Few subjects discontinued study participation due to an adverse experience."

P684-724:
"Table 14-8. Number (%) of Subjects With New Medical History (Incidence >0% in One or More Vaccination Groups) by System Organ Class (Vaccination Period) (All Vaccinated Subjects)."

After all these pages, this is still not the table of interest, as it only refers to the vaccination period, i.e. only up to month 7 even though all the Future trials ran for four years. This is irrelevant if one wants to study the safety of a vaccine. This is the penultimate of the 186 tables.

P725-795:
Table 14-9. Number (%) of Subjects With New Medical History (Incidence >0% in One or More Vaccination Groups) by System Organ Class (Follow-Up Period) (All Vaccinated Subjects).

This is the last of the 186 tables. If a reviewer for a drug regulator should ever come this far in a Merck study report, I wonder if that person would know if the events presented in the first type of table, usually called "After Day 1" but in this case "Vaccination period" (p684) are incorporated in the other type of table, "Follow-up period." Logically, this should be the case, since "After Day 1" does not have an upper limit. "After Day 1" also includes events noted during follow up. Confusing the issues further, the follow-up period is also called "post month 7." I checked if the data in Table 12-9 on p615, "incidence ≥1% … (Vaccination period)" were included in the data in Table 12-10 on p618, "incidence ≥1% … (Follow-Up Period)." These events seemed to be mutually exclusive, which the main text also indicated (p614). For example, for influenza, there were 19 (1.0%) vs 25 (1.3%) cases in Table 12-9 but there was no entry for influenza in Table 12-10.

It can be seen on p614 that "Vaccination period" for Future 3 is not the same as "After Day 1" for Future 2 and Future 3: "Table 14-8 and Table 14-9, in Section 14.4 summarize, by system organ class, the number and percentage of subjects with new medical conditions with an incidence of >0% in at least one vaccination group Day 1 through Month 7 and after Month 7, respectively."

It appears there is no table that reports all the events that occurred in the whole trial period of 4 years, in all the reports of the Future trials. If the aim is to study whether the vaccine causes harms such as POTS and CRPS, which may be diagnosed both early, within the first 7 months, or later, after the first 7 months, such an analysis would be necessary. Without a table that includes the whole 4-year period, any attempt at elucidating rare but important harms will run into the double counting problem, as the same patient may suffer from fainting both before and after 7 months, for example.

The published report for this study[45] was problematic for multiple reasons.

[45] Muñoz N, Manalastas R Jr, Pitisuttithum P, et al. Safety, immunogenicity, and efficacy of quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine in women aged 24-45 years: a randomised, double-blind trial. Lancet 2009;373:1949-57.

1) The study was called “placebo-controlled,” which was not true.

2) Even though safety was a primary objective, which the Methods section in the *Lancet* article also stated: “The primary safety objective was to show that a three-dose regimen of quadrivalent HPV vaccine was generally well tolerated,” the only mention in the abstract of safety was: “We recorded no vaccine-related serious adverse events.” For a vaccine to be given to healthy people, of which very few will experience any benefit, non-serious adverse events are very important. Addressing only vaccine related serious adverse events, which in the large Gardasil 9 trial constituted only 0.05% of all adverse events (see above), is a serious violation of generally accepted research practices. See also item four below.

3) The statistical analysis section contained nothing about testing for safety.

4) Even though the trial register noted that the time frame for reporting serious adverse events was four years,[46] the Results section only mentioned serious adverse events, and only if they had occurred within the first two weeks after each vaccination. This is highly inappropriate for a four-year trial and for which 90% of the serious adverse events are expected to occur outside the two-week intervals (see page 104 below). It might be defensible to take an interest only in serious adverse events if the patients have life-threatening cancer and are treated with cytotoxic drugs, but not for a vaccine to be given to healthy people.

As the trial ended in April 2009 and was published one month later, there should have been plenty of time to include the full data set. There cannot have been any need to publish quickly, as two larger trials with the same design, the Future 1 and 2 trials, had been published two years earlier.

Merck reported 3 vs 7 patients with serious adverse events in *Lancet* within the two-week periods after each vaccination, but this was inaccurate. In the main study report (V501 P019 CSR), there was a table on page 577 that showed when the serious adverse events had occurred. To be consistent, I used the summary tables for my meta-analyses even when there were contradictory data elsewhere. In this case, there were 14 vs 16 events, both in the summary table and in the table on page 577. But, as noted above, two more serious adverse events, one of Gardasil and one on adjuvant, were described in the text, on page 575, which “were mistakenly not incorporated into the Clinical Trials Systems (CTS) database but were reported in the worldwide adverse experience system (WAES) database.” Even when I included these two extra patients, there were only 3 vs 6 patients for which the serious adverse event (the first one, if there were more than one) had occurred within the two-week periods after each vaccination (the other events had occurred from day 44 until day 1059 after a vaccination). Merck reported 14 vs 16 in its summary table in the study report, but also two more cases, and there were also 15 vs 15 in the US trial register. Thus, there were four sets of data for serious adverse events: 15 vs 17, 14 vs 16, 3 vs 7 and 3 vs 6.

5) There was a table of adverse events in the article, which I compared with the data in Merck’s study report:

[46] https://clinicaltrials.gov/ct2/show/results/NCT00090220?view=results

	Merck's study report		Journal article	
Subjects with adverse events	**Gardasil**	**Adjuvant**	**Gardasil**	**Adjuvant**
adverse events	1645	1535	1642	1532
injection-site adverse events	1450	1213	1450	1212
systemic adverse events	1121	1135	1118	1131
vaccine related adverse events	1565	1391	1565	1389
injection-site adverse events	1449	1213	1449	1212
systemic adverse events	746	697	745	695
serious adverse events	14	16	3	7

There were discrepancies for all the events, with differences of up to 4 patients, apart from the difference in serious adverse events (see just above).

6) There were no p-values or confidence intervals in the table of adverse events, even though safety was a primary objective, and there were no comments about the large difference in injection-site adverse events ($p = 6 \times 10^{-17}$) or the non-significant difference in systemic adverse events considered vaccine related ($p = 0.11$).

7) There was nothing about safety in the Discussion and no conclusion about safety other than the meaningless sentence in the abstract: “We recorded no vaccine-related serious adverse events” (none of the 3 vs 7 events were considered vaccine related).

8) There was no mention of new medical history at all even though this is about adverse events; even though Merck included this in its study reports; and even though there were 1458 such events.

9) There was no mention that some patients died. Whether considered drug related or not, deaths must be reported in a clinical trial. Merck’s reporting to the US trial register, which was last updated in 2017, was confusing. The numbers were different to those in Merck’s study report, e.g. there seemed to be no deaths, even though 7 vs 1 died (whereas the numbers of serious adverse events were correct):

All-Cause Mortality

	qHPV Vaccine: Base Study		Placebo: Base Study	
	Affected / at Risk (%)		Affected / at Risk (%)	
Total	--/--		--/--	

Serious Adverse Events

	qHPV Vaccine: Base Study		Placebo: Base Study	
	Affected / at Risk (%)	# Events	Affected / at Risk (%)	
Total	15/1890 (0.79%)		17/1888 (0.90%)	

There were numerous tables, e.g. 26 for primary outcomes, 8 for secondary outcomes and 7 for other prespecified outcomes. I found only one entry where I could see the number of deaths:

4. Primary Outcome

Title	Number of Participants With an SAE Resulting in Death After Vaccine Administration
Description	An adverse event (AE) is any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the study vaccine. Any worsening of a preexisting condition which is temporally associated with the use of the study vaccine is also an adverse event. A serious adverse event (SAE) is an AE that results in death, is life threatening, results in persistent or significant disability or incapacity, results in or prolongs a hospitalization, is a congenital anomaly or birth defect, is a cancer, or is an overdose.
Time Frame	qHPV in Base Study: Up to Month 120; Placebo in Base Study: approximately Month 60 up to Month 120

Outcome Measure Data

Analysis Population Description

Participants who received >=1 qHPV vaccination in the Base Study or EXT1 and had safety follow-up

Arm/Group Title	qHPV in Base Study: All Participants	Base Study: Placebo
Arm/Group Description:	Participants received qHPV vaccination at Day 1, Month 2, and Month 6 in the Base Study	Participants who received placebo or an incomplete qHPV regimen in the Base Study and were offered open-label qHPV vaccine starting at approximately Month 60 in EXT1
Overall Number of Participants Analyzed	1890	1327
Measure Type: Number Unit of Measure: Participants		
	8	4

There seemed to be 8 vs 4 deaths while there were 7 vs 1 deaths in Merck's study report (and none in *Lancet*). The discrepancy between 12 and 8 deaths is unexplained.

Nine of the 18 authors were employees of Merck and potentially owned stock or stock options in Merck; four had received fees from Merck or acted as consultants (which are usually salaried); two had received grants from Merck; two had undertaken HPV vaccine studies for Merck; and six were members of the Merck HPV steering committee. Only three authors had not declared any conflicts.

This was not a setup that was likely to lead unbiased trial conduct and unbiased reporting. On top of this, the principal investigators had an agreement with Merck that restricted their rights to discuss or publish trial results after the trial was completed.[47]

V501 P019 V1 CSR

The report is dated 29 November 2007, which is two years before the final report above.

Index on p9.

P4:
"Each dose of qHPV vaccine contained 20 µg HPV 6 L1 VLP, 40 µg HPV 11 L1 VLP, 40 µg HPV 16 L1 VLP, and 20 µg HPV 18 L1 VLP, along with 225 µg of aluminum as amorphous aluminum hydroxy phosphate sulfate (Merck Aluminum Adjuvant). Each dose of placebo contained Merck standard aluminum diluent (225 µg alum) in normal saline, USP (NaCl 0.9%)."

Again, it is grossly inaccurate to write that the "placebo" just contained a "diluent" (see above, under Future 2).

P417:
"12.2.1 Brief Summary of Adverse Experiences.
Table 12-1 displays a summary of clinical adverse experiences reported by subjects at any time during the study through visit cut-off date of 13-Jul-2007."

[47] https://clinicaltrials.gov/ct2/show/results/NCT00090220?view=results

The Future trial reports did not list all "new medical history" events that occurred in the whole trial period, however, there is a table, including all events, also those beyond the vaccination period of 7 months, but not for new medical history, only for clinical adverse experiences. It is only a summary table showing numbers with adverse events. None of the report's 216 tables show numbers of patients with MedDRA defined events, as in other Merck trials.

Since it is wholly arbitrary and obscure whether an event should be called an adverse experience or new medical history, reporting the totals only for adverse events confuses the issues further.

P418:
"Table 12-3 displays the number and percentage of subjects who reported any clinical adverse experience by maximum intensity rating within 15 days following any vaccination visit by vaccination group. Overall, the number of mild or moderate adverse experiences per subject with follow-up was slightly higher in the qHPV vaccine group. The proportion of subjects who reported a severe intensity adverse experience was higher in the group that received qHPV vaccine compared with the placebo group."

The text on p418 is incorrect. The table the text refers to, table 12-3 is not about "any clinical adverse experience" but only about injection-site adverse experiences, see table 12-3 just below. Furthermore, I was unable to find any data substantiating this narrative account. "Any clinical adverse experience" includes both injection-site adverse reactions and systemic adverse reactions. I found a table of systemic adverse reactions by maximum intensity rating on p452 (table 12-12, see below) but none about "any clinical adverse experience." These data are missing. None of the 216 tables in the report were about this. I went through all of them manually and also searched in the report on "any clinical adverse experience," but I did not find anything, apart from the narrative on p418.

P423:

Table 12-3

Number (%) of Subjects Who Reported Specific Injection-Site Adverse Experiences by Maximum Intensity Rating
(Days 1 to 5 Following Any Vaccination Visit) (All Vaccinated Subjects)

	qHPV (N= 1908)		Placebo (N=1902)	
	n	(%)	n	(%)
Number of subjects with follow-up	1889		1886	
Number (%) of subjects without Injection-Site adverse experiences	446	(23.6)	676	(35.8)
Number (%) of subjects with Injection-Site adverse experiences	1443	(76.4)	1210	(64.2)
Number (%) of subjects by maximum intensity rating of Injection-Site adverse experiences				
Mild	907	(48.0)	885	(46.9)
Moderate	447	(23.7)	277	(14.7)
Severe	89	(4.7)	48	(2.5)

Percentages are calculated based on the number of subjects with follow-up.
N = Number of subjects who received only the clinical material indicated in the given column.
For the measured adverse experiences of redness and swelling, Mild = 0 to 1 inch, Moderate >1 to <2 inches, and Severe >2 inches. Subjects were counted by their worst severity rating.

There are far more patients with injection-site reactions in the vaccine group than in the "placebo" group, 1443 vs 1210 ($p = 2 \times 10^{-16}$), and far more of these reactions are severe, 89 vs 48 ($p = 0.0005$, Fisher's exact test, my calculation). There were also far more that were severe or moderate, 536 vs 325 ($p = 3 \times 10^{-16}$, my calculation). Merck did not provide any such significance tests.

I could not find any table listing the severity of systemic adverse events in this Future 3 report going beyond the two-week intervals after each vaccination, only many tables listing various injection-site symptoms. In the final report, I searched "Maximum Intensity Rating." There were many entries and tables, but they were all about what happened when all patients, after the randomised trial phase was over, were offered a dose

of the active vaccine. There were only 104 vs 120 patients in the two groups. Later, I found a table 12-12 in the earlier report listing the severity of systemic adverse events but only for the two-week intervals.
P434:

Table 12-8

Comparison of qHPV Vaccine and Placebo Groups With Respect to the Number (%) of Subjects Who Reported Severe Injection-Site Adverse Experiences
(Days 1 to 5 Following Any Vaccination Visit)

	qHPV Vaccine (N= 1,908)		Placebo (N= 1,902)		Risk Difference (qHPV Vaccine - Placebo)	95% Confidence Interval
	n	(%)	n	(%)		
Number of subjects without follow-up	19		16			
Number of subjects with follow-up	1889		1886			
Number (%) of subjects with severe injection-site adverse experiences Days 1 to 5 following any vaccination visit	90	(4.8)	48	(2.5)	2.20	(1.0 , 3.5)

Percentages calculated as 100*(n/number of subjects with follow-up).
N = Number of subjects who received only the clinical material indicated in the given column. There were 7 subjects (qHPV vaccine=2, placebo=5) who received mixed treatment regimen who were not included in the summaries provided in this table.
n = Number of subjects with the indicated characteristic.
qHPV = Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine.

In this table, the number of patients with severe injection-side experiences are 90 vs 48, but they were 89 vs 48 in table 12-3. This discrepancy was not explained.

P435:
"The proportion of subjects who reported pain in the extremity was higher (the lower limit if the 95% Cl of the difference in percentages was greater than 0.0%) in the qHPV vaccine group than in the placebo group (see Table 12-10)" (which only showed events occurring in at least 1% of the patients).

This is the first I saw of any mention of pain in extremities, which is a key symptom in CRPS.

P435:
"For both vaccination groups the frequency of systemic clinical adverse experiences were [sic] somewhat higher following vaccination Visit 1" (there are tables for each visit separately).

P437:

Table 12-9

Number (%) of Subjects With Systemic Clinical Adverse Experiences (Incidence ≥1% in One or More Vaccination Groups) by System Organ Class
(Days 1 to 15 Following Any Vaccination Visit)

	qHPV (N=1908)				Placebo (N=1902)			
	All Adverse Experiences		VR		All Adverse Experiences		VR	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in analysis population	1908				1902			
Subjects without follow-up	19				16			
Subjects with follow-up	1889				1886			
Number (%) of Subjects with one or more systemic adverse experiences	1118	(59.2)			1131	(60.0)		
Number (%) of Subjects with no systemic adverse experience	771	(40.8)			755	(40.0)		

In this table 12-9, systemic adverse experiences only counted if the incidence was at least 1% in one of the vaccination groups, and only if they occurred within the first two weeks following any of the three

vaccination visits. In table 12-1 (p419), the systemic adverse experiences had no 1% limitation in order to count, and they included both vaccination and follow-up periods (days 1 to 9999):

Table 12-1

Clinical Adverse Experience Summary
(Vaccination and Follow-up Periods, Days 1 to 9999) (All Vaccinated Subjects)

	qHPV (N=1908)		Placebo (N=1902)	
	n	(%)	n	(%)
Subjects in analysis population	1908		1902	
Subjects without follow-up	19		16	
Subjects with follow-up	1889		1886	
Number (%) of subjects:				
with no adverse experience	244	(12.9)	352	(18.7)
with one or more adverse experiences	1645	(87.1)	1534	(81.3)
injection-site adverse experiences	1450	(76.8)	1212	(64.3)
systemic adverse experiences	1121	(59.3)	1133	(60.1)

It is odd that table 12-9, with its two serious limitations (at least a 1% incidence and only if reported within two-week intervals), reports 1118 vs 1131 patients with systemic adverse experiences while table 12-1, with no such limitations, reports only five more patients (0.2% more), 1121 vs 1133.

I searched to see how these two types of tables compared with Future 2 and Future 1, but only found both types of tables in the final report for Future 1:

P3920 in Future 1:

Clinical Adverse Experience Summary
(Days 1 to 15 Following Any Vaccination Visit)

	FMP Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=1779)		PMM Monovalent HPV 16 L1 VLP Vaccine (N=304)		Placebo (N=1789)	
	n	(%)	n	(%)	n	(%)
Subjects in analysis population	1779		304		1789	
Subjects without follow-up	27		5		39	
Subjects with follow-up	1752		299		1750	
Number (%) of subjects:						
with no adverse experience	110	(6.3)	21	(7.0)	173	(9.9)
with one or more adverse experiences	1642	(93.7)	278	(93.0)	1577	(90.1)
injection-site adverse experiences	1540	(87.9)	250	(83.6)	1376	(78.6)
systemic adverse experiences	1194	(68.2)	211	(70.6)	1139	(65.1)

P13 in Future 1:

Clinical Adverse Experience Summary
(Days 1 to 9999 Following Any Vaccination Visit)

	qHPV (N=2713)		HPV 16 L1 VLP Vaccine (N=304)		Placebo (N=2724)	
	n	(%)	n	(%)	n	(%)
Subjects in analysis population	2713		304		2724	
Subjects without follow-up	40		5		52	
Subjects with follow-up	2673		299		2672	
Number (%) of subjects:						
with no adverse experience	176	(6.6)	21	(7.0)	267	(10.0)
with one or more adverse experiences	2497	(93.4)	278	(93.0)	2405	(90.0)
injection-site adverse experiences	2353	(88.0)	250	(83.6)	2133	(79.8)
systemic adverse experiences	1746	(65.3)	211	(70.6)	1701	(63.7)

The first table has fewer subjects than the second one because it represents a substudy whose purpose was to compare the immunogenicity of the final manufacturing process with the pilot manufacturing process (protocol 012).

There were 3447 subjects with systemic adverse experiences in the two main vaccine groups (ignoring the few patients randomised to monovalent vaccine) among 5437 subjects (63%) when there were no time limitations, and 2333 among 3568 subjects (65%) with the limitation that the events should occur within two weeks after each vaccination. One would have expected the opposite: more systemic adverse experiences when there was no time constraint.

Coming back to Table 12-9 about systemic adverse experiences in the Future 3 interim report:

	qHPV (N=1908)				Placebo (N=1902)			
	All Adverse Experiences		VR		All Adverse Experiences		VR	
	n	(%)	n	(%)	n	(%)	n	(%)
Infections And Infestations(Cont.)								
Tonsillitis	18	(1.0)	5	(0.3)	22	(1.2)	5	(0.3)
Upper respiratory tract infection	37	(2.0)	16	(0.8)	25	(1.3)	7	(0.4)
Injury, Poisoning And Procedural Complications	**24**	**(1.3)**	**4**	**(0.2)**	**25**	**(1.3)**	**1**	**(0.1)**
Musculoskeletal And Connective Tissue Disorders	**196**	**(10.4)**	**99**	**(5.2)**	**167**	**(8.9)**	**57**	**(3.0)**
Back pain	45	(2.4)	12	(0.6)	55	(2.9)	12	(0.6)
Myalgia	27	(1.4)	16	(0.8)	14	(0.7)	11	(0.6)
Neck pain	19	(1.0)	7	(0.4)	13	(0.7)	3	(0.2)
Pain in extremity	88	(4.7)	58	(3.1)	42	(2.2)	19	(1.0)

Pain in extremity, a key symptom both for POTS and CRPS, was more conspicuous when judged vaccine related (VR), 58 vs 19, than when also non-vaccine related events were included, 88 vs 42. This becomes clearer if one calculates the two risk ratios: risk ratio 3.04 for vaccine related events, (58/1908)/(19/1902), and 2.09 for all events. The difference in vaccine related pain in extremity was highly statistically significant (p = 0.000,008, Fisher's exact test, my calculation). For all events, the difference was also highly significant (p = 0.000,05).

For events that could be related to POTS, there was a similar tendency, but the risk ratios were rather similar, 0.98 vs 0.96 for dizziness and 1.07 vs 1.01 for headache:

Dizziness	79	(4.2)	55	(2.9)	82	(4.3)	56	(3.0)
Headache	526	(27.8)	401	(21.2)	518	(27.5)	375	(19.9)

P444:
Table 12-10 is a similar table but with risk differences and confidence intervals:

Adverse Experience Term	qHPV Vaccine (N= 1,908)		Placebo (N= 1,902)		Risk Difference (qHPV Vaccine - Placebo)	95% Confidence Interval
	n	(%)	n	(%)		
Musculoskeletal And Connective Tissue Disorders	**196**	**(10.4)**	**167**	**(8.9)**	**1.50**	**(-0.4 , 3.4)**
Back pain	45	(2.4)	55	(2.9)	-0.50	(-1.6 , 0.5)
Myalgia	27	(1.4)	14	(0.7)	0.70	(0.0 , 1.4)
Neck pain	19	(1.0)	13	(0.7)	0.30	(-0.3 , 1.0)
Pain in extremity	88	(4.7)	42	(2.2)	2.40	(1.3 , 3.6)

This table violated the declared primary safety endpoint which was the proportion of subjects with vaccine-related serious adverse events (p203 in final report):

9.7.1.3.2 Primary and Other Safety Endpoints

The primary safety endpoint was the proportion of subjects with vaccine-related SAE.

By including non-vaccine-related serious adverse events, the random noise increases, which makes it more difficult to find out if the vaccine might cause CRPS or POTS. Even though the primary endpoint was serious vaccine-related adverse events, it is clear in Merck's reports that Merck emphasizes those events that the investigators consider vaccine-related, whether serious or not.

It is of interest that dizziness and headache occurred together in some patients, as these are key symptoms for POTS that often come together (the total number of nervous system events was 597 but adding the three symptoms, one gets 642):

Nervous System Disorders	**597**	**(31.6)**	**590**	**(31.3)**	**0.30**	**(-2.7 , 3.3)**
Dizziness	79	(4.2)	82	(4.3)	-0.20	(-1.5 , 1.1)
Headache	526	(27.8)	518	(27.5)	0.40	(-2.5 , 3.2)
Migraine	37	(2.0)	40	(2.1)	-0.20	(-1.1 , 0.8)

P508:
"12.2.8 New Medical History"

Like in the final report, there is no table that includes all events from day 1 till the follow-up period ended.

P529:
"13.1.8.1 Overall Safety Findings. Administration of the qHPV vaccine was generally well tolerated."

This was the foregone conclusion drawn before the trial even started.

V501 P019 x02 (aka P019-21) CSR

Index on p25 and on p285.

P1:
"Long-Term Follow-Up Safety, Immunogenicity, and Effectiveness Observational Study in Columbian Women."

Trial Initiation Date: 14-Jan-2011
Trial Completion Date: 24-March-2016
Report Date: 14-Sep-2016

P3-5:
"This trial was conducted at 5 trial centers in Colombia ... An extension phase (V501-019-10) offered qHPV vaccine to subjects who had received placebo or who had received incomplete qHPV vaccine regimens in the base study ... No study vaccinations were provided within the context of this LTFU study ... Safety endpoints. Serious Adverse Experiences (SAEs) (as defined in the detailed protocol) judged by the study investigator to be possibly, probably, or definitely related to prior administration of qHPV vaccine or a study procedure; death of a study subject; new medical conditions; pregnancy and infant follow-up outcomes."

As explained above, in relation to a similar long-term follow-up study of Future 2 (see p108), this report is unhelpful in relation to safety because comparisons between the two groups will be biased.

P6:
This is a flow chart. Numbers of patients are described as 1910 vs 1907, of which 1610 (42%) were from Colombia. Of these, 685 were in the early vaccination group, 651 in the catch-up vaccination group and 25 did not get the vaccine, 1361 patients in total.

P23:
"Safety summaries were conducted at Year 6, Year 8, and Year 10. The primary safety analysis was conducted in subjects enrolled in the LTFU study who had received at least 1 dose of qHPV vaccine in the base study or V501-19-10 extension."

"Summary
No SAEs were judged by the investigator to be related to the qHPV vaccine in the V501-019-21 LTFU study. A total of 3 events were reported as SAEs for 3 subjects: Two SAEs resulted in the death of the subject, 1 subject in the EVG died due to ventricular tachycardia and 1 subject in the CVG died due to leiomyosarcoma. A third subject experienced a deep vein thrombosis (DVT), which was reported to have resolved. While this DVT event did not meet the criteria for reporting in the LTFU study, it was included in previous analyses (Years 6 and 8 interim analyses) and was therefore included in the SAE listing for this report."

Additional errors, contradictions, and missing data in the Future reports

The protocol for Future 2 states on p776 in the final report (V501 P015 CSR_protocol P005-10 pg 1917) that the investigator will evaluate "all adverse experiences" as to their maximum intensity:
— Mild is awareness of sign or symptom, but easily tolerated;
— Moderate is discomfort enough to cause interference with usual activity;
— Severe is incapacitating with inability to work or do usual activity.

The protocols for Future 1 and 3 have the same information (p129 in V501 P01 CSR_with P013-10 pg 712 and p156 in V501 P019 CSR, respectively), but they explicitly divide the adverse experiences into "injection-site adverse experiences" and "systemic clinical adverse experiences."

For Future 3, I found tables that had divided injection site adverse experiences and systemic adverse experiences according to whether they were mild, moderate or severe (p423 and 452 in V501 P019 V1 CSR). I was unable to analyze events that included all the randomised patients in all three Future trials because no such tables for Future 1 and Future 2 appear to exist.

In my review of the three Future trials, which are large pivotal trials for Gardasil, the reports of which contain a great amount of detail (50,000+ pages in total), I found the following:

After the randomised trial phase of 6 months and the follow-up period of four years was over, patients in the Future trials were offered Gardasil, which meant that those on "placebo" (Merck's adjuvant) were offered three Gardasil injections and that those on Gardasil received a fourth vaccination (V501 P015 CSR_protocol P005-10 pg 1917, p1918-9). In Future 2, 6019 vs 6031 girls had follow-up data, but data were available in the final study report from only 113 vs 127 who received a fourth vaccination. This final report contained errors.

P5224:
“4.5.1 Adverse Experience Summary.
Primary Series of GARDASIL™ Plus Challenge Dose of GARDASIL™.
Table 4-20 presents a clinical adverse experience summary Days 1 to 15 following vaccination Visit 4 for subjects enrolled in the extension of Protocol 007 who received a fourth dose of GARDASIL™. There were 104 subjects who received a fourth dose of GARDASIL™ during the extension phase. All of these 104 subjects had safety follow-up data available.”

This is not correct. In most of the safety tables, there are 127 such subjects, not 119. This discrepancy is not explained.

P5225:
“Placebo Primary Series Plus GARDASIL™.
Table 4-22 presents a clinical adverse experience summary Days 1 to 15 following any vaccination visit in which GARDASIL™ was administered during the extension phase to subjects who received placebo in the main study and GARDASIL™ only during the extension phase. Overall, 120 subjects received placebo primary series in the main study plus GARDASIL™ during the extension phase. Of these 120 subjects, 119 subjects had safety follow-up data available.

This is not correct. In most of the safety tables, there are 127 such subjects, not 119. This discrepancy is not explained.

The first set of safety tables, where the events had been divided into mild, moderate and severe, included 104 vs 119 females.

These tables are incomplete and inconsistent. There are only two tables for clinical adverse experiences, on p5228 and p5231:

Table 4-21

Number (%) of Subjects Who Reported Any Clinical Adverse Experience by Maximum Intensity Rating
(Days 1 to 15 Following Vaccination Visit 4 for Subjects Who Received a Primary Series of GARDASIL™ in the Main Study and a Challenge Dose of GARDASIL™ in the Extension Phase)

Table 4-23

Number (%) of Subjects Who Reported Any Clinical Adverse Experience by Maximum Intensity Rating
(Days 1 to 15 Following Any Vaccination Visit for Subjects Who Received a Primary Series of Placebo in the Main Study and GARDASIL™ in the Extension Phase)

Table 4-21 shows data from visit 4 for girls who received Gardasil in the trial plus a fourth dose of Gardasil after 4 years whereas table 4-23 is not about visit 4 but any vaccination visit for girls who received “placebo” in the trial.

This violates basic scientific rules about comparing like with like. The “placebo” group would be expected to have more adverse events, as they have been collected over four vaccination visits.

P020

V501 P020 CSR_protocols P020-04 pg 958

A Study to Evaluate the Efficacy of GARDASIL™ in Reducing the Incidence of HPV 6-, 11-, 16-, and 18-Related External Genital Warts, PIN, Penile, Perianal and Perineal Cancer, and the Incidence of HPV 6-, 11-, 16-, and 18-Related Genital Infection in Young Men.

Study Initiation Date (FPI): 03-Sep-2004
Study Completion Date (LPO): 31-Jul-2009
Interim CSRs for the same Protocol: 05-Dec-2008
Footnote: 27-Jan-2010.

This is the final report. There are 205 tables.

Index on p10.
List of references on p920 that starts with p3107 and ends with p7078.
List of appendices on p936; ends with p7089.

P4:
"Subjects received vaccination with quadrivalent (Types 6, 11, 16, 18) Human Papillomavirus vaccine (referred to as the qHPV vaccine in this document) or placebo in a 1:1 ratio at Day 1, Month 2, and Month 6. All subjects were followed for safety from the day of vaccination plus 14 calendar days after administration of each dose. The current clinical study report is the end of study report for Protocol 020. and presents the primary analysis of the MSM Substudy efficacy endpoint. Results of analyses of the primary and secondary efficacy hypotheses, and primary analyses of safety and immunogenicity, were reported in the original CSR. In addition to the MSM Substudy analysis, the current CSR provides updated analyses of the primary and secondary efficacy endpoints, safety, and immunogenicity."

2032 vs 2033 young men were randomised. MSM means men having sex with men.

P5:
"Each dose of placebo contained Merck standard aluminum diluent (225 µg alum) in normal saline."

Thus, there was no placebo, as the "placebo" group received Merck's adjuvant.

P6:
Assessment of safety was equally inadequate as in other Merck trials:

"Safety: The primary objective for safety was to demonstrate that qHPV vaccine was generally well tolerated. The following measures were collected from each study subject to assess safety; (1) temperatures (oral or oral equivalent) 4 hours after vaccination and daily for the next 4 days; (2) all adverse experiences that occurred within 14 calendar days following vaccination; (3) all serious clinical adverse experiences that occurred within 14 days following vaccination; and (4) all serious clinical adverse experiences that resulted in the death of the subject or were determined to be related to the study vaccine or a study procedure that occurred at any time during the study."

P8:

“Safety: Administration of the qHPV vaccine was generally well tolerated. Since the reporting of safety results in the original CSR, there were no new safety outcomes reported from Day 1 to 15 following any vaccination. In addition, no new serious adverse experiences were reported.”

P92:
Procedures inadequate and very similar to other Merck trials:

“Each subject received a VRC (vaccine report card) on which to record oral temperatures 4 hours following vaccination and daily for the next 4 days, any systemic or local adverse experiences that occurred on Day of vaccination or within 14 calendar days following vaccination, and medications received on the Day of vaccination or during the 14 days following vaccination. Study site personnel reviewed the VRC for completeness with study subjects.”

P120:
“9.7.1.3.2 Primary Safety Endpoints
The safety objective was addressed by summarizing:
• the number and percent of subjects with serious adverse experiences Days 1 to 15 following any vaccination visit
• the number and percent of subjects with serious vaccine-related adverse experiences at any time during the study
• the number and percent of subjects with one or more injection-site adverse experiences, with ≥ 1% incidence Days 1 to 5 following any vaccination visit
• the number and percent of subjects with severe injection-site adverse experiences Days 1 to 5 following any vaccination visit
• the number and percent of subjects with specific systemic clinical adverse experiences with ≥ 1% incidence Days 1 to 15 following any vaccination visit
• the number and percent of subjects with maximum oral temperature >37.8°C (>100°F) Days 1 to 5 following any vaccination visit

For each endpoint, point estimates and 95% confidence intervals were provided for the risk difference between the qHPV vaccine and placebo group. Statistical testing of no difference between the qHPV vaccine and placebo groups was performed for serious adverse experiences, serious vaccine-related adverse experiences, specific injection-site adverse experiences prompted for on the VRC, and maximum oral temperature. No statistical testing was performed for severe injection-site adverse experiences or specific systemic clinical adverse experiences.”

No statistical testing is performed at all for systemic adverse events or for severe injection-site adverse events. This design was biased in favour of not finding any safety signals.

P347:
“• The proportion of subjects who reported at least one clinical adverse experience was slightly higher in the qHPV vaccine group than in the placebo group;
• The proportion of subjects who reported at least one injection-site adverse experience was slightly higher in the qHPV vaccine group than in the placebo group;
• The proportion of subjects who reported at least one systemic adverse experience was generally comparable between the vaccine and placebo groups.”

P347:
“A total of 3 subjects died in the qHPV vaccine group and a total of 10 subjects died in the placebo group. None of the deaths were vaccine related.”

P348-9:

Clinical Adverse Experience Summary
(Days 1 to 9999 Following Any Vaccination Visit) (All Vaccinated Subjects)

	qHPV (N=2020)		Placebo (N=2029)	
	n	(%)	n	(%)
Subjects in analysis population	2020		2029	
Subjects without follow-up	75		79	
Subjects with follow-up	1945		1950	
Number (%) of subjects:				
with no adverse experience	599	(30.8)	698	(35.8)
with one or more adverse experiences	1346	(69.2)	1252	(64.2)
injection-site adverse experiences	1169	(60.1)	1047	(53.7)
systemic adverse experiences	617	(31.7)	622	(31.9)
with vaccine-related[†] adverse experiences	1242	(63.9)	1134	(58.2)
injection-site adverse experiences	1169	(60.1)	1046	(53.6)
systemic adverse experiences	275	(14.1)	283	(14.5)
with serious adverse experiences[§]	8	(0.4)	11	(0.6)
with serious vaccine-related adverse experiences	0	(0.0)	0	(0.0)
who died	3	(0.2)	10	(0.5)
discontinued[‡] due to an adverse experience	5	(0.3)	14	(0.7)
discontinued due to a vaccine-related adverse experience	2	(0.1)	3	(0.2)
discontinued due to a serious adverse experience	3	(0.2)	10	(0.5)
discontinued due to a serious vaccine-related adverse experience	0	(0.0)	0	(0.0)

† Determined by the investigator to be possibly, probably, or definitely related to the vaccine.
‡ Discontinued = Subject discontinued from therapy.
§ Three (3) subjects enrolled more than once and were excluded from this table. AN 72648, AN 73819, AN 73858 each had an SAE of overdose. See Section 10.2 and 12.2 for details.
Percentages are calculated based on the number of subjects with follow-up.

Although there were 8% more clinical adverse events with the vaccine than with the adjuvant, the difference of 1346 vs 1252 is called "slightly higher." I calculated that p = 0.001 for the difference. Merck also stated that injection-site adverse events were "slightly higher" (12% more, p = 0.000,07). These differences are not "slightly higher."

P365:
"Final data support the original report, and show that the proportions of subjects who reported new medical history consistent with potential autoimmune phenomena were comparable between the vaccination groups."

P371:

Table 12-7

Number (%) of Subjects With New Medical History
(Incidence >0% in One or More Vaccination Groups) by System Organ Class
(After Day 1) Potentially Consistent With Autoimmune Phenomena

	qHPV (N= 2020)		Placebo (N= 2029)	
	n	(%)	n	(%)
Subjects in analysis population	2020		2029	
Subjects with one or more new Medical History	14	(0.7)	23	(1.1)
Subjects with no new secondary diagnosis	2006	(99.3)	2006	(98.9)
Cardiac Disorders	**1**	**(0.0)**	**1**	**(0.0)**
Myocarditis	1	(0.0)	1	(0.0)

P366ff:
New Medical History.

P377-8
"13.4 Overall Study Safety Findings
Data in the original CSR showed the qHPV vaccine to be generally well-tolerated in men 16-26 years of age. Overall, the proportions of subjects who reported serious adverse experiences or who discontinued due to an adverse experience were low and comparable between vaccination groups. Final data confirm these findings. Importantly, no additional serious adverse experiences were reported between the original CSR and the current analyses, and there were no vaccine-related SAEs for the entire duration of the study. The favorable clinical adverse event profile observed upon final analysis of Protocol 020 is consistent with what has been previously observed for the qHPV vaccine."

This statement is unsupported, given the above.

P379:
"13.5.3 Safety Conclusion
• Prophylactic administration of a 3-dose regimen of qHPV vaccine is generally well tolerated in men 16-26 years of age."

P738:

Table 14-85

Number (%) of Subjects Who Reported Specific Injection-Site Adverse Experiences by Maximum Intensity Rating
(Days 1 to 5 Following Any Vaccination Visit)

	qHPV (N= 2020)		Placebo (N= 2029)	
	n	(%)	n	(%)
Number of subjects with follow-up	1945		1950	
Number (%) of subjects without Injection-Site adverse experiences	779	(40.1)	904	(46.4)
Number (%) of subjects with Injection-Site adverse experiences	1166	(59.9)	1046	(53.6)
Number (%) of subjects by maximum intensity rating of Injection-Site adverse experiences				
Mild	936	(48.1)	868	(44.5)
Moderate	199	(10.2)	155	(7.9)
Severe	25	(1.3)	19	(1.0)
Unknown	6	(0.3)	4	(0.2)

Percentages are calculated based on the number of subjects with follow-up.
N = Number of subjects who received only the clinical material indicated in the given column.
For the measured adverse experiences of redness and swelling, Mild = 0 to 1 inch, Moderate >1 to <2 inches, and Severe >2 inches. Subjects were counted by their worst severity rating.

Data Source: [16.4.2.1]

P749:

Number (%) of Subjects Who Reported Specific Systemic Adverse Experiences by Maximum Intensity Rating
(Days 1 to 15 Following Any Vaccination Visit)
All Subjects

	qHPV (N= 2020)		Placebo (N=2029)	
	n	(%)	n	(%)
Number of subjects with follow-up	1945		1950	
Number (%) of subjects without Systemic adverse experiences	1329	(68.3)	1337	(68.6)
Number (%) of subjects with Systemic adverse experiences	616	(31.7)	613	(31.4)
Number (%) of subjects by maximum intensity rating of Systemic adverse experiences				
Mild	308	(15.8)	286	(14.7)
Moderate	256	(13.2)	274	(14.1)
Severe	51	(2.6)	53	(2.7)
Unknown	1	(0.1)	0	(0.0)

Percentages are calculated based on the number of subjects with follow-up.
N = Number of subjects who received only the clinical material indicated in the given column.
Subjects were counted by their worst severity rating.

Data Source: [16.4.2.1]

P852:

Number (%) of Subjects With New Medical History
(Incidence >0% in One or More Vaccination Groups) by System Organ Class
(Vaccination Period, Day 1 Through Month 7)

	qHPV (N= 2020)		Placebo (N= 2029)	
	n	(%)	n	(%)
Subjects in analysis population	2020		2029	
Subjects with one or more new Medical History	498	(24.7)	463	(22.8)

Many of the new medical history events, 498 vs 463, were gastrointestinal disorders, 73 vs 57, of which 22 vs 15 were diarrhoea.

There were five protocol amendments (p1080, 1205, 1345, 1487 and 1626) with significant changes to the original protocol but none of them were related to any changes in the statistical analysis of possible harms.

V501 P020 V1_protocol P020-04

Dated 5-Dec-2008 in a footnote, one year before the final report.

V501 P020-21 LTFU_Analysis #1

This long-term study does not have a “placebo” group. Subjects who were vaccinated with qHPV vaccine in the base study at 16 to 26 years of age are referred to as the "Early Vaccination Group" (EVG) in this report. Subjects who were vaccinated with placebo in the base study were later vaccinated with a 3-dose regimen of qHPV vaccine during the first extension of the base study at 20 to 31 years of age (V501 Protocol 020-10) and are referred to as the "Catch-up Vaccination Group" (CVG) in this report.

“Out of the 2,966 subjects who completed the Protocol 020 base study, 1,805 subjects have participated in the long term study as of the data cutoff date of 01-Jun-2012.”

“two SAEs have been reported in the context of this long-term follow-up study. Both of them were not vaccine related. Approximately 99% of all subjects reported no new medical conditions. There was no specific pattern of new medical conditions in either group.”

V501 P020-21 LTFU_Analysis #2

Statistical report. Interim Analysis #2.

”This interim analysis report summarizes data collected as of the data cut-off of 02-Mar-2015. A future analysis is planned in 2017 (end-of-study analysis).”

I have not seen any end-of-study analysis.

V501 P023 CSR

An immunogenicity and safety study of GARDASIL™ (human papillomavirus [types 6, 11,16, 18) recombinant vaccine) in females 9 to 23 years of age in Korea.

Study Initiation Date (FPI): 20-0ct-2005
Study Completion Date (LPO): 24-Jun-2006
Clinical Study Report Date: 18-Sep-2006

Only 117 vs 59 subjects in the trial. The “placebo” is not a placebo as it contains aluminium adjuvant: “The placebo contains all excipients except HPV L1 VLPs.”

P5:
There is no conclusion about safety in the Synopsis:
“Safety: The safety objective of this study was to demonstrate that a 3-dose regimen of GARDASIL® is generally well tolerated in females 9 to 23 years of age in Korea. The table that follow s displays a summary of clinical adverse experiences reported from Days 1 through 15 following any vaccination visit by vaccination group.”

P6:

Clinical Adverse Experiences Summary
(Days 1 to 15 Following Any Vaccination Visit)

	GARDASIL® (N = 117)		Placebo (N = 59)	
	n	(%)	n	(%)
Number of subjects vaccinated	117		59	
Subjects with safety follow-up	117		59	
Number (%) of subjects				
with no adverse experience	26	(22.2)	17	(28.8)
with one or more adverse experiences	91	(77.8)	42	(71.2)
injection-site adverse experiences	85	(72.7)	33	(55.9)
systemic adverse experiences	37	(31.6)	26	(44.1)
with vaccine-related† adverse experiences	85	(72.7)	35	(59.3)
injection-site adverse experiences	84	(71.8)	33	(55.9)
systemic adverse experiences	14	(12.0)	4	(6.8)
with serious adverse experiences	0	(0.0)	1	(1.7)
with serious vaccine-related† adverse experiences	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)
discontinued‡ due to an adverse experience	0	(0.0)	0	(0.0)
discontinued‡ due to a vaccine-related† adverse experience	0	(0.0)	0	(0.0)
discontinued‡ due to a serious adverse experience	0	(0.0)	0	(0.0)
discontinued‡ due to a serious vaccine-related† adverse experience	0	(0.0)	0	(0.0)

† Determined by the investigator to be possibly, probably, or definitely related to the study vaccine.
‡ Discontinued = Subject discontinued from therapy.
Calculation of percentage: The number of vaccinated subjects with adverse experience divided by the number of subjects with follow-up.
N = Number of subjects randomized; n = Number of vaccinated subjects with adverse experience.

P36:
“With 85 evaluable subjects in the vaccine group, the power to declare success for all 4HPV types was greater than 80%.”

This is a very low power, with a beta of 20%, which is an unusually high risk for overlooking that the vaccine produces antibodies against HPV strains. And the trial did not obtain this low number of patients, as there were only 59 in the “placebo” group.

P58:
Similarly inadequate means of collecting safety data as in other Merck trials.

P60-2:
Adverse events were classified as to severity, mild, moderate and severe, but there were no data on severity overall, only for separate symptoms:

Table 12-3
Number (%) of Subjects With Injection-Site Adverse Experiences
(Incidence ≥ 1% in One or More Vaccination Groups) by Maximum Intensity
(Days 1 to 5 Following Any Vaccination Visit)

	GARDASIL® (N = 117, m = 117)								Placebo (N = 59, m = 59)							
	Unknown		Mild		Moderate		Severe		Unknown		Mild		Moderate		Severe	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Injection site pain	0	(0.0)	74	(63.2)	8	(6.8)	3	(2.6)	0	(0.0)	28	(47.5)	2	(3.4)	0	(0.0)
Injection site pruritus	0	(0.0)	5	(4.3)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.7)	0	(0.0)	0	(0.0)
Injection site tenderness	0	(0.0)	2	(1.7)	0	(0.0)	0	(0.0)	0	(0.0)	3	(5.1)	0	(0.0)	0	(0.0)
Injection site warmth	0	(0.0)	2	(1.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

Percentages are calculated based on the number of subjects with follow-up.
A given adverse experience asigned multiple internsity ratings is reported only once under the highest associated internsity rating.
N = Number of subjects randomized; n = Number of vaccinated subjects with injection-site adverse experience.
m = Number of subjects with follow-up.

P69:
One subject died in a car accident despite the fact that no deaths were reported in the table above (which includes only events occurring within two weeks after each vaccination).

P74:
“The higher proportion of vaccine-related systemic adverse experience was reported in vaccine group compared with placebo group, and most of them were fever which intensity was mild and non-serious in every subject.”

There is no table of the severity of systemic adverse events despite the fact that the protocol mentions that their severity will be classified into mild, moderate and severe (p32).

V501 P024 CSR

An Open-label, Randomized, Multicenter Study of the Safety, Tolerability, and Immunogenicity of GARDASIL™ Given Concomitantly With REPEVAX™ in Healthy Adolescents 11-17 Years of Age.”

The design is the same as in V501 P025 just below and in Gardasil 9 protocol 005. Subjects were randomised to be vaccinated also with a vaccine against “diphtheria, tetanus, pertussis [acellular, component] and poliomyelitis [inactivated]” at day 1 or after a month. 843 people were randomised.

P7:
“SAFETY: Administration of qHPV vaccine was generally well tolerated in each of the vaccination groups. The table that follows presents a summary of clinical AEs at any time during the study by vaccination group. There were no deaths, few non-fatal SAEs (<1% in any vaccination group), no vaccine-related SAEs, and no discontinuations due to an AE.”

P8:

Clinical Adverse Experience Summary
by Vaccination Group (Concomitant vs. Non-Concomitant)
(Vaccination and Follow-up Periods, Days 1 to 9999) (All Vaccinated Subjects)

	qHPV Vaccine† + REPEVAX™ (Concomitant‡) (N=420)		qHPV Vaccine† + REPEVAX™ (Non-Concomitant§) (N=423)	
	n	(%)	n	(%)
Subjects in analysis population	420		423	
Subjects without follow-up	0		0	
Subjects with follow-up	420		423	
Number (%) of subjects:				
with no adverse experience (AE)	15	(3.6)	17	(4.0)
with one or more AEs	405	(96.4)	406	(96.0)
injection-site AEs	397	(94.5)	390	(92.2)
systemic AEs	255	(60.7)	250	(59.1)
with vaccine-related‖ AEs	400	(95.2)	392	(92.7)
injection-site AEs	397	(94.5)	390	(92.2)
systemic AEs	144	(34.3)	125	(29.6)
with serious AEs	1	(0.2)	3	(0.7)
with serious vaccine-related AEs	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)
discontinued¶ due to an AE	0	(0.0)	0	(0.0)
discontinued due to a vaccine-related AE	0	(0.0)	0	(0.0)
discontinued due to a serious AE	0	(0.0)	0	(0.0)
discontinued due to a serious vaccine-related AE	0	(0.0)	0	(0.0)

† Combined qHPV vaccine (CMF) and qHPV vaccine (FMF).
‡ qHPV vaccine and REPEVAX™ administered on Day 1 at different injection sites.
§ qHPV vaccine administered on Day 1 followed by REPEVAX™ administered at Month 1.
‖ Determined by the investigator to be possibly, probably, or definitely related to the vaccine.
¶ Discontinued = Subject discontinued from therapy.
Percentages are calculated based on the number of subjects with follow-up.
CMF = Current manufacturing facility; FMF = Final manufacturing facility.

No randomisation to placebo or another vaccine.

V501 P025 CSR

An Open-Label, Randomized, Multicenter Study of the Safety, Tolerability, and Immunogenicity of Quadrivalent HPV Vaccine Given Concomitantly With Menactra™ and ADACEL™ in Healthy Adolescents 11-17 Years of Age.

The design is the same as in Gardasil 9 protocol 005. Subjects were randomised to be vaccinated also with a meningococcal vaccine (Menactra) and a vaccine against tetanus, diphtheria and pertussis (Adacel) at day 1 or after one month. 1042 people were randomised.

P7:

SAFETY: The safety analyses demonstrate that concomitant administration of a first dose of qHPV vaccine with **Menactra™** and **ADACEL™** is generally well tolerated compared to when the first dose of qHPV vaccine is given separately from **Menactra™** and **ADACEL™**. The table that follows presents a summary of clinical AEs at any time during the study by vaccination group. There were no deaths, there were few non-fatal SAEs (<1% in any vaccination group), a single vaccine-related SAE was observed, and there were no discontinuations due to an AE.

P8:

Clinical Adverse Experience Summary
(Vaccination and Follow-up Periods) (All Vaccinated Subjects)

	qHPV Vaccine + Menactra™ + ADACEL™ (Concomitant) (N=522)		qHPV Vaccine + Menactra™ + ADACEL™ (Non -Concomitant) (N=498)	
	n	(%)	n	(%)
Subjects in analysis population	522		498	
Subjects without follow-up	2		0	
Subjects with follow-up	520		498	
Number (%) of subjects:				
with no adverse experience	39	(7.5)	40	(8.0)
with one or more adverse experiences	481	(92.5)	458	(92.0)
injection-site adverse experiences	471	(90.6)	443	(89.0)
systemic adverse experiences	278	(53.5)	270	(54.2)
with vaccine-related† adverse experiences	473	(91.0)	445	(89.4)
injection-site adverse experiences	471	(90.6)	443	(89.0)
systemic adverse experiences	135	(26.0)	129	(25.9)
with serious adverse experiences	0	(0.0)	2	(0.4)
with serious vaccine-related adverse experiences	0	(0.0)	1	(0.2)
who died	0	(0.0)	0	(0.0)
discontinued‡ due to an adverse experience	0	(0.0)	0	(0.0)
discontinued due to a vaccine-related adverse experience	0	(0.0)	0	(0.0)
discontinued due to a serious adverse experience	0	(0.0)	0	(0.0)
discontinued due to a serious vaccine-related adverse experience	0	(0.0)	0	(0.0)

† Determined by the investigator to be possibly, probably, or definitely related to the vaccine.

‡ Discontinued = Subject discontinued from therapy. Percentages are calculated based on the number of subjects with follow-up.

N = number of subjects in analysis population. One (1) subject from each vaccination group, was randomized but did not receive any vaccination. Five (5) subjects who were randomized into the Non-concomitant Vaccination Group unintentionally received vaccine according to the Concomitant Vaccination Group schedule. 20 subjects who had been randomized into the Non-concomitant Vaccination Group were classified into a third vaccination group titled Protocol Non-compliant Regimen.

No randomisation to placebo or another vaccine.

V501 P028 CSR

The company is Banyu, which is Japanese. Study compares quadrivalent vaccine with “placebo” (p124) in 82 vs 25 subjects; that it was reported in 2010; and that the “placebo” contained adjuvant (p4):

治験薬	含量	ロット番号	包装
V501	HPV 6型、11型、16型及び18型の L1 VLP をそれぞれ20/40/40/20 µg 及び 225 µg アルミニウムアジュバント／0.5 mL	WL00014881	0.75 mL 単回接種バイアル
プラセボ	225 µg アルミニウム アジュバント／0.5 mL	WL00019363	0.75 mL 単回接種バイアル
HPV：ヒトパピローマウイルス、L1：主要カプシドたん白質、VLP：ウイルス様粒子			

V501 P029 CSR_India

Date of report: 15 April 2008

110 people all received the quadrivalent vaccine, no control group.

V501 P030_Statistical Analysis_China

Dated 19 July 2009 in a footnote. The report is of poor quality.

“Approximately 600 subjects was randomized in a 1:1 ratio to receive either quadrivalent HPV vaccine or aluminum-containing placebo.”

P5:
“Study vaccine or placebo was administered at the Day 1, Month 2, and Month 6 visits. All subjects was followed for Adverse Experiences (AEs).”

Study design was very similar to other Merck studies.

P13:
“302 of them received GARDASIL™ (qHPV Vaccine) and 298 of them received Placebo.”
P16:

Table 7.3.1 Summary of Adverse Experiences (Safety Population)

AEs	qHPV Vaccine(N=302)			Placebo(N=298)		
	n subj.	n events	% subj.	n subj.	n events	% subj.
Any AE(Day 1 to Day 14 following each vaccination)	153	372	50.66	131	291	43.96
Vaccine-related AEs*	123	269	40.73	100	193	33.56
Discontinued due to AE**	0	0	0.00	0	0	0.00
Injection-site AE (Day 1 to Day 5 following each vaccination)	66	128	21.85	40	55	13.42
Vaccine-related injection-site AE*	66	127	21.85	40	55	13.42
Discontinued due to injection-site AE**	0	0	0.00	0	0	0.00
Systemic AE (Day 1 to Day 14 following each vaccination)	129	241	42.72	119	234	39.93
Vaccine-related systemic AE*	87	139	28.81	82	136	27.52
Discontinued due to systemic AE**	0	0	0.00	0	0	0.00
SAE (Day 1 to Day 14 following each vaccination)	0	0	0.00	1	1	0.34
Vaccine-related SAE*	0	0	0.00	0	0	0.00
Discontinued due to SAE**	0	0	0.00	0	0	0.00

*Determined by the investigator to be possibly, probably, or definitely related to the vaccine.
**Did not complete the study.

For number of events, the differences were larger than for number of subjects with events.

P47:
There is nothing in the protocol about dividing adverse events into mild, moderate and severe, but on p47, local reactions are so divided. However, not a single patient seems to have experienced any redness, swelling or induration at the injection site, or nausea or vomiting, headache or “other.” These were the only categories in the tables after each vaccination, which looked like this:

Table 8.3.1.3 Other reactions within half an hour after the second vaccination by vaccination group (Safety Population)

Time	qHPV Vaccine	Placebo
Injection site redness		
Not exist	297(100.00%)	294(100.00%)
Mild	0(0.00%)	0(0.00%)
Moderate	0(0.00%)	0(0.00%)
Severe	0(0.00%)	0(0.00%)
Life threatening	0(0.00%)	0(0.00%)
Total	297	294

Headache		
Not exist	297 (100.00%)	294 (100.00%)
Mild	0 (0.00%)	0 (0.00%)
Moderate	0 (0.00%)	0 (0.00%)
Severe	0 (0.00%)	0 (0.00%)
Life threatening	0 (0.00%)	0 (0.00%)
Total	297	294

Pain was not included in the severity tables even though many patients would have experienced pain within half an hour after an injection. Further, many people had headaches, and there are these tables on p16 and 18, respectively:

Table 7.3.2 Frequency of VRC-prompted injection-site AE by vaccination group (Safety population)

AEs	qHPV Vaccine(N=302)			Placebo(N=298)			P value	risk difference and its 95%CI(%)
	n subj.	n events	% subj.	n subj.	n events	% subj.		
Total	66	128	21.85	40	55	13.42		
INDURATION	6	6	1.99	1	1	0.34	0.060	1.7(-0.1,4.0)
PAIN/TENDERNESS/SORENESS	61	94	20.20	39	46	13.09	0.020	7.1(1.2,13.1)
PRURITUS	12	16	3.97	2	3	0.67	0.007	3.3(1.0,6.2)
REDNESS	3	3	0.99	2	2	0.67	0.664	0.3(-1.5,2.3)
SWELLING	9	9	2.98	2	3	0.67	0.035	2.3(0.2,5.0)

Note : Risk difference was counted by qHPV Vaccine minus Placebo.

Table 7.3.5 Frequency of systemic AE reported in ≥4 subjects by preferred term and vaccination group (Safety population)

AEs	qHPV Vaccine(N=302)			Placebo(N=298)			risk difference and its 95%CI(%)
	n subj.	n events	% subj.	n subj.	n events	% subj.	
MYALGIA	11	16	3.64	12	12	4.03	-0.4(-3.7,2.9)
HEADACHE	16	20	5.30	18	20	6.04	-0.7(-4.6,3.1)
DIARRHEA	9	11	2.98	10	10	3.36	-0.4(-3.5,2.6)
NAUSEA	8	9	2.65	12	14	4.03	-1.4(-4.6,1.6)
VOMITING	8	9	2.65	12	14	4.03	-1.4(-4.6,1.6)
COUGH	11	12	3.64	10	16	3.36	0.3(-2.9,3.5)
UPPER RESPIRATORY TRACT INFECTION	18	21	5.96	13	14	4.36	1.6(-2.1,5.4)
ALLERGIC REACTION	8	9	2.65	2	2	0.67	2.0(-0.1,4.6)
FATIGUE	17	24	5.63	22	25	7.38	-1.8(-5.9,2.3)
FEVER	71	83	23.51	70	85	23.49	0.0(-6.8,6.8)

Note : Risk difference was counted by qHPV Vaccine minus Placebo.

On p57 is a table, but not all three categories of severity are shown:

Table 8.3.3.2.2 Frequency of VRC-prompted injection-site AE by intensity and vaccination group (Safety Population)

AEs	qHPV Vaccine(N=302)			Placebo (N=298)		
	n subj.	n events	% subj.	n subj.	n events	% subj.
Total	66	128	21.85	40	55	13.42
INDURATION	6	6	1.99	1	1	0.34
Mild	5	5	1.66	0	0	0.00
Moderate	1	1	0.33	1	1	0.34
PAIN/TENDERNESS/SORENESS	61	94	20.20	39	46	13.09
Mild	61	93	20.20	37	44	12.42
Moderate	1	1	0.33	2	2	0.67
PRURITUS	12	16	3.97	2	3	0.67
Mild	11	15	3.64	2	3	0.67
Severe	1	1	0.33	0	0	0.00
REDNESS	3	3	0.99	2	2	0.67
Mild	2	2	0.66	2	2	0.67
Moderate	1	1	0.33	0	0	0.00
SWELLING	9	9	2.98	2	3	0.67
Mild	7	7	2.32	1	2	0.34
Moderate	2	2	0.66	1	1	0.34

It is not credible that not one of 600 subjects experienced severe induration, pain, redness or swelling at the injection site.

In Future 1, 4.9% of the patients experienced a severe injection reaction on Gardasil and 2.1% on adjuvant, or 3.2% on average. Using this average, there should have been 19 patients with severe injection reactions in the Chinese study among 600 patients but there were none. A statistical comparison of 122/3502 versus 0/600 gives p = 5 x 10-9. This extremely small p-value shows beyond doubt that the Chinese trial is not reliable.

P031

V501 P031-02_Final Report

Surveillance, about 190,000 subjects. Kaiser Permanente. See next report just below.

V501 P031-02_Revised Final Report

Surveillance, about 190,000 subjects. Kaiser Permanente. Revised final report.

A Post-Licensure Surveillance Program for the Safety of GARDASIL™ in a Managed Care Organization Setting. Revised Final Report. December 2010.

Index on p3.

P10:
"No safety signals associated with vaccination with GARDASIL™ were detected for pre-specified autoimmune conditions from the same population of 189,629 females. Additionally, with the exception of syncope on the day of vaccination and possibly cellulitis, no safety signals were detected for any health event resulting in an ER visit or hospitalization within 60 days of each vaccination with GARDASIL™."

The study was flawed.

Kaiser did not examine the medical records of all potential cases in either vaccinated or unvaccinated populations. Kaiser did not examine at all the cohort of unvaccinated patients and only did a random sampling of vaccinated cases. For the unvaccinated cohort, Kaiser acted as though the data for the unvaccinated group were missing and estimated a background rate using a non-standard Rubin's multiple imputation model. But the data were not missing, they just were not examined.

Even so, the study did show a statistically significant elevated risk for the autoimmune condition Hashimoto's disease in the vaccinated population.

Both vaccinated and unvaccinated patients' records should have been reviewed equally for a proper analysis.

The study cannot rule out the possibility that Gardasil causes important harm in some people. If such harms are rare, they may easily be overlooked in studies of this type as the signal could be drowned in all the background "noise." Furthermore, it is insufficient to look only at hospital visits within 60 days of each vaccination. For example, it can take years after the vaccinations before POTS, and likely also CRPS, gets diagnosed, if it gets diagnosed at all, as the symptoms are often diffuse.

V501 P033-00_Final Study Report

"This report provides final study results for the GARDASIL (Recombinant Human Papillomavirus [types 6,11,16,18] Vaccine) Vaccine Impact in Population (VIP) Study that was conducted in four Nordic countries (Denmark, Iceland, Norway, and Sweden). The VIP study was based on a combination of registry data and primary data collection that took a series of cross-sectional snap shots at the general female population in various Nordic countries between 2004 and 2011 (up to 2012 for primary data collection). There were four components in the VIP study, including 1) surveillance of HPV-related disease incidence; 2) pregnancy safety; 3) HPV typing in cervical samples; and 4) questionnaire surveys. The first two components utilized the existing nationwide registry data in the Nordic countries while the last two components were based on cross-sectional collections of samples and data in the general female population."

N/A

V501 P035 CSR China

Not a randomised study: "An Open-Label, Single-Dose, Safety and Tolerability Study of Quadrivalent HPV (Types 6,11,16,18) LI Virus-Like Particle (VLP) Vaccine in Chinese Female Subjects Aged 9 to 26 Years."

"40 subjects were vaccinated in two divided stages, no severe or serious adverse reaction was observed, tolerance was well."

V501 P041 CSR_synopsis only_Chinese

This trial compared the quadrivalent vaccine with its adjuvant (225 µg in both cases) in 3006 Chinese women (1503 in each group). Clinical Trial Registry Number: NCT 00834106.

First subject first visit: 03-Jan-2009
Last subject last visit: 30-Sep-2016
Database lock: 17-Jan-2017
REPORT DATE: 26th Jun 2017

The design is very similar to that of other Merck trials, including "new medical history." Vaccination at Day 1, Month 2, and Month 6. "This study includes base phase (until Month 30 visit) and extension phase (until Close-out visit). All subjects were followed for adverse events by using Vaccine Reporting Card (VRC) for 14 calendar days after administration of each dose. Serious adverse events were collected during the entire study. All subjects were followed for efficacy evaluation through Month 78 visit.

Duration of extension phase: "not pre-defined. The study was case-driven."

The safety objectives were even more rudimentary than in the Future trials. Even though it was a randomised study, there was apparently no initial intention of comparing safety outcomes in the vaccine group with those in the adjuvant group (p3):

"Primary Safety Objective: To describe the incidence of vaccine or procedure-related serious adverse experiences and incidence of death in women 20 to 45 years of age who received Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Vaccine.

Secondary Safety Objective: To describe the pregnancy outcome in women 20 to 45 years who received Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Vaccine."

The conclusion about safety was the usual (p21): "The qHPV vaccine was generally well tolerated and showed good safety profile in healthy Chinese females aged 20-45 years old."

P20:
There was a summary table for adverse events reported in the "Entire Study Period," which was not explicitly defined but was likely the base phase of 30 months. On p2, it was explained that "All subjects were followed for adverse events by using Vaccine Reporting Card (VRC) for 14 calendar days after administration of each dose. Serious adverse events were collected during the entire study." There was no information about how non-serious adverse events were collected.

P20:

Adverse Event Summary
(Entire Study Period)
(20 to 45 Year-Olds)
(All Vaccinated Subjects)

	qHPV Vaccine		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population with follow-up	1,499		1,498		2,997	
with one or more adverse events	926	(61.8)	856	(57.1)	1,782	(59.5)
injection-site	564	(37.6)	417	(27.8)	981	(32.7)
non-injection-site	770	(51.4)	750	(50.1)	1,520	(50.7)
with no adverse event	573	(38.2)	642	(42.9)	1,215	(40.5)
with vaccine-related† adverse events	846	(56.4)	773	(51.6)	1,619	(54.0)
injection-site	564	(37.6)	416	(27.8)	980	(32.7)
non-injection-site	639	(42.6)	628	(41.9)	1,267	(42.3)
with serious adverse events	38	(2.5)	43	(2.9)	81	(2.7)
with serious vaccine-related adverse events	0	(0.0)	1	(0.1)	1	(0.0)
who died	2	(0.1)	0	(0.0)	2	(0.1)
discontinued‡ due to an adverse event	2	(0.1)	3	(0.2)	5	(0.2)
discontinued due to a vaccine-related adverse event	2	(0.1)	2	(0.1)	4	(0.1)
discontinued due to a serious adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious vaccine-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)

† Determined by the investigator to be related to the vaccine.
‡ Study medication withdrawn.

21-page synopsis for a study of 3006 women only.

V501 P046 CSR_Africa

Evaluation of Safety and Immunogenicity of GARDASIL in Healthy Females Between 9 and 26 Years of Age in Sub-Saharan Africa.

Study Initiation Date (FPE): 21-Mar-2011
Study Completion Date (LPLV): 23-Mar-2012 (Primary Endpoint)
Date of report in a footnote: 19-Feb-2013

P3:
"PRIMARY THERAPY PERIOD: 21-March-2011 (first subject vaccinated) to 23-Mar-2012 (last subject visit for Month 7). The study is ongoing, with safety follow-up planned for Month 12 of Phase A and the vaccination of placebo subjects with safety follow-up Week 4 Postdose 3 in Phase B.

DURATION OF TREATMENT: Vaccination at Day 1, Month 2, and Month 6 with 14 calendar days of clinical follow-up after administration of each dose. All subjects were followed to assess safety and immunogenicity through Month 7."

“Phase A of the study was a randomized, double-blind study to observe the safety, tolerability and immunogenicity of a 3-dose regimen of GARDASIL™ in approximately 250 healthy SubSaharan African females with safety follow up through Month 12. In Phase B of the study, all subjects who received placebo in Phase A were offered the option to return to the study site and receive a 3-dose regimen of GARDASIL™. Approximately 20 healthy females between 9 and 12 years of age (at initial enrollment in Phase A of the study) received GARDASIL™. All subjects in Phase B were to be followed for reporting of any serious adverse experiences regardless of causality or time of onset through Week 4 Postdose 3. This Clinical Study Report (CSR) addresses visits conducted between Day 1 and Month 7 (1 month postdose vaccination 3) of Study Phase A, inclusive.”

P4:

Disposition of Subjects
(All Randomized Subjects by Age Strata)

	GARDASIL™ 9 to 12 years old		GARDASIL™ 13 to 15 years old		GARDASIL™ 16 to 26 years old		Placebo 9 to 12 years old		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Not Randomized									7	
Subjects in population	80		30		120		20		250	

This study is inadequate for an assessment of vaccine harms; only 20 subjects are randomised to placebo; the age distribution is different in the Gardasil groups where only one group of 80 subjects has the same age distribution as the placebo group. Furthermore, I do not have any final report even though the study was ongoing in 2013, which is the date of the current report. I did not read any further.

V501 P059_Korea

Surveillance study. qHPV.

3,605 subjects whose case report forms were reviewed for safety. CRFs filled out between 2007 and 2013 were retrieved from 171 doctors at 142 hospitals in Korea.

P7:

Clinical testing data of various countries from the developmental stage of the drug did not uncover significant problems. Therefore there was no special issue in this study. During the Re-examination period, very rare cases of serious adverse events that did not have a definite causal relationship with GARDASIL as well as unexpected cases of serious adverse events were observed and investigated.

The focus was on serious adverse events. None were reported. Other events occurred in 1% of the subjects. There was no control group.

P070, qHPV

V501 P070-01 3rd report

Surveillance study. See 5th report below.

V501 P070-01 4th report

Surveillance study. See 5th report below.

V501 P070-01 5th report

Surveillance study.

Post-Licensure Observational Study of the Safety of GARDASIL in Males

Fifth Annual Interim Report
Data Accrual Period: 16-0ctober-2009 through 31-December-2015 with Follow-up through 29-February-2016
Final Report Date: 09-December-2016

Cohort of 106,110 males.

P9:
"Background: GARDASIL® is a quadrivalent human papillomavirus (HPV) vaccine licensed by Merck. The vaccine was approved in 2006 by the United States (US) Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the prevention of several diseases caused by HPV types 6, 11, 16, and 18 in females. In October 2009, the US FDA approved an additional indication for GARDASIL®: use in boys and men, ages 9 through 26 years, for the prevention of external genital warts (condyloma acuminata) caused by HPV types 6 and 11. A further indication for GARDASIL® was approved by the US FDA in December 2010: use in males and females, 9 through 26 years of age, for the prevention of anal intraepithelial neoplasia (AIN) grades 1,2, and 3 caused by HPV types 6 ,1 1 ,1 6 , and 18, and for the prevention of anal cancer caused by HPV types 16 and 18

… This is the 5th Annual Interim Report of an observational study of the safety of GARDASIL® in males conducted by Optum (Merck Protocol V501-070-01), which is a post-licensure regulatory commitment to the US FDA following the October 2009 approval for the use of GARDASIL® in males. This cohort study includes males who received GARDASIL® in the course of routine clinical care from 16-0ctober-2009 through 31-December-2015 and were followed for study outcomes through 29-February-2016 (i.e., approximately 2 months from the last potential accrual date ...

Objectives: The primary objective of this study is to describe the general safety of GARDASIL® among males within 60 days following the administration of each dose of the vaccine by estimating:
a) the incidence of health outcomes resulting in emergency room (ER) visits or hospitalizations occurring in the combined 60-day risk periods after each dose of GARDASIL®; and b) the rates of such health outcomes as compared to rates in a post-vaccination self-comparison reference period (relative rate).
The 3 secondary objectives of this study are:
1. To describe the general safety of a first dose of GARDASIL® in males;

2. To provide descriptive epidemiology of new onset of 20 pre-specified autoimmune conditions for a period of 6 months after each dose of GARDASIL®, including comparison of incidence of these conditions to background incidence within the male population; and
3. To describe the general safety of GARDASIL® on the day of vaccination (i.e., Day 0).

Considering that this is a safety study required by the FDA, the means of collecting possible harms of the vaccine are insufficient, as in all other Merck studies. It can take much longer than 60 days before an important harm gets diagnosed, and the other health outcomes considered are only those that result in visits to a hospital, occur on the day of the vaccination, or are autoimmune disorders diagnosed within 6 months after the vaccination, which is also too short a follow-up period. This study cannot be used to "describe the general safety of a first dose of GARDASIL® in males."

P10:
General safety outcomes were identified by claims corresponding to an ER visit or hospitalization and the associated International Classification of Diseases, Ninth Revision (ICD-9) and International Classification of Diseases, Tenth Revision (ICD-10) diagnosis codes. All of the specific diagnosis codes from these claims were grouped according to hierarchical, clinically meaningful categories developed by the Healthcare Cost Utilization Project (HCUP).

P12:
The occurrence of 20 autoimmune conditions was evaluated within 6 months after each dose of the vaccine among the autoimmune cohort and among a propensity-matched comparison group comprised of males of similar age to the autoimmune cohort matched at the time of a physician visit and who had not received a dose of GARDASIL® prior to the time of the matching

… Between 16-0ctober-2009 and 31-December-2015, a total of 189,892 doses of GARDASIL® were administered to the regimen initiator cohort of 106,110 males (an average of 1.8 doses each).

P12-3:
The 8 HCUP categories with significantly elevated RRs [risk ratios] corresponded to 'coma; stupor; and brain damage' (HCUP 6.6); 'ear conditions' (HCUP 6.8); 'otitis media and related conditions' (HCUP 6.8.1); 'skin and subcutaneous tissue infections' (HCUP 12.1); 'cellulitis and abscess of arm' (HCUP 12.1.1.3); 'injury and poisoning' (HCUP 16); 'concussion' (HCUP 16.4.1); and 'sprains and strains' (HCUP 16.7). Following multiple-comparison adjustment, 4 HCUP categories remained statistically significant in the Days 1-60 for all doses combined analysis: 'ear conditions' (HCUP 6.8) (RR 1.32; 95% Cl 1.05-1.67); 'otitis media and related conditions' (HCUP 6.8.1) (RR 1.55; 95% Cl 1.03-2.35); 'cellulitis and abscess of arm' (HCUP 12.1.1.3) (RR 1.97 (1.02-4.02); and 'concussion' (HCUP 16.4,1) (RR 1.24; 95% Cl 1.00-1.54). In last year's report there were 8 HCUP categories with at least one significantly elevated RR; 6 of the 8 HCUP categories in the current report had significantly elevated RRs in the last annual report.

Twenty-six HCUP categories had significantly decreased RRs, and 12 of those were embedded within a more general HCUP category that was also identified; 4 HCUP categories had RRs that remained significant after multiple comparisons adjustment: 'mental illness' (HCUP 5) (RR 0.74; 95% Cl 0.63-0.87); 'diseases of musculoskeletal system and connective tissue' (HCUP 13) (RR 0.84; 95% Cl 0.76-0.92); 'intracranial injury' (HCUP 16.4) (RR 0.45; 95% Cl 0.24-0.82); 'concussion' (HCUP 16.4.1) (RR 0.35; 95% Cl 0.17-0.67). In last year's 4th Annual Interim Report, there were 32 HCUP categories with decreased RRs; of those, 18 HCUP categories had significantly decreased RRs also in the current report.

According to the report, concussion both increased and decreased with Gardasil: 'concussion' (HCUP 16.4,1) (RR 1.24; 95% CI 1.00-1.54) and 'concussion' (HCUP 16.4.1) (RR 0.35; 95% CI 0.17-0.67). The discrepancy is not explained.

P13:
New-onset Autoimmune Conditions: there were no data in the summary.

P14, conclusions:
"The small elevations observed in the RRs for the general safety outcomes could be attributed to uncontrollable artifacts or other possible explanations, such as seasonality (e.g., timing of the risk period relative to the self-control period with respect to the increased number of injuries during the summer), chance, or pre-existing conditions. The observed decreased RRs for the general safety analyses may represent delayed workup for possible conditions identified at the vaccine visit, or the healthy vaccinee effect, or may be due to chance or uncontrollable artifacts. The VTE [deep vein thrombosis] and autoimmune analyses are ongoing, pending case review and/or adjudication of study outcomes. The study data overall do not suggest an alteration in the existing safety profile of GARDASIL®."

P15, Risk vs. Self Comparison Period:
Coma; stupor; and brain damage: RR 2.23 (95% CI 1.13-4.64)
Concussion: RR 1.24 (1.00-1.54)
Sprains and strains: 1.11 (1.01-1.23)

Risk of confounding, as also indicated by Merck.

V501 P110 CSR_Japan, qHPV

In Japanese. There seems to be only one group.

V501 P122 V01 CSR_Japan, qHPV

In Japanese; some tables are in English.

Index on p23 (in Japanese). Another index on p276.

Actual Enrollment: 1124 participants
Masking: Triple (Participant, Investigator, Outcomes Assessor)
Official Title: A Phase III Placebo-controlled Clinical Trial to Study the Tolerability, Immunogenicity and Efficacy of V501 in 16- to 26-year-old Japanese Men
Actual Study Start Date: June 27, 2013
Actual Primary Completion Date: August 30, 2017
Actual Study Completion Date: August 30, 2017
This was a study in 1124 Japanese males that started in 2013 and was completed in 2017. Although this was recent, it was designed in the same way as the Future trials including the category, "New Medical History," even though this had been heavily criticised by EMA in 2014 (see above).

The study ran for 3 years, but the time frame for reporting systemic adverse events was only two weeks after each vaccination. This resulted in a table that described that no one experienced any serious adverse events, even though one patient died outside the two-week interval.

As the study report was written in Japanese, I supplemented the study report with the published report of the trial[48] and with information from the US trial register from where I furthermore downloaded the Study Protocol and Statistical Analysis Plan (84 pages). There were identifiers in two additional trial registers:

132237 (Registry Identifier: JAPIC-CTI) and
2015-002931-16 (EudraCT Number). The EU trial register had similar outcome data as the US register. I did not look up the Japanese trial register.
Clinical Trials.gov Identifier NCT01862874, https://clinicaltrials.gov/ct2/show/NCT01862874

The published report showed that Merck did not distinguish between adverse experiences and new medical history despite its claims to the contrary: "Tolerability, based on adverse events (AEs), vaccination-related AEs, and new medical conditions, was also assessed as a primary objective." Nowhere in the published trial report was there any account of adverse events that had occurred beyond the two-week periods after each vaccination, and new medical history was not mentioned at all, apart from the Methods section, even though six of its eight authors were from Merck.

The Japanese study report had tables in English that showed how reported adverse events and new medical history should be translated into MedDRA terms, e.g. feeling of weakness was coded as asthenia. Since adverse events and new medical history were coded in the same way with MedDRA terms, this is an additional reason why it makes no sense that Merck operated with both categories in its trials.

The frequency threshold for reporting "other adverse events" to the trial register was 5%, which is arbitrary, too high and a violation of Merck's own protocol where the threshold was 1%. The rates were 329/554 (59.4%) on the vaccine vs 303/559 (54.2%) on the adjuvant. In the published trial report, there were 57 more (9% more) patients with adverse events than in the trial register. One would think that this was because there was no 5% threshold for reporting in the journal article. However, the data were the same for systemic adverse events, even though there should be more such events without a threshold. Therefore, the explanation for the discrepancy cannot be the lack of a threshold in the trial publication. This discrepancy between the data in the trial register and the data in the published trial report is unexplained.

The trial publication mentioned in the Discussion that the injection-site adverse events were reported by similar proportions of Japanese men as in earlier trials with males whereas the incidence of systemic adverse events was lower, 14.4% on vaccine vs 15.4% on the adjuvant, as compared to 31.6% vs 31.4% internationally.

This is important information, as it shows that the reporting of different types of adverse events can vary considerably from trial to trial, even when the procedures for collecting adverse events are the same.

Merck restricted its statistical testing of differences in adverse experiences to injection-site reactions and temperature. It is inappropriate not to test for systemic adverse events. Further, Merck did not report to the trial registry whether the adverse events were mild, moderate or severe.

Participants received 0.5 mL intramuscular injection at Day 1, Month 2, and Month 6. Follow-up was up to Month 36. "Each dose of the qHPV vaccine contained HPV6/11/16/18 L1 viral-like particles 20/40/40/20 mg, respectively, and 225 µg aluminum (as aluminum hydroxyphosphate sulfate adjuvant). The placebo doses contained the adjuvant alone" (from published trial report).

[48] Mikamo H, Yamagishi Y, Murata S, et al. Efficacy, safety, and immunogenicity of a quadrivalent HPV vaccine in Japanese men: A randomized, Phase 3, placebo-controlled study. Vaccine 2019;37:1651-8.

Primary Outcome Measures related to safety:

Percentage of Participants With Maximum Temperature ≥37.5°C Reported on the Vaccination Report Card [Time Frame: Up to 5 days after any vaccination].

Percentage of Participants With an Injection-site Adverse Event Prompted on the Vaccination Report Card [Time Frame: Up to 5 days after any vaccination].

Percentage of Participants With a Systemic Adverse Event [Time Frame: Up to 15 days after any vaccination].

Percentage of Participants With a Vaccine-related Systemic Adverse Event [Time Frame: Up to 15 days after any vaccination].

P21 in study report:

Adverse Event Summary
(Day 1 to 15 Following Any Vaccination Visit)
(All Vaccinated Subjects)

	V501		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population with follow-up	554		559		1,113	
with one or more adverse events	354	(63.9)	335	(59.9)	689	(61.9)
injection-site	331	(59.7)	309	(55.3)	640	(57.5)
non-injection-site	80	(14.4)	86	(15.4)	166	(14.9)
with no adverse event	200	(36.1)	224	(40.1)	424	(38.1)
with vaccine-related[†] adverse events	337	(60.8)	316	(56.5)	653	(58.7)
injection-site	330	(59.6)	308	(55.1)	638	(57.3)
non-injection-site	19	(3.4)	28	(5.0)	47	(4.2)
with non-serious adverse events	354	(63.9)	335	(59.9)	689	(61.9)
with serious adverse events	0	(0.0)	0	(0.0)	0	(0.0)
with serious vaccine-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)
who died due to a vaccine-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued[‡] due to an adverse event	0	(0.0)	3	(0.5)	3	(0.3)
discontinued due to a vaccine-related adverse event	0	(0.0)	3	(0.5)	3	(0.3)
discontinued due to a serious adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious vaccine-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)

[†] Determined by the investigator to be related to the vaccine.
[‡] Study medication withdrawn.
Percentages are calculated based on the number of subjects with follow-up.

P126:

Subjects With Injection Site Adverse Events by Maximum Intensity
(Incidence > 0% in One or More Vaccination Groups)
(Days 1 to 5 Following Any Vaccination Visit)
(All Vaccinated Subjects)

	Intensity Grading	V501		Placebo		Total	
		n	(%)	n	(%)	n	(%)
Subjects in population with follow-up		554		559		1,113	
With one or more adverse events	Total	329	(59.4)	309	(55.3)	638	(57.3)
	Mild	271	(48.9)	266	(47.6)	537	(48.2)
	Moderate	34	(6.1)	13	(2.3)	47	(4.2)
	Severe	1	(0.2)	0	(0.0)	1	(0.1)
	Unknown	23	(4.2)	30	(5.4)	53	(4.8)

P132:

Subjects With Systemic Adverse Events by Maximum Intensity
(Incidence > 0% in One or More Vaccination Groups)
(Days 1 to 15 Following Any Vaccination Visit)
(All Vaccinated Subjects)

	Intensity Grading	V501 n	V501 (%)	Placebo n	Placebo (%)	Total n	Total (%)
Subjects in population with follow-up		554		559		1,113	
With one or more adverse events	Total	80	(14.4)	86	(15.4)	166	(14.9)
	Mild	53	(9.6)	55	(9.8)	108	(9.7)
	Moderate	25	(4.5)	27	(4.8)	52	(4.7)
	Severe	2	(0.4)	4	(0.7)	6	(0.5)

P155:

表 12-13　自己免疫疾患の可能性がある有害事象又は新たな医学的事象
（Day 1 からデータカットオフ日まで）
（いずれかの接種群で発現割合 0%超）
Subject With Adverse Events and/or New Medical History Conditions
(Incidence >0% in One or More Vaccination Groups)
Potentially Indicative of an Autoimmune Disorder by System Organ Class
(Day1 to Cut-Off Date)
(All Vaccinated Subjects)

	V501 n	V501 (%)	Placebo n	Placebo (%)
Subjects in population	554		559	
With one or more events/conditions	4	(0.7)	2	(0.4)
With no events/conditions	550	(99.3)	557	(99.6)
筋骨格系および結合組織障害	**3**	**(0.5)**	**2**	**(0.4)**
関節痛	1	(0.2)	1	(0.2)
関節炎	1	(0.2)	1	(0.2)
末梢関節炎	1	(0.2)	0	(0.0)
皮膚および皮下組織障害	**1**	**(0.2)**	**0**	**(0.0)**
円形脱毛症	1	(0.2)	0	(0.0)

P260:
Analysis of Subjects With Systemic Adverse Events (Incidence >0% in One or More Vaccination Groups) (Days 1 to 15 Following Any Vaccination Visit). This table provides data on all the individual terms.

P3642-4243:
Listing of Subjects With Adverse Events (All Vaccinated Subjects) (Day 1 to Cut-Off Date). Also, a list of local and systemic events, and of events considered vaccine related.

P4244-4310:
New Medical History.

In the report, Merck does not distinguish between adverse experiences and new medical history:

“Tolerability, based on adverse events (AEs), vaccination-related AEs, and new medical conditions, was also assessed as a primary objective.”

The published trial report does not account for any patients with new medical history.

P4314-9:
A table showing how reported events were translated into MedDRA terms, e.g. feeling of weakness was coded as asthenia.

P4321-30.
Similar table for New Medical History.

Since adverse events and new medical history were coded in the same way with MedDRA terms, this is an additional reason why it makes no sense that Merck operated with both categories in its trials.

From the trial register:

Individual Participant Data (IPD) Sharing Statement:
Plan to Share IPD: Yes
Plan Description: http://engagezone.msd.com/doc/ProcedureAccessClinicalTrialData.pdf
URL: http://engagezone.msd.com/ds_documentation.php

Via the URL, this information appears:

Access to Our Clinical Trial Data

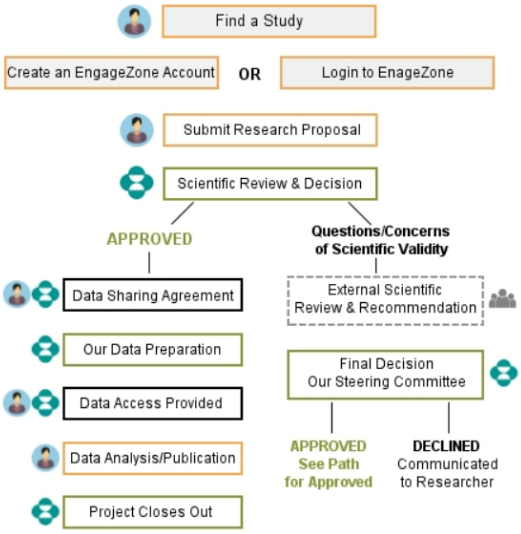
The Company is fully committed to providing qualified scientific researchers access to anonymized patient level data and full clinical study reports (CSRs) from our clinical trials. Qualified researchers with appropriate competencies, engaged in rigorous, independent scientific research can submit a data request for patient-level data or a full CSR.

Scope of Data
The Company will provide access to patient-level data and CSRs for clinical trials performed by the Company for which results are posted on the clinicaltrials.gov registry (dating back to September 2007) for products or indications that have been approved by regulators in the US and EU. In general, data will be made available for request approximately 18 months after clinical trial completion and acceptance of a primary results manuscript. Data from Phase I trials in healthy volunteers and consumer health care studies are out of scope.

View our procedure on access to Clinical Trial Data
Start a Proposal
To start the request proposal, you can search for any of our Clinical Trials using the search form below. Once you locate a trial you are interested in you can request a proposal by clicking on the Trial Data link, then the Request Data button.

Merck provided a flow chart about access or no access to their data:

Visual Overview



Although Merck states it will share its data, it also has the right to decline proposals for access to data.

The frequency threshold for reporting "other adverse events" in the trial register was 5%, which is arbitrary and inappropriate. The rates were 329/554 (59.4%) on the vaccine vs 303/559 (54.2%) on the adjuvant. The data in the published trial report were slightly different:

Table 5
AE summary among all vaccinated participants (Days 1–15 following any vaccination visit).

n (%)	qHPV vaccine (N = 554)	Placebo (N = 559)
Any AE	354 (63.9)	335 (59.9)
Injection-site AEs	331 (59.7)	309 (55.3)
Systemic AEs	80 (14.4)	86 (15.4)
Vaccination-related AE	337 (60.8)	316 (56.5)
Injection-site AEs	330 (59.6)	308 (55.1)
Systemic AEs	19 (3.4)	28 (5.0)
SAE	0	0
Death	0	0
Discontinued due to AE	0	3 (0.5)
Discontinued due to vaccination-related AE	0	3 (0.5)
Most common vaccination-related AEs (>1%)		
Injection-site pain[a]	303 (54.7)	271 (48.5)
Injection-site erythema[a]	136 (24.5)	121 (21.6)
Injection-site swelling[a]	118 (21.3)	81 (14.5)
Injection-site pruritus[a]	6 (1.1)	4 (0.7)
Pyrexia[b]	8 (1.4)	9 (1.6)
Headache	2 (0.4)	7 (1.3)

AE, adverse event; qHPV, quadrivalent human papillomavirus; SAE, serious adverse event.
[a] Days 1–5 following any vaccination.
[b] Pyrexia was defined as ≥37.5 °C.

There are now 57 more (9% more) adverse events than in the trial register. One would think that this was because there was no 5% threshold for reporting in the journal article. However, the data are the same for systemic adverse events, 14.4% with the vaccine vs 15.4% with the adjuvant, and there should be more such events without a threshold, e.g. the publication stated that, "The most common vaccine-related systemic AEs were pyrexia (qHPV: 1.4%; placebo: 1.6%) and headache (qHPV: 0.4%; placebo: 1.3%)." This means that the explanation for the discrepancy cannot be the lack of a threshold in the trial publication. There is

therefore an unexplained discrepancy between the data in the trial register and the data in the published trial report.

The trial publication mentions in the Discussion that, "Injection-site AEs were reported by similar proportions of Japanese men in the current study (qHPV: 59.7%; placebo: 55.3%) as previously by international male clinical trial participants (qHPV: 60.1%; placebo: 53.7%) [16]. The incidence of systemic AEs appeared to be lower in this study (qHPV: 14.4%; placebo: 15.4%) than in the international study (qHPV: 31.6%; placebo: 31.4%)."

This is important information. It shows that the reporting of systemic adverse events can vary hugely from trial to trial. In this case, there were double as many reported events outside Japan as in Japan even though the procedures for collecting adverse events were the same as in other Merck trials:

"The Vaccination Report Card (VRC) "will be utilized to collect subject's (1) oral temperature and local (i.e., injection-site) AEs (including erythema, swelling and pain/tenderness) for 5 days starting the day of each vaccination, (2) systemic AEs and serious adverse events (SAEs) for 15 days (14 days following each vaccination), and (3) vaccine-related SAEs and deaths throughout the study" (information in the trial protocol, downloaded from clinicaltrials.gov).

P52 in the protocol:
"To provide an overall assessment, summary measures such as the incidence of (a) any adverse experiences; (b) any injection-site experiences; (c) any systemic adverse experiences; and (d) any vaccine-related adverse experiences will be summarized in both groups ... To address specific adverse experiences, the incidences of injection-site adverse experiences Days 1 to 5 and specific systemic adverse experiences within 14 days postvaccination occurring in at least 1% of the subjects will be tabulated ... Statistical testing of no difference in safety parameters between the vaccine and placebo group will be restricted to injection site adverse experiences prompted for on the VRC (namely, injection site pain, redness and swelling), and for temperature elevations (maximum oral equivalent temperature ≥37.5°C), across all vaccination visits ... Tables of specific adverse experiences will be restricted to those events occurring in at least 1% of either vaccination group ... The incidence of greatest adverse experience intensity (mild, moderate, severe) reported by a subject will be tabulated for: all injection site adverse experiences (Day 1 to Day 5 following any vaccination visit); all systemic adverse experiences (Day 1 to Day 14 following any vaccination visit); any adverse experience (Day 1 to Day 14 following any vaccination visit) ... Similar tables will be produced summarizing the greatest intensity per subject for each of the prompted adverse experiences individually."

Merck violated its own protocol when it reported its results to the trial registries, as Merck used a 5% threshold and not a 1% threshold. It is inappropriate to restrict statistical testing to injection-site adverse events and temperature and not to test also systemic adverse events. Further, Merck did not report to the trial registry whether the adverse events were mild, moderate or severe.

V501 P125 CSR, qHPV

Surveillance study in India.

A Post Marketing Surveillance to Assess the Safety of Gardasil® in Females of 9 to 45 Years in Routine Clinical Care.

Study Initiation Date 29-JAN-2016 first participant first visit
Study Completion Date 30-JUN-2018 last participant last visit

Report Date 16-MAY-2019

P2:
“METHODOLOGY: Protocol V501-125 was an active post marketing, nonrandomized, observational, multicenter study to assess the safety of Gardasil® administered to Indian females age 9 to 45 years. Subjects who opted for vaccination with Gardasil® in routine clinical care and consented to participate were enrolled in the study. After vaccination with Gardasil®, subjects were under active surveillance for serious adverse events (SAEs) occurring within 30 days after administration of any dose of Gardasil®. Subjects were advised to follow the recommended vaccination schedule (ie, second dose after 2 months and third dose after 6 months of first dose, respectively).”

Study only interested in serious adverse events occurring within 30 days after a vaccination, and no control group, and only 188 women participated, therefore insufficient study of safety. It is misleading to call this study “A Post Marketing Surveillance to Assess the Safety of Gardasil.”

V501 P200 V01_Japan, qHPV

In Japanese. Study identifier is NCT02576054. There is only one treatment group:

“This is a study of V501 [quadrivalent Human Papillomavirus (HPV) (Type 6, 11, 16 and 18) L1 virus-like particle (VLP) vaccine] in healthy Japanese boys. This study will consist of two periods. Period I of the study is to evaluate the immunogenicity and tolerability of V501 up to Month 7. Period II of the study is to evaluate the long-term immunogenicity and safety from Month 7 to Month 30. Two analyses are planned. The first analysis will be conducted when all subjects have completed their Month 7 visit or have been discontinued before that time. The second analysis will be conducted at the end of study. The primary hypothesis tested in this study is that seroconversion rates for the vaccine HPV types will be >90% at 4 weeks postdose 3.”

V501_Extension Safety Summaries_P005-10, 007-20, 013-10, 015-10, and 016-10, qHPV

Quadrivalent HPV (Types 6, 11,16, 18) L1 VLP Vaccine. Safety Summary. Protocol Extensions 005-10, 007-20, 013-10, 015-10, and 016-10.

The report is not formally dated but “06-Oct-2010” appears in a footnote.

The report summarised “in detail, the serious clinical adverse experiences, pregnancies and pregnancy/infant outcomes that occurred in the Extension Protocols 005-10, 007-20, 013-10, 015-10 and 016-10.”

Gardasil was provided to people who: “(1) received placebo in the base study; (2) received monovalent HPV 16 vaccine in the base study; (3) received an incomplete vaccine regimen of qHPV vaccine in the base study; or (4) did not meet the protocol specified criteria for seroconversion (Protocol 016 only).”

There appeared to be 1862 patients in total who were called randomised even though the extension studies were not randomised. There was no information about how many of the originally randomised patients in the studies that were offered participation in the extension studies, or about how many declined and for what reasons. Without this information, the report is uninterpretable.

The report did not even describe for how long the patients were followed in the studies. This information was only provided indirectly: “This report includes data for the study extensions for visits conducted through 31-Jul-2009 for P005-10; 14-Sep-2009 for P007-20; 29-Jan-2009 for P011-10, 11-Feb-2009 for P012-10 (sub-study for P013-10); 10-Mar-2008 for P015-10; and 12-Feb-2009 for P016-10.” One would therefore need to consult other reports to find this out.

Visits were numbered from 1 to 25, all with the label “OB”, e.g. 1.0B, 2.0B, which was not explained.

The discontinuation rate was 26%, which is far above the discontinuation rates in Merck’s other studies.

The narratives of serious adverse events operated with a new category called “other important medical event.” After having read over 100,000 pages of Merck reports, this was the first time I can recall encountering this category for adverse events. Other reports operated with adverse events and new medical history. It is unknown what this third category is about and how it is defined, as there was no definition in the study report. A headache that lasted six months, which the investigator determined was possibly related to the vaccine, was called an “other important medical event.”

One woman who had received adjuvant in the base study “experienced a mild allergic reaction” after the first Gardasil dose. After the second dose, she “experienced a classic allergic reaction of severe intensity.” “The investigator felt the classic allergic reaction was probably related to the study vaccine and was to be another important medical event.”

P5:
“1. Executive Summary
The purpose of this document is to summarize, in detail, the serious clinical adverse experiences, pregnancies and pregnancy/infant outcomes that occurred in the Extension Protocols 005-10, 007-20, 013-10, 015-10 and 016-10. The purpose of the extension studies was to provide quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine 20/40/40/20 mcg dose (GARDASIL™) (hereafter referred to as qHPV vaccine) to subjects who: (1) received placebo in the base study; (2) received monovalent HPV 16 vaccine in the base study; (3) received an incomplete vaccine regimen of qHPV vaccine in the base study; or (4) did not meet the protocol specified criteria for seroconversion (Protocol 016 only).

No serious clinical adverse experiences that resulted in death were reported. Overall, 8 subjects reported serious clinical adverse experiences. Four (4) of the 8 subjects reported serious clinical adverse experiences that were determined by the investigator to be possibly, probably or definitely vaccine-related. These events included:

Headache (possibly vaccine-related)
Pharyngitis (possibly vaccine-related)
Allergy to vaccine (probably vaccine-related)
Overdose (definitely vaccine-related).”

P9:
“In the Extension studies, enrolled subjects were followed for serious adverse experiences, occurrence of pregnancy, and pregnancy/infant outcomes. The Extension studies did not use Vaccination Report Cards (VRCs) to collect non-serious adverse experiences. The data was entered on Case Report Forms and was entered into the Clinical Trial Database for review.”

1862 subjects in total (p11), which are called “randomized” even though the extension studies were not randomised. There is no information about how many of the originally randomised subjects in the studies

that were offered to participate in the extension studies and how many declined and for what reasons. Without this data, the report is unusable.

The report does not describe for how long the subjects were followed in the study. This information is only provided indirectly, and one therefore needs to consult other reports to find this out (p10):

"3.3 Data Sources
This report includes data for the study extensions for visits conducted through 31-Jul-2009 for P005-10; 14-Sep-2009 for P007-20; 29-Jan-2009 for P011-10, 11-Feb-2009 for P012-10 (sub-study for P013-10); 10-Mar-2008 for P015-10; and 12-Feb-2009 for P016-10."

26% of the subjects discontinued the study (p12), which is far above the discontinuation rates in Merck's other studies.

P14, narratives of serious adverse events:

Protocol 005
AN 2022, a White female who was 21 years of age at enrollment (31 years of age at the time of AE), received 3 vaccinations of monovalent HPV 16 L1 VLP vaccine in the base study. She was vaccinated with her first and second doses of qHPV vaccine on 10-Jan-2008 and 07-Jul-2008, respectively. On Day 2 (08-Jul-2008), Postdose 2, the subject experienced flu-like symptoms including headache. The flu-like symptoms were resolved but the headache persisted. The subject discontinued from the study due to the headache. She had a MRI, (22-Sep-2008) which was normal. The headache resolved in Jan-2009. The investigator determined the headache was possibly related to the vaccine and considered the headache as an "other important medical event".

A headache that lasted six months was considered to be an "other important medical event." It is not clear what is meant by this term.

Protocol 011
AN 20159, a multi-racial female who was 22 years of age at enrollment (27 years of age at the time of AE), received three vaccinations of placebo in the base study. In the Extension study, she was vaccinated with her first dose of qHPV vaccine on **redacted** 2007. On Day 12 **redacted** -2007), Postdose 1, the subject was hospitalized. An endoscopy was performed and the results indicated a gastric ulcer. She was treated with omeprazole 20mg/bid from 20-Mar-2007 to 03-Apr-2007 and sucralfate 1 g from 20-Mar-2007 to 03-Apr-2007. She was discharged **redacted** 2007. On 15-Aug-2007, the subject had a follow-up visit and confirmed an additional planned endoscopy was not performed. On 30-May-2007 the subject recovered from gastric ulcer. The reporting investigator determined the gastric ulcer was definitely not related to the qHPV vaccine.

AN 25413, a multi-racial female who was 23 years of age at enrollment (28 years of age at time of AE), received three vaccinations of placebo in the base study. She had a history of ventricular arrhythmia. In the Extension study she was vaccinated with her first and second doses of qHPV vaccine on 13-Mar-2007 and **redacted** -2007, respectively. There was no concomitant medication. On Day 74 **redacted** -2007), Postdose 2, the subject went to the clinic with left hemiparesia and paresthesias; and she was admitted to the ER. On **redacted** 2007, she was discharged from the hospital with the diagnosis of transient ischemic attack (TIA). She took Aspirin 100 mg qd since 28-Jul-2007 to Sep-2007 (day unknown) and Propaferona once a day since 05-Aug-2007 to 25-Aug-2007. She recovered on 29-Jul-2007 and the etiology of the event was not determined. The reporting investigator felt the TIA was probably not related to qHPV vaccine.

Protocol 012
AN 30849, an Asian female who was 22 years of age at enrollment (27 years of age at time of AE), received three vaccinations of placebo in the base study. In the Extension study, she was vaccinated with the first, second, and third doses of qHPV vaccine on 01-Mar-2007, 08-May-2007, and **redacted** 2007, respectively. On Day 1 **redacted** 2007) (day of vaccination), 10 hours after her final vaccination, the subject experienced diarrhea (10 times) and vomiting (3 times) and was admitted to the hospital. During her stay in the hospital, she received normal saline solution (NNS) IV drip, hyoscine IV, Metoclopramide IV, norfloxacin (oral), hyoscine (oral rehydrate solution and loperamide (oral) PRN. The subject was discharged on **redacted**2007 and the symptoms resolved on 18-Aug-2007. The diagnosis was acute gastroenteritis. The reporting investigator felt the acute gastroenteritis was not related to the qHPV vaccine.

AN 32216, an Asian female who was 22 years of age at enrollment (26 years of age at time of AE), received three vaccinations of placebo in the base study. In the Extension study, she was vaccinated with the first, second, and third doses of qHPV vaccine on 26-Mar-2007, 28-May-2007, and **redacted** 2007, respectively. On Day 1 **redacted** 2007) (day of 3rd vaccination), the subject experienced fever with chills, myalgia, cough, sore throat, runny nose and vomiting. The physical examination was remarkable for infected pharynx and mild costovertebral angle. The subject was hospitalized and received paracetamol1000 mg PRN Q 6 hr, lincomycin 600 mg IM, dexamethasone 4 mg IM, roxithromycin300 mg/day (until 27-Sep-2007), dexromethorphan 15 mg (+) guaifenesin 100 mg (+)terpin hydrate 3 tablets/day (until 25-Sep-2007), mixture tussis PRN, domperidone 30mg/day and 5% dextrose in half strength of normal saline IV drip. On **redacted** 2007, the subject was discharged and recovered on 27-Sep-2007. The final diagnosis was acute pharyngitis. The reporting investigator felt the acute pharyngitis was possibly related to the vaccine.

AN 33469, a White female who was 22 years of age at enrollment (27 years of age at time of AE), received three vaccinations of placebo in the base study. In the Extension study, she was vaccinated with her first and second doses of qHPV vaccine on 12-Dec-2007 and 13-Feb-2008. Concomitant therapy included ethinyl estradiol (+) levonorgestrel (MICROGYNON). On 12-Dec-2007 following the first vaccination, the patient experienced a mild allergic reaction (non-serious). On approximately Day 6 (18-Feb-2008), Postdose 2, the subject experienced a classic allergic reaction of severe intensity. It was reported after the first vaccination the subject's reaction was mild but the symptoms were severe after the second vaccination. The subject was prescribed steroids and epinephrine hydrochloride (EPIPEN). The subject recovered from the classic allergic reaction on 29-Feb-2008. The investigator felt the classic allergic reaction was probably related to the study vaccine and was to be another important medical event.

The severe allergy was likely caused by the vaccine because it became worse on rechallenge, which is a classical method used in clinical pharmacology to establish cause-effect relationships.

AN 30066, a Hispanic female who was 22 years of age at enrollment (27 years of age at time of AE), received three vaccinations of qHPV vaccine in the base study. In the Extension study, she was inadvertently vaccinated with her 4th dose of qHPV vaccine on 29-Aug-2007. Administration of a 4th dose of vaccine was considered an overdose (per protocol definition). The subject was not hospitalized. The subject did not experience any signs or symptoms within the 30 minute observation nor during the 14-day follow up. The investigator reported the incorrect dose of vaccine administered/overdose was definitely related to study vaccine. Of note, subsequent to frozen file, the investigator changed the causality from definitely related to not related.

Protocol 015
AN 41232, a While female who was 22 years of age at enrollment (27 years of age at time of AE), received three vaccinations of placebo in the base study. The subject had generalized anxiety disorder since Jan-2006. In the Extension study, she was vaccinated with her first dose of qHPV vaccine on **redacted** 2007. On

approximately Day 4 (**redacted** 2007) Postdose 1, the subject experienced a panic crisis and was hospitalized. **redacted** 2007, the subject recovered was discharged from the hospital. She was treated with fluoxetine 20 mgr, alrprzolm [sic] 0.25 mgr and clonazepam 7 drops/day. The reporting investigator felt the panic crisis was probably not related to the study therapy. The panic crisis was considered to be immediately life-threatening.

V501 Protocol GDS03E, qHPV

16 Feb 2012.

Index on p12.

Report of a case-control study of autoimmunity. Apparently made by independent researchers. There is no description of conflicts of interest.

The information offered is not consistent:

The authors of the report are these (p1):

Lamiae Grimaldi-Bensouda
Elodie Aubrun
Pamela Leighton
Michel Rossignol
Lucien Abenhaim

But the research team is different (p2):

Research Team

		Signature
Lamiae Grimaldi-Bensouda, PharmD, MSc, PhD	Pharmacoepidemiology (Principal Investigator)	
Jacques Benichou, MD, PhD	Epidemiology Biostatistics	
Michel Rossignol, MD, MSc	Clinical epidemiology	
Lucien Abenhaim, MD, PhD	Pharmacoepidemiology	

The scientific committee is this one (p2):

Validation of the report by the scientific committee

I certify that I have validated independently the following report version 2.2, 16 February 2012, in the context of the Scientific Committee "Gardasil® and autoimmune diseases use the PGRx information system".

		Signature
Paul-Henri Lambert	Immunology (president)	Paul H Lambert
Bertrand Godeau	Internal Medicine	
Didier Guillemot	Epidemiology	
Alfred Mahr	Internal Medicine /Clinical Epidemiology	

But on p22, wider teams are listed, now with six in the scientific committee and seven in the research team:

Gardasil® & autoimmune disorders - Scientific committee

– Scientific Committee organised by SPMSD – Supervised

Paul-Henri Lambert	Immunology	University of Geneva, Centre of Vaccinology in the Department of Pathology and Immunology
Bertrand Godeau	Internal Medicine	CHU Henri Mondor, Creteil
Didier Guillemot	Epidemiology	Pasteur Institute /Inserm U657, Paris
Charles Thivolet	Endocrinology	CHU Lyon South, Lyon
Kumaran Deiva	Neurology	CHU Kremlin-Bicêtre, Paris (left the committee in 2011)
Alfred Mahr	Internal Medicine /Clinical Epidemiology	Saint-Louis Hospital, Paris

Composition of the PGRx/LASER Research team

Lamiae Grimaldi-Bensouda	Pharmacoepidemiology	Conservatoire National des Arts & Metiers & Pasteur Institute, Paris
Elodie Aubrun	Pharmacoepidemiology	Paris
Jacques Benichou	Biostatistics	University of Rouen
Yann Hamon	Datamanagement/statistics	Paris
Anais Sitruk	Statistics	Paris
Michel Rossignol	Pharmacoepidemiology	CRR andMcGill University, Montreal
Lucien Abenhaim	Pharmacoepidemiology	London School of Hygiene & Tropical Medicine

Four of the six members of the scientific committee and four of the seven members of the research team signed the report. One of the authors of the report (Leighton) is not a member of the research team and have not signed the report, and three members of the research team (Benichou, Hamon and Sitruk; all statisticians, it seems) are not authors.

P12:

Disclosure

This study was conducted by using the database accrued by the PGRx Information System. This system collects cases of diseases and a reference pool of controls independently of any exposure to drugs. The system and the data collected belong to LA-SER, a private corporation. Interested parties, such as pharmaceutical companies or other organisations, obtain copies of the database (with aggregated data) by a system of subscription. Several parties can subscribe to the same data, for similar or for different purposes. The reference pool is subscribed by all users. This was the case for the study presented here, where cases were subscribed by SPMSD, which commercialises Gardasil®. Several pharmaceutical companies have subscribed to the system for other studies, including several using part of the cases used in this study and all using the same reference pool (in all or in part).

So, LA-SER is a private company. It explained on p19 that SPMSD is Sanofi Pasteur MSD.

P13:

Context

Health authorities have requested that autoimmune disorders (AIDs) be surveyed in relation to vaccination against the human papillomavirus (HPV). This study employed a systematic case-referent methodology through the PGRx (Pharmacoepidemiologic General Research eXtension) system to investigate whether the HPV vaccine Gardasil® is associated with a modified risk of AIDs in the French population. The PGRx system prospectively and routinely collects: incident and validated cases of AID, a large pool of referent patients from general practices (from which controls matched to cases are drawn) and information concerning cases' and controls' vaccinations, drug use and a variety of potential risk factors. Methods for the collection of cases and referents, control selection and data gathering are standardised, audited, and have been validated previously (Grimaldi-Bensouda *et al.* 2010 a, b and c).

The French authorities identified the following AIDs to be studied: idiopathic thrombocytopenic purpura (ITP), central demyelination and multiple sclerosis (CDMS), connective tissue disorders (CTD: lupus, rheumatoid arthritis, undifferentiated connective tissue diseases, myositis and dermatomyositis), type 1 diabetes mellitus (T1DM), auto-immune thyroid disorders (AITD: Grave-Basedow and Hashimoto diseases) and Guillain-Barré Syndrome (GBS). The study of uveitis had been envisioned but found not feasible. This study was carried out in females aged 14 to 26 years; the population of individuals most likely to have been vaccinated with Gardasil®.

P15:

The case-control study was too small to rule out associations between autoimmune diseases and Gardasil, as evidenced by the wide confidence intervals, e.g.:

Conclusions

No evidence of an increased risk of the studied autoimmune disorders was observable following vaccination with Gardasil® for the time window of study available. The study lacked the power to conclude on individual disorders taken separately. From the monitoring goal viewpoint, the study observed no unusual accrual, in a large series of centres specialised in autoimmune disorders, of incident cases of any of the diseases surveyed in young females, at a time when one-third of them were getting vaccinated against HPV, mainly by Gardasil®.

Appendix D

Gardasil 9 Clinical Trials

Review Notes

Contents

Placebo-controlled study of Gardasil 9

P006

"A Phase III Randomized, International, Placebo-Controlled, Double-Blind Clinical Trial to Study the Tolerability and Immunogenicity of V503, a Multivalent Human Papillomavirus (HPV) L1 Virus-Like Particle (VLP) Vaccine, Given to Females 12-26 Years of Age Who Have Previously Received GARDASIL™ (Protocol 006)."

Study Initiation Date (FPE): 25-Feb-2010

Study Completion Date (LPLV): 10-Jun-2011
Report not dated, at the bottom of pages are both 09-Jan-2012 and 10-Jan-2012.

Index on p10.
P3:
"Subjects were administered a standard 3-dose regimen (Day 1, Month 2, and Month 6) of 9-valent HPV (9vHPV) vaccine or placebo. All vaccinated subjects were followed for safety from Day 1 through Month 7. Subjects were assessed for immunogenicity at Day 1, Month 2, and Month 7."

Those who had not tolerated Gardasil well previously, which they had all received, would likely decline being randomised. It is therefore not a genuine placebo-controlled trial, as such a trial would tell us something reliably about Gardasil's harms.

OBJECTIVE(S):

Primary Objective: To evaluate the tolerability of the 9-valent HPV L1 VLP vaccine in adolescent girls and young women 12 to 26 years of age who have previously received a 3-dose regimen of GARDASIL™.

Primary Hypothesis: 9-valent HPV L1 VLP vaccine when administered to adolescent girls and young women 12 to 26 years of age who have previously received a 3-dose regimen of GARDASIL™ is generally well-tolerated.

Secondary Objective: To demonstrate that the 9-valent HPV L1 VLP vaccine is immunogenic with respect to HPV Types 31, 33, 45, 52, and 58 in adolescent girls and young women 12 to 26 years of age who have previously received a 3-dose regimen of GARDASIL™.

Secondary Hypothesis: 9-valent HPV L1 VLP vaccine generates acceptable immune responses in adolescent girls and young women 12 to 26 years of age who have previously received a 3-dose regimen of GARDASIL™ as measured by the percentage of subjects who are seropositive to each of HPV Types 31, 33, 45, 52, and 58 at 4 weeks post-dose 3. (Each vaccine component will be analyzed separately. Acceptability is defined as the lower bound of the two-sided 95% confidence interval for the seropositivity percentage being greater than 90 %.)

Safety is a primary objective. A secondary objective is to see if vaccination with five more antigens than those contained in Gardasil will provide acceptable immunity to each of these additional antigens in females who have all received three doses of Gardasil previously.

P4:

	9vHPV vaccine		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Not Randomized					11	
Subjects in population	618		306		924	

P5:

DOSAGE/FORMULATION NOS.: Subjects received one 0.5-mL intramuscular dose of 9vHPV vaccine at Day 1, Month 2, and Month 6. Formulation and dosage for the clinical material are found in the following table:

Clinical Supplies-Control Numbers, Formulation Numbers, Dosage and Package Information for 9-valent HPV Vaccine and Placebo Formulations Used in V503-006

Vaccine	Control Number	Bulk Lot ID/Formulation Number	Potency	Packaging
9vHPV Vaccine	WL00040547	WL00033284	60/80/120/80/40/40/40/40 /40 ug/mL	0.5-mL, single-dose vial
9vHPV Vaccine	WL00037291	WL00033284	60/80/120/80/40/40/40/40 /40 ug/mL	0.5–mL, single-dose vial
Normal Saline Placebo	WL00040547	WL00036598	9 mg/mL	0.5–mL, single-dose vial
Normal Saline Placebo	WL00037291	WL00036598	9 mg/mL	0.5–mL, single-dose vial

It appears that the two batches of vaccine were actually the same batch (Bulk Lot) but the control numbers are different. Why did Merck produce two different portions of placebo, if this is what the control numbers mean, as placebo was normal saline without the vaccine adjuvant.

P5:
"subject has received a 3-dose regimen of marketed GARDASIL™ within a 1-year period, has received the third dose of GARDASIL™ at least 1 year prior to enrollment, and has not received any other HPV vaccine."

Despite the fact that they had all received three doses of Gardasil earlier, 22 of 618 discontinued on the vaccine vs 6 of 306 on placebo (p4).

P6:

> **Safety**: The following measures were collected from each study subject to assess safety: 1) temperatures (within 5 days following any vaccination); 2) all adverse events (Days 1 to 15 following any vaccination); 3) all serious adverse experiences that occurred from Day 1 through 30 days following the last vaccination; 4) all serious adverse experiences that resulted in death or were determined to be related to the study vaccine that occurred at any time during the study. All subjects who received at least one injection of study vaccine and had safety follow-up data were included in the safety summary.

P6:
"Statistical p-Values were computed only for those adverse experiences that were prompted for on the VRC [vaccine report card] (pain/tenderness/soreness, swelling, and redness) and elevated temperatures."

P69:
"9.5.3.2.1 Primary Safety and Tolerability Parameters
The important variables of interest for safety/tolerability were the occurrence of injection site adverse experiences prompted for on the VRC (such as redness, swelling, and pain/tenderness/soreness occurring Day 1 through Day 5 following any vaccination) and elevated temperature (≥100.0°F [≥37.8°C]), from Day 1 to Day 5 following any vaccination. Other important variables of interest included severe injection-site adverse experiences and the incidence of any vaccine-related serious adverse experiences ... Follow-up at Months 2, 6, and 7 after the first injection included an interview to assess general safety. The interview solicited broadly for any serious adverse experiences that the subject may have encountered."

This is not an appropriate way to study safety. Systemic adverse experiences are not even mentioned (apart from those very few that are considered serious, e.g. are life-threatening or lead to hospital admission), and before interviewing people at follow-up visits, the investigators were instructed to only take an interest in serious adverse events.

P8:

> **Safety:** The frequency of injection-site clinical adverse experiences (Days 1 to 5 following any vaccination) was higher in the 9vHPV vaccine group than in the placebo group (91.1% and 44.3%, respectively). The frequencies of systemic adverse experiences (Days 1 to 15 following any vaccination) were generally comparable between the 2 groups (61.5% in the 9vHPV vaccine group, and 58.0% in the placebo group). The frequency of elevated temperatures (Days 1 to 5 following any vaccination) was slightly higher in the 9vHPV vaccine group than in the placebo group (6.5% and 3.0%, respectively). Only 3 subjects discontinued from the study due to a vaccine-related adverse experience, all in the 9vHPV vaccine group. Six (6) serious adverse experiences were reported over the entire duration of the study, regardless of causality, including 3 events in subjects in the 9vHPV vaccine group and 3 events in subjects in the placebo group. Two (2) serious vaccine-related adverse experiences were reported over the entire duration of the study, including 1 event in subjects in the 9vHPV vaccine group and 1 event in subjects in the placebo group. Overall, administration of the 9vHPV vaccine in prior GARDASIL™ vaccine recipients was generally well tolerated.

P8:

Adverse Event Summary
(Vaccination and Follow-up Periods, Day 1 to End of Study) (All Vaccinated Subjects)

	9vHPV vaccine		Placebo	
	n	(%)	n	(%)
Subjects in population with follow-up	608		305	
with one or more adverse events	583	(95.9)	229	(75.1)
injection-site	554	(91.1)	135	(44.3)
non-injection-site	374	(61.5)	177	(58.0)
with no adverse event	25	(4.1)	76	(24.9)
with vaccine-related[†] adverse events	566	(93.1)	175	(57.4)
injection-site	554	(91.1)	135	(44.3)
non-injection-site	186	(30.6)	79	(25.9)
with serious adverse events	3	(0.5)	3	(1.0)
with serious vaccine-related adverse events	1	(0.2)	1	(0.3)
who died	0	(0.0)	0	(0.0)
discontinued[‡] due to an adverse event	3	(0.5)	0	(0.0)
discontinued due to a vaccine-related adverse event	3	(0.5)	0	(0.0)
discontinued due to a serious adverse event	0	(0.0)	0	(0.0)
discontinued due to a serious vaccine-related adverse event	0	(0.0)	0	(0.0)

[†] Determined by the investigator to be related to the vaccine.
[‡] Study medication withdrawn.

P9:
Conclusion in synopsis: "generally well tolerated."

Merck claimed that Gardasil 9 was "generally well tolerated" despite the fact that 91% of the patients experienced injection site adverse events on Gardasil 9 versus only 44% on placebo. These percentages come from the table just above (554/608 vs 135/305). I calculated that $p = 1 \times 10^{-52}$ for this difference (Fisher's exact test).

I do not recall ever seeing a p-value in biomedical research that is so low or anywhere near being so low. The likelihood that this huge difference occurred by chance is the same as the likelihood that a person can guess correctly a number with 52 digits, e.g.: 507,457,386,833,556,284,307,831,635,422,839,574,205,395,244,737,850,8.

Merck's conclusion, that its vaccine is well tolerated, is written before the trials were undertaken, and it does not seem to matter what Merck finds in its trials. The foregone conclusion remains unaltered.

Given these data, it is misleading to claim that the vaccine was "generally well tolerated." As it could be argued that this is less important because it is stated in a report to drug regulators, to which the public does not have access, I looked at Merck's published report of the study.

I looked up the trial in a publicly available trials register[1] (NCT01047345) and it mentions three publications based on the trial:

"Garland SM, Cheung TH, McNeill S, Petersen LK, Romaguera J, Vazquez-Narvaez J, Bautista O, Shields C, Vuocolo S, Luxembourg A. Safety and immunogenicity of a 9-valent HPV vaccine in females 12-26 years of age who previously received the quadrivalent HPV vaccine. Vaccine. 2015 Nov 27;33(48):6855-64. doi: 10.1016/j.vaccine.2015.08.059. Epub 2015 Sep 26.

[1] A study of V503, a 9-valent human papillomavirus (9vHPV) vaccine in females 12-26 years of age who have previously received GARDASIL™ (V503-006). https://clinicaltrials.gov/show/NCT01047345.

Moreira ED Jr, Block SL, Ferris D, Giuliano AR, Iversen OE, Joura EA, Kosalaraksa P, Schilling A, Van Damme P, Bornstein J, Bosch FX, Pils S, Cuzick J, Garland SM, Huh W, Kjaer SK, Qi H, Hyatt D, Martin J, Moeller E, Ritter M, Baudin M, Luxembourg A. Safety Profile of the 9-Valent HPV Vaccine: A Combined Analysis of 7 Phase III Clinical Trials. Pediatrics. 2016 Aug;138(2). pii: e20154387. doi: 10.1542/peds.2015-4387. Epub 2016 Jul 15.

Publications automatically indexed to this study by ClinicalTrials.gov Identifier (NCT Number):

Moreira ED, Giuliano AR, de Hoon J, Iversen OE, Joura EA, Restrepo J, Van Damme P, Vandermeulen C, Ellison MC, Krick A, Shields C, Heiles B, Luxembourg A. Safety profile of the 9-valent human papillomavirus vaccine: assessment in prior quadrivalent HPV vaccine recipients and in men 16 to 26 years of age. Hum Vaccin Immunother. 2018 Feb 1;14(2):396-403. doi: 10.1080/21645515.2017.1403700. Epub 2017 Dec 14."

The published trial report by Garland et al. mentions the huge difference in injection site reactions in the abstract of 91% vs 44% but provides no p-value and concludes, like in Merck's internal report, that the vaccine is "generally well tolerated." Four of the ten authors are from Merck. The two other publications describe results from several studies.

In Merck's study report, this colossal difference between vaccine and placebo is described this way (p141):

"As shown in Table 12-3, the proportion of subjects in the 9vHPV vaccine group who reported at least one injection-site adverse experience within 5 days of any vaccination (554/608 [91.1%]) was numerically higher than the proportion of subjects in the placebo group who reported at least one injection-site adverse experience within 5 days of any vaccination (134/305 [43.9%])."

For some unknown reason, there was one patient less in the placebo group, 134 in total, on p141 than in the summary table on p8 where there were 135. I have come across many such small discrepancies in Merck's reports that I have not commented upon.

To say "numerically higher" about such a large difference is misleading. This is an expression researchers usually only use if the numbers are higher, but not statistically significantly higher. Furthermore, the p-value Merck provided in a table – but not in the text – was $p < 0.001$ (p144). Not $p = 1 \times 10^{-52}$.

On p186, Merck states:

"The overall safety and tolerability profile of the 9vHPV vaccine administered to 12- to 26-year-old adolescent girls and young women who were previously vaccinated with qHPV vaccine was acceptable. Safety and tolerability findings in that population were generally consistent with the overall safety and tolerability findings previously reported in 9- to 26-year-old girls and women following administration of a 3-dose regimen of the qHPV vaccine."

There are at least three problems with this statement.

Firstly, Merck concludes that the indisputable and substantial harm "was acceptable."

Secondly, the doubling of females with injection-site reactions from 44% to 91% is far from being consistent with the findings in the other Merck trials. There is extreme heterogeneity in the results of Merck's trials (see Appendix A, which contains my meta-analyses), which means that Merck's findings are highly inconsistent.

Thirdly, Merck's result raises the suspicion that people might tolerate poorly being vaccinated six times with Gardasil, which might be because they mount an immune reaction to the repeated vaccinations. This phenomenon is well-known for some other vaccines, e.g. against pneumococci.

P43:
"Four of the five HPV types of interest (Types 31, 45, 52, 58) have been previously tested in V502-001, a 7-month, qHPV vaccine-controlled, dose-ranging, immunogenicity and safety study of an aluminum-containing 8-valent HPV (Types 6 , 11, 16, 18, 31, 45, 52, 58) L1 VLP vaccine in 16- to 23-year-old women. This study showed that the 8-valent vaccine formulations are generally well-tolerated and highly immunogenic in that population."

P44:
"The low-dose, mid-dose, and high-dose formulations contained respectively 5, 20 and 40 mcg of each of these VLPs. Anti-HPV 31, 45, 52, and 58 GMTs in the 8-valent vaccine cohorts at 4 weeks post-dose 3 appeared to be dose-dependent. Differences in anti-HPV 31, 45, 52, and 58 GMTs were most apparent between the low-dose and mid-dose formulations."

P44:
"V504 Protocol 001: 5-Valent HPV Vaccine (HPV 31. 33. 45. 52. 581 Administered Concomitantly With qHPV Vaccine."

P46:
"The subjects, investigators (and his/her staff), laboratory staff, and Sponsor remained blinded to subject vaccine allocation for the duration of the study. Because the 9vHPV vaccine and normal saline placebo can be visibly distinguished, the vaccine/placebo in this study had to be prepared by an unblinded third party who was otherwise not involved in the conduct of the study."

P53:
"The use of a saline placebo allowed an overall evaluation of the safety and tolerability profile of all vaccine components, including antigenic proteins and adjuvant. Because the 9vHPV vaccine and saline placebo are visually distinct (vaccine is a whitish, semi-translucent suspension; placebo is a clear colorless liquid), the study involved unblinded and blinded site personnel. Unblinded personnel were to prepare and administer the vaccine and have no further contact with study subject, while blinded personnel were to be in charge of the safety evaluation. A similar approach was previously used in the qHPV vaccine clinical program (V501 Protocol 018 [16.1.12.57])."

P62:
"This unblinded third party was responsible for preparation and administration of study material, but did not disclose the contents of the syringe to the subject, the parent/legal guardian, the blinded study personnel/ investigator, or Sponsor's personnel ... The unblinded study personnel were responsible for obtaining the subject's AN [number that identify the patient in the trial], selecting the appropriate vial from the refrigerator, withdrawing, and verifying the volume and contents of the syringe."

There is a great risk that the investigators and patients were not kept blind. Why were the vials not produced centrally, by Merck, which is normal practice in drug trials, but at each study site, which creates a huge risk of unblinding? The vials were produced in advance and stored in a refrigerator and could therefore have been produced by Merck instead.

It would have been easy to add something to the saline placebo that would have made it a "whitish, semi-translucent suspension," indistinguishable from the vaccine, and there are other easy ways of blinding injections that do not run such a huge risk of unblinding the investigators.

P62-3:
"After completing administration of the study material, the unblinded study personnel established that the subject was stable and then left the examination room to allow the blinded study personnel to continue with study procedures ... The blinded study personnel waited outside the examination room while the unblinded personnel administered the vaccine/placebo and entered the examination room only when the unblinded personnel completed their responsibilities."

This is scientifically unacceptable. The unblinded study personnel had contact with ALL the subjects enrolled in the trial. I do not recall ever seeing such inappropriate handling of blinding in a trial. Breaking the blinding is highly problematic for a trial that has safety as its only primary outcome. We are even told that "A similar approach was previously used in the qHPV vaccine clinical program" (p53). On top of all this, Merck used additional unblinded personnel, which seems totally unnecessary (p63):

P63:
"9.4.5.5 Roles of Unblinded Sponsor Clinical Personnel: Unblinded Clinical Scientist, Unblinded Clinical Research Associate, and Unblinded Project Manager
Because the vaccine and placebo used in this study were visually distinguishable, the vaccine/placebo was prepared and administered by unblinded study personnel not otherwise involved in subject management. An unblinded CRA was assigned to the study to monitor study procedures that involved the administration and accountability of the vaccine/placebo. An unblinded PM was assigned to review all monitoring visit reports (MVR), track all unblinded MVRs and collate site issues provided by the unblinded CS and unblinded CRA. In addition, an in-house unblinded CS was assigned to the study to ensure that no in-house Merck personnel directly involved in the conduct of the study were accidentally unblinded based on the appearance of the vaccine/placebo when communicating with the study sites."

I have not seen such detailed revelations in Merck's other studies.

P47:
"All subjects were to be monitored for safety from Day 1 through 1 month following the last vaccination. All subjects were to receive a Vaccination Report Card (VRC) at the Day 1, Month 2, and Month 6 study vaccination visits. On the VRC, the subject or the parent/guardian of the subject were to be asked to record the subject's oral temperature in the evening after each study vaccination and daily for 4 days after each study vaccination for the purpose of identifying febrile events. Also, beginning after each study vaccination and for a total of 15 days including the day of vaccination, the subject was to be asked to record injection-site and systemic adverse experiences, concomitant medications, and concomitant vaccinations on the VRC.

Serious adverse experiences were to be collected regardless of causality from Day 1 through 1 month following the last vaccination.

Pregnancy and lactation information was also to be collected. Pregnancies and associated adverse experiences were to be followed to outcome.

In addition, new medical conditions not present at baseline and not reported as an adverse experience were to be collected throughout the study. Pregnancy and associated adverse experiences, lactation (if a

subject received study vaccine while breastfeeding during the Day 1 through Month 7 period), and serious adverse experiences in study subjects and infants were to be followed to outcome."

P53:
"The pre-specified adverse experiences of interest included VRC-prompted injection-site adverse experiences, VRC-prompted systemic clinical adverse experiences, serious clinical adverse experiences, and fever."

P50:
"9.1.2 Study Extension
Each subject was to be followed for approximately 7 months. Once the final database is unblinded (i.e., all subjects have completed Month 7 and data are audited and analyzed), subjects randomized to receive placebo will be eligible to receive 9vHPV vaccine under a study extension if vaccine tolerability and immunogenicity is demonstrated."

P78-9:
"To assess the risks of adverse experiences temporally associated with vaccination, a multi-tiered approach was used for the analysis of safety parameters. Tier-1 adverse experiences included (1) injection-site adverse experiences prompted for on the VRC, such as redness, swelling, and pain/tenderness/soreness occurring Day 1 through Day 5 following any vaccination, and (2) elevated temperature (≥100.0°F [37.8°C]), from Day 1 to Day 5 following any vaccination. For Tier-1 adverse experiences, the risk difference between the 9vFIPV vaccine group and placebo group, the corresponding two-sided 95% Cl on the risk difference, and the p-value for the test of significance of the risk difference (2-sided <0.05 level) were provided. All risk differences, 95% CIs, and p-values were calculated using the methods proposed by Miettinen and Nurminen [16.1.12.60].

The Tier-2 adverse experience summaries included (1) specific systemic adverse experiences within 14 days following any vaccination occurring in ≥1% of subjects in any vaccination group, (2) injection-site adverse experiences not prompted for on the VRC occurring Day 1 to Day 5 following any vaccination in ≥1% of subjects in any vaccination group, (3) serious adverse experiences occurring within 14 days following any vaccination, (4) serious vaccine-related adverse experiences observed at any time during the study, and (5) severe injection-site adverse experiences Day 1 through Day 5 following any vaccination visit. Risk differences and 95% CIs between the two vaccination groups were estimated for all Tier-2 adverse experiences using the methodology proposed by Miettinen and Nurminen [16.1.12.60].

Tier-3 adverse experiences included summaries (counts and proportions) by vaccination group for any other adverse experiences, including all injection-site adverse experiences occurring from Day 1 to Day 5 following each vaccination visit and all systemic adverse experiences occurring within 14 days of each vaccination visit."

Even though this was a placebo-controlled trial, the collection of possible harms of the vaccine was entirely inadequate, just like in other Merck trials, limiting the adverse events to those occurring in at least 1% of the patients and serious adverse events to those considered vaccine related, which is a subjective decision made by investigators some of whom very likely had financial conflicts of interest in relation to Merck. This is not a trustworthy trial.

P86:
Denmark contributed with 305 of the 924 randomised subjects.

P138:
"Adverse experience data for the entire study period is presented in Appendix [16.4]."

This appendix is missing. It is mentioned again on p467, which is the last page in the report:

16. LIST OF APPENDICES (CONT.)

Appendix		Application Starting Page
16.3:	CASE REPORT FORMS	
	Individual subject case report forms are not provided within the clinical study report.	
16.4:	INDIVIDUAL SUBJECT DATA LISTINGS	
	The Data Definition File page contains a list of the individual case report tabulations.	

P139:

Adverse Event Summary
(Days 1 to 15 Following Any Vaccination Visit) (All Vaccinated Subjects)

	9vHPV vaccine		Placebo	
	n	(%)	n	(%)
Subjects in population with follow-up	608		305	
with one or more adverse events	581	(95.6)	225	(73.8)
injection-site	554	(91.1)	134	(43.9)
non-injection-site	363	(59.7)	170	(55.7)
with no adverse event	27	(4.4)	80	(26.2)
with vaccine-related† adverse events	566	(93.1)	174	(57.0)
injection-site	554	(91.1)	134	(43.9)
non-injection-site	186	(30.6)	79	(25.9)
with serious adverse events	2	(0.3)	1	(0.3)
with serious vaccine-related adverse events	1	(0.2)	1	(0.3)
who died	0	(0.0)	0	(0.0)
discontinued‡ due to an adverse event	3	(0.5)	0	(0.0)
discontinued due to a vaccine-related adverse event	3	(0.5)	0	(0.0)
discontinued due to a serious adverse event	0	(0.0)	0	(0.0)
discontinued due to a serious vaccine-related adverse event	0	(0.0)	0	(0.0)

† Determined by the investigator to be related to the vaccine.
‡ Study medication withdrawn.

Data Source: [16.4]

On p8 in the report (repeated on p140), there is a similar table, but it includes not only events during two weeks after each vaccination but events occurring during the entire trial period of 7 months:

Adverse Event Summary
(Vaccination and Follow-up Periods, Day 1 to End of Study) (All Vaccinated Subjects)

	9vHPV vaccine		Placebo	
	n	(%)	n	(%)
Subjects in population with follow-up	608		305	
with one or more adverse events	583	(95.9)	229	(75.1)
injection-site	554	(91.1)	135	(44.3)
non-injection-site	374	(61.5)	177	(58.0)
with no adverse event	25	(4.1)	76	(24.9)
with vaccine-related† adverse events	566	(93.1)	175	(57.4)
injection-site	554	(91.1)	135	(44.3)
non-injection-site	186	(30.6)	79	(25.9)
with serious adverse events	3	(0.5)	3	(1.0)
with serious vaccine-related adverse events	1	(0.2)	1	(0.3)
who died	0	(0.0)	0	(0.0)
discontinued‡ due to an adverse event	3	(0.5)	0	(0.0)
discontinued due to a vaccine-related adverse event	3	(0.5)	0	(0.0)
discontinued due to a serious adverse event	0	(0.0)	0	(0.0)
discontinued due to a serious vaccine-related adverse event	0	(0.0)	0	(0.0)

† Determined by the investigator to be related to the vaccine.
‡ Study medication withdrawa.

A comparison of these two tables show that the registration of adverse events in this trial, and therefore in all Merck's trials, is insufficient. The numbers are virtually the same, e.g. there were 806 subjects with adverse events in the first table of events registered during two weeks after each vaccination, and only 6 more subjects in the second table of events registered from day 1 till the end of the study. For systemic events (called non-injection-site events), the numbers were 533 vs 551, or only 18 (3%) more subjects.

P148:

Subjects With Injection Site Adverse Events by Maximum Intensity
(Incidence >0% in One or More Vaccination Groups)
(Days 1 to 5 Following Any Vaccination Visit) (All Vaccinated Subjects)

		9vHPV vaccine		Placebo	
	Intensity Grading	n	(%)	n	(%)
Subjects in population with follow-up		608		305	
All Injection Site AEs	Total	550	(90.5)	124	(40.7)
	Mild	310	(51.0)	112	(36.7)
	Moderate	216	(35.5)	11	(3.6)
	Severe	24	(3.9)	1	(0.3)

These differences are very large; for 24 vs 1 severe injection-site reactions, p = 0.0008, and for 240 vs 12 moderate or severe reactions, p = 6 x 10^{-36} (my calculations; Merck made no such calculations).

P151:

Analysis of Subjects With Severe Injection Site Adverse Events
(Incidence >0% in One or More Vaccination Groups)
(Days 1 to 5 Following Any Vaccination Visit) (All Vaccinated Subjects)

	9vHPV vaccine		Placebo		Difference in % vs Placebo
	n	(%)	n	(%)	Estimate (95% CI)†
Subjects in population with follow-up	608		305		
With one or more Severe injection site adverse events	68	(11.2)	3	(1.0)	10.2 (7.5, 13.1)

† Based on Miettinen & Nurminen method.
For the measured adverse experiences of erythema and swelling, Severe is defined as >2 inches.
Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.

Data Source: [16.4]

There are more severe events in this table because erythema and swelling were included. Again, there is a huge difference between vaccine and placebo in severe injection-site adverse events, 68 vs 3, p = 2 x 10^{-9} (my calculation).

P152:
"12.2.2.2.2 Comparison of Systemic Adverse Experiences
Comparison between the 9vHPV vaccine group and placebo group with respect to the number and percentage of subjects who reported specific systemic clinical adverse experiences (incidence ≥1% in one or more vaccination groups) by system organ class from Day 1 to 15 following any vaccination visit is provided in Table 12-9. As shown in the table, the 95% CIs of the risk difference between 9vHPV vaccine and placebo groups generally included zero, except in a few cases, including:
- Abdominal Discomfort (higher frequency in 9vHPV vaccine group).
- Nausea (higher frequency in 9vHPV vaccine group).
- Pyrexia (higher frequency in 9vHPV vaccine group).
- Dizziness (higher frequency in 9vHPV vaccine group)."

The data in table 12-9 for these events were:

	9vHPV vaccine		Placebo		Difference in % vs Placebo
	n	(%)	n	(%)	Estimate (95% CI)[†]
Abdominal discomfort	8	(1.3)	0	(0.0)	1.3 (0.1, 2.6)
Nausea	52	(8.6)	12	(3.9)	4.6 (1.2, 7.7)
Pyrexia	41	(6.7)	10	(3.3)	3.5 (0.3, 6.2)
Dizziness	30	(4.9)	6	(2.0)	3.0 (0.3, 5.3)

Table 12-9 has 12 general categories (like nervous system disorders) and a total of 29 separate events (like dizziness). If the vaccine had no harms at all, one would expect 5% of these 29 events to be statistically significant by chance, and half of them (2.5%) to be more common with the vaccine than with the placebo, which is 0.7 events. However, there were 4 such events, which is six times more common than expected by chance.

It is noteworthy that, apart from pyrexia, these symptoms are very common in patients with POTS. In Brinth's cohort of 53 POTS patients, 70% had abdominal pain, 91% had nausea and 96% had orthostatic intolerance (which is a kind of dizziness).[2] Since abdominal pain is not the same as abdominal discomfort, I looked at all the gastrointestinal events in table 12-9:

Gastrointestinal disorders	**108**	**(17.8)**	**41**	**(13.4)**	**4.3 (-0.8, 9.0)**
Abdominal discomfort	8	(1.3)	0	(0.0)	1.3 (0.1, 2.6)
Abdominal pain	10	(1.6)	4	(1.3)	0.3 (-1.8, 1.9)
Abdominal pain upper	22	(3.6)	6	(2.0)	1.7 (-0.9, 3.8)
Diarrhoea	9	(1.5)	7	(2.3)	-0.8 (-3.3, 0.9)
Nausea	52	(8.6)	12	(3.9)	4.6 (1.2, 7.7)
Toothache	6	(1.0)	5	(1.6)	-0.7 (-2.9, 0.8)
Vomiting	13	(2.1)	4	(1.3)	0.8 (-1.3, 2.6)

A footnote to the table explains that, "Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class."

[2] Brinth L, Theibel AC, Pors K, et al. Suspected side effects to the quadrivalent human papilloma vaccine. Dan Med J 2015;62:A5064.

Adding the upper three categories, abdominal discomfort, pain or upper pain, one gets 40 vs 10 events, or double as many as expected in the vaccine group, which is double as large as the placebo group.

Adding nausea and vomiting, which are closely related, one gets 65 vs 16 events, also double as many as expected in the vaccine group.

There is a similar table in the study report for the only other placebo-controlled trial, where carrier solution was used as placebo (on p291-6 in V501 P018 LTFU CSR_ w protocols P018-05, -06, -10 and -11):

	Quadrivalent HPV (Types 6,11,16,18) L1 VLP Vaccine (N=1179)				Non-Alum Placebo (N=594)			
	All Adverse Experiences		VR		All Adverse Experiences		VR	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in analysis population	1179				594			
Gastrointestinal Disorders	**150**	**(12.9)**	**51**	**(4.4)**	**91**	**(15.6)**	**30**	**(5.1)**
Abdominal pain	19	(1.6)	7	(0.6)	12	(2.1)	7	(1.2)
Abdominal pain upper	38	(3.3)	12	(1.0)	17	(2.9)	3	(0.5)
Diarrhoea	43	(3.7)	11	(0.9)	21	(3.6)	3	(0.5)
Nausea	38	(3.3)	18	(1.5)	22	(3.8)	13	(2.2)
Vomiting	26	(2.2)	10	(0.9)	18	(3.1)	6	(1.0)
Pyrexia	100	(8.6)	74	(6.4)	45	(7.7)	32	(5.5)
Dizziness	25	(2.1)	19	(1.6)	9	(1.5)	7	(1.2)

VR means vaccine related. For abdominal pain, the two categories add up to 57 vs 29, which is not an increase because the vaccine group is double as large as the placebo group. For nausea and vomiting, the total numbers are 64 vs 40, less than expected. For pyrexia, they are 100 vs 45, a little more than expected.

For dizziness, the numbers are 25 vs 9, a little more than expected. Taken together, the two placebo-controlled trials found more dizziness on vaccine than on placebo. I did a meta-analysis with the Comprehensive Meta Analysis program and found a risk ratio of 1.69 (95% confidence interval 1.42 to 2.01), p < 0.00001, with no heterogeneity ($I^2 = 0$). This is an important finding because dizziness is a key symptom in POTS. It is often this symptom that lands the POTS patients in hospital for the first time. The number needed to harm was only 56.

That the vaccine seems to cause pyrexia is supported by the actually measured temperatures (p160):

Analysis of Maximum Temperatures
(Days 1 to 5 Following Any Vaccination Visit) (All Vaccinated Subjects)

	9vHPV vaccine		Placebo		Difference in % vs Placebo	
	n	(%)	n	(%)	Estimate (95% CI)†	p-value†
Subjects in population	613		305			
Without temperature data (Days 1 to 5)‡	9		1			
With temperature data (Days 1 to 5)	604		304			
Maximum Temperature (Oral or Oral Equivalent)						
≥37.8 °C (100.0 °F)	39	(6.5)	9	(3.0)	3.5 (0.5, 6.2)	0.026

Even though Merck found a statistically significant difference in the occurrence of fever after vaccination and also reported this in a table (see just above, p = 0.026), Merck dismissed this finding (p186): "The proportion of subjects who reported a fever during the 5 days following any vaccination was low in both vaccination groups and within the range reported in previous qHPV vaccine studies."

P155-6:
This table describes subjects with systemic clinical adverse experiences, although it doesn't say so but says "adverse events" (which includes injection-site adverse events). The table heading is therefore misleading:

Subjects With Adverse Events by Maximum Intensity Rating
(Days 1 to 15 Following Any Vaccination Visit) (All Vaccinated Subjects)

	9vHPV vaccine		Placebo	
	n	(%)	n	(%)
Subjects in population with follow-up	608		305	
With one or more adverse events	363	(59.7)	170	(55.7)
With no adverse events	245	(40.3)	135	(44.3)
Subjects by maximum intensity rating of adverse events				
MILD	109	(17.9)	57	(18.7)
MODERATE	190	(31.3)	78	(25.6)
SEVERE	63	(10.4)	34	(11.1)
UNKNOWN	1	(0.2)	1	(0.3)
Each subject is counted a single time according to the highest non-missing intensity grading.				

Data Source: [16.4]

There were more systemic clinical adverse experiences of moderate or severe intensity with the vaccine than with placebo, 253 (41.6%) vs 112 (36.7%). This difference was not statistically significant (p = 0.17, calculated by me), but with very few enrolled patients, it is difficult to obtain statistical significance even if the signal is real. Merck should have used placebo as comparator in all its trials instead of adjuvant.

P165:
There were three serious adverse events in each group. One patient reported syncope with an onset 14 days after the second vaccination, of moderate intensity, lasting three days. This patient had a positive tilt test and was diagnosed with dysautonomia (p444):

"AN 37083, a 15 year old white female from Columbia with dysmenorrhoea, anaemia, atopic dermatitis, citrus allergy, menstrual cycle irregularity and urticaria and a medical history of acute rhinosinusitis diagnosed on 8-Nov-2010 received two doses of 9vHPV vaccine (1st dose 02-SEP-2010, 2nd dose **redacted** 2010). The patient was previously vaccinated with Gardasil vaccine in 2007/2008. On **redacted** -2010 (13 days post-dose 2), at 11:00 a.m, the subject had an episode of syncope for about 30 minutes after having presented with global headache of moderate intensity. She was hospitalized. There was no previous neurologic medical history. Hemoleukogram was normal. Brain trans-axial tomography and electroencephalogram (EEG) were normal, cerebrospinal fluid (CSF) from lumbar puncture was normal (no leukocytosis, no polymorphonucleocytes (PMN), normal glucose, normal protein, presence of leukocytes). Lab testing: hemogram, Blood Urea Nitrogen (BUN), creatinine, ionogram all normal. There was no evidence of infection. The initial diagnosis was epilepsy and epileptic symptoms. The subject was treated with sodic fenitoine, midazolam, ranitidine, alizapride, dipyrone, omeprazole, ketoprofen and ondansetron. On **redacted**-2010, the subject recovered from syncope and was discharged from the hospital. The discharge diagnosis was epileptic syndrome symptomatic with focalization and simple partial attacks, syncope and collapse. A control EEG was planned and new metabolic testing was expected. Fasting glucose on 14-JAN-2011 was normal. The subject was seen by a neurologist on 18-JAN-2011; the neurologist concluded syncope and collapse with tachycardia of non-specified cause. On 03-FEB-2011, tilt-test showed

positive for neurocardiogenic syncope mixed and positive for syncope mix cardiogenic. Following the Tilt test, the cardiologist provided a diagnosis of dysautonomia. The subject received her third dose of 9vHPV vaccine on 09-FEB-2011. The reporting investigator felt that syncope was not related to 9vHPV vaccine."

This patient is the one that came closest to a diagnosis of POTS that I have seen in all Merck's study reports, but this diagnosis was not made by the cardiologist despite a positive tilt test and Merck did not use the word POTS in its study report. I searched on POTS in the study report but did not find anything. I also searched on postural, which led me to the document, V503 P006 CSR Section 16.1.4.3_Investigator List, which included the curriculum vitae for Jesper Mehlsen, the head of the Danish Syncope Unit and five of his publications that contained the word "postural:"

HESSE B., MEHLSEN J., BOESEN F,, SCHMIDT J. F., ANDERSEN E. B., WALDEMAR G., ANDERSEN A. R., PAULSON O. B. & VORSTRUP S. (2002) Regulation of cerebral blood flow in patients with autonomic dysfunction and severe postural hypotension. *Clin Physiol Fund Imaging,* **22, 241-247.**

MEHLSEN J., HAEDERSDAL C. & STOKHOLM K. H. (1994a) Dependency of blood pressure upon cardiac filling in patients with severe postural hypotension. *Scand J Clin Lab Invest,* **54,281-284.**

MEHLSEN J., STADEAGER C. & TRAP-JENSEN J. (1993c) Differential effects of betaadrenoceptor partial agonists in patients with postural hypotension. *Eur J Clin Pharmacol,* **44,7-11**

MEHLSEN J. & TRAP-JENSEN J. (1986) Xamoterol, a new selective beta-1-adrenoceptor partial agonist, in the treatment of postural hypotension, *Acta Med Scand,* **219, 173-177.**

MEHLSEN J. & TRAP-JENSEN J. (1990) Haemodynamics in postural hypotension—effects of the beta-adrenoceptor partial agonist xamoterol, and pindolol. *Eur Heart J,A1* **Suppl A, 56-58.**

P172:
"Three (3) subjects discontinued from the study and/or did not complete the 3-dose regimen due to serious or nonserious clinical adverse experiences … One subject experienced abdominal pain and diarrhea. Another subject experienced a swollen tongue. A third subject experienced injection-site swelling and erythema. The adverse experiences in these subjects were judged by the investigator to be vaccine related. All of these adverse experiences resolved after a few days and were judged to be nonserious adverse experiences."

V503 P006 CSR Section 16.1.3.3_consent form

The consent forms, state (P5):

"Common Vaccine-Related Side Effects:

The common side effects listed below for GARDASIL™ or 9-valent HPV vaccine occurred in 1 or more out of 100 subjects. For the GARDASIL™ studies, which included a matching imitation (placebo) vaccine group for comparison, side effects are included below if they were reported more commonly in subjects who received GARDASIL™ than in subjects who received placebo.

- Pain, swelling, redness, itching and bruising at the injection site
- Fever
- Nausea
- Dizziness

• Headache
• Pain in extremity (pain in arm or leg)
• Cold symptoms
• Feeling Tired
• Diarrhea

P6:
The following additional side effects have been reported by people receiving marketed GARDASIL™. These side effects were voluntarily reported from a group of people of unknown size. It is not possible to estimate the frequency of these side effects or the relationship of these side effects to the vaccine.

• Syncope (fainting) sometimes resulting in falling with injury sometimes with shaking/jerking movements and seizure-like activity.
• Anaphylaxis (severe allergic reaction)
• Swollen glands (neck, armpit, or groin)
• Guillain-Barre syndrome (tingling, numbness or muscle weakness in limbs which may lead to limited or generalized paralysis)
• Autoimmune hemolytic anemia (decrease in red blood cells)
• Idiopathic thrombocytopenic purpura (low number of a certain type of cells with no known cause)
• Pancreatitis (inflammation of the pancreas)
• Asthenia (feeling weak)
• Death
• Fatigue
• Autoimmune diseases (a type of severe allergic disease)
• Hypersensitivity reactions (allergic reaction)
• Bronchospasm (narrowing of the airways)
• Hives
• Acute disseminated encephalomyelitis (disease in the brain that produces lesions in the brain or spinal cord)
• Motor neuron disease (nerve disease causing muscle weakness)
• Paralysis (loss or impairment of movement in a body part)
• Seizures (convulsions)
• Transverse myelitis (inflammation of the spinal cord)
• Deep venous thrombosis (blood clots in blood vessels)
• Pulmonary embolus (blood clots in the lungs)
• Chills

There are other less common side effects that your study doctor can identify for you. The study doctor or staff will discuss these with you. There can be other side effects that are not presently known about GARDASIL™ or the 9-valent HPV vaccine."

Comparisons of Gardasil 9 with Gardasil and other studies

P001

V503 P001 CSR

The report is of 8000+ pages.

Study Initiation Date (FPE): 26-SEP-2007
Study Completion Date (LPLV): 10-APR-2013 (also called visit cut-off date)
Report Date 30-OCT-2013

There are no interim reports.
Dose-ranging substudy: 1242 females (see below).
Efficacy substudy: 14,215 females (see below).

The design is very similar to that for the Future trials, with vaccinations at day 1, month 2, and month 6, but the subjects were not followed for 4 years but for 3.5 years (month 42).

This is a pivotal study because it is very large, 14,215 females, and compared Gardasil 9 with Gardasil, but it is not well-reported, and essential data are missing.

The dose-ranging substudy compared three different doses of Gardasil 9 (nine-valent HPV vaccine) with quadrivalent HPV vaccine (qHPV vaccine, trade name Gardasil):

P118:
"9.2.1.2 Dose selection
The dose selection strategy was guided by prior findings that the addition of new HPV types in the vaccine negatively impacts anti-HPV responses to the original HPV types compared with qHPV vaccine ... The trend toward lower immunogenicity observed in these prior Phase II studies was relatively small, with a 10 to 20% decrease in immunogenicity compared with qHPV vaccine ... The dose formulations of 9vHPV vaccine tested in Protocol V503-001 [the current study] were designed with the goal to achieve similar immunogenicity for 9vHPV vaccine compared with qHPV vaccine with respect to the original vaccine HPV types. Two distinct approaches were considered to try to prevent lower immunogenicity for the original types. The first approach was based on increasing the adjuvant-to-antigen ratio in 9vHPV vaccine compared with qHPV vaccine. The second approach relied on increasing the amount of antigen for original types in 9vHPV vaccine compared with qHPV vaccine. The 3 dose formulations of 9vHPV vaccine tested in Protocol V503-001 are shown in Table 9-3. The low-dose formulation contains the same amounts of HPV 6, 11, 16, and 18 VLPs as the qHPV vaccine and has a higher adjuvant-to-antigen ratio than the qHPV vaccine. The mid-dose formulation contains increased amounts of HPV 6, 16, and 18 VLPs than the qHPV vaccine and has an adjuvant-to-antigen ratio that is similar to that of the qHPV vaccine. The high-dose formulation contains increased antigen amounts for the 7 oncogenic types compared with the mid-dose formulation."

P119, Table 9-3:

Protocol V503-001: 9vHPV Vaccine Dose Formulations Used for Dose Selection

	HPV 6 (mcg)	HPV 11 (mcg)	HPV 16 (mcg)	HPV 18 (mcg)	HPV 31 (mcg)	HPV 33 (mcg)	HPV 45 (mcg)	HPV 52 (mcg)	HPV 58 (mcg)	Total VLP (mcg)	AAHS (mcg)	AAHS /VLP ratio
qHPV vaccine	20	40	40	20	0	0	0	0	0	120	225	1.88
Low-dose formulation	20	40	40	20	20	20	20	20	20	220	500	2.27
Mid-dose formulation	30	40	60	40	20	20	20	20	20	270	500	1.85
High-dose formulation	30	40	80	55	30	30	30	30	30	355	500	1.41
Antigen and adjuvant amounts based on a 0.5-mL dose of vaccine AAHS – Amorphous Aluminum Hydroxyphosphate Sulfate (Merck's aluminum adjuvant)												

It is difficult to find out exactly which women, and how many, were represented in which analyses because the explanations are scattered around in various places in the study report, which describes three substudies (p4):

"1) A dose-ranging substudy including all subjects enrolled in Part A with an evaluation of immunogenicity and safety from Day 1 through Month 7.

2) An efficacy substudy including all subjects who received the selected dose formulation of 9vHPV vaccine or qHPV vaccine with an efficacy and safety evaluation from Day 1 through at least Month 42.

3) An immunogenicity substudy including all subjects enrolled in Part B with an immunogenicity evaluation from Day 1 through Month 42."

Thus, the results from the efficacy substudy included results from one of the three tested doses of Gardasil 9 and the Gardasil group in the dose-ranging substudy. Since the two other doses are not relevant, and the groups were quite small, I did not review the results obtained with them.

The protocol describes that there would be approximately 1240 healthy young women in the dose-ranging substudy and that approximately 13,380 additional women were to be enrolled in the efficacy substudy (p103-4). Thus, with half of the women from the dose-ranging substudy being transferred to the efficacy substudy, there should be about 14,000 women in the efficacy substudy, which is close to the 14,225 in the trial (table 10-2, p198).

The mid-dose of Gardasil 9 was chosen for the main study (p195). The main text and the tables are confusing (see below) for those who want to find out the exact number of women randomised to the two substudies and there is no subject flow chart that shows this.

Index, missing tables, missing subjects and empty content

There is an index on p27-40 that ends on p40 with two headings:

The following pages, p41-71, is an index of 388 tables, starting with table 12-1. There is no table 13. There are no tables 14.1-1, etc., either, but there is a table 14.2-13, so the number 13 was not avoided altogether.

Since there was no table 14.1 listed in the index, I searched on "table 14.1" in the report. I found this: "Table 14.1 - 79 in Section 14.2 summarizes the detection of DNA to multiple qHPV vaccine HPV types (HPV 6, 11, 16, 18) at Day 1 by vaccination group in the efficacy substudy" (p247). Next, I searched on "section 14.2," but as this was mentioned numerous times in the report, I went back to the index:

The heading "Baseline characteristics" was misleading, as the first table was "Table 14.2-1. Study Entry Criteria Not Met by Non-Randomized Subjects" (5 pages). This is not baseline characteristics, which describe those randomised, not those not randomised.

The next table is “14.2-2. V503-001 Protocol Violators” (three pages). This is the top of the table:

Category	Allocation Number	Subject Disposition in Per-Protocol Analyses of Efficacy and Immunogenicity
Subjects who were incorrectly randomized	19984	Excluded
Subjects who received an inactivated vaccine within ±14 days of injection study HPV vaccine; or received a live virus vaccine within −21 to 14 days of injection of study HPV vaccine	Subject allocation numbers will be identified from the CDR database through SAS programming and incorporated in the creation of the efficacy analysis datasets.	Excluded

One incorrectly randomised subject was excluded from efficacy analyses, but what about safety analyses? And what happened to those who had received a vaccine dose too close to the randomisation; were they excluded altogether, and was this before or after randomisation, and were they included in the total number of randomised patients in the various tables?

Subject received immunosuppressives prior to the Month 7 visit	68053, 19805, 71582, 10593, 20387, 20638, 72132, 20460, 68191, 70757, 20564, 10174, 10221, 11015, 19714	Excluded

What about these subjects, were they in- or excluded in the safety analyses? I remembered having seen in the report that those who received at least one dose of vaccine were included in the safety analyses. Since Merck’s report is of 8000+ pages, one cannot assume that readers can remember everything. Furthermore, according to good scientific practice, tables should be self-explanatory so that readers would not need to read the main text to understand them. Conversely, the main text should also be clear so that readers would not need to read the tables to understand the text.

Baseline characteristics do not start until p974. Elsewhere, the tables start with the dose-ranging substudy, but this table is missing for “Subject characteristics.” There are only four such tables for efficacy substudy, and there are not any totals:

Table 14.2 - 3

Subject Characteristics
(All Vaccinated Subjects, Efficacy Substudy) (Asia-Pacific)

	9vHPV Vaccine		qHPV Vaccine		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	905		909		1,814	

The table starts by describing subjects from Asia-Pacific. As I wanted to see if there were any totals in the main text, I searched on “Table 14.2 – 3” in the report and found that, after the index had ended, on p40, with this information:

Another index, of tables, started on p41, and in this index, one can see what is contained on the 695 pages of 102 tables:

The number of subjects in the four regions were:

Asia-Pacific	905	909
Europe	2406	2409
Latin America	2372	2372
North America	1423	1419
Total	7106	7109

The totals of 7106 vs 7109 also appear in another table that shows that 11 subjects were never vaccinated (7099 vs 7105 were vaccinated at visit 1) (p198):

Table 10-2

Disposition of Subjects
(Day 1 to Month 7) (All Randomized Subjects, Efficacy Substudy)

	9vHPV Vaccine		qHPV Vaccine		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	7,106		7,109		14,215	
Vaccinated at						
Vaccination 1	7,099	(99.9)	7,105	(99.9)	14,204	(99.9)
Vaccination 2	7,015	(98.7)	7,015	(98.7)	14,030	(98.7)
Vaccination 3	6,928	(97.5)	6,934	(97.5)	13,862	(97.5)

In the synopsis for the study, there is a table summarising adverse events (p25):

Adverse Event Summary
(Vaccination and Follow-up Periods, Day 1 through Visit Cut-Off Date) (All Vaccinated Subjects, Efficacy Substudy)

	9vHPV Vaccine		qHPV Vaccine	
	n	(%)	n	(%)
Subjects in population with follow-up	7,071		7,078	
with one or more adverse events	6,661	(94.2)	6,444	(91.0)

There are now only 7071 vs 7078 subjects. Thus, 28 vs 27 subjects are missing even though "All subjects who received at least one dose of 9vHPV vaccine or qHPV vaccine were followed for safety" (p744). The discrepancy is unexplained.

The next tables are these ones:

The first time there is anything about the subjects who participated in the dose-ranging substudy, is a table about their sexual history at enrolment (p985):

	Low-Dose 9vHPV Vaccine (N =315)		Mid-Dose 9vHPV Vaccine (N =307)		High-Dose 9vHPV Vaccine (N =310)		qHPV Vaccine (N =310)		Total (N =1,242)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects With Sexual History Data at Enrollment	314		307		310		310		1,241	

Since the mid-dose was chosen for the efficacy substudy, it appears that 307 + 310 subjects were included in the efficacy substudy. This suggests that 7106 + 7109 – 307 – 310 = 13,598 subjects were randomised to the efficacy substudy, provided no one dropped out or was lost to follow-up before they were included in this new cohort. To see whether this was correct, I searched "13598," "13,598," "6799," and "6,799" (which is 7106 – 307) in the report. I found the numbers I had calculated were correct (p902):

"13.1.2 Study Cohort. Overall, 14,840 healthy subjects were randomized in the study, including 1,242 women, 16 to 26 years of age, in Part A and 13,598 women, 16 to 26 years of age, in Part B."

The only place in the report where the number of females randomised de novo for the efficacy substudy was given was in the Discussion section:

The number of randomised subjects should not be deferred to the Discussion section. Scientific reports should contain a Background section, a Methods section, a Results section, and a Discussion section. Merck's report is disorganized where there are no such divisions in the index although it is very detailed and runs over 14 pages (p27-40). The first data on results come on page 194:

Section 10.1 mentions that, "A total of 15,334 subjects were screened to participate in V503-001. Of these, approximately 97% (n=14,840) were randomized and 3% (n=494) were not randomized." The total number of 14,480 is correct (see just above) but there is no mention of the numbers in the two compared groups.

It should not require intensive investigation to find out what happened in a clinical trial, particularly not to find out which numbers were randomised to two groups. Furthermore, it is concerning to discover, when doing this, that some patients are missing without explanation.

I discovered that not only was there no table 13 in the report; there was also no table 14.1, which the index also revealed:

As noted above, p247 in the report erroneously states that the report contains a table 14.1 -79 that summarizes the detection of DNA. I did not find table 14.1 – 79, or any of the foregoing 78 tables, but I found 23 tables about this under 14.2, which were not numbered chronologically but were tables 14.2 – 51 to 56 and 67 to 83.

As already noted, the primary index ends on p40 with this:

P2597 starts with this:

15 LIST OF REFERENCES

Once again, the numbering is confusing. The references to publications should have been 15.1.11 and 15.1.12 and not 16.1.11 and 16.1.12.

The page numbers start with 5674. There is no explanation about what is contained on the 3,077 pages from page 2597 to page 5673, but this comes on p2610 (List of appendices). This list ends with "publications based on the study" and "important publications referenced in the CSR [clinical study report] (p2612), as just above, and all the references to the individual publications are listed once again, over 14 pages. The important publications, those which are not derived from the study, are shown as printed in medical journals over 1448 pages, till p7123 in the report.

Not until p2625, is it revealed what is contained in the rest of the report:

The fact that, this late in the report, and after 1448 pages of printed scientific papers that were not derived from the study, there are additional tables about safety makes it difficult to navigate through the study report. We now see, for the first time, on page 7153, information about patients with non-serious adverse events with an "incidence = 5%," which must be a printing error, as few events would have an incidence of exactly 5%. However, the exact 5% is repeated in the table header on p7153:

16.2.7.2 Patients With Non-Serious Adverse Events (Incidence = 5% in One or More Treatment Groups)

Subjects With Non-serious Adverse Events, to be Reported to www.clinicaltrials.gov (Incidence > 5% in One or More Vaccination Groups)
(Non-Injection Site AEs - Days 1 to 15 Following Any Vaccination AND Injection Site AEs - Days 1 to 5 Following Any Vaccination)

	Low-Dose 9vHPV Vaccine			Mid-Dose 9vHPV Vaccine			High-Dose 9vHPV Vaccine			qHPV Vaccine		
	n	(%)	Number of Events	n	(%)	Number of Events	n	(%)	Number of Events	n	(%)	Number of Events
Subjects in population with follow-up	310			7,071			305			7,078		
with one or more non-serious adverse events that met the incidence cutoff	278	(89.7)	1227	6,549	(92.6)	29361	280	(91.8)	1179	6,267	(88.5)	23865
with no non-serious adverse events that met the incidence cutoff	32	(10.3)		522	(7.4)		25	(8.2)		811	(11.5)	
Gastrointestinal disorders												
Nausea	22	(7.1)	23	512	(7.2)	616	18	(5.9)	20	459	(6.5)	551

Nausea is the only gastrointestinal adverse experience in this table. The heading says "Incidence = 5%," the subheading says "Incidence > 5%" while Merck in all its other reports operates with a third limitation, which in this case would have been "Incidence ≥ 5%." Why nausea, as the only gastrointestinal adverse experience, is "to be Reported to www.clinicaltrials.gov" is unclear.

There are two more pages of this type. The first one speaks about non-injection site adverse experiences, and general disorders but nonetheless starts by listing four injection-site adverse events:

Subjects With Non-serious Adverse Events, to be Reported to www.clinicaltrials.gov (Incidence > 5% in One or More Vaccination Groups)
(Non-Injection Site AEs - Days 1 to 15 Following Any Vaccination AND Injection Site AEs - Days 1 to 5 Following Any Vaccination)

	Low-Dose 9vHPV Vaccine			Mid-Dose 9vHPV Vaccine			High-Dose 9vHPV Vaccine			qHPV Vaccine		
	n	(%)	Number of Events	n	(%)	Number of Events	n	(%)	Number of Events	n	(%)	Number of Events
General disorders and administration site conditions												
Injection site erythema	100	(32.3)	157	2,407	(34.0)	3590	91	(29.8)	140	1,810	(25.6)	2563
Injection site pain	267	(86.1)	684	6,356	(89.9)	15359	273	(89.5)	672	5,910	(83.5)	12989
Injection site pruritus	18	(5.8)	21	388	(5.5)	493	14	(4.6)	16	282	(4.0)	341
Injection site swelling	100	(32.3)	154	2,830	(40.0)	4517	103	(33.8)	168	2,035	(28.8)	2988
Pyrexia	30	(9.7)	35	469	(6.6)	563	17	(5.6)	19	463	(6.5)	551
Infections and infestations												
Influenza	20	(6.5)	22	311	(4.4)	342	12	(3.9)	12	295	(4.2)	313
Nasopharyngitis	10	(3.2)	11	376	(5.3)	412	12	(3.9)	13	388	(5.5)	419
Nervous system disorders												

Subjects With Non-serious Adverse Events, to be Reported to www.clinicaltrials.gov (Incidence > 5% in One or More Vaccination Groups)
(Non-Injection Site AEs - Days 1 to 15 Following Any Vaccination AND Injection Site AEs - Days 1 to 5 Following Any Vaccination)

	Low-Dose 9vHPV Vaccine			Mid-Dose 9vHPV Vaccine			High-Dose 9vHPV Vaccine			qHPV Vaccine		
	n	(%)	Number of Events	n	(%)	Number of Events	n	(%)	Number of Events	n	(%)	Number of Events
Nervous system disorders												
Dizziness	17	(5.5)	20	346	(4.9)	405	11	(3.6)	13	307	(4.3)	368
Headache	65	(21.0)	100	1,876	(26.5)	3064	66	(21.6)	106	1,755	(24.8)	2782

Every subject is counted a single time for each applicable non-serious adverse event. Serious adverse events are not counted in this report.
A specific non-serious adverse event appears on this report only if its incidence in one or more of the columns is greater than the percent incidence specified in the report title, prior to rounding. A system organ class appears on this report only if one or more specific non-serious adverse events in that system organ class appear on this report.

Data Source: [16.4]

Next, comes the table "CIOMS Adverse Experience Reports" (p7156-8731). Although 1576 pages are devoted to these reports, I could not find much information about what it is: "In addition to the narratives provided in Section 14.6, Serious Adverse Experience Reports (CIOMS) are attached in [16.2.7.3], The CIOMS reports are derived from data in the safety data base as reported at the time of the event. For the complete patient data see the data tabulations from the clinical data base" (p2454).

I have not seen anywhere a definition of "data tabulations from the clinical data base" and do not have access to "the complete patient data." I did not find them in Merck's study report.

The patient identifiers in these reports were patient initials, country and birth date (redacted). There was no AN number as in the narratives of adverse events (but there was a "Patient ID" under "Remarks" further below on the page), and there was no check box for the intensity of the events, although, according to the protocol, all events should be classified as mild, moderate or severe (p141).

An index on p2625 in the report pointed to important data located over 6,000 pages later:

This is the content of the empty pages:

16.2.8 Listings of Individual Laboratory Measurements by Subject

No content

16.3 CASE REPORT FORMS

Individual subject case report forms are not provided within the clinical study report.

16.4 INDIVIDUAL SUBJECT DATA LISTINGS

The Data Definition File page contains a list of the individual case report tabulation.

I do not know why these pages were described in the index when the information is not provided. There were not even blank case report forms. We therefore have no idea about how possible harms of the vaccine were collected, in contrast to the Future trials where there were blank case report forms.

As there was no "Data Definition File page," I searched in the report for "Data Definition File," but page 8734 was the only place where this term was used. There were no such definitions in the report.

Additional tables in the study report

The tables of vaccine-related systemic adverse events start by showing only those after visit 1 and only those that were recorded for two weeks, which is a subgroup of a subgroup (p1920). After similar tables for visits 2 and 3 there are still no tables for all patients for the whole trial period, and then a table of "Subjects With Serious Adverse Events (Excluding Events of Fetal Loss) (Day 1 Through Visit Cut-Off Date)" suddenly appears on p1940. Injection-site adverse events occurred for 6399 vs 5988 patients when prompted for on

the vaccination report cards (p763) but for 60 more subjects when there was no such limitation (6423 vs 6024, p25).

The tables in the beginning of the report, including a little interspersed text, take up 2,346 pages (from p108 to p2453). The tables of adverse events start on p748. After tables of systemic adverse events with an incidence of at least 1% during two weeks (p783), there are tables of temperature during days 1 to 5, tables of systemic adverse events with an incidence of at least 1% during two weeks (again, but this time judged vaccine related), serious adverse events (not limited to systemic ones), pregnancy related events, "New Medical History Conditions," autoimmune disorders, subjects never randomised, subject characteristics, a lot about the patients' sexual and gynaecological history, contraceptive use, efficacy results, and then, on p1767, there are suddenly tables again on adverse events.

The effect of this is to drown and confuse the reader with unnecessary detail, which means that important things might easily go unnoticed. Many of the tables provide very similar information, with slightly different headings, in a confusing order, which make them very hard to follow, and mistakes are easily made, if one is not extremely careful.

I searched for a table of systemic adverse events by system organ class (incidence > 0% in one or more vaccination groups) (day 1 trough visit cut-off date) (all vaccinated subjects, efficacy substudy). There were such tables in the three Future trials, but I could not find any such table in the Gardasil 9 trial. I searched "systemic adverse events" in the index, but in vain. I found 24 tables on "systemic adverse events," but they showed only selected data: from just one vaccination visit, or from just the two weeks after each vaccination, or only for those with an incidence ≥ 1%. The table that came closest was Table 14.5-33 that listed "clinical adverse events." It included data for the whole trial period with no incidence limitation, but it had not separated injection-site events from systemic events, and the table only described three patients who "received a noncompliant regimen" (p1891-4). The table that came second-closest was Table 14.5-17 that listed subjects with systemic adverse events by system organ class (incidence > 0% in one or more vaccination groups), but only during days 1 to 15 following any vaccination visit (p1810-32).

Merck's presentation of the data was disorganized. It is well known that regulatory agencies are understaffed, which means it is unlikely they would be able to undertake a thorough review of Merck's data as presented. The 388 tables in the main body of the report take up 895 pages, but suddenly yet another set of tables appear by the end, including the 1576 pages of "CIOMS adverse experience reports" described above. These CIOMS have no allocation numbers and therefore they cannot be compared with the narratives of adverse events or with other tables of adverse events.

It is deeply concerning that Gardasil 9 was ever approved for marketing in any country based on this and other deficient reports, but it confirms observations made by many researchers that drug regulation is insufficient.[3]

[3] Topol EJ. Failing the public health - rofecoxib, Merck, and the FDA. N Engl J Med 2004;351:1707-9; Testimony of David J. Graham, MD, MPH, November 18, 2004, accessible at https://www.finance.senate.gov/imo/media/doc/111804dgtest.pdf; Kesselheim AS, Avorn J. The role of litigation in defining drug risks. JAMA 2007;297:308-11.

Study design, particularly in relation to safety

P2:
“Subjects received 9vHPV vaccine or qHPV vaccine at Day 1, Month 2, and Month 6. All subjects were followed for safety Day 1 through Month 7. Subjects were assessed for immunogenicity at Month 7. Subjects who received the selected 9vHPV vaccine dose formulation or qHPV vaccine were followed for efficacy through at least Month 42, followed for persistence of antibody responses through Month 42, and followed for safety for the duration of the trial. Subjects who received the 9vHPV vaccine dose formulations that were not selected for further evaluation completed the study at Month 7.”

“Primary Objectives
(1) Objective: To evaluate the tolerability of the 9-valent HPV L1 VLP vaccine when administered to 16- to 26-year-old women. Hypothesis: 9-valent HPV L1 VLP vaccine administered to 16- to 26-year-old women is generally well-tolerated.
(2) Objective: To demonstrate that administration of 9-valent HPV L1 VLP vaccine will reduce the combined incidence of HPV 31-, 33-, 45-, 52-, and 58-related high-grade cervical abnormalities (CIN 2/3), Adenocarcinoma In Situ (AIS), invasive cervical carcinoma, high-grade Vulvar Intraepithelial Neoplasia (VIN 2/3), high-grade Vaginal Intraepithelial Neoplasia (ValN 2/3), vulvar cancer, or vaginal cancer, compared with GARDASIL™ in 16- to 26-year-old adolescent and young adult women who are seronegative at Day 1 and PCR negative Day 1 through Month 7 to the relevant HPV type.”

P4:
“Approximately 1240 subjects were to be enrolled in Part A and equally randomized to 3 dose formulations of 9vHPV vaccine or qHPV vaccine. One dose formulation was selected based on interim immunogenicity results. Approximately 13,380 subjects were to be enrolled in Part B and equally randomized to the selected dose formulation of 9vHPV vaccine or qHPV vaccine.
Three substudies were conducted:
1) A dose-ranging substudy including all subjects enrolled in Part A with an evaluation of immunogenicity and safety from Day 1 through Month 7
2) An efficacy substudy including all subjects who received the selected dose formulation of 9vHPV vaccine or qHPV vaccine with an efficacy and safety evaluation from Day 1 through at least Month 42
3) An immunogenicity substudy including all subjects enrolled in Part B with an immunogenicity evaluation from Day 1 through Month 42.
… All subjects were to be followed for safety for the duration of the study.”

P12:
Gardasil 9 adjuvant contains 500 µg adjuvant, Gardasil contains 225 µg.

P13:
“Safety: The following measures were collected from each study subject to assess safety:
1) temperatures (within 5 days following any vaccination);
2) all adverse events (within 14 days following any vaccination);
3) all serious adverse experiences that occurred from Day 1 through 180 days following the last vaccination;
4) all serious adverse experiences that resulted in death or were determined to be related to the study vaccine or study procedure that occurred at any time during the study.

All subjects that received at least one injection of study vaccine and had safety follow-up data were included in the safety summary. In addition to the above safety endpoints, this CSR summarizes: (1) new medical conditions…”

Even though this trial started six years after the Future 1 trial and three years after the Future 3 trial, the procedures for collection of safety data are still inadequate, with only a two-week period for collection of adverse events after each vaccination, and after day 180, serious events were only collected if someone (not specified who) determined them to be vaccine related or related to a study procedure. This is particularly concerning given that the first primary objective mentioned was to evaluate the tolerability of Gardasil 9.

P13 and 15:
"STATISTICAL PLANNING AND ANALYSIS.
… Adverse experiences were summarized descriptively as frequencies and percentages by vaccination group and type of adverse experience, by vaccination visit and across all vaccination visits. Elevated temperatures (≥100° F, ≥37.8° C, oral or oral equivalent) within 5 days following each vaccination were summarized in a similar manner. In addition, risk differences and associated 95% confidence intervals were computed comparing the groups across all vaccination visits with respect to injection site adverse experiences on the VRC [vaccination report card], specific systemic adverse events, severe injection site adverse event [sic], serious adverse events and elevated temperatures, p-values were computed only for those adverse experiences that were prompted for on the VRC (pain/tenderness/soreness, swelling, and redness) and elevated temperatures."

This is inadequate for a study which has a main safety objective. In contrast to the Future trials:

1) *there is nothing about events the investigators considered vaccine related (but there are data described on p141 that this judgment was to be made in relation to the two-week registration periods;*
2) *there is nothing about moderate injection-site events, only severe events;*
3) *there is nothing about whether the systemic adverse events are mild, moderate or severe;*
4) *p-values are only calculated for less important outcomes, temperature and injection-site events.*

Merck violated its own prespecified methods by failing to calculate a confidence interval when it turned out that there were significantly more serious adverse events with Gardasil 9 than with Gardasil (see below).

Thus, already 15 pages into the 8000+ page study report, it was clear that this trial was flawed. Merck effectively avoided arriving at the result that Gardasil 9 is more harmful than Gardasil, which one would expect, given that it contains five more antigens and more than double as much adjuvant than Gardasil, 500 µg versus 225 µg.

P27, safety conclusion in the synopsis:
"Safety: Administration of a 3-dose regimen of 9vHPV vaccine is generally well tolerated in young women, 16 to 26 years of age."

This has been Merck's mantra for all of its trials, formulated before the trials were carried out ("Hypothesis: 9-valent HPV L1 VLP vaccine administered to 16- to 26-year-old women is generally well-tolerated") on page 2 in the report and repeated when the trial has been finished ("is generally well tolerated"), no matter what was found in the trial, in this case even significantly more serious adverse events with Gardasil 9 than with Gardasil.

P81:
"5.3.2 Incentives
The generic Sponsor-approved written informed consent document(s) in Section [16.1.3] were developed in accordance with ICH E6 4.8.10 and include a description of the type of incentives, if any, that were provided to study subjects/patients. The specific amount and schedule of payments were individually

determined by each investigative site and approved by the overseeing IEC in accordance with local country regulations. The details of such payments and incentives are available upon request."

Only payments to trial subjects are mentioned here. As it is very costly in terms of time and resources for clinical departments to participate in such trials, there is always payments to the departments, and sometimes also to the investigators, as a personal honorarium, or there are other benefits, e.g. participation in international conferences, and paid speaking engagements, consultancies and participation on advisory boards. Something should be said about this in the protocol. Payments to departments and doctors can generate a loyalty towards the sponsor that reduces the likelihood that important harms of the investigational drugs get reported.[4]

P110:
"9.1.2.4 Safety Assessment
An important goal of the study was to evaluate the safety and tolerability of the 9vHPV vaccine in the study population ... New medical conditions not present at baseline and not reported as an adverse experience were to be collected throughout the study."

I, and others, including drug regulatory staff, have criticised this arbitrary practice of calling some adverse events new medical conditions, see my report on the Future trials and below.

P111:
"9.1.4 Long Term Follow-up
Subjects who are enrolled in Scandinavian countries that have appropriate centralized registry infrastructures have been asked to participate in a sub-study for long-term follow-up. This sub-study will be initiated after a subject has completed her Protocol 001 scheduled study visits and will use cervical cancer screening registries to capture Pap test and biopsy results to assess the long-term vaccine effectiveness for at least 10 years following completion of the Protocol 001 scheduled study visits. The long term follow-up study will also assess antibody persistence and selected new medical history events."

Although "An important goal of the study was to evaluate the safety and tolerability of the 9vHPV vaccine," adverse events were not collected during long-term follow-up, not even new medical history events, but only "selected new medical history events."

P126:
"9.2.1.5 Safety Assessment
Safety information was collected for the duration of the study as outlined in Section 9.1.2.4. This approach was generally similar to that used in registration studies in the clinical development program of the qHPV vaccine (V501 program). However, with some respects, collection of safety information was more comprehensive than in the V501 program: (1) in the V503 program, VRC [vaccination report card] were provided to all study participants as opposed to a subset of participants in the V501 program; (2) in the V503 program, SAEs [serious adverse events] were collected for a more extended period compared to the V501 program …"

This looks good in a protocol, but Merck violated its own protocol when the company found more serious adverse events with Gardasil 9 than with Gardasil, see below.

P128:
As in the Future trials, immunocompromised females were excluded from participation.

[4] Gøtzsche PC. Deadly psychiatry and organised denial. Copenhagen: People's Press; 2015.

P141:
“All VRC information was to be recorded in the eCRFs. The physician investigator/subinvestigator was to determine causality of systemic and injection-site adverse experiences recorded on the VRC using the reporting guidelines given in the protocol and were to classify each event as a SAE or non-serious adverse experience (NSAE).”

“The tolerability of the study vaccine at each injection site was evaluated by the subject and noted on the VRC.” Systemic clinical adverse experiences were also evaluated by the subject, and both types of experiences were ranked as mild, moderate or severe.

P143:
“9.5.1.4.6 Other Safety Events Collected During the Study
New Medical History
New medical history consists of new medical conditions that were not considered adverse experiences (i.e., they occurred outside the Day 1 through Day 15 post-vaccination visit period and/or were not considered by the study investigator to be SAEs). New medical history was collected from Day 1 through the end of the study.”

As noted for the Future trials, this approach to collecting and reporting possible harms is inappropriate. Investigators cannot use “New medical history” for events that occur within the two-week intervals after each vaccination, but investigators are nevertheless told to collect “New medical history” events from day 1, i.e. including the first two weeks where they are not allowed to use this category for events. What should an investigator do if he/she finds that an event that occurs outside the two-week intervals is an adverse experience and wants to call it an adverse experience and not “New medical history?” This is explicitly forbidden by Merck, unless the event is serious, but investigators have repeatedly broken this rule. I have shown for several of Merck’s studies, including this one (see just below), that there are more systemic adverse events in the whole trial period than in the three two-week periods after each vaccination.

P148:
“9.5.3.3.1 Primary Safety and Tolerability Parameters
The important variables of interest for safety/tolerability were the occurrence of injection site adverse experiences prompted for on the VRC (such as redness, swelling, and pain/tenderness/soreness occurring Day 1 through Day 5 following any vaccination) and elevated temperature (≥100.0°F [≥37.8°C]), from Day 1 to Day 5 following any vaccination. Other important variables of interest included severe injection-site adverse experiences and the incidence of any vaccine-related SAEs.”

Although “An important goal of the study was to evaluate the safety and tolerability of the 9vHPV vaccine,” what is considered important are primarily rather banal injection-site reactions and temperature elevations occurring within two-weeks after each vaccination. P149: “Follow-up at Months 2, 3, 6, and 7 after the first injection included an interview to assess general safety. The interview solicited broadly for any SAEs that the subject may have encountered. Participants were instructed to notify the study physician immediately if any unexpected or severe adverse experience occurred.”

This approach shows a lack of interest in elucidating “other important variables of interest,” even though these included vaccine-related serious adverse events. And, as to other vaccine-related events, some of which, as we have seen in the Future trials, are moderate or severe in intensity, there is no clear directive on how such data should be collected.

P215-20:
Of the 14,215 subjects enrolled in the main study, 3686 (26%) were from Denmark, which is a remarkably high proportion because the United States, Mexico, Taiwan, Colombia, Peru, Norway, Brazil, Hong Kong, Chile, Thailand, South Korea, Japan, Canada, Germany, Puerto Rico, New Zealand, Austria and Sweden also recruited people. The biggest recruiter was Danish physician Jesper Mehlsen, with 2042 females (14% of all subjects).

Adverse events

P748, adverse events in dose-ranging substudy:

Table 12-1
Adverse Event Summary
(Days 1 to 15 Following Any Vaccination Visit) (All Vaccinated Subjects, Dose-Ranging Substudy)

	Low-Dose 9vHPV Vaccine		Mid-Dose 9vHPV Vaccine		High-Dose 9vHPV Vaccine		qHPV Vaccine	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population with follow-up	310		303		305		308	
with one or more adverse events	287	(92.6)	280	(92.4)	283	(92.8)	278	(90.3)
injection-site	273	(88.1)	270	(89.1)	279	(91.5)	258	(83.8)
non-injection-site	166	(53.5)	171	(56.4)	156	(51.1)	163	(52.9)
with no adverse event	23	(7.4)	23	(7.6)	22	(7.2)	30	(9.7)
with vaccine-related† adverse events	279	(90.0)	275	(90.8)	283	(92.8)	268	(87.0)
injection-site	273	(88.1)	270	(89.1)	279	(91.5)	258	(83.8)
non-injection-site	104	(33.5)	93	(30.7)	91	(29.8)	90	(29.2)
with serious adverse events	2	(0.6)	2	(0.7)	0	(0.0)	1	(0.3)
with serious vaccine-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued‡ due to an adverse event	2	(0.6)	1	(0.3)	0	(0.0)	0	(0.0)
discontinued due to a vaccine-related adverse event	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious vaccine-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

† Determined by the investigator to be related to the vaccine.
‡ Study medication withdrawn.

Data Source: [16.4]

P745:
"The proportion of subjects in the dose-ranging substudy who reported at least one injection-site adverse experience within 15 days of any vaccination (Table 12-1) was higher among subjects who received one of the 3 dose formulations of 9vHPV vaccine (88.1%, 89.1%, and 91.5% in the low-dose, mid-dose and high-dose 9vHPV vaccine cohorts, respectively) compared to those who received qHPV vaccine (83.8%)."

The occurrence of injection-site adverse experiences was not only higher, it was statistically significantly higher (822/918 vs 258/308 gives p = 0.008, Fisher's exact test, my calculation). Merck violated again its own trial protocol: "p-values were computed only for those adverse experiences that were prompted for on the VRC (pain/tenderness/soreness, swelling, and redness) and elevated temperatures" (p15). The adverse experiences in table 12-1 were those prompted for on the VRC, but Merck did not do a significance test.

For my meta-analyses of Merck's data, I did not include data in the two small dose groups that were not selected for the main study, as these would not be marketed.

For adverse events in the efficacy substudy, two of the tables are identical (those on p25 and on p751):

Adverse Event Summary
(Vaccination and Follow-up Periods, Day 1 through Visit Cut-Off Date) (All Vaccinated Subjects, Efficacy Substudy)

	9vHPV Vaccine		qHPV Vaccine	
	n	(%)	n	(%)
Subjects in population with follow-up	7,071		7,078	
with one or more adverse events	6,661	(94.2)	6,444	(91.0)
injection-site	6,423	(90.8)	6,024	(85.1)
non-injection-site	4,052	(57.3)	3,957	(55.9)
with no adverse event	410	(5.8)	634	(9.0)
with vaccine-related[†] adverse events	6,519	(92.2)	6,202	(87.6)
injection-site	6,422	(90.8)	6,024	(85.1)
non-injection-site	2,088	(29.5)	1,930	(27.3)
with serious adverse events	233	(3.3)	183	(2.6)
with serious vaccine-related adverse events	2	(0.0)	2	(0.0)
who died	5	(0.1)	5	(0.1)
discontinued[‡] due to an adverse event	8	(0.1)	4	(0.1)
discontinued due to a vaccine-related adverse event	5	(0.1)	3	(0.0)
discontinued due to a serious adverse event	3	(0.0)	1	(0.0)
discontinued due to a serious vaccine-related adverse event	1	(0.0)	0	(0.0)

[†] Determined by the investigator to be related to the vaccine.
[‡] Study medication withdrawn.

On p750, there is another table, with events occurring within two weeks after each vaccination:

Table 12-3
Adverse Event Summary
(Days 1 to 15 Following Any Vaccination Visit) (All Vaccinated Subjects, Efficacy Substudy)

	9vHPV Vaccine		qHPV Vaccine	
	n	(%)	n	(%)
Subjects in population with follow-up	7,071		7,078	
with one or more adverse events	6,640	(93.9)	6,419	(90.7)
injection-site	6,423	(90.8)	6,023	(85.1)
non-injection-site	3,948	(55.8)	3,883	(54.9)
with no adverse event	431	(6.1)	659	(9.3)
with vaccine-related[†] adverse events	6,519	(92.2)	6,200	(87.6)
injection-site	6,422	(90.8)	6,023	(85.1)
non-injection-site	2,086	(29.5)	1,929	(27.3)
with serious adverse events	25	(0.4)	17	(0.2)
with serious vaccine-related adverse events	2	(0.0)	1	(0.0)
who died	1	(0.0)	1	(0.0)
discontinued[‡] due to an adverse event	7	(0.1)	3	(0.0)
discontinued due to a vaccine-related adverse event	5	(0.1)	3	(0.0)
discontinued due to a serious adverse event	2	(0.0)	0	(0.0)
discontinued due to a serious vaccine-related adverse event	1	(0.0)	0	(0.0)

[†] Determined by the investigator to be related to the vaccine.
[‡] Study medication withdrawn.
Data Source: [16.4]

I compared these two tables to see if the numbers presented were consistent:

	Days 1 to 15		**Whole trial period**	
	Gardasil 9	**Gardasil**	**Gardasil 9**	**Gardasil**
with one or more adverse events	6640	6419	6661	6444
injection-site	6423	6023	6423	6024
non-injection-site	3948	3883	4052	3957
with vaccine-related' adverse events	6519	6200	6519	6202
injection-site	6422	6023	6422	6024
non-injection-site	2086	1929	2088	1930
with serious adverse events	25	17	233	183
with serious vaccine-related adverse events	2	1	2	2

Combining the two groups, 42 patients experienced serious adverse events during the three two-week intervals, which increased to 416 for the whole trial period. Thus, 90% of all serious adverse events occurred outside the two-week intervals after each vaccination.

Since serious adverse events are a subgroup of all adverse events, the difference between 416 and 42, which is 386, should also be the difference in all adverse events. This was not the case. There were 13,105 patients with adverse experiences in the whole trial period and 13,059 in the three two-week periods, a difference of

only 46 patients when it should have been 386 patients. Merck did not describe this discrepancy and did not offer any explanation for it. The numbers do not add up.

The investigators considered only 4 of the 416 (1%) serious adverse events vaccine related.

This trial shows how important it is to look not only at the occurrence of adverse events but also at their severity, i.e. whether they are serious or not (see also the classification into mild, moderate and severe below). Compared to the total number of adverse events, there is a very large difference:

Adverse event summary	During 6 weeks		Whole trial period		Risk ratio of events
	Gardasil 9	Gardasil	Gardasil 9	Gardasil	Whole trial/6 weeks
Total subjects	7971	7078	7971	7078	
Subjects with adverse events	6640	6419	6661	6444	1.00
Subjects with serious adverse events	25	17	233	183	9.90

Even though there were more adverse events and more serious adverse events on Gardasil 9 than on Gardasil, the risk ratio for adverse events was the same for the whole trial period (called Day 1 through Visit Cut-Off Date, which means 42 months) as for the six weeks after each vaccination, whereas it was ten times bigger for serious adverse events.

P746 (how Merck interpreted the data):
"Efficacy substudy - A summary of clinical adverse experiences occurring by vaccination group from Day 1 to Day 15 following any vaccination visit during the Efficacy Substudy is provided in Table 12-3. Table 12-4 displays a summary of clinical adverse experiences, reported from Day 1 through the visit cut-off date of 10-Apr-2013, by vaccination group in this substudy cohort. A listing of all efficacy substudy subjects' clinical adverse experiences during the entire study period can be found in [16.4]. The following observations can be made among these subjects with follow-up data:
• The proportion of subjects in the efficacy substudy cohort reporting at least one adverse experience within 15 days of any vaccination (Table 12-3) was higher among the subjects who received 9vHPV vaccine (93.9%) compared to those who received qHPV vaccine (90.7%).
• The proportion of subjects in this substudy who reported at least one injection-site adverse experience within 15 days of any vaccination (Table 12-3) was higher among subjects who received 9vHPV vaccine (90.8%) compared to those who received qHPV vaccine (85.1%).
• The proportion of subjects in this substudy who reported at least one systemic adverse experience within 15 days of any vaccination (Table 12-3) was generally comparable among subjects who received 9vHPV vaccine (55.8%) compared to those who received qHPV vaccine (54.9%).
• As shown in Table 12-4, 12 subjects in the efficacy substudy discontinued study medication due to an adverse experience, including 8 in the 9vHPV vaccine group and 4 in qHPV vaccine group. Of these, 8 were vaccine-related, including 5 in the 9vHPV vaccine group and 3 in qHPV vaccine group.
• Four hundred seventeen (416) SAEs were reported during the entire course of this substudy, including 233 in the 9vHPV vaccine group and 183 in qHPV vaccine group (Table 12-4). Reported SAEs in the efficacy substudy included 4 vaccine-related SAEs (2 in the 9vHPV vaccine group and 2 in qHPV vaccine group) and 10 deaths (5 in the 9vHPV vaccine group and 5 in qHPV vaccine group). None of the deaths were vaccine-related."

Despite the fact that Merck chose the table with the most events for the synopsis (table 12-4), they started by quoting the table with fewer events, table 12-3, and then used table 12-4 in the last two paragraphs.

P763:

"Table 12-9. Analysis of Subjects With Injection Site Adverse Events Prompted for on the VRC (Incidence >0% in One or More Vaccination Groups) (Days 1 to 5 Following Any Vaccination Visit) (All Vaccinated Subjects, Efficacy Substudy)."

Vaccination	n	(%)	Difference in % vs qHPV Vaccine: Estimate (95% CI)†	Difference in % vs qHPV Vaccine: p-value†
Subjects in population with follow-up				
9vHPV Vaccine	7,071			
qHPV Vaccine	7,078			
General disorders and administration site conditions				
9vHPV Vaccine	6,399	(90.5)	5.9 (4.8, 7.0)	<0.001
qHPV Vaccine	5,988	(84.6)		
Injection site erythema				
9vHPV Vaccine	2,407	(34.0)	8.5 (7.0, 10.0)	<0.001
qHPV Vaccine	1,810	(25.6)		
Injection site pain				
9vHPV Vaccine	6,356	(89.9)	6.4 (5.3, 7.5)	<0.001
qHPV Vaccine	5,910	(83.5)		
Injection site swelling				
9vHPV Vaccine	2,830	(40.0)	11.3 (9.7, 12.8)	<0.001
qHPV Vaccine	2,035	(28.8)		

The incidence of injection-site erythema, pain and swelling is far greater with Gardasil 9 than with Gardasil. Numbers needed to harm vary between only 9 and 16 subjects. There was also significantly more injection site swelling and pruritus although this was not prompted for on the vaccination report card (90 vs 46, and 388 vs 282, respectively, p765-6).

P780:

Subjects With Injection Site Erythema or Injection Site Swelling by Maximum Size
(Incidence >0% in One or More Vaccination Groups)
(Days 1 to 5 Following Any Vaccination Visit) (All Vaccinated Subjects, Efficacy Substudy)

	Size Rating (inches)	9vHPV Vaccine n	9vHPV Vaccine (%)	qHPV Vaccine n	qHPV Vaccine (%)
Subjects in population with follow-up		7,071		7,078	
Injection site erythema	Total	2,407	(34.0)	1,810	(25.6)
	0 to ≤ 1	1,921	(27.2)	1,555	(22.0)
	>1 to ≤ 2	370	(5.2)	197	(2.8)
	>2 to ≤ 3	85	(1.2)	53	(0.7)
	>3 to ≤ 4	19	(0.3)	4	(0.1)
	>4 to ≤ 5	7	(0.1)	0	(0.0)
	>5 to ≤ 6	2	(0.0)	0	(0.0)
	>7 to ≤ 8	1	(0.0)	0	(0.0)
	Unknown	2	(0.0)	1	(0.0)
Injection site swelling	Total	2,830	(40.0)	2,035	(28.8)
	0 to ≤ 1	1,958	(27.7)	1,594	(22.5)
	>1 to ≤ 2	597	(8.4)	332	(4.7)
	>2 to ≤ 3	220	(3.1)	93	(1.3)
	>3 to ≤ 4	40	(0.6)	13	(0.2)
	>4 to ≤ 5	7	(0.1)	1	(0.0)
	>5 to ≤ 6	3	(0.0)	0	(0.0)
	>6 to ≤ 7	0	(0.0)	1	(0.0)
	>7 to ≤ 8	2	(0.0)	1	(0.0)
	Unknown	3	(0.0)	0	(0.0)

Every subject is counted a single time for each applicable specific injection site adverse event, and is classified according to the highest non-missing size rating.

A specific injection site adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the percent incidence specified in the report title, after rounding.

The swellings were much larger with Gardasil 9 than with Gardasil and they could be very big: 272 vs 109 subjects had swellings at least two inches in size.

The injection-site reactions were not trivial. Reactions of moderate intensity (discomfort enough to cause interference with usual activities), or severe intensity (incapacitating with inability to work or do usual activity) occurred in 37.6% vs 27.0% of the subjects (p775), which means that the number needed to harm is only 9 (= 1/(37.6%-27.0%)) for Gardasil 9 compared with Gardasil.

Numbers with severe injection-site reactions were 315 (4.5%) vs 190 (2.7%) when the follow-up period was five days (p775) but 555 (7.8%) vs 310 (4.4%) when it was 15 days (p781). Number needed to harm was 56 vs 29. Thus, injection reactions were double as harmful with the 9-valent vaccine compared to the 4-valent vaccine when the follow-up was longer than just the first five days.

This indicates injection-site reactions have been seriously underestimated in Merck's other trials where such reactions are only followed for five days and not for 15 days.

P782:
"Table 14.5 - 17 in Section 14.5 displays the number and percentage of subjects with systemic clinical adverse experiences (incidence >0% in one or more vaccination groups) by system organ class from Day 1 to 15 following any vaccination visit. Table 14.5 - 18, Table 14.5 - 19, and Table 14.5 - 20 provide the number and percentage of subjects with clinical adverse experiences (incidence >0% in one or more vaccination groups) by system organ class from Day 1 to 15 following vaccination visit 1, vaccination visit 2, and vaccination visit 3, respectively. The frequency of systemic clinical adverse experiences numerically decreased across vaccination visits within each vaccine group."

P789:
"Table 12-20. As shown in the table, the 95% CIs of the risk difference between 9vHPV vaccine and qHPV vaccine groups generally included zero, except for the adverse experience of headache (higher frequency in the 9vHPV vaccine group)."

Headache was not the only interesting neurological finding (p805). There were three MedDRA terms (Medical Dictionary for Regulatory Activities) in the table:

Vaccination	n	(%)	Difference in % vs qHPV Vaccine Estimate (95% CI)[1]
Nervous system disorders			
9vHPV Vaccine	2,137	(30.2)	2.0 (0.5, 3.5)
qHPV Vaccine	1,999	(28.2)	
Dizziness			
9vHPV Vaccine	346	(4.9)	0.6 (-0.1, 1.3)
qHPV Vaccine	307	(4.3)	
Headache			
9vHPV Vaccine	1,876	(26.5)	1.7 (0.3, 3.2)
qHPV Vaccine	1,756	(24.8)	
Migraine			
9vHPV Vaccine	84	(1.2)	-0.0 (-0.4, 0.3)
qHPV Vaccine	85	(1.2)	

There were significantly more patients with nervous system disorders on Gardasil 9 than on Gardasil, p = 0.01) and also more patients with dizziness, but the difference was not statistically significant, p = 0.12. For headache, p = 0.02 (my calculations).

This table was for events occurring in at least 1% of the patients. The corresponding table for new medical history only had two MedDRA terms (p892):

Nervous system disorders	**515**	**(7.3)**	**491**	**(6.9)**
Headache	278	(3.9)	243	(3.4)
Migraine	105	(1.5)	97	(1.4)

Thus, also for new medical events, there were more patients with nervous system disorders and with headache on Gardasil 9 than on Gardasil. Since dizziness was missing in this table, I looked up the table for new medical history that included all events, not just those with an incidence of at least 1% (p2160):

Dizziness	67	(0.9)	64	(0.9)
Dizziness postural	3	(0.0)	0	(0.0)

Thus, even though the differences were small, there were more patients with dizziness and postural dizziness on Gardasil 9 than on Gardasil.

This demonstrates that, by splitting adverse events into two groups, Merck made it more difficult to detect vaccine harms.

P808:
"The majority of subjects across the vaccination groups experienced systemic adverse experiences, most of which were of mild or moderate intensity."

This statement is misleading and downplays what Merck found. For a drug to be given prophylactically, to healthy girls at a certain age, it is evident that the focus should be on serious, severe and moderate systemic events, not on mild and moderate events. It was a primary research objective to evaluate the tolerability of Gardasil 9 (p2 in the report), which is repeated on p110: "An important goal of the study was to evaluate the safety and tolerability of the 9vHPV vaccine." However, Merck failed to compare the two vaccines in this summary statement. The table that gave rise to this statement followed two pages later:

P810:

Table 12-22

Subjects With Systemic Adverse Events by Maximum Intensity Rating
(Days 1 to 15 Following Any Vaccination Visit) (All Vaccinated Subjects, Efficacy Substudy)

	9vHPV Vaccine		qHPV Vaccine	
	n	(%)	n	(%)
Subjects in population with follow-up	7,071		7,078	
With one or more Systemic adverse experiences reported	3,948	(55.8)	3,883	(54.9)
With no Systemic adverse experiences reported	3,123	(44.2)	3,195	(45.1)
Subjects by maximum intensity rating of Systemic adverse experiences reported				
MILD	1,168	(16.5)	1,255	(17.7)
MODERATE	1,954	(27.6)	1,864	(26.3)
SEVERE	826	(11.7)	761	(10.8)
UNKNOWN	0	(0.0)	3	(0.0)

Each subject is counted a single time according to the highest non-missing intensity grading.

Data Source: [16.4]

I calculated that, for severe events, p = 0.08 for the difference between Gardasil 9 and Gardasil, and for moderate or severe events, p = 0.007 (Fisher's exact test). I also calculated that, for moderate or severe systemic adverse events, the number needed to harm is only 45.

The conclusion about safety in Merck's synopsis is: "Safety: Administration of a 3-dose regimen of 9vHPV vaccine is generally well tolerated in young women, 16 to 26 years of age" (p27). This is misleading, considering also that only events occurring within two weeks after each vaccination were listed in the table.

P825:
"Efficacy substudy - Table 12-31 presents the number and percentage of subjects with serious adverse experiences (incidence >0% in one or more vaccination groups) by system organ class from Day 1 through visit cut-off [my comment: which is the same as study completion date]. Approximately 2.9% (n=416) of subjects reported one or more serious adverse experiences during the safety follow-up period in the efficacy substudy (3.3% (n=233) in the 9vHPV vaccine group, 2.6% (n=183) in the qHPV vaccine group). The proportion of subjects with serious adverse experiences occurring between Day 1 and the visit cut-off date in the efficacy substudy was low and comparable between the 9vHPV vaccine groups and the qHPV vaccine group. Most SAEs were related to pregnancy, which was expected, given that the study population primarily consisted of young women of childbearing age. Moreover, since the Sponsor required that events be reported as SAEs, a large proportion of the SAEs were events of elective and spontaneous abortion. In both vaccination groups, the most common serious adverse experiences were abortion induced and spontaneous abortion ..."

This is scientifically inappropriate, for at least six reasons.

1) The difference in serious adverse events, 233 (3.3%) vs 183 (2.6%), is statistically significant, p = 0.01 (my calculation), and the number needed to harm is 143. Merck called these two rates "comparable."

2) Merck stated in the statistical planning and analysis section in the synopsis for the report that "risk differences and associated 95% confidence intervals were computed comparing the groups across all vaccination visits with respect to … serious adverse events." (p15). This synopsis is misleading. It gives the impression that a 95% confidence interval for the difference in serious adverse events will compare Gardasil 9 with Gardasil only across the vaccination visits, which means the three two-week periods after each vaccination and not for the whole trial period. This is not true. An index on p2611-2 shows that there are four statistical analysis plans:

The first one was dated 2.5 months after the trial started. It shows (p5068) that a 95% confidence interval and a p-value will be computed for vaccine-related (VR) serious adverse events for the whole trial period:

Planned Analyses of Adverse Experience Endpoints

Adverse Experience Endpoint	Follow-Up Period				Summaries/Analyses		
	After Any Vaccination Visit						
	Day 1 to Day 5†	Day 1 to Day 15†	Day 1 through Month 7	Any Time During Study	Incidence	Risk Difference§ and 95% CI	P-Value
Clinical AEs							
– Any AE		•			•		
– Deaths				•	•		
Injection site AEs							
AEs of pain/tenderness, swelling, and redness	•				•	•	•
– Severe injection site AEs	•				•	•	
– Number (%) of subjects by maximum intensity rating, across the categories of pain/tenderness, swelling‡, and redness‡	•				•		
– Maximum intensity ratings of injection site AEs, across the categories of pain/tenderness, swelling‡, and redness‡	•				•		
– Maximum intensity rating of injection site AEs, within each of the categories of pain/tenderness, swelling‡, and redness‡	•				•		
Systemic AEs							
– Systemic AEs		•			•	•†	
– Number (%) of subjects by maximum intensity rating, over all systemic AEs		•			•		
– Maximum intensity rating of systemic AEs, over all systemic AEs		•			•		
Temperatures							
– Elevated temperatures#	•				•	•	•
– Maximum temperatures††	•				•		
AEs of Special Interest							
– Serious AEs		•			•	•	•
– Serious VR AEs				•	•	•	•
– New medical conditions			•	•	•		
– Serious AEs of infants exposed to study vaccine during conception			•	•	•		

This information is repeated in the three updates of the statistical analysis plan (on p5147, p5227 and p5308).

3) There are inconsistencies in the table just above. Serious adverse events were only analysed if they occurred within the three two-week periods after each vaccination whereas serious adverse events considered vaccine related by the investigators were NOT analysed for this restricted period, only for the whole trial period. It is scientifically inappropriate to analyse and report the most important harms data this way. Whether considered vaccine related or not, serious adverse events must be analysed for the whole trial period, which Merck failed to do.

I have seen no explanation for this conduct, and the main text in the statistical analysis plan does not explain why this decision was made (p5066):

"Statistical analyses of adverse experiences will follow the 3-tiered analysis approach commonly used by the SPONSOR when conducting safety assessments ... Tier 2 analysis follows the tier 1 analysis approach, except p-values are not computed. The Tier-2 adverse experience summaries include (1) specific systemic adverse experiences within 14 days following any vaccination occurring in ≥1% of subjects in any vaccination group, (2) injection-site adverse experiences not prompted for on the VRC occurring Day 1 to Day 5 following any vaccination in ≥1% of subjects in any vaccination group, (3) serious adverse experiences occurring within 14 days (Day 1 to Day 15) following any vaccination, (4) serious vaccine-related adverse experiences observed at any time during the study, and (5) severe injection-site adverse experiences Day 1 through Day 5 following any vaccination visit."

It is stated that serious adverse experiences observed at any time during the study are only those considered vaccine related.

4) Among Merck's 388 tables, I found only two with confidence intervals, on p839 and p841:

Table 12-34

Analysis of Subjects With Serious Adverse Events
(Incidence >0% in One or More Vaccination Groups)
(Days 1 to 15 Following Any Vaccination Visit) (All Vaccinated Subjects, Efficacy Substudy)

Vaccination	n	(%)	Difference in % vs qHPV Vaccine Estimate (95% CI)[†]
Subjects in population with follow-up			
9vHPV Vaccine	7,071		
qHPV Vaccine	7,078		
with one or more serious adverse events			
9vHPV Vaccine	25	(0.4)	0.1 (-0.1, 0.3)
qHPV Vaccine	17	(0.2)	

[†] Based on Miettinen & Nurminen method.
Every subject is counted a single time for each applicable row.
Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.
A bolded term or specific adverse event appears on this report only if its incidence in one or more of the vaccination groups meets the incidence criterion in the report title, after rounding.

Data Source: [16.4]

Table 12-35

Analysis of Subjects With Serious Vaccine-related Adverse Events
(Incidence >0% in One or More Vaccination Groups)
(Day 1 Through Visit Cut-Off Date) (All Vaccinated Subjects, Efficacy Substudy)

Vaccination	n	(%)	Difference in % vs qHPV Vaccine Estimate (95% CI)[†]
Subjects in population with follow-up			
9vHPV Vaccine	7,071		
qHPV Vaccine	7,078		
with one or more adverse events			
9vHPV Vaccine	2	(0.0)	0.0 (-0.1, 0.1)
qHPV Vaccine	2	(0.0)	

[†] Based on Miettinen & Nurminen method.
Every subject is counted a single time for each applicable row.
Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.
A bolded term or specific adverse event appears on this report only if its incidence in one or more of the vaccination groups meets the incidence criterion in the report title, after rounding.

Data Source: [16.4]

This is scientifically inappropriate and misleading. The large difference in serious adverse events, 233 vs 183 disappears. Instead, readers are presented with very small numbers, 25 vs 17 and 2 vs 2, none of which are statistically significant.

I searched in the whole document for the term "95% CI." After having seen hundreds of occurrences of 95% CI and many concrete 95% confidence intervals, all related to the benefits of the HPV vaccines, with a few exceptions, I found the first 95% confidence interval related to adverse effects, which was on p757 in the report.

5) Merck tried to explain away the difference of 233 vs 183 by saying that many of the events were related to pregnancy. However, in a randomised trial, one will expect pregnancy outcomes to be similarly distributed in the two compared groups, which Merck even confirmed: "In both vaccination groups, the most common serious adverse experiences were infections and pregnancy-related events. These events occurred at generally comparable frequencies among both vaccination groups" (p848).

The correct analysis is to include all events that are serious.

6) Merck claimed that most serious adverse events were related to pregnancy. I found this statement to be false. There were 233 vs 183 serious adverse events and 243 vs 192 MedDRA terms (because a few patients had more than one serious adverse event). I found 130 MedDRA terms related to pregnancy, which is only 30% of the total and therefore not "most." Furthermore, exclusion of the pregnancy events did not make much of a difference. Before I excluded them, the difference in MedDRA terms was 51, and after it was 35.

Serious adverse events by system organ class

P827:

Table 12-31
Subjects With Serious Adverse Events by System Organ Class
(Incidence > 0% in One or More Vaccination Groups)
(Day 1 Through Visit Cut-Off Date) (All Vaccinated Subjects, Efficacy Substudy)

	9vHPV Vaccine		qHPV Vaccine	
	n	(%)	n	(%)
Subjects in population with follow-up	7,071		7,078	
with one or more serious adverse events	233	(3.3)	183	(2.6)
with no serious adverse events	6,838	(96.7)	6,895	(97.4)
Blood and lymphatic system disorders	**1**	**(0.0)**	**1**	**(0.0)**
Anaemia	1	(0.0)	1	(0.0)
Cardiac disorders	**1**	**(0.0)**	**0**	**(0.0)**

P834:
"The proportion of subjects with serious adverse experiences occurring between Days 1 and 15 following any vaccination visit in the efficacy substudy was low and comparable between the 2 vaccination groups."

As already noted, it is scientifically inappropriate to report serious adverse experiences during only two weeks after each vaccination. Merck concludes that the occurrence of serious adverse experiences was "comparable" between the two vaccination groups. Actually, the risk ratio is larger for the two-week intervals than for the whole study period, 1.47 (25/17) vs 1.27 (183/233), but there are fewer events, and Merck erroneously concludes they are "comparable." Merck provides a statistical analysis to "prove" its point: the difference in occurrence is 0.1%, with a 95% confidence interval of -0.1% to 0.3%, which means that the difference is not statistically significant (p839). Merck went so far as to analyse 2 vs 2 patients with serious vaccine-related adverse events on p841 while not testing 233 vs 183.

P840:
"There were 4 reports of vaccine-related serious adverse experiences in the efficacy substudy (2 in the 9vHPV vaccine group and 2 in the qHPV vaccine group)." The events were pyrexia (lasted 2 days), allergy (23 hours), headache (1.8 months) and hypoaesthesia (1.7 years).

P894:
Subject With Adverse Events and/or New Medical History Potentially Indicative of an Autoimmune Disorder by System Organ Class (Day 1 Through Visit Cut-off Date, Efficacy Substudy).

Table 12-49

Subject With Adverse Events and/or New Medical History Potentially Indicative of an Autoimmune Disorder by System Organ Class
(Day 1 Through Visit Cut-off Date, Efficacy Substudy)

	9vHPV Vaccine		qHPV Vaccine	
	n	(%)	n	(%)
Subjects in population	7,106		7,109	
With one or more events[1]	254	(3.6)	235	(3.3)
With no events	6,852	(96.4)	6,874	(96.7)
Blood and lymphatic system disorders	**1**	**(0.0)**	**1**	**(0.0)**
Antiphospholipid syndrome	1	(0.0)	0	(0.0)
Idiopathic thrombocytopenic purpura	0	(0.0)	1	(0.0)

There were 254 v 235 patients with one or more events, of which 57 vs 44 were considered autoimmune conditions by the reporting investigator (p897). Merck did not distinguish between adverse events and new medical history for this analysis, which the company has otherwise separated in all its other analyses (even though this, as already explained, is scientifically inappropriate and arbitrary).

P915:
Under "Discussion and Conclusions," Merck notes that, "The proportion of subjects who reported systemic clinical adverse experiences was generally comparable in the 2 vaccine groups."

As there are no further explanations, or any reservations, this is Merck's conclusion. However, 4052 vs 3957 patients reported such events (p = 0.10) and 2088 vs 1930 (p = 0.003) (my calculations) were considered vaccine-related by the investigators (p25). As Merck considers vaccine-related events much more important than all events, it is inappropriate to claim that these rates are "comparable."

P1810:
"Subjects With Systemic Adverse Events by System Organ Class (Incidence > 0% in One or More Vaccination Groups) (Days 1 to 15 Following Any Vaccination Visit) (All Vaccinated Subjects, Efficacy Substudy)."

There were only 3948 vs 3883 patients whereas there were 4052 vs 3957 patients when the time period was not limited to two weeks after each vaccination (p25). Thus, there were only 178 (2%) more patients when the whole trial period was included. This suggests that reporting of adverse events was insufficient. For events considered vaccine related, the differences were even smaller, 2086 vs 1929 (p1910) and 2088 vs 1930 (p25), a difference of only 3 patients (0.07%). As noted above, the numbers do not add up because serious systemic adverse events were to be reported for the whole trial period, which was 42 months: "Subjects who received the selected 9vHPV vaccine dose formulation or qHPV vaccine were followed for efficacy through at least Month 42, followed for persistence of antibody responses through Month 42, and followed for safety for the duration of the trial" (p2).

P2454:
"In addition to the narratives provided in Section 14.6, Serious Adverse Experience Reports (CIOMS) are attached in [16.2.7.3]."

P2454-2537 (84 pages):
14.6.1 Serious Adverse Experiences (Excluding Events of Fetal Loss)

P2538-40 (3 pages): Fetal Congenital Anomalies.

P2541-67 (27 pages): 14.6.3 Serious Adverse Experiences Reported in Infants Who Were Born to Subjects Enrolled in This Study.

P2568-96 (29 pages): 14.6.4 Incident Conditions Potentially Indicative of Autoimmune Disorder.

Merck chose not to use its arbitrary division of adverse events and new medical history by providing tables that combined these two, but also provided three tables, which were not that different:

Table 12-49 Subject With Adverse Events and/or New Medical History Potentially Indicative of an Autoimmune Disorder by System Organ Class (Day 1 Through Visit Cut-off Date, Efficacy Substudy) **894**

Table 12-50 Subject With Adverse Events and/or New Medical History Potentially Indicative of an Autoimmune Disorder by System Organ Class - Events Considered As Autoimmune Conditions by the Reporting Investigator (Day 1 Through Visit Cut-off Date, Efficacy Substudy) **897**

Table 12-51 Subject With Vaccine-Related Adverse Events and/or New Medical History Potentially Indicative of an Autoimmune Disorder by System Organ Class (Day 1 Through Visit Cut-off Date, Efficacy Substudy) **899**

One would expect tables 12-50 and 12-51 to be quite similar because, in both cases, presumably it is the investigator who decides if an event is "vaccine-related" or "potentially indicative of an autoimmune disorder."

Further tables are provided:

Table 14.5 - 48 Listing of Adverse Experiences and New Medical Conditions Considered Potentially Indicative of Autoimmune Disorders **2186**

Table 14.5 - 49 Listing of Subjects With Adverse Events and/or Medical History Potentially Indicative of an Autoimmune Disorder (Day 1 Through Visit CutOffDate) (All Vaccinated Subjects).... **2188**

The wording changes, which only adds to the confusion. What exactly is the difference between these two additional tables, coming over 1000 pages later in the report, and the three earlier tables?

I looked up all five tables and determined that, in the first three tables, the number of people with events decreased from table to table: 254 vs 235, 57 vs 47 and 17 vs 20. There were more events on Gardasil 9 than on Gardasil but the difference in the occurrence of these events dropped from 19 to 10 to -3 over the three tables. It is impossible to know what to make out of these tables, if anything.

The fourth table was a very broad list of 77 conditions, which might be considered autoimmune, starting with Alopecia areata, Ankylosing spondylitis, Antinuclear antibody positive, Antiphospholipid syndrome, Arthralgia, Arthritis, Arthritis reactive, Arthropathy, Anaemia haemolytic autoimmune, Autoimmune hepatitis, Autoimmune thrombocytopenia and Autoimmune thyroiditis.

In the fifth table, concrete subjects were listed, with intensity and outcome (e.g. resolved or persisting).

I did not find a table of adverse events or one of new medical history that could be autoimmune disorders, only combination tables. Below is the top of each of the three first tables:

P894:

Table 12-49

Subject With Adverse Events and/or New Medical History Potentially Indicative of an Autoimmune Disorder by System Organ Class
(Day 1 Through Visit Cut-off Date, Efficacy Substudy)

	9vHPV Vaccine		qHPV Vaccine	
	n	(%)	n	(%)
Subjects in population	7,106		7,109	
With one or more events[†]	254	(3.6)	235	(3.3)
With no events	6,852	(96.4)	6,874	(96.7)
Blood and lymphatic system disorders	**1**	**(0.0)**	**1**	**(0.0)**
Antiphospholipid syndrome	1	(0.0)	0	(0.0)
Idiopathic thrombocytopenic purpura	0	(0.0)	1	(0.0)

P897:

Table 12-50

Subject With Adverse Events and/or New Medical History Potentially Indicative of an Autoimmune Disorder by System Organ Class - Events Considered As Autoimmune Conditions by the Reporting Investigator
(Day 1 Through Visit Cut-off Date, Efficacy Substudy)

	9vHPV Vaccine		qHPV Vaccine	
	n	(%)	n	(%)
Subjects in population	7,106		7,109	
With one or more events[†]	57	(0.8)	47	(0.7)
With no events	7,049	(99.2)	7,062	(99.3)
Blood and lymphatic system disorders	**1**	**(0.0)**	**1**	**(0.0)**
Antiphospholipid syndrome	1	(0.0)	0	(0.0)
Idiopathic thrombocytopenic purpura	0	(0.0)	1	(0.0)

P899:

Table 12-51

Subject With Vaccine-Related Adverse Events and/or New Medical History Potentially Indicative of an Autoimmune Disorder by System Organ Class
(Day 1 Through Visit Cut-off Date, Efficacy Substudy)

	9vHPV Vaccine		qHPV Vaccine	
	n	(%)	n	(%)
Subjects in population	7,106		7,109	
With one or more events[†]	17	(0.2)	20	(0.3)
With no events	7,089	(99.8)	7,089	(99.7)
Endocrine disorders	**1**	**(0.0)**	**0**	**(0.0)**
Goitre	1	(0.0)	0	(0.0)
Hyperthyroidism	1	(0.0)	0	(0.0)

Even though this trial started six years after the Future 1 trial, the procedures were even more inadequate. There was only a two-week period for collection of adverse events after each vaccination, and after day 180, serious adverse events were only collected if someone (not specified by whom) determined them to be vaccine related or related to a study procedure. This is particularly concerning given that it was a primary objective to evaluate the tolerability of Gardasil 9.

The statistical analyses of adverse events were also more inadequate than in the Future trials (p15 in the study report). P-values were computed only for those adverse experiences that were prompted for on the vaccination report card (two-week periods only) and for fever. Risk differences and 95% confidence intervals were computed for injection site adverse experiences, “specific systemic adverse events,” severe injection-site adverse events, serious adverse events, and fever.

V503 P021-01_Stat Report

A Registry-Based Extension of Protocol V503-001. “First interim analysis.”

P8:
“Subjects were followed in the base study (Protocol V503-001) for up to 6 years post-dose 1 (median: 4 years). A long-term follow-up (LTFU) study (Protocol V503-021) was implemented as an extension of the base study to assess effectiveness, immunogenicity and safety of the vaccine for an additional 10 years following the end of the V503-001 base study. This protocol number (021) differs from the protocol number (001), to allow the establishment of a new, separate clinical electronic database by the Sponsor.

This LTFU study is designed to assess effectiveness of the 9vHPV vaccine up to at least 14 years after the start of vaccination (including approximately 4 years of follow-up in the V503-001 base study and 10 years of follow-up in the V503-021 study extension). It includes participants from Denmark, Norway and Sweden and uses national health registries from these countries.”

“a final report is to be prepared after the end of the study. This first interim report summarizes effectiveness and safety analyses conducted through Year 2 of the study extension through a cut-off date of 01-Jan-2016.”

“There were 1363 subjects who contributed to the follow-up out of 1782 eligible subjects in the per-protocol efficacy population.”

P9:
“Through the first interim analysis period, 36.3% of subjects who received 9vHPV vaccine in the base study (Cohort 1) and 35.1% of subjects who received qHPV vaccine in the base study (Cohort 2) had at least one new medical condition during the first two years of the V503-021 study extension.”

P34:
“4453 subjects were enrolled from Denmark, Norway, and Sweden for efficacy evaluation in the V503-001 base study.”

P61:
“4.4 Safety
Table 4-17 displays the number and percentage of subjects with new medical history (incidence >0%) by system organ class in the follow-up study for each cohort. For this reporting period, new medical history was only collected for Denmark and Norway; new medical history for Sweden from the beginning of the LTFU study will be provided starting with the second interim analysis report.”

P62:

Subject New Medical History Conditions
(Incidence >0% in One or More Vaccination Groups)
(All Long-Term Follow-up Study Participants)

	Cohort 1		Cohort 2	
	n	(%)	n	(%)
Subjects in population	2,029		2,036	
With one or more new conditions	736	(36.3)	715	(35.1)

This was all there was about safety, called new medical history.

Misleading trial report in *New England Journal of Medicine*

The published trial report[5] is of overriding importance because this is where doctors and patients can get information about what the trial showed.

This article was misleading on eight counts.

1) The article stated that 14,215 women had been randomised, which was incorrect; the correct number was 14,840. Contrary to the usual scientific standard, there was no flow chart of patients, which would have revealed that the information on number of randomised women was off.

2) The only mention of adverse events in the abstract was: "Adverse events related to injection site were more common in the 9vHPV group than in the qHPV group." This downplayed the differences between the two vaccines. There were statistically significant differences in adverse events related to the injection site with extremely low p-values (my calculations; Merck did not provide any such calculations in its study report or in the published trial report); for example:

Injection-site vaccine related adverse events: $p = 8 \times 10^{-26}$ (p32 above, table)
Injection-site pain: $p = 3 \times 10^{-29}$ (p32, table)
Injection-site swelling: $p = 3 \times 10^{-45}$ (p32, table)
Severe injection-site adverse events: $p = 10^{-8}$ (V503 P001 CSR, p775)
Severe or moderate injection-site adverse events: $p = 6 \times 10^{-41}$ (V503 P001 CSR, p775).

As noted above, the number needed to harm was only between 9 and 16 patients for injection-site erythema, pain and swelling. These harms were far more common on Gardasil 9 than on Gardasil.

3) The Background section noted that, "Analyses of clinical trial and post-licensure safety data have not identified safety concerns associated with HPV vaccination." There were eight references to this mendacious statement. One would have expected one of them to be to the most relevant trial, the placebo-controlled trial of Gardasil published 8 years earlier,[6] but it was not quoted. One would also have expected Merck to quote one or more of the large and pivotal Future trials, but none of them were quoted.

Not a single one of Merck's previous trials was quoted. All eight references for this highly important but false claim were to observational studies or reviews. The most relevant one was a review[7] that stated in the abstract that it described five clinical trials, with a total of 21,480 participants, who had received qHPV (Gardasil) or placebo. This was also false. Only one of the five trials had used a placebo; the other four trials had used adjuvant as control. Two of the other trials reviewed were Future 1 and Future 2; Future 3 was not included (the study report was dated 17 November 2009, three months before the review was published). It was also false when the abstract stated that, **"**All serious and non-serious adverse experiences (AEs) and new medical conditions were recorded for the entire study period(s)," as non-serious adverse experiences were only recorded for the three two-week periods after each vaccination. The review

[5] Joura EA, Giuliano AR, Iversen O-E, et al. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. N Engl J Med 2015;372:711-23.
[6] Reisinger KS, Block SL, Lazcano-Ponce E, et al. Safety and persistent immunogenicity of a quadrivalent human papillomavirus types 6, 11, 16, 18 L1 virus-like particle vaccine in preadolescents and adolescents: a randomized controlled trial. Pediatr Infect Dis J 2007;26:201-9.
[7] Block SL, Brown DR, Chatterjee A, et al. Clinical trial and post-licensure safety profile of a prophylactic human papillomavirus (types 6, 11, 16, and 18) l1 virus-like particle vaccine. Pediatr Infect Dis J 2010;29:95-101.

had 12 authors of which 7 were employees of Merck and held stock or stock options; the remaining 5 had all received personal financial support from Merck and four of them had received research grants from Merck. The author team could therefore not claim that they did not know better.

4) The 277-word long section in *New England Journal of Medicine*, "Primary hypotheses and end points," contained nothing about safety even though safety was one of the two primary objectives for the trial (see above). It was all about efficacy.

5) The 657-word long section "Statistical analysis" contained nothing about safety analyses even though safety was one of the two primary objectives for the trial. It was all about efficacy.

6) The reporting of adverse events was false, as it violated Merck's own protocol on several counts. There were no p-values and no confidence intervals and the cut-off for reporting was 2% and not 1%. About injection-site events, it was noted that "Events of severe intensity were more common in the 9vHPV group" (I found $p = 10^{-8}$ for this difference). There was nothing about serious adverse events in the text: "All the serious adverse events are listed according to system organ class in Tables S6 and S7 in the Supplementary Appendix."

There was a table of adverse events, listed for each group separately but without a single p-value or confidence interval. This table shows a line with "Serious adverse event," with 233 (3.3%) versus 183 (2.6%), but as it has 34 lines, this line can easily be overlooked. P = 0.01 for this difference (my calculation).

7) There was no mention of new medical history at all even though this is about adverse events; even though Merck put great emphasis on this in its study reports; and even though there were over 10,000 such events (see Appendix A).

8) The Discussion section only mentioned that "Most adverse events related to the injection site were mild or moderate in intensity. Few participants discontinued study vaccination because of a vaccine-related adverse event." This was misleading. There was no information about the number needed to harm.

Seven of the 27 authors were current or former employees of Merck and held stock or stock options in Merck; nine had received personal honoraria or other financial support from Merck; two had received a grant from GlaxoSmithKline, another HPV vaccine manufacturer; and one also personal honoraria. Only eight authors had not reported any conflicts of interest. On top of this, the principal investigators had an agreement with Merck that restricted their rights to discuss or publish trial results after the trial was completed.[8]

P002

A Phase III Clinical Trial to Study the Immunogenicity, Tolerability, and Manufacturing Consistency of V503 (A Multivalent Human Papillomavirus [HPV] L1 Virus-Like Particle [VLP] Vaccine) in Preadolescents and Adolescents (9 to 15 year olds) with a Comparison to Young Women (16 to 26 year olds).

No randomisation to vaccine and placebo or another vaccine.

[8] https://www.clinicaltrials.gov/ct2/show/results/NCT00543543

Synopsis:

“Safety: Administration of the 9vHPV vaccine was generally well tolerated. The frequencies of clinical adverse experiences were generally comparable among the 3 demographic cohorts. Only 1 subject discontinued from the study due to a vaccine-related adverse experience. Forty-two (42) SAEs were reported over the entire duration of the study, regardless of causality, including 2 vaccine-related SAEs.”

P003

A Phase III Clinical Trial to Study the Tolerability and Immunogenicity of V503, a Multivalent Human Papillomavirus (HPV) L1 Virus-Like Particle (VLP) Vaccine, in 16- to 26-Year-Old Men and 16- to 26-YearOld Women.

P3:
It was about “Prevention of external genital lesions, anal cancers and related precancers, and persistent infection.” The types of participants were obscure, as abbreviations were not explained. I had no idea what HM and MSM were: “This was a Phase III, open-label, international, multicenter, clinical study to evaluate the immunogenicity and tolerability of the 9-valent HPV L1 VLP (9vHPV) vaccine in healthy young HM men (16 to 26 years of age) in comparison to healthy young women (16 to 26 years of age). Approximately 1100 healthy young HM (16 to 26 years of age) and approximately 1 1 0 0 healthy young women (16 to 26 years of age) were to be enrolled. In addition, approximately 300 MSM subjects (16 to 26 years of age) were to be enrolled and evaluated separately.”

P6:
In a footnote to a table, it was explained that “HM = Heterosexual men, MSM = Men having sex with men.”

No randomisation to vaccine and placebo or another vaccine.

P005

I started with this one: V503 P005 CSR

A Phase III Open-Label Clinical Trial to Study the Immunogenicity and Tolerability of V503 (A Multivalent Human Papillomavirus [HPV] L1 Virus-Like Particle [VLP] Vaccine) Given Concomitantly with Menactra™ and Adacel™ in Preadolescents and Adolescents (11 to 15 Year Olds).

1241 subjects were randomised to be vaccinated also with a meningococcal vaccine (Menactra) and a vaccine against tetanus, diphtheria and pertussis (Adacel) at day 1 or after a month.

P14:

SAFETY:

When compared to non-concomitant administration, concomitant administration of a first dose of 9vHPV vaccine with Menactra™ and Adacel™ was generally well tolerated and demonstrated a favorable safety profile. The table that follows displays a summary of clinical AEs, reported from Day 1 through the end of the study, by vaccination group. There were no deaths, few SAEs (<1% in either vaccination group), and no vaccine-related SAEs. The frequency of AEs was generally comparable between the 2 groups, and only one discontinuation in each group due to an AE.

Adverse Event Summary
(Day 1 to End of Study - All Vaccinated Subjects)

	9vHPV Vaccine + [Menactra™ + Adacel™] Concomitant		9vHPV Vaccine + [Menactra™ + Adacel™] Non-concomitant		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population with follow-up	613		611		1,224	
with one or more adverse events	553	(90.2)	542	(88.7)	1,095	(89.5)
injection-site	531	(86.6)	509	(83.3)	1,040	(85.0)
non-injection-site	344	(56.1)	339	(55.5)	683	(55.8)
with no adverse event	60	(9.8)	69	(11.3)	129	(10.5)
with vaccine-related[†] adverse events	538	(87.8)	522	(85.4)	1,060	(86.6)
injection-site	531	(86.6)	509	(83.3)	1,040	(85.0)
non-injection-site	168	(27.4)	168	(27.5)	336	(27.5)
with serious adverse events	5	(0.8)	5	(0.8)	10	(0.8)

No randomisation to vaccine and placebo or another vaccine.

P007

V503 P007 CSR

A Phase III Open-Label Clinical Trial to Study the Immunogenicity and Tolerability of Y503, a Multivalent Human Papillomavirus (HPV) L1 Virus-Like Particle (VLP) Vaccine, Given Concomitantly With REPEVAX™ in Preadolescents and Adolescents (11 to 15 Year Olds).

Randomised trial testing Repevax (against diphtheria, tetanus, pertussis and polio) when given concomitantly with Gardasil or one month later. N/A. The vaccine was “generally well tolerated” (p205), but on this occasion, the safety profile was not favourable as usual, but only “acceptable” (p207).

P009

4000+ pages.

Study initiation date: 23 February 2011 (First Visit First Subject)
Study completion date: 20 December 2011 (Last Visit Last Subject)
Date of the report: 06 December 2012.

Index on p17 but only up to page 271. After this, appendices are listed, with no page numbers for the remaining 3823 pages in the report.

P3:
“All subjects were randomized to be administered a standard 3-dose regimen (Day 1, Month 2, Month 6) of either 9vH PV vaccine or qHPV vaccine.”

The study compared Gardasil 9 with Gardasil in 600 girls.

Table 2. Schedule of Safety Measurements

	ICF signed	Visit 1 Day 1			Visit 2 Month 2			Visit 3 Month 6			Visit 4 Month 7
		Dose 1			Dose 2			Dose 3			
		VRC			VRC			VRC			
Oral temperature		5 days*			5 days*			5 days*			
Solicited ISR		5 days*			5 days*			5 days*			
Other ISR		15 days**		(a)	15 days**		(a)	15 days**		(a)	
Systemic AE		15 days**		(a)	15 days**		(a)	15 days**		(a)	
SAE	From signature of ICF until approximately 4 weeks after the third vaccination regardless of causality										
Death	From signature of ICF until last visit										

* Day 1 to Day 5
** Day 1 to Day 15
Day 1 = day of vaccination
AE = Adverse Event
ICF = Informed Consent Form
ISR = Injection-site Reaction
(a) any new medical event was recorded as a MHNC = Medical History and New Conditions
SAE = Serious Adverse Event
Solicited = Prompted for on the VRC
VRC = Vaccination Report Card

Table 1. Schedule of Vaccination and Immunogenicity Measurements

Event/Test	Day 1 (Visit 1)	Month 2 (Visit 2)	Month 6 (Visit 3)	Month 7 (Visit 4)
		2 months after Day 1, ±3 weeks	6 months after Day 1, ±4 weeks	3 to 7 weeks after Month 6
Serum for anti-HPV antibody testing	X			X
Vaccination	X	X	X	

P5:
"Subjects were followed up to Month 7, i.e. approximately 4 weeks following the third vaccination."

P8:

Table 7. Clinical Adverse Event Summary (Day 1 Through Month 7 Following Any Vaccination) - Safety Set

	9vHPV Vaccine (N=299)	qHPV Vaccine (N=300)
Number of subjects with	**N subj (%)**	**N subj (%)**
No adverse event	12 (4.0%)	19 (6.3%)
One or more adverse event	287 (96.0%)	281 (93.7%)
with one or more vaccine-related adverse event	279 (93.3%)	271 (90.3%)
Injection-site adverse reaction from Days1 to 5	274 (91.6%)	265 (88.3%)
Solicited injection-site adverse reaction	274 (91.6%)	265 (88.3%)
Injection site erythema	102 (34.1%)	88 (29.3%)
Injection site pain	267 (89.3%)	265 (88.3%)
Injection site swelling	143 (47.8%)	108 (36.0%)
Other injection-site adverse reaction	35 (11.7%)	42 (14.0%)
Systemic adverse event from Days 1 to 15	142 (47.5%)	156 (52.0%)
Vaccine-related systemic adverse event	62 (20.7%)	73 (24.3%)
Serious adverse event at any time	1 (0.3%)	2 (0.7%)
Serious vaccine-related adverse reaction	-	-
Death	-	-
Withdrawn due to an adverse event at any time	1 (0.3%)	1 (0.3%)
Withdrawn due to a vaccine-related adverse reaction	-	-
Withdrawn due to a serious adverse event	1 (0.3%)	1 (0.3%)

Although it is a summary of clinical adverse events from day 1 to month 7, systemic adverse events are limited to days 1 to 15 even though harms of vaccines can occur much later, and even though systemic harms can be far more serious than transient local harms at the injection site. There was no table in the report of systemic adverse events through month 7.

P45:
"9.4.6. Blinding
Blinded vaccines had visually identical presentations and were presented in an indistinguishable packaging."

P100-1:
"12.3.1.3.2.2. Adverse Event of Special Interest

Apart from the CPAs [Condition of Particular Attention] no AEs referenced in the Sanofi Pasteur MSD Specification 005261 List of Adverse Event of Special Interest (AESIs) for qHPV vaccine have been reported in the study, and specifically neither allergic reaction considered by the Investigator related to study vaccine nor syncope with fall resulting in injury.

Six subjects experienced one episode of syncope or presyncope during the study, 2 episodes occurred after 9vHPV vaccine and 4 episodes occurred after qHPV vaccine. None of these events was serious and considered of clinical interest; 3 cases were considered vaccine-related and 3 cases were considered as not vaccine-related by the investigator:

■ Subject AN 50246 experienced fainting post-dose 1 of 9vHPV vaccine. The event was of mild intensity and considered vaccine-related.
■ Subject AN 50138 experienced syncope post-dose 1 of 9vHPV vaccine. The event was of moderate intensity and assessed as not vaccine-related by the investigator.
■ Subject AN 50172 experienced syncope post-dose 1 of qHPV vaccine. The event was of mild intensity and considered vaccine-related. For this subject, Dose 1 of qHPV vaccine was administered in full but it was injected in two times due to the syncope.
■ Subject AN 50181 experienced a vasovagal episode: immediately after vaccination with qHPV vaccine (Dose 1), the subject lost consciousness for few seconds then she recovered and had nausea and weakness for about 15 minutes. The event was of moderate intensity and assessed as not vaccine-related by the investigator.
■ Subject AN 51212 experienced fainting 6 days post-dose 1 of qHPV vaccine associated with mild abdominal pain. The event was of moderate intensity and assessed as not vaccine-related by the investigator.
■ Subject AN 50060 experienced lipothymic episode and pale clammy skin (presyncope) post-dose 2 of qHPV vaccine. The event was of mild intensity and considered vaccine-related.

It is of interest that Merck, in 2011, took an interest in cases of syncope. I did not see this in Merck's previous studies. Six cases in 600 girls are 1%.

Merck operates with Condition of Particular Attention and with the Sanofi Pasteur MSD Specification 005261 List of Adverse Event of Special Interest (AESIs). Unclear whether there is a difference.

P101, three narratives:
"12.3.2.2. Other Serious Adverse Events

Subject AN 51128 (E2011-02911) - PARTIAL COMPLEX EPILEPSY – Not related

A 14-year-old white girl from Sweden experienced partial complex epilepsy **redacted** days after she had received the first dose of qHPV vaccine on 02 April 2011.

The subject had no familial history of neurological disease or epilepsy. She was healthy, did not take any medicine, nor contraceptives and was socially active.

On **redacted** 2011, she had a left-sided occipital headache after a run. She went to bed and was woken up by her father about one hour later. He found that she had aberrant rapport, but thought that this was due to the fact that she was half asleep. She slept for another hour and when she woke up she still had

headache, vomited once and was dysphasic.

When she arrived at the Emergency Unit Care her condition worsened. She could not orientate herself in time or place. The right pupil was dilated but reacted normally to light. She also had episodes similar to apnoea. CT scan of the skull was normal. She received 2 doses of sumatriptan (Imigran) with no effect. Lumbar puncture was normal. She was admitted to hospital. CT angiography was normal.

The day after (09 May 2011), she was tired but fully oriented, with no apparent dysphasia. There was a slight anisochoria. EEG showed several short seizures starting in the left temporal lobe but also regional slowing. MRI with and without contrast was normal. Chest X-ray was also normal. She was treated with Oxacarbezin (Trileptal). During hospitalisation, she had headache with dizziness, assessed predominantly as adverse reaction to medicine. Ophthalmologic exam was normal. On 11 May 2011 headache and anisochoria worsened, which led to another EEG showing clear improvement. A new lumbar puncture was performed, which was normal. Serology of possible encephalitis was also performed (no results were provided). The subject's condition improved and she was discharged on **redacted** 2011. The subject received Dose 2 (on 11 June 2011) and Dose 3 (on 9 October 2011) of qHPV vaccine and did not experience any adverse event.

The latest information received on March 2012 was that the subject was doing fine. She was still treated with Oxacarbezin (Trileptal) and had no more seizures.

According to the Investigator, the event was not related to study vaccine or study procedure.

Subject AN 50011 (E2011-05155) - HENOCH-SCHONLEIN PURPURA – Not related

A 12 year-old white girl from Finland experienced a Henoch-Schonlein purpura of moderate intensity 46 days following administration of the second dose of qHPV vaccine on 2 May 2011. She had received a first dose of qHPV vaccine on 2 March 2011.

The subject was healthy and was not taking any concomitant treatment.

On 15 June 2011 the subject had otitis media treated with Amoxicillin trihydrate and ciproxin-hydrocortison eardrops. On 17 June 2011 purpura and swelling of lower limbs and hands were noticed. Amoxicillin and eardrops were stopped. Then the subject complained of stomach pain and had diarrhoea and arthralgia in elbow, wrists and calves.

She was hospitalised on **redacted** 2011. Physical exam was normal except tender calves. Lab tests showed leukocytosis at 14,000 with mainly neutrophils at 66%, haemoglobin at 145, CRP at 64 and normal thrombocytes value. Urine sample showed 10 leukocytes and 5 erythrocytes per visual fields. The subject was treated with cefuroxim with paracetamol for pain. On **redacted** 2011 the urine culture did not show any pathogens and antibiotics were stopped. Urine albumin/creatinine ratio was (slightly) increased at 5.42 mg/mmol. The subject was discharged in good general condition on **redacted** 2011. Henoch-Schonlein purpura was diagnosed. On 7 July 2011 the subject had still petechia without other symptoms. Lab test showed 1 erythrocyte per visual fields. Urine albumin/creatinine ratio was increased at 13.6 mg/mmol. She had 2 other control visits on 18 August 2011 and 01 September 2011. On 10 November 2011 the subject was considered as recovered, as her physical examination was normal as well as all lab values.

The subject was withdrawn from the study due to the serious adverse event.

According to the investigator the adverse event was considered as not related to study vaccine or procedure, as well as not related to Amoxicillin and ciproxin-hydrocortisone eardrops.

Subject AN 51204 (E 2011-05623) – PULMONARY VASCULITIS and ANEMIA – Not related

A 13-year-old white girl from Spain developed pulmonary vasculitis and anemia diagnosed approximately 2 months after receiving the second dose of 9vHPV vaccine on 23 June 2011. She had received a first dose of 9vHPV vaccine on 19 April 2011.

The subject was healthy, with no relevant medical family history. She had menarche in December 2010, with cycles every 15-20 days, lasting approximately 5 days, with profuse bleeding and no dysmenorrhoea. She had been hospitalised in March 2011 for abdominal pain due to ovarian cyst.

On 1 September 2011, the subject presented tiredness for approximately four months, with dyspnoea for 2 months, tachycardia on slight exertion, appetite decrease with weight loss of 5 kg since the symptoms started, and frequent headache treated with analgesics. She had an episode of fever (max. 39.5°C), nausea and headache, which spontaneously resolved within 24 hours. Lab tests showed anaemia. Chest X-ray showed baseline multifocal illness with poorly defined “nodular” images in both inferior lobes, indicating oedema or haemorrhage, with probable interstitial thickening.

The subject was hospitalized on **redacted** 2011. Physical exam was normal except a slight pallor of skin and mucous membranes. Lab investigations on admission showed Haemoglobin 8.4 g/dl, Hematocrit 27.3%, MCV 85.2 fl, Leukocytes 4,130/mm3 (59% neutrophils, 30% lymphocytes, 5.3% monocytes), Platelets 355,000/mm3. ESR: 40 mm 1st hour. Iron metabolism test: iron 31 mcg/dL, transferrin saturation index 13%, ferritin normal. LDH was 421 1U/1 and the other biochemical parameters were within the normal range. Urine analysis test showed hematuria and proteinuria and the remainder was normal. Complement testing (C2, C3, C4, CI150) was within normal range. Antinuclear Antibodies (ANA) were positive at 1/1280 as well as anti-DNA antibodies; Anti-neutrophils cytoplasmic antibodies (ANCA), anti-proteinase 3, antimyeloperoxidase, antireticulin, and anti glomerular basement membrane antibodies testing were negative. ENA, anti-Ro antibodies, anti-La antibodies, anti-RNP antibodies, anti SCL-70 antibodies and anti-SM antibodies were pending at discharge. Anti-transglutaminase and antiendomysial antibodies were negative. Viral serology were negative (HBV, HCV, HIV, herpes simplex virus, CMV, Adenovirus and Parvovirus B19). Chest CT scan showed extensive diffuse bilateral opacities predominantly in the inferior lobes, and small parenchymatous consolidations in both lung bases, also in middle lobe. Lung function tests showed lung disorder of restrictive nature consistent with the suspected diagnosis of vasculitis or haemosiderosis. Fibrobronchoscopy showed that bronchial trees contained erythematous mucosa and traces of blood. Result of histology from transbronchial biopsy in the right inferior lobe showed extensive areas of alveolar bleeding, both old and recent, combined with small areas of inflammation of the interalveolar septum (focal capillaritis). These morphological findings are consistent with the variant of alveolar haemorrhage and capillaritis found in Wegener’s disease, microscopic polyangiitis and other diseases associated with capillaritis, such as acute lupus pneumonia, rheumatoid arthritis, polymyositis and connective tissue disease. Given that there were elevated ANA, the spectrum of diagnostic options is restricted to other diseases associated with capillaritis, such as lupus pneumonia, and other processes, such as Wegener’s disease and microscopic polyangiitis, are ruled out.

The subject received oral ferrous sulphate, cyclophosphamide (750 mg intra-venous, once every month, planned for 6 courses) and oral prednisone (40 mg/day). During hospitalisation, her condition gradually improved. The subject was discharged on **redacted** 2011. Haemogram prior to discharge was Haemoglobin 10.1 g/dL with Hematocrit 32.6%.

Diagnoses at discharge were diffuse alveolar haemorrhage due to focal pulmonary capillaritis, with elevated antinuclear antibodies and positive anti-DNA antibodies, secondary haemosierosis, iron deficiency, dysfunctional uterine haemorrhage and multifactorial anaemia. This was suggesting of a possible connective tissue disorder although not fulfilling any category yet.

Final diagnosis was isolated pulmonary capillaritis with positive ANA and multifactorial anemia. Anaemia was mainly related to profuse menstrual bleeding cycles before the current disease but was mainly exacerbated by diffuse alveolar haemorrhage secondary to main diagnosis. It was considered to be resolved on 5 December 2011 as the last Haemoglobin (1 December 2011) was 13.8 g/dL.

The latest information received on March 2012 was that the subject was asymptomatic since 21 December 2011, considered as the date of resolution of the SAE pulmonary vasculitis. Thoracic CT-scan showed resolution of previous lesions. ANA: 1/1280 with anti-DNA antibody: 25 (Normal: 0-10) on 12 September 2011 and ANA: 1/320 with anti-DNA antibody: 13 on 03 February 2012. The subject had received 5 cures of cyclophosphamide and the last is planned. Prednisone was stopped on 23 February 2012.

The subject was withdrawn from the study due to adverse event, because the drug used to treat pulmonary capillaritis was immunosuppressive.

According to the investigator, the diagnosis of diffuse alveolar haemorrhage secondary to focal pulmonary capillaritis, together with the high level of antinuclear antibodies suggested an underlying connective tissue disease. Anemia was mainly related to profuse menstrual bleeding cycles before the current disease but was exacerbated by diffuse alveolar haemorrhage secondary to main diagnosis. The investigator assessed the relationship of both SAEs to vaccine as not related.

Unredacted date of onset later in report, compare: "A 14-year-old white girl from Sweden experienced partial complex epilepsy ***redacted*** *days after she had received the first dose of qHPV vaccine on 02 April 2011." On p107, it states:*

"Three subjects reported serious adverse events, none of them assessed by the investigator as vaccine-related:

■ *a 14-year old girl had partial complex epilepsy 36 days after the first dose of qHPV vaccine."*

On p99, there was a table where the birth dates for the three patients with serious adverse events had not been redacted, whereas in a similar table on p252, the birth dates had been redacted:

Table 12.14. Summary of Serious Adverse Events – Safety Population

Subject AN Birth date Gender	SAE description (a)	Intensity	Dates of vaccination	Start date	Onset (Day)	Stop date	Duration (days)	SAE leading to premature withdrawal
9vHPV Vaccine								
51204 1998-02-08 F	Anemia/ Anaemia (Blood and lymphatic system disorders)	Moderate	1st: 19Apr2011 2nd: 23Jun2011	01Jul 2011 (b)	Day 9	05Dec 2011	158	Yes
	Isolated pulmonary capillaritis with positive ANA/ Pulmonary vasculitis (Respiratory, thoracic and mediastinal disorders)	Moderate	1st: 19Apr2011 2nd: 23Jun2011	01Jul 2011 (b)	Day 9	21Dec 2011	174	Yes
qHPV vaccine								
50011 1998-09-13 F	Henoch-Schönlein purpura/ Henoch-Schönlein purpura (Skin and subcutaneous tissue disorders)	Moderate	1st: 02Mar2011 2nd: 02May2011	17Jun 2011	Day 47	10Nov 2011	147	Yes
51128 1996-07-06 F	Partial complex epilepsy/ Complex partial seizures (Nervous system disorders)	Severe	1st: 02Apr2011 2nd: 11Jun2011 3rd: 09Oct2011	08May 2011	Day 37			No

In the table on p252, the number of days for the girl with epilepsy was not redacted: First vaccination date was 2 April 2011 and onset of epilepsy was 8 May 2011:

Listing 14.1. Overview of serious adverse events - Safety set*

Allocation number Center Number Birth date Gender	SAE description Reported term / MedDRA Preferred Term (MedDRA Primary SOC)	Intensity	Dates of vaccination (day/month/ year)	Start date (day/month /year)	Onset (Day)	Stop date (day/month /year)	Dura-tion (days)	Related to 9vHPV vaccine	Related to qHPV vaccine	SAE leading to premature withdrawal
9vHPV Vaccine										
51204 0502 1998 [redacted] F	Anemia/ Anaemia (Blood and lymphatic system disorders)	Moderate	1st: 19Apr2011 2nd: 23Jun2011	01Jul2011	9	05Dec2011	158	No	No	Yes
51204 0502 1998 [redacted] F	Isolated pulmonary capillaritis with positive ANA/ Pulmonary vasculitis (Respiratory, thoracic and mediastinal disorders)	Moderate	1st: 19Apr2011 2nd: 23Jun2011	01Jul2011	9	21Dec2011	174	No	No	Yes
qHPV Vaccine										
50011 0305 1998 [redacted] F	Henoch-Schönlein purpura/ Henoch-Schönlein purpura (Skin and subcutaneous tissue disorders)	Moderate	1st: 02Mar2011 2nd: 02May2011	17Jun2011	47	10Nov2011	147	No	No	Yes
51128 0603 1996 [redacted] F	Partial complex epilepsy/ Complex partial seizures (Nervous system disorders)	Severe	1st: 02Apr2011 2nd: 11Jun2011 3rd: 09Oct2011	08May2011	37			No	No	No

* Safety Set included subjects who received at least one dose of the study vaccine and who have safety follow-up data

P104:

Table 12.15. Comparison of 9vHPV Vaccine and qHPV Vaccine with Respect to The Number (%) of Subjects with Serious Adverse Event - Safety Set

	9vHPV Vaccine (N=299)		qHPV Vaccine (N=300)			
	n subjects (%)	95%CI	n subjects (%)	95%CI	Risk difference (%)	95%CI
Serious adverse event from Days 1 to 15 following any dose	1 (0.3%)	[<0.1%;1.8%]	0 (0%)	[0%;1.2%]	0.3	[-0.9;1.9]
Serious vaccine-related adverse event from Day 1 through Month 7	0 (0%)	[0%;1.2%]	0 (0%)	[0%;1.2%]	0.0	[-1.3;1.3]

n subjects (%): number of subjects (percentage) presenting at least once the considered event.

This table provides incorrect information. It states that only one patient experienced a serious adverse event from day 1 till month 7 when the correct number is three patients. The table on p8 is also a "safety set" table, from the same time period, but there are three patients:

Table 7. Clinical Adverse Event Summary (Day 1 Through Month 7 Following Any Vaccination) - Safety Set

	9vHPV Vaccine (N=299)	qHPV Vaccine (N=300)
Number of subjects with	**N subj (%)**	**N subj (%)**
No adverse event	12 (4.0%)	19 (6.3%)
One or more adverse event	287 (96.0%)	281 (93.7%)
with one or more vaccine-related adverse event	279 (93.3%)	271 (90.3%)
Injection-site adverse reaction from Days1 to 5	274 (91.6%)	265 (88.3%)
Solicited injection-site adverse reaction	274 (91.6%)	265 (88.3%)
Injection site erythema	102 (34.1%)	88 (29.3%)
Injection site pain	267 (89.3%)	265 (88.3%)
Injection site swelling	143 (47.8%)	108 (36.0%)
Other injection-site adverse reaction	35 (11.7%)	42 (14.0%)
Systemic adverse event from Days 1 to 15	142 (47.5%)	156 (52.0%)
Vaccine-related systemic adverse event	62 (20.7%)	73 (24.3%)
Serious adverse event at any time	1 (0.3%)	2 (0.7%)
Serious vaccine-related adverse reaction	-	-
Death	-	-
Withdrawn due to an adverse event at any time	1 (0.3%)	1 (0.3%)
Withdrawn due to a vaccine-related adverse reaction	-	-
Withdrawn due to a serious adverse event	1 (0.3%)	1 (0.3%)

The index for the report has this information on p22:

In order to conduct a meta-analysis of the number of serious adverse events in Merck's trials, the obvious starting point would be the index, but the table on p99 has three events whereas the one on p105 has only one event. Merck's tables are thus unreliable.

P106:

Table 12.18. Comparison of 9vHPV Vaccine and qHPV Vaccine with Respect to the Number of Subjects (%) with Maximum Oral Temperature ≥37.8°C (Days 1 to 15 Following Any Dose) – Safety Set

	9vHPV Vaccine (N=299)		qHPV Vaccine (N=300)				
	n subjects (%)	95%CI	n subjects (%)	95%CI	Risk difference (%)	95%CI	p
Maximum temperature (Oral) ≥ 37.8°C	20 (6.7%)	[4.1%;10.1%]	10 (3.3%)	[1.6%;6.0%]	3.4	[-0.1;7.2]	0.059

n subjects (%): number of subjects (percentage) presenting at least once the considered event.
All subjects had one or more temperature measurement.

This supports other findings that Merck's vaccines seem to cause pyrexia (p = 0.059) and that the harms increase with the number of antigens and the amount of adjuvant in the vaccine. The compositions of the two vaccines were the usual ones (p43).

P108:
"The significance of the finding of higher incidence of swelling in subjects administered 9vHPV vaccine vs. subjects administered qHPV vaccine is uncertain. It could be either due to lack of multiplicity adjustment (i.e. false positive finding) or possibly related to the higher amount of VLPs and adjuvant contained in the 9vHPV vaccine compared to qHPV vaccine."

The higher amounts of antigens and of adjuvant in Gardasil 9 compared to Gardasil show more harms. Merck reported p < 0.05 in the text; the exact p-value is 0.004 (my calculation). It is therefore not likely that this is a chance finding. Furthermore, Merck's other trials support the finding that more antigens and more adjuvant leads to more harm, as would be expected. See also p175 just below.

P175:

Table 14.48. Number (%) of subjects with injection-site adverse reactions (excluding erythema and swelling) by maximum intensity (Days 1 to 5 following any dose) - Safety Set

	9vHPV Vaccine (N=299)	qHPV Vaccine (N=300)
	N subj (%)	N subj (%)
All injection-site adverse reaction*	267 (89.3%)	265 (88.3%)
Mild	139 (46.5%)	157 (52.3%)
Moderate	111 (37.1%)	96 (32.0%)
Severe	17 (5.7%)	12 (4.0%)

P208:

Table 14.63. Number (%) of subjects with systemic adverse events by maximum intensity rating (Days 1 to 15 following any dose) - Safety Set				
	9vHPV Vaccine (N=299)		qHPV Vaccine (N=300)	
	All	Vaccine-related	All	Vaccine-related
	Nb subj (%)	Nb subj (%)	Nb subj (%)	Nb subj (%)
All systemic adverse event	142 (47.5%)	62 (20.7%)	156 (52.0%)	73 (24.3%)
Mild	50 (16.7%)	22 (7.4%)	46 (15.3%)	25 (8.3%)
Moderate	72 (24.1%)	31 (10.4%)	81 (27.0%)	33 (11.0%)
Severe	17 (5.7%)	9 (3.0%)	27 (9.0%)	14 (4.7%)
Missing	3 (1.0%)	0 (0%)	2 (0.7%)	1 (0.3%)

P1996:

CRFs FOR

OTHER SERIOUS ADVERSE EVENTS

Subject Identification Number	Reaction(s)	Case Reference Number
Allocation number: 50011 Baseline number: 0305-00001	HENOCH-SCHONLEIN PURPURA	E2011-05155
Allocation number: 51204 Baseline number: 0502-00010	ISOLATED PULMONARY CAPILLARITIS WITH POSITIVE ANA MULTIFACTORIAL ANEMIA	E2011-05623
Allocation number: 51128 Baseline number: 0603-00017	PARTIAL COMPLEX EPILEPSY	E2011-02911

P2000-4094:
There were 2094 pages with case report forms. I searched for the girl with epilepsy and found there were three different identifiers for the girl: AN 51128, baseline number 0603-00017, and case reference number E2011-02911. When I searched epilepsy, the first hit was on p2941. It was the correct baseline number, 0603-00017, and the date diagnosed was correct, 8 May 2011. The epilepsy was described on p3002 onwards. The event was serious for two reasons: the patient was hospitalised, and it was “Persistent or significant disability/incapacity.” Nonetheless, the investigator did not consider the epilepsy of clinical interest, which is hard to understand:

If Death :

Event reported in autopsy as cause of death ?
- ☐ No
- ☐ Yes
- ☐ Autopsy not performed

Is the AE an event of clinical interest ?
- ☒ No
- ☐ Yes

Two more adverse events were described for this patient, headache and throat pain.

Many pages later, on p3060-2, there is a more comprehensive narrative than the one in the main text of the study report (see just above; it is on p101 in the study report):

ADVERSE EVENT REPORT

Sanofi Pasteur MSD (Europe)
8 rue Jonas Salk
LYON Cedex 07
69367
FRANCE

AER NO: E2011-02911()
?

REPORT TYPE : Serious
INITIAL RECEIVED DATE: 09/MAY/2011
PROVINCE/COUNTRY: SWEDEN
OTHER ID NOS:

FROM:
LATEST RECEIVED DATE: 02/APR/2012

PATIENT ID	DOB	AGE	AGE GROUP	SEX
UNKNOWN	REDA... 1996	14 Years	Adolescent	Female

This narrative describes in much more detail the precursor events and also shows that she had two other episodes of seizure while she was hospitalized, on 9 and 11 May. This narrative does not have as identifiers AN 51128, or the baseline number 0603-00017, but the case reference number E2011-02911.

My little exercise shows that it can be difficult to follow individual patients in Merck's reports.

CRS 140 pages. Some forms were blank.

It is clear that much more comprehensive narratives of serious adverse events exist than those Merck has provided in most of its clinical study reports. The narrative had an "EUDRACT NUMBER: 2010-023393-39," but this is not a fourth identifier for the patient but an identifier for the trial, used in the European Union.

P010

V503 P010 CSR

Trial Initiation Date: 16-Dec-2013 (first subject first visit)
Trial Completion Date: Ongoing, visit cut-off date for this report (19-Jun-2015)
Report Date: 13-NOV-2015.

P1:
"This is a Phase III, open-label, international, multicenter, 3-year safety and immunogenicity study to compare the immunogenicity of 2 doses of 9vHPV vaccine administered at Day 1 and Month 6 (or Day 1 and Month 12) in girls and boys, 9 to 14 years of age, to 3 doses of 9vHPV vaccine administered at Day 1, Month 2, and Month 6 in young women, 16 to 26 years of age."

The study compared Gardasil 9 with itself, given as 2 or 3 doses in a study that was not blinded; 1518 people were randomised. Age groups were not comparable.

P3:
"A Vaccination Report Card (VRC) was not used in this study because the safety profile of the 9vHPV vaccine has been thoroughly investigated in clinical studies involving over 15,000 subjects. Although a VRC was not used and non-serious AEs were not solicited, subjects and investigators had the opportunity to report these events in the study database."

P5-7:
There were three primary objectives, three secondary objectives, three primary hypotheses, and three secondary hypotheses, which were all about antibodies. There wasn't a single mention of safety.

P17:
"Summary: Administration of the 9vHPV vaccine was generally well tolerated.

1. One subject discontinued from the study due to a vaccine-related adverse event.
2. Twenty two (22) subjects experienced serious adverse events.
There were no vaccine-related SAEs.
3. No subject died during the course of the study."

P193:
"In general, the proportion of subjects who reported at least one adverse event were higher among subjects who received (0, 2, 6) regimen compared to the corresponding proportion among subjects who received (0, 6) or (0, 12) regimen, for the apparent reason that 3-dose regimen (0, 2, 6) recipients have 1 more vaccination episode around which adverse events can occur compared to 2-dose regimen [(0, 6) and (0, 12)] recipients."

P198:
Narratives for subjects with serious adverse events are contained within the CIOMS reports in [16.2.7.3].

In a separate file: V503 P010 CSR Section 16.2.7.3_CIOMS Adverse Event Reports. One syncope seemed to have been caused by rotavirus gastroenteritis.

P364:

364

V503 PAGE 29
CLINICAL STUDY REPORT P 010

14.3.1 Narratives of Deaths, Other Serious and Significant Adverse Events

Serious Adverse Event Reports in [16.2.7] are derived from data in the safety database. For the complete subject data, see the data tabulations from the clinical database.

Among the files, one described serious adverse events in 22 (1.5%) of the 1496 patients (V503 P010 CSR Section 16.2.7_AEs).

P020

Approximately 3000 pages.

Study initiation date: 24 March 2014 (First Visit First Subject)
Study completion date: 22 April 2015 (Last Visit Last Subject)
Date of the report: 15 December 2015.

Index on p15.

The study is very similar to P009 but included 16- to 26-year-old men; 249 vs 251 were randomised.

All subjects were randomised to be administered a standard 3-dose regimen (Day 1, Month 2, Month 6) of 9vHPV vaccine or qHPV vaccine. Serum samples were collected at Day 1 and Month 7.

P9:

Table 8. Clinical Adverse Event Summary (Days 1 to 15 following any vaccination*) - Safety Set

	9vHPV Vaccine (N=248)	qHPV Vaccine (N=248)
Number of subjects with	**N subj (%)**	**N subj (%)**
No adverse event	44 (17.7)	45 (18.1)
One or more adverse event	204 (82.3)	203 (81.9)
with one or more vaccine-related adverse event	202 (81.5)	196 (79.0)
Injection-site adverse reaction from Days 1 to 5	196 (79.0)	179 (72.2)
Solicited injection-site adverse reaction	195 (78.6)	177 (71.4)
Injection site erythema	38 (15.3)	43 (17.3)
Injection site swelling	36 (14.5)	23 (9.3)
Injection site pain	193 (77.8)	174 (70.2)
Other injection-site adverse reaction	24 (9.7)	23 (9.3)
Severe injection-site adverse reaction from Days 1 to 5	3 (1.2)	4 (1.6)
Systemic adverse event	101 (40.7)	100 (40.3)
Vaccine-related systemic adverse event	57 (23.0)	54 (21.8)
Serious adverse event	0 (0)	0 (0)
Serious vaccine-related adverse reaction at any time	0 (0)	0 (0)
Vaccine-related serious adverse event leading to death at any time	0 (0)	0 (0)

*Period of reporting of Adverse Events is Day 1 to Day 15 if not otherwise specified

Although this table is a summary of clinical adverse events from day 1 to month 7, systemic adverse events are limited to days 1 to 15 even though harms of vaccines can occur much later, and even though systemic harms can be far more serious than transient local harms at the injection site. There was no table in the report of systemic adverse events through month 7.

P83:
"a comparable percentage of subjects reported at least one injection-site reaction from Day 1 to Day 5 following administration of the 9vHPV vaccine (79.0%) and qHPV vaccine (72.2%), although numerically more subjects reported swelling (14.5% after 9vHPV vaccine compared to 9.3% after qHPV vaccine) and pain (77.8% after 9vHPV vaccine compared to 70.2% after qHPV vaccine)."

Merck claims that numbers are "comparable," which they were not. There were 17 more patients with injection-site reactions on Gardasil 9 than on Gardasil (p = 0.09, my calculation), see the table just above. It is scientifically inappropriate to claim that events are comparable in a study that is too small to find differences, and when larger studies have shown that Gardasil 9 is NOT comparable to Gardasil but causes far more harm.

P87:

Table 12.5. Number (%) of Subjects with Injection-Site Adverse Reaction by Maximum Intensity Rating (Days 1 to 5 Following Any Dose) – Safety Set

	9vHPV Vaccine (N=248)	qHPV Vaccine (N=248)
	n (%)	n (%)
Injection-site adverse reaction from Day 1 to Day 5	**196 (79.0)**	**179 (72.2)**
Mild	154 (62.1)	139 (56.0)
Moderate	39 (15.7)	36 (14.5)
Severe	3 (1.2)	4 (1.6)

P93-4:
"12.2.3.2. Systemic Adverse Events
Comparison of systemic adverse events occurring in at least 4 subjects in either group did not show statistically significant differences between 9vHPV and qHPV vaccines (without adjustment of the

significance level for multiplicity) except for lymphadenopathy, which was more frequent in the group receiving the 9vHPV vaccine; the risk difference for this adverse event was 2.41 (95% CI: 0.7; 5.2).

Lymphadenopathy was reported in 6 subjects in the 9vHPV group:

• AN 53071: swelling of the neck, side not specified, starting 5 days after injection of Dose 1 of 9vHPV vaccine and lasting 59 days; the lymphadenopathy did not recur after Dose 2 or Dose 3.
• AN 53237: swollen cervical lymph glands, side not specified, starting the same day as injection of Dose 1 of the 9vHPV vaccine and lasting 3 days; the lymphadenopathy did not recur after Dose 2 or Dose 3.
• AN 53287: swollen cervical glands, side not specified, starting 4 days after injection of Dose 1 of 9vHPV vaccine and lasting <1 day; the lymphadenopathy did not recur after Dose 2 or Dose 3.
• AN 53001: swollen axillary lymph nodes on the left side, i.e., the same side as the injection, starting 4 days after injection of Dose 1 of 9vHPV and lasting 11 days; this subject reported nasopharyngitis beginning 1 day before the onset of lymphadenopathy, and the lymphadenopathy did not recur after Dose 2 or Dose 3.
• AN 53035: swollen supraclavicular lymph glands, side not specified, starting 6 days after injection and lasting 30 days; this subject also reported injection-site lymphadenopathy after Dose 2 and Dose 3.
• AN 53057: swollen cervical glands, side not specified, starting the same day as injection of Dose 1 of 9vHPV vaccine and lasting 3 days; the lymphadenopathy did not recur after Dose 2 or Dose 3.

All 6 cases of lymphadenopathy were considered vaccine-related by the Investigator. The area in which the lymphadenopathy was observed was plausibly related to the injection site in the arm (axillary for I subject, supraclavicular for 1 subject, and cervical for 1 subject). The relationship with the injection could be considered questionable for 2 of the subjects (AN 53237 and AN 53057), as the adverse event began on the same day as the injection of Dose 1 of 9vHPV vaccine; for the other subjects, lymphadenopathy occurred between 4 and 6 days after Dose 1. When the side on which the lymphadenopathy was located was reported (only for AN 53001), it was found to be on the same side as the injection of Dose 1 of 9vHPV vaccine. A possible confounding factor was only found for one subject (AN 53001), who concurrently reported nasopharyngitis. The lymphadenopathy did not reoccur after subsequent injections, except in one subject (AN 53035), who also reported injection-site lymphadenopathy after Dose 2 and Dose 3. The cases of lymphadenopathy were mild, except in one subject (AN 53237), who reported moderate lymphadenopathy. All cases resolved spontaneously, mostly within a few days, except for one case that lasted 1 month (AN 53035), and one case that lasted 2 months (AN 53071)."

Merck operated with a new criterion for evaluating systemic adverse events. As they should occur in at least 4 patients in either group, it means that events with an incidence below 1.6% did not count. In Merck's other studies, the criterion for non-reporting was 1%.

All 6 cases of lymphadenopathy were considered vaccine-related by the investigator and they all occurred in the Gardasil 9 group. Merck considered the relationship with the injection questionable for 2 of the cases because the adverse event began on the same day as the injection whereas it began between 4 and 6 days for the other 4 patients.

P189:

Table 14.51. Number (%) of subjects with systemic adverse events by maximum intensity rating from Day 1 to Day 15 following any dose – Safety Set				
	9vHPV Vaccine (N=248)		qHPV Vaccine (N=248)	
	All	Vaccine-related	All	Vaccine-related
	n (%)	n (%)	n (%)	n (%)
Systemic adverse events from Day 1 to Day 15*	101	57 (23.0)	100	54 (21.8)
Mild	58 (23.4)	32 (12.9)	47 (19.0)	27 (10.9)
Moderate	32 (12.9)	20 (8.1)	40 (16.1)	21 (8.5)
Severe	10 (4.0)	4 (1.6)	13 (5.2)	6 (2.4)

Appendix E

Narrative Review of Gardasil Clinical Trials

Contents

Placebo-controlled study of Gardasil (P018)

This study, P018, is the only “placebo-controlled” study Merck has ever carried out on its monovalent and quadrivalent vaccines, and it was done because a regulatory agency required it.

The so-called placebo was not a placebo

Merck described the placebo as the “carrier solution,” but nowhere in the report could I find the composition of this carrier solution. My research group has done extensive work on this issue and found out that, according to the FDA: "Each 0.5-mL dose of the vaccine contains approximately 225 mcg of aluminum (as Amorphous Aluminum Hydroxyphosphate Sulfate adjuvant), 9.56 mg of sodium chloride, 0.78 mg of L-histidine, 50 mcg of polysorbate 80, 35 mcg of sodium borate, <7 mcg yeast protein/dose, and water for injection."[1]

[1] https://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm111263.pdf

These substances are not placebos. Polysorbate 80 is used to stabilize aqueous formulations of medications for parenteral administration.[2] Influenza vaccines contain 2.5 µg of polysorbate 80 per dose whereas Merck put 20 times as much in its "placebo," 50 µg, without explaining why. Like other surfactants, polysorbate 80 "is not an inert compound … In drug formulations, polysorbate 80 has been implicated in a number of systemic reactions (e.g., hypersensitivity, nonallergic anaphylaxis, rash) and injection- and infusion-site adverse events (ISAEs; e.g., pain, erythema, thrombophlebitis)."[3]

Sodium borate may be harmful if inhaled; may cause respiratory tract irritation; may be harmful if swallowed; may be harmful if absorbed through skin; may cause skin irritation; and may cause eye irritation.[4] Sodium borate is used against sunburn, diaper rash, insect bites and stings, and to prevent otitis externa.[5]

According to the WHO,[6] "There is a theoretical risk of contamination of vaccines with yeast antigens with resultant mimicry between peptides of yeast and human myelin proteins. T-cells might be activated, with a resultant cross-reaction with myelin proteins."

Thus, at least two of the four substances in the carrier solution, polysorbate 80 and yeast proteins, might be immunogenic. It is not appropriate that Merck calls this carrier solution placebo, and by doing so, Merck contradicts its own definition of what a placebo is: "A placebo is made to look exactly like a real drug but is made of an inactive substance, such as a starch or sugar."[7]

In the US trial register, clinicaltrials.gov, the trial number is NCT00092547. The main trial publication[8] is listed in this register. Even though 6 of the publication's 12 authors are Merck employees, the abstract states that the control group received "saline placebo." Water for injection is not saline, and Merck's carrier solution is not a saline placebo. Drug regulators and other authorities, e.g. the Danish Board of Health, believe that this was a saline placebo-controlled trial.[9]

Unequal randomisation

Merck randomised the participants in a 2:1 ratio, which reduces the chance of detecting any harms of the vaccine, compared to the usual 1:1 ratio. Since Merck had already randomised several thousand people to receive the vaccine in its earlier trials, Merck should have used a 1:1 ratio and should have conducted a much larger trial; its placebo trial had only 594 people in the analyses.

Inadequate statistical testing

The trial's primary objective was to study the safety of the vaccine, which was requested by a drug regulator, but statistical testing was only done for elevated temperatures and for adverse experiences with an incidence of at least 1% in either group if they were prompted for on the vaccination report card and were reported within 14 days after each vaccination on this card, although the study ran for 18 months and although harms of vaccines may not be detected so quickly. This is a problem with all Merck's trials. **There were 1179 patients in the vaccine group, so if 11 patients (0.9%) experienced an important harm versus none of the 594**

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[2] https://en.wikipedia.org/wiki/Polysorbate_80
[3] Schwartzberg LS, Navari RM. Safety of Polysorbate 80 in the Oncology Setting. Adv Ther 2018;35:754–67.
[4] https://www.abcam.com/index.html?pageconfig=resource&rid=13171
[5] https://www.rxwiki.com/sodium-borate
[6] https://www.who.int/vaccine_safety/committee/topics/yeast/jan_2005/en/
[7] Merck: Placebos. https://www.merckmanuals.com/home/drugs/overview-of-drugs/placebos.
[8] Reisinger KS, Block SL, Lazcano-Ponce E, et al. Safety and persistent immunogenicity of a quadrivalent human papillomavirus types 6, 11, 16, 18 L1 virus-like particle vaccine in preadolescents and adolescents: a randomized controlled trial. Pediatr Infect Dis J 2007;26:201-9.
[9] Gøtzsche PC. Vaccines: truth, lies, and controversy. New York: Skyhorse; 2021.

patients in the placebo group, this would be ignored, even though p = 0.02 for this difference (Fisher's exact test).

Inappropriate prespecification of adverse experiences

The emphasis was on "prespecified adverse experiences: vaccine-related adverse experiences …" Since a placebo-controlled trial had never been carried out before, no one could know which harms the vaccine might cause, and it was therefore inappropriate to prespecify these. Both the 1% limit and the prespecifications meant that unanticipated harms, e.g. those suggesting the occurrence of postural orthostatic tachycardia syndrome (POTS), complex regional pain syndrome (CRPS) or autoimmune diseases, would very likely be ignored.

Lack of blinding

Merck did not make the vaccine and the placebo visually indistinguishable, which is essential for a safety study. Merck decided to run a huge risk that the study would be unblinded by using site personnel that was not blinded to administer the vaccines. I cannot see any justification for not blinding the vaccines centrally, which would have been easy.

Merck furthermore partially unblinded some of the onsite clinical investigators ("coordinating investigators") who reviewed the clinical study report while the trial was still running (Appendix C, p6). I do not recall ever seeing this for any clinical trial and cannot see any justification for writing and reviewing the clinical study report before the trial is finished, and indeed, in an unblinded fashion.

Finally, "In order to conduct the Month 7 analysis, inhouse Merck personnel were unblinded to treatment group after the Month 7 data were reviewed and the database was frozen" (Appendix C, p6).

The lack of appropriate blinding measures made the trial unreliable in relation to its safety results because the detection, recording, coding, analysis and reporting of possible harms is a subjective process that is highly vulnerable to bias. Merck left the door wide open to biased coding of adverse events, biased analysis and biased reporting even though, as I argued with examples from my own randomised trials already in 1996, in a widely cited and well-known article, it is easy to blind data analysis and writing of reports.[10]

The safety analyses did not include the full trial period

Although "All subjects will be followed for persistence of antibody response and safety evaluation through Month 18" (Appendix C, p3), "The main analyses of immunogenicity and safety presented in this CSR are based on data collected up to 1 month Postdose 3 (i.e., the Month 7 visit)" (Appendix C, p6). Further, there were only fourteen days of clinical follow-up after administration of each dose.

It is highly problematic that the safety analyses did not include the full trial period through month 18, as some vaccine harms take a long time to develop or to be diagnosed. For example, the influenza vaccine Pandemrix caused narcolepsy in over 1300 people, a life-long, seriously debilitating condition with poor treatment options where people suddenly fall asleep, with an onset from about two months after vaccination and up to at least two years later.[11] [12] Its manufacturer, GlaxoSmithKline, has acknowledged the causal link,[13] and the

[10] Gøtzsche PC. Blinding during data analysis and writing of manuscripts. Controlled Clin Trials 1996;17:285-90.
[11] Institutet för Hälsa och Välfärd. Förhöjd narkolepsirisk i två år efter Pandemrix-vaccinationen. 2014; June.
[12] Nohynek H, Jokinen J, Partinen M, et al. AS03 adjuvanted AH1N1 vaccine associated with an abrupt increase in the incidence of childhood narcolepsy in Finland. PLoS One 2012;7:e33536.
[13] Vogel G. Why a pandemic flu shot caused narcolepsy. Science 2015; July 1.

likely mechanism is an autoimmune cross-reaction in people with a particular tissue type between the active component of the vaccine and receptors on brain cells controlling the day rhythm.

Merck narrowed the target *within* the clinical study report

Merck even raised the bar for reporting adverse events *within* the clinical study report (Appendix C, p7-8). On p29 in the report, Merck wrote: "Safety: The primary objective of this study related to the safety of the vaccine ... In order to address this objective, the study called for a detailed tolerability analysis, with emphasis on the following prespecified adverse experiences: vaccine-related adverse experiences, vaccination report card (VRC)-prompted injection-site adverse experiences (swelling/redness and pain/tenderness/soreness), VRC-prompted systemic adverse experiences (muscle/joint pain, headaches, hives, rashes, diarrhea), severe adverse experiences, and fever."

However, on p75, Merck wrote: "The important variables of interest for safety/tolerability were the occurrence of severe injection-site adverse experiences and the incidence of any vaccine related serious adverse experiences."

Merck's initial "emphasis" on injection-site adverse experiences became narrowed into *severe* injection-site adverse experiences; vaccination report card prompted systemic adverse experiences and severe adverse experiences became narrowed into *vaccine related serious* adverse experiences, which are something entirely different and exceedingly rare. If Merck had applied these criteria on its trial that compared Gardasil 9 with Gardasil (see below), it would have had dramatic consequences. There were 7071 vs 7078 patients with follow-up data; 4052 vs 3957 with systemic adverse events; 233 vs 183 with serious adverse events; and 2 vs 2 with vaccine-related serious adverse events. If Merck had applied these criteria on its trial that compared Gardasil 9 with Gardasil, the 8009 patients with systemic adverse events would have been reduced to 4 patients with vaccine related serious adverse events, a reduction of 99.95% in patients with systemic adverse events. Thus, even if all the 1165 patients in the vaccine group in the placebo-controlled trial had experienced systemic adverse events, only one would be expected to have been serious and vaccine related. This raises very serious concerns.

It is scientifically inappropriate to define vaccine related serious adverse experiences as the important variable of interest in a placebo-controlled safety study. It is subjective to decide if a serious adverse experience is vaccine related, and the investigators did not know what to expect, as this was the first placebo-controlled trial. Furthermore, many other events than those that are serious are relevant for the patients, their relatives and their doctors, e.g. those of moderate or severe intensity (see below).

In Merck's trials, including this one, Merck defined serious adverse events in the usual way for drug trials, and added a few more (Appendix C, p7):

A serious adverse experience is any adverse experience occurring at any dose that:

- Results in death; or
- Is life threatening (places the subject/patient, in the view of the investigator, at immediate risk of death from the experience as it occurred. [Note: This does not include an adverse experience that, had it occurred in a more severe form, might have caused death.]); or
- Results in a persistent or significant disability/incapacity (substantial disruption of one's ability to conduct normal life functions); or
- Results in or prolongs an existing inpatient hospitalization (hospitalized is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation.) (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse experience); or

- Is a congenital anomaly/birth defect (in offspring of subject taking the product regardless of time to diagnosis); or

ALSO:

Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the subject/patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

In addition, Merck requires the collection of the following:

cancer, or
overdose (whether accidental or intentional) (Note: Overdose in this study was defined as a subject receiving >3 doses (0.5-mL) of vaccine or placebo throughout the study or receiving >0.75 mL of vaccine or placebo in any 1 dose).

Underreporting of serious adverse events

It is inadequate to instruct investigators to report, in addition to deaths, only those serious adverse experiences that occur during two weeks after each vaccination or if they are considered by the investigator to be possibly, probably, or definitely vaccine related (p78 in the study report, V501 P018 V1 CSR_missing P018-05 and -06). These instructions, which led to substantial underreporting of serious adverse events, are included in Merck's other protocols as well (see, for example, the Future 1 study below).

Fallacious reporting of serious adverse events

The reporting of serious adverse events appears fallacious. There were 5 events on the vaccine vs 0 on placebo in the study report but 6 vs 0 in the US trial register.[14] It was difficult to compare the entries, as they were described with different terms, but only four of the total of 11 patients were the same. Thus, there seemed to be 7 vs 0 with serious adverse experiences.

In the register, which was last updated on 20 February 2018, the 6 events were:

1) Haemorrhagic anaemia
2) Colitis ulcerative
3) Appendicitis
4) Localised infection
5) Type 1 diabetes mellitus
6) Pain in extremity

All six serious adverse events were stated to have been "collected by non-systematic assessment," which is not reassuring for a safety study. The five events in the study report were:

1) Heavy menstrual bleeding (also diagnosed with haemorrhagic anaemia)
2) Appendicitis
3) Right finger fracture (and acute renal failure)
4) Insulin dependent diabetes mellitus
5) Infected toe (with pain).

[14] https://clinicaltrials.gov/ct2/show/NCT00092547

Three patients appeared in both listings, those with haemorrhagic anaemia, appendicitis and diabetes. If we assume that the patient with localised infection is the same as the one with an infected toe, this leaves three additional patients that do not appear to be the same: colitis ulcerative, pain in extremity, finger fracture and renal failure. This shows that Merck's reporting of serious adverse events cannot be trusted and that we therefore do not know how many patients experienced severe adverse events in the trial. I believe it was at least 7 – all on the vaccine - whereas Merck only reported 5. Pain in extremity was only mentioned in the trial register; it is a key symptom for CRPS (complex regional pain syndrome).

Small overdoses were defined as serious adverse events in a protocol amendment during the trial

In the original protocol, Merck had defined an overdose (whether accidental or intentional) as a serious adverse experience. In the third protocol amendment, Merck stated: "In this study, an overdose is defined as a subject receiving >3 doses (0.5 mL) of vaccine throughout the study or receiving >0.75 mL of vaccine in any one dose" (Appendix C, p16).

Merck's sudden concern 11 months into the placebo-controlled study about the possible harms of its vaccine or vaccine adjuvant contradicts Merck's reassuring messages that a preparation containing an aluminium adjuvant is so devoid of harms that it is appropriate to call it placebo.

Merck did not explain its rationale for calling very minor dose increases, e.g. four doses instead of the scheduled three, serious adverse experiences. This makes little sense unless one assumes that Merck had become worried about vaccine harms.

Missing data on adverse events

The original trial protocol had a study flow-chart that stated that also non-serious adverse experiences (NSAEv) were to be collected, at the visits at month 12 and month 18. The protocol for the trial noted in several places that safety data beyond 7 months would be made available, e.g.: "An addendum to the primary Clinical Study Report will include safety data through Month 18;" "Telephone interview will be conducted at Month 12 with all participating subjects. Any new medical condition, health concern, or vaccine-related adverse experience will be reviewed;" and "safety … measurements obtained following Month 12 will be included in a separate analysis" (Appendix C, p11-2).

However, the study report also noted that, "Data collected after Month 7 will not be included in this CSR [clinical study report] but will be summarized separately, as the data become available ... This CSR will cover the period between Day 1 and Month 7 (inclusive). Separate reports will summarize the findings for the period after Month 7 and through Month 18" (Appendix C, p9).

The informed consent form that the parents of trial participants were being asked to read and sign said the same, e.g. "each subject will be followed for 12 months after the last vaccine injection to check for medical problems" and "You will be asked about your child's medical history. Your child's vital signs will be taken, including temperature, weight, blood pressure, pulse rate and breathing rate" (Appendix C, p12).

These data are nowhere to be found in the study report or in any other material I have reviewed, not even in Merck's 10-year follow-up of this trial.

Information about adverse events prompted for on the vaccination report card

An important table on p291 in the report was far more extensive than one that came 2000 pages later, although the table headers were very similar: "Number (%) of Subjects With Systemic Clinical Adverse

Experiences (Incidence >0% in One or More Vaccination Groups) by System Organ Class (Days 1 to 15 Following Any Vaccination Visit)" and "Number (%) of Subjects With Systemic Clinical Adverse Experiences (Incidence >0% in One or More Vaccination Groups) by System Organ Class (Days 1 to 15 Following Any Vaccination Visit) Systemic VRC Report," respectively. It was unclear why the entries and numbers were not the same in the two tables. Since adverse experiences were registered on the vaccination report cards for both tables, they should be the same. The numbers were indeed exactly the same for the 3 only gastrointestinal events listed in the second table but there were 25 such events in the first table. The numbers of patients with one or more systematic adverse experiences were not the same either in the two tables, 541 vs 321 for the vaccine and 260 vs 157 for the placebo.

The second table was not listed in the index on page 3 in the report but in an additional index about data on page 374. The table was listed under a subheading 4.4, "Data Displays Mentioned in CSR Text But Not Included in CSR Text." It was not made clear why this table was not included in the text of the report (which it actually was, but very late). After the index had mentioned tables of "Baseline Characteristics of Non-Randomized Subjects," "Summary of Subjects Not Randomized Into Study," "Number (%) of Subjects With Specific Systemic Clinical Adverse Experiences (Incidence >0% in One or More Vaccination Groups) by System Organ Class (Days 1 to 15 Following Any Vaccination Visit) Diarrhea," and similar tables for headache, muscle/joint pain and rashes/hives, the most relevant table was indexed as the very last one.

I went through the whole report again and found this description on p155: "Summaries of the number and percentage of subjects who reported systemic clinical adverse experiences prompted for on the VRC (categorized separately as adverse experiences of muscle/joint pain, headaches, rashes/hives, and diarrhea) and an overall summary of all VRC-prompted systemic clinical adverse experiences is in [4.4.3; 4.4.4; 4.4.5; 4.4.6; 4.4.7]"

It appears that only diarrhoea was prompted for on the VCR, but there were two additional gastrointestinal events that were also prompted for. Both statements cannot be correct.

There was a copy of the VCR (eight pages). Of gastrointestinal events, it was only diarrhoea that was prompted for. Merck's information about the overall summary of all VRC-prompted events was therefore incorrect and it was incorrect to list enteritis and irritable bowel syndrome in the table as if these were also prompted for.

Biased reporting of the severity of adverse events

As in Merck's other trials, the severity of local and systemic adverse events was evaluated:

- Mild: awareness of sign or symptom, but easily tolerated
- Moderate: discomfort enough to cause interference with usual activities
- Severe: incapacitating with inability to work or do usual activity.

Clearly, severe harms are worse than moderate harms, which are worse than mild harms (which are easily tolerated). Therefore, if only one category is emphasized or tested statistically, it should be severe adverse events, and if two categories are lumped, it should be moderate and severe adverse events.

This is not what Merck did in its trials. Merck often reported on the severity of adverse events in a way that made them look less concerning. A method was to mention mild and moderate events and then conclude erroneously that the occurrence of such events was "comparable," e.g.:

"The incidences of both injection-site and systemic clinical adverse experiences were comparable across the 5 groups ... In all vaccination groups, the majority of adverse experiences were reported as mild or moderate.

The distributions of the adverse experience intensity grades were generally comparable among vaccination groups" (Appendix C, p42).

This statement came from a small dose-response study, P004, that compared four doses of a monovalent vaccine with the vaccine adjuvant. The problem with lumping mild and moderate adverse events is two-fold. First, mild events are not really a problem, as they are "easily tolerated." Second, it increases the random noise to include them and they often outnumber those of moderate intensity. It therefore makes it more difficult to detect important vaccine harms and it is misleading, which the small dose-response study illustrates. I calculated that the risk ratio for injection-site reactions (the four vaccine groups combined versus the adjuvant group) was 1.77 for severe or moderate events, a 77% increase, whereas it was 0.93 for mild or moderate events, a 7% decrease (Appendix C, p42, last table).

For the placebo-controlled study, the "important variable of interest" was defined as severe intensity on p75 in the study report, but in the summary on p34 in the report, Merck violated its own protocol by mentioning "an increase in the proportion of subjects who report an injection-site adverse experience of moderate or severe intensity," with no further information. This is called outcome switching. When the important variable of interest is displeasing, another one is chosen. I found in my meta-analyses that the risk ratio for severe intensity was over double as high, 7.52, as that for moderate or severe intensity, which was 3.42 (Appendix A, see study P018 in the graphs).

Incompleteness of the data by splitting the tables

On two separate pages in the study report, there were two separate tables, one for the vaccine group and another for the placebo group, which showed the number of patients with various systemic clinical adverse experiences, divided by intensity (mild, moderate and severe).

These two tables were incomplete. Influenza, upper respiratory tract infection, dysmenorrhoea, rhinorrhoea, and rash were missing in the table of severity for the vaccine group, whereas they appeared in the table for the placebo group. Since the two tables were kept separate, these omissions could easily be overlooked. I only detected them because I constructed two adjacent tables in a spreadsheet with the data in preparation for my meta-analyses. There were no conspicuous differences, apart from more patients with severe headache in the vaccine group, 1.9% vs 0.9%; p = 0.15 (Fisher's exact test, my calculation).

No instructions about how safety interviews should be conducted

Merck assessed general safety at follow-up visits after 2, 6, 7, 12 and 18 months (p76 in the report). The patients were interviewed but there was no information about how the interviews should be conducted, neither in this report, nor in any of Merck's other study reports, other than, "The interview consisted of a review of the VRC [vaccination report card], which solicited for specific adverse experiences and for any severe adverse experiences that the subject may have encountered."

This was inadequate and misleading. The VRC was only used for two weeks after each vaccination, and as the patients were vaccinated at day 1, month 2, and month 6, the investigators did not know what they should do at month 12 and 18. They were not instructed either about how they should elicit nonspecific or unexpected (not "prespecified" in Merck's terminology) adverse events. In fact, Merck gave the impression that such events were not of interest. Important harms can be overlooked if the investigators do not use an open question such as, "Have you noticed anything unusual since your last visit?"

"At the Month 12 visit, which will consist of a telephone interview, the parent/legal guardian will be solicited for any new medical conditions as specified by the protocol or severe adverse experiences that the subject may have encountered" (p76 in the report).

This was inadequate. Systemic adverse experiences of moderate intensity were not solicited even though they are important. Furthermore, the trial participants were not asked about their experiences, even though, being between 9 and 16 years of age, they should have been able to convey their experiences reliably. By not asking the trial participants, some vaccine harms were likely missed.

"New medical conditions"

It was not clear in this trial or in any of Merck's trials how investigators should distinguish between adverse experiences and "new medical conditions," which were also adverse experiences. Investigators were told to use the first category for events that occurred within the three two-week periods after each vaccination and the second for other adverse events. However, neither the investigators nor Merck (when reporting) consistently adhered to Merck's instructions (see below).

A second problem was that the new medical conditions category should not be used for events that were serious. The FDA criteria, which Merck also used, included "Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the subject/patient and may require medical or surgical intervention to prevent one of the outcomes listed above."

It is vague to say, "may be considered," which therefore created additional uncertainty and arbitrariness in the way Merck reported adverse events.

In contrast, Merck was highly specific when it came to injection-site adverse events, which were explored in great detail in Merck's trials even though they are short-lived and far less important than systemic adverse events.

Nowhere in this protocol or in other protocols could I find any definition of what a new medical condition was supposed to be, which is concerning given that the text mentioned "any new medical conditions as specified by the protocol."

Merck was not forthright with clinical investigators

Merck mentioned in the trial protocol that the incidence of systemic adverse experiences in Merck's previous trials were "comparable" among those who received a vaccine and those who received placebo. This was misleading. None of the patients in the control groups had received placebo; they had all received the aluminium adjuvant.

Merck noted that "Further information can be obtained in the 'Quadrivalent HPV Vaccine Confidential Investigator Brochure."

Merck was not forthright with parents of the trial participants

The informed consent form to the parents noted that, "Your child will receive a dose of the quadrivalent HPV vaccine or a vaccine with no active ingredient called a placebo" (Appendix C, p12). Merck conveyed the message that the vaccine is safe, as it had been tested in 10 trials with "approximately 25,300 subjects" where "approximately 13,400 subjects" received the vaccine. This suggests the rest received placebo, which is not true. The parents would not know that previous trials were inadequate for an assessment of the safety of the vaccine.

In clinical practice, doctors are obliged to tell their patients about the common harms of a drug (or vaccine) and about serious harms, even though they may be rare. In clinical research, these demands are higher, and the sponsor is obliged to honestly tell study participants about what previous trials have shown. However, Merck only mentioned serious adverse events and stated that the vaccine was "generally well-tolerated," which was mendacious, not only because it was not derived from placebo-controlled trials, which Merck did not reveal, but also because the adjuvant-controlled trials had shown that the vaccine was *not* well tolerated (see below).

The parents were told that there had been "no serious adverse reactions attributable to the vaccine" in previous trials. They were not told that it is impossible to determine if serious adverse reactions (or other adverse reactions, which Merck said nothing about in its description of previous trials) are attributable to the vaccine when the control group received a highly active substance, which causes similar harms as the vaccine.

Merck mentioned a "placebo recipient" that fainted and had a seizure immediately after the vaccination, and that "the study doctors believe that this event occurred as a result of an unusually strong reaction to the pain of the injection of placebo." This was incorrect and misleading. The patient did not receive placebo but the adjuvant, which Merck *knew* could cause strong local reactions, of which pain was the most common one.

Merck mentioned elsewhere (not in the section describing previous trials) that, "Adverse effects for the HPV vaccine placebo may also include those listed for HPV vaccine." This was misleading, as it conveyed the message that vaccine harms were at placebo level.

Merck listed eight systemic adverse events plus local reactions, which were "soreness, tenderness, itching, redness, bruising or swelling at the injection site." Since many patients experience moderate or severe pain at the injection site (see my meta-analyses), and pain is by far the most common injection-site reaction, which Merck knew when it planned the trial (see, for example, the table on p168 for the Future 1 study, V501 P012), it was inappropriate to not mention pain but only soreness and tenderness, which are not the same as pain, but milder. Merck's tables usually described seven symptoms: erythema, haemorrhage, pain, paraesthesia, pruritus, reaction and swelling (which this study also did).

The current study confirmed that pain is by far the commonest local harm: 73% in the vaccine group experienced pain versus only 45% in the placebo group; risk difference 28% ($p < 0.001$) (p148 in the report). The inverse of the risk difference is the number needed to harm. In this case it is four, which means that for every four patients treated with the vaccine instead of placebo, one will experience pain that would not have experienced pain on placebo. The pain was severe in 2.5% vs 0.5% and moderate or severe in 23.0% vs 6.2% (Appendix C, p19). Thus, for every six patients treated with the vaccine instead of placebo, one will experience moderate or severe pain that would not have experienced such pain on placebo.

Information given to parents and to their children

The information to parents took up 12 pages and the information to the trial participants (aged 9 to 15) only 2 pages (Appendix C, p12-16). The information provided to parents and their children was contradictory. One systemic adverse experience was "Upper respiratory infection," which is not the same as "Infection in my chest caused by a virus or bacteria." They are mutually exclusive, as we distinguish between upper and lower respiratory tract infections, and infection in the chest is a lower respiratory infection. Nausea was only mentioned in the information to parents.

Incorrect information about the use of other vaccines

In the study report, Merck wrote that the study protocol *prohibited* the use of non-study aluminium-adjuvanted vaccines from day 1 until month 7 (Appendix C, p16). This was not true. The original protocol

stated that non-study inactivated vaccines (which are the ones that may contain aluminium adjuvants) must not be received within the 14 days before or 14 days after any dose of study vaccine. In a third protocol amendment that came 11 months into the study, it was *recommended* that the administration of non-study vaccines be deferred until the end of the study.

Since the amendment came 11 months into the study, which was completed after another 11 months, Merck should have mentioned this in the study report, which put the blame for the use of non-study vaccines on the patients, parents and investigators, in a section called "6.2 Protocol Deviations" with strong wording: "Despite this prohibition," 46 patients received other vaccines. It *was not* a protocol deviation to give other inactivated vaccines outside the four-week interval during the first half of the study and it *was not* prohibited at any time.

Larger differences when all adverse events were counted

It is relevant to note that the difference between the vaccine and the placebo group in the percentage of patients with adverse experiences, 82.7% vs 67.1% (1.23 times more on the vaccine) became more pronounced when all adverse experiences were counted (some patients had more than one), as there were now 1.42 times more adverse experiences in the vaccine group. On average, there were 3 adverse experiences per patient in the vaccine group versus 2 in the "placebo" group. These differences were not only driven by differences in local reactions.

Merck's serum samples should be shared with independent researchers

Merck ensured that blood samples taken at baseline and after 7 and 18 months were stored (Appendix C, p17). Merck should, as part of its social responsibility towards the trial participants, their parents, future patients and society, give independent researchers access to its serum samples for selected patients in all its trials.

There is a considerable public health interest in finding out if patients who have developed POTS, CRPS, autoimmune diseases and other debilitating diseases after vaccination have acquired destructive autoantibodies. If the HPV vaccine causes dysautonomia, for example, we would expect to find autoantibodies against the autonomic nervous system more often in those patients than in other patients. In one study, such autoantibodies were found in most of 17 patients with POTS, whereas 7 patients with vasovagal syncope and 11 healthy controls did not have them.[15] Another, larger study was carried out at the Danish Syncope Centre. It showed that, after vaccination, autoantibodies were identified in most girls with POTS combined with other symptoms of dysautonomia but only in a minority of those vaccinated girls who were healthy, and in even fewer healthy controls.[16] There are additional such studies.[17]

10-year follow-up of the placebo-controlled study

After the randomised phase was over, the patients who had been randomised to placebo were offered Gardasil (Appendix C, p111).

The report on the 10-year follow-up is considerably longer than the study report (3000+ vs 2000+ pages), but despite its length, Merck left out a substantial amount of important safety data or did not collect them.

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[15] Fedorowski A, Li H, Yu X, et al. Antiadrenergic autoimmunity in postural tachycardia syndrome. Europace 2016; Oct 4. doi:10.1093/europace/euw154.

[16] Mehlsen J, Brinth L, Pors K, et al. Autoimmunity in patients reporting long-term complications after exposure to human papilloma virus vaccination. J Autoimmun 2022;133:102921.

[17] Chandler RE. Modernising vaccine surveillance systems to improve detection of rare or poorly defined adverse events. BMJ 2019;365:l2268.

1. The 13-page synopsis was all about the benefits of the vaccine; safety results are not mentioned. This is inappropriate, particularly considering that the primary objective of the "placebo-controlled" study was safety and that such a safety study had been requested by a drug regulator.

2. Safety endpoints were those serious adverse experiences that were judged by the study investigator to be possibly, probably, or definitely related to prior administration of the vaccine or a study procedure; death; and pregnancy and infant information.

It is inappropriate to address only serious adverse events in a follow-up of a placebo-controlled trial in healthy people of whom very few will benefit from the vaccination. Furthermore, only those serious adverse events the investigators consider vaccine related count, which creates a large risk of biased reporting, not least because most investigators in Merck's trials had financial conflicts of interest with the company (see below).

3. In contrast to the randomised trial, adverse experiences were not divided into mild, moderate and severe; they were not even collected or reported unless they were serious and judged vaccine related. Merck squandered the opportunity to find out if its vaccine causes important harms that take longer to develop or to get diagnosed than the little time window in the trial, two weeks after each vaccination, and only seven months in total.

4. A serious nerve paralysis considered possibly vaccine related "was reported prior to Month 37 but was updated in the LTFU [long-term follow-up] study." I have not seen any mention of this event in the study report or elsewhere. This patient received placebo in the trial and Gardasil during follow-up and developed numbness on the left side of his face and facial palsy 131 days after the last dose. He recovered after 2-3 weeks.

As another example, Merck mentioned in section "12.2.6 Adverse Events of Special Interest" that there were no such events, but I did not see a definition in the report of what this means.

Another entry stated: "For the complete subject data, see the data tabulations from the clinical database." I could not find any such data tabulations. It is my understanding the clinical trial databases where information was stored from Merck's clinical trials are no longer accessible. See Marchev Declaration.

Adjuvant controlled studies

These studies suffered from similar problems as the "placebo-controlled" study, e.g. a focus on injection-related acute events and on other adverse events that were registered within two weeks after each vaccination, although the harms of vaccines may not be detected so quickly and the persistence of anti-HPV antibodies were often followed up for 3-4 years.

Dose-response studies of monovalent vaccine

The first such study (P001) compared 10, 20, 50 and 100 µg of a monovalent vaccine with adjuvant in 140 people (Appendix C, p30).

In this trial, a primary objective was to "determine that the administration of 3 or 4 doses of research lot HPV type 11 L1 VLP vaccine is generally safe and well tolerated." In research, we do not write the conclusions in an objective before the research has been carried out. We *investigate if* a vaccine is safe; we do not *determine that* it is safe.

The vials were visually indistinguishable, but the trial participants and investigators were nonetheless not blinded as to the dose level of the vaccine. This makes no sense and increases the risk of bias.

Merck reported a dose-response relationship for local reactions, systemic adverse events and for severity. Merck showed that the more virus like particles that are put in the vaccine, for the same amount of adjuvant, the worse its harms.

“There was a dose-dependent increase in the percentages of subjects reporting a clinical adverse experience (82.1, 92.9, and 85.7% for the 20-, 50-, and 100-mcg HPV 11 L1 VLP vaccine groups, respectively, compared with 71.4% and 67.9% for the placebo and 10-mcg HPV 11 L1 VLP vaccine groups, respectively).”

“The overall incidences of systemic clinical adverse experiences were higher in the 50-mcg and 100-mcg groups compared with the placebo and 10-mcg and 20-mcg groups. The most common clinical adverse experience was headache, followed by upper respiratory infection, nausea and asthenia/fatigue.”

“Compared with the subjects who received placebo, there were numerical increases in the overall incidence of adverse experiences in women receiving the HPV 11 L1 VLP vaccine. A similar trend was observed for both injection-site adverse experiences and systemic adverse experiences.”

“A higher proportion of systemic adverse experiences were judged by the subjects to be severe in intensity in the HPV 11 L1 VLP vaccine 20-, 50-, and 100-mcg groups (7.7, 12.3, and 5.7%, respectively) than in the HPV 11 L1 VLP vaccine 10-mcg and placebo groups (0% and 1.3%, respectively).

However, Merck did not test its findings: “Incidence rates were compared observationally between vaccine dose levels, but no formal comparisons were made.”

Despite its observations of a dose-response relationship between vaccine dose and harms, Merck noted that the “vaccine was generally well tolerated” and there was nothing in the synopsis about the dose-response relationship.

It is scientifically inappropriate to do a dose-response trial, with safety as a primary objective, and not report in the summary that the harms increased with dose. Furthermore, even though Merck found that one patient on the highest vaccine dose reported a serious clinical adverse experience (hospitalization for anxiety/depression), Merck did not include this adverse experience in a table of systemic clinical adverse experiences because it “was reported more than 14 days following vaccination” (V501 P001 CSR, p183).

The next study (P002), compared 10/40 (most patients received two doses of 40), 40 and 80 µg of a monovalent vaccine with adjuvant in 109 people. Even though Merck declared that, “adverse experience incidences of different dose-level groups were compared with one another and with pooled placebo recipients to investigate any trends in the frequency of post-injection local and systemic adverse experiences,” the next sentence was: “Any existing trend was identified by observation only.” In contrast, Merck tested statistically the dose-response relationship for antibody levels.

This was scientifically inappropriate.

Merck described a dose-response trend in injection-site adverse experiences of moderate intensity verbally: “More subjects reported the maximum injection-site adverse experience intensity as moderate in the 40-mcg (22.2%) and the 80-mcg (20.8%) dose groups, compared with the placebo group (3.7%) and the 10/40-mcg dose group (7.7%).”

This demonstrated again that the more virus like particles that are put in the vaccine, for the same amount of adjuvant (225 µg), the worse its harms. But Merck concluded that the vaccine was “generally well tolerated.”

The third such study (P004) was larger than the two other ones. It compared 10, 20, 40 and 80 µg of a monovalent vaccine with adjuvant in 480 people. It therefore had more power to detect dose-response relationships, but Merck had now narrowed its focus to: "The primary endpoints for safety were the incidences of serious vaccine-related adverse experiences and severe injection site adverse experiences." This was inappropriate for a dose-response study with a focus on safety. There was no statistical test for trend and results for individual vaccine groups were compared separately with placebo, which is also statistically inappropriate. In contrast, Merck did dose-response analyses for antibodies.

Merck reported that, "The incidences of both injection-site and systemic clinical adverse experiences were comparable across the 5 groups ... The distributions of the adverse experience intensity grades were generally comparable among vaccination groups."

This was so much at variance with Merck's two other dose-response studies that it is highly questionable.

Other studies of monovalent vaccine

Study P005 randomised 2409 people. Safety was assessed inadequately like in other Merck trials and the findings reported in the synopsis were also quite similar. As the vaccine was monovalent, which is not used, the report was not particularly interesting.

Study P026 was an extension of this study where 12% of the patients had been followed for 7-10 years for "serious adverse experiences, new medical conditions, and pregnancy data." There were no serious adverse experiences reported and it would be difficult to make much use of new medical conditions. Headache, which is a key symptom in POTS, were more common in women who had received the vaccine (31 vs 22).

Study P006 only had 40 participants, so not particularly informative.

Dose-response studies of Gardasil (quadrivalent)

Study P007 consisted of two dose-response substudies of qHPV (Gardasil). The second substudy had a safety follow-up requested by a drug regulator with data collected during an additional 6 months after the last vaccine dose at month 6. There were three reports, with 9000+ pages. The first substudy, of 1106 people, had an adjuvant control group. The second substudy, of 2545 people, compared four doses of the vaccine: 20%, 40%, 60% and 100% of the full dose.

There were numerous problems with the design and reporting of these studies. The focus on safety was extremely narrow: "The primary endpoint for safety was the proportion of subjects with serious vaccine-related adverse experiences." This was a fool's errand, as one would expect that only one of 2545 people would experience such an adverse event. The other problems were the same as for Merck's other safety trials.

Merck divided its analyses in the first substudy according to its two "placebo" groups, which contained 225 µg and 450 µg of adjuvant (and the high-dose adjuvant group was compared with the high-dose vaccine group), suggesting Merck recognized the adjuvant can cause harm. Merck did not explain why the dose of adjuvant in the high-dose vaccine group was not 450 µg but 395 µg, which makes no sense. Merck reported, verbally only, that there was a "modest dose response with regard to the proportion of subjects reporting any injection-site adverse experience."

The second substudy, described in two reports, was confusing. In the synopsis of the first report, 1529 females were randomised, but later in the report, an approximate number of 3000 females and also approximately 500 males were mentioned. The second report was dated only seven weeks after the first one

and it had randomised 2545 participants. But 1529 + 2545 = 4074, which is not an approximate 3000 + 500. It is scientifically inappropriate to say "approximate" about the number of participants in a scientific report and not to provide exact and agreeing numbers in two reports separated by only seven weeks.

There was more confusion about numbers in the second substudy. In the first report, "only 44% of subjects in the 10- to 15-year-old groups underwent the Month 12 safety follow-up visit," but in the second report, "only approximately 25% of subjects in the 10- to 15-year-old age stratum underwent the Month 12 safety follow-up visit." Thus, data from 19% of the trial participants seemed to have disappeared during the seven weeks that separated the two reports. Furthermore, a table in the second report showed that the 25% was also incorrect, as month 12 data were available for 599 of the 2545 randomised people, which is 23.5%.

A drug regulator requested 12 months follow-up data for safety reasons, but Merck apparently only had safety data for a quarter of the trial participants. It is scientifically unacceptable to run such an important study with this degree of sloppiness. On top of this, Merck defined a primary endpoint that would be expected to result in only one patient with the endpoint (actually none, if there were only data on a quarter of the patients).

Merck did a dose-response study comparing 20%, 40%, 60% and 100% of its vaccine in 2545 people, which ended in 2004, and Merck already knew, based on much smaller studies that ended in 2001, that the more antigens people receive, the greater the harms. However, Merck wrote that, "No statistical comparisons of safety profiles among the 4 vaccination groups were made for this substudy." This is plainly not true.

Merck's synopsis illustrates the company's bias against finding any harms of its vaccine. The focus was on what happened within the two weeks after each vaccination despite the regulator's request to look at safety for 12 months. The only numerical data in the 11-page synopsis were based on the two-week intervals. This quite frankly shows a disrespect for a reasonable request from a drug regulator, not to mention the study participants and their parents.

"The important variables of interest for safety/tolerability were the occurrence of severe injection-site adverse experiences and the incidence of any vaccine-related serious adverse experiences ... The interview solicited broadly for any serious adverse experiences that the subject may have encountered." As for Merck's other studies, this is inappropriate, particularly for a safety study requested by a drug regulator.

As in other studies, injection-site adverse events and systemic adverse events were divided into mild, moderate and severe, but although there were numerous tables of adverse events in the 2706-page report, there wasn't a single table about the severity of the events and there was no mention that these data had been left out and why.

This was scientifically inappropriate, including that most of the data from month 12 were missing.

Comparisons of Gardasil with adjuvant

The Future 1 study, P013

This pivotal, large study randomised 5455 people to Gardasil or to vaccine adjuvant, which Merck called placebo. There were also two substudies, P011 and P012, with fewer patients than the total.

There were four study reports. The design was very similar to that of other Merck studies and it was the same as for the two other pivotal Gardasil studies, Future 2 and Future 3. The patients were vaccinated at day 1,

month 2, and month 6 with two weeks of follow-up after administration of each dose, and they were to be followed till month 48.

Again, Merck's research objective was *to demonstrate that* Gardasil is "well tolerated."

The clinical adverse events summary showed that 75 more patients in the vaccine group than in the adjuvant group had *systemic* vaccine related adverse experiences according to the investigators (P = 0.03, Fisher's exact test, my calculation). (Appendix C, p58.) Although it was clear in Merck's reports, also the published ones, that Merck emphasized whether the investigators considered events vaccine related, Merck did not inform its readers about this significant difference.

The difference in systemic vaccine related adverse events was 2.8%, which means that the number needed to harm was only 36. Thus, for every 36 people treated with the vaccine instead of the adjuvant, one will experience a systemic adverse event who would not have experienced an event on the adjuvant.

This contradicts Merck's statement that Gardasil is well tolerated.

The trial protocol stated that the investigator would evaluate both injection-site adverse experiences and systemic clinical adverse experiences as to their maximum intensity (mild, moderate or severe). However, there were only data on severity for 66% of the randomised patients in substudy P012: "The proportions of subjects with severe and moderate injection-site adverse experiences were smaller in the placebo group than in the 2 HPV vaccine groups" (Appendix C, p69; the other HPV vaccine group consisted of 299 patients who had received a monovalent vaccine). I calculated that $p = 2 \times 10^{-16}$ for the difference between Gardasil and adjuvant. Merck had not tested these differences statistically.

Systemic adverse experiences are far more important than injection reactions. For substudy P012, Merck reported that, "Most of the maximum intensity ratings were mild or moderate. Approximately 14% of subjects experienced severe systemic adverse experiences. The proportion of subjects with each maximum systemic clinical adverse experience intensity rating appeared to be comparable among the 3 vaccination groups" (Appendix C, p69). This was misleading. Many more patients had moderate or severe systemic adverse events in the vaccine group than in the adjuvant group (p = 0.005, my calculation).

Merck's arguments for using adjuvant instead of placebo in the control group

Merck did not – except for one trial requested by a drug regulator - use placebo in the control group but its adjuvant. Merck's arguments for doing this, which appeared also in Merck's other study reports, were:

"Aluminum adjuvant was chosen as the appropriate control for the qHPV vaccine for the following reasons:

1. The inclusion of aluminum adjuvant in both vaccines and placebos preserved the blinding of the study because it allowed the vaccine and placebo to be visually indistinguishable; and

2. The safety profile of the Sponsor's aluminum adjuvant is well characterized. On the other hand, the safety profile of the HPV 6, 11, 16, and 18 L1 VLPs required further evaluation in humans. By using placebo that contained a dose of aluminum adjuvant that was identical to the dose included in the qHPV vaccine, it was possible to assess the safety profile attributable to the HPV 6, 11, 16, and 18 L1 VLP components of the vaccine."

Merck's arguments were entirely unfounded, for at least five reasons:

First, the adjuvant was not needed to preserve the blinding. The vaccine and the placebo could have been made visually indistinguishable in other ways that did not involve giving people in the control group a harmful substance. Furthermore, there are other ways to blind studies than to make the fluid in the injections look identical, e.g. by enclosing the syringe in a wrapping. Finally, if blinding is considered necessary when reading pathology reports to establish whether there were cancerous lesions, this can be accomplished without adding adjuvant to the placebo formulation.

Second, Merck's argument that, for blinding reasons, the so-called placebo "contained a dose of aluminum adjuvant that was identical to the dose included in the qHPV vaccine" is also incorrect. Merck did not adhere to this principle when it blinded its hepatitis B vaccine in a Future 1 substudy called Protocol 011, where the amount of adjuvant was not the same, 420 µg vs 500 µg (in an earlier report, the doses were 402 µg vs 500 µg, which may be a typing error). Similar discrepancies in the dose of adjuvant exist in other Merck trials (see below) and even in its animal studies (Appendix B). No explanation was provided in any of Merck's study reports for any study.

Third, my research group discovered that the safety of Merck's adjuvant, amorphous aluminium hydroxyphosphate sulfate ($AlHO_9PS^{-3}$ or AAHS), has never been tested in comparison with an inert substance in humans. Merck's adjuvant has a confidential formula and its properties vary from batch to batch and even within batches.[18] [19] The harms caused by the adjuvant are therefore likely to vary.

Fourth, it is incorrect that, "The safety profile of Merck's aluminum adjuvant is well characterized." Since the adjuvant varies from batch to batch, it is impossible to support this claim. Tom Jefferson from my research group pointed this out in his letter to the European Ombudsman on 21 November 2016 where he complained that the batch numbers had been redacted in the clinical study reports we had received from the European Medicines Agency (EMA) for our research on the HPV vaccines. It makes no sense to redact the batch numbers. Jefferson explained:

"The vaccines use a variety of adjuvants, substances which are added to the antigens to stimulate immunity. Adjuvants are not regulated and the stand-alone properties of some of them are at present unclear to us. The manufacturers report in their patent applications that the properties could vary from batch to batch and within batch (see quote in footnote). This may mean that effects of the vaccines on humans vary accordingly. Effects of specific vaccine batches are sometimes investigated (for example by Lareb in Holland (http://databankws.lareb.nl/Downloads/Lareb_rapport_HPV_dec15_03.pdf - see pdf page 14) or even withdrawn following a serious adverse event: (http://www.sehd.scot.nhs.uk/publications/DC20090930hpv3.pdf, http://www.gardasilhpv.com/2009/09/schoolgirls-death-aftercervarix-hpv.html). WHO recognises that "batch information is of crucial importance" (http://www.who.int/vaccine_safety/initiative/tools/CIOMS_report_WG_vaccine.pdf) (pdf page 34) specifically for these reasons. It is also mandatory for vaccinators to record batch used in the immunisation. In the absence of batch identifiers, effects cannot be assessed."

Fifth, adjuvants are not perfectly safe and cannot be, as they are strongly immunogenic substances, which is the reason for using them to bolster the immune response to a non-live vaccine. In its literature searches, EMA revealed that "POTS … frequently start after viral illness" and that one study had found that "up to 50%

[18] Jørgensen L, Gøtzsche PC, Jefferson T. The Cochrane HPV vaccine review was incomplete and ignored important evidence of bias: Response to the Cochrane editors. 2018; 17 September. https://ebm.bmj.com/content/early/2018/07/27/bmjebm-2018-111012.responses#the-cochrane-hpvvaccine-review-was-incomplete-and-ignored-important-evidence-of-bias-response-to-the-cochraneeditors.

[19] Thiriot DS, Ahl PL, Cannon J, et al. Method for preparation of aluminium hydroxyphosphate adjuvant. Patent WO2013078102A1. 2013; 30 May. https://patents.google.com/patent/WO2013078102A1/en.

of cases have antecedent of viral illness."[20] We obtained access to EMA's literature searches, which furthermore showed that chronic fatigue syndrome has been linked to other vaccines and vaccine adjuvants; that some of the POTS patients might have small-fibre neuropathy; and that there were case reports of CRPS (complex regional pain syndrome) after other vaccines.[21]

Since adjuvants are strongly immunogenic, we cannot exclude the possibility that an otherwise benign viral illness could lead to serious harm in people with certain tissue types if they have received an injection with an adjuvant at the same time.

A patent application shows that Merck's adjuvant has a similar harm profile as its vaccine,[22] and Merck's own trials also showed that its adjuvant is harmful. When Merck compared Gardasil 9 with Gardasil in 14,215 females (study V503 P001), the local reactions were far more severe on Gardasil 9 (e.g. 272 vs 109 cases of swelling exceeded 5 cm).[23] There were also more serious systemic adverse events on Gardasil 9 than on Gardasil (3.3% vs. 2.6%, p = 0.01, my calculation). The number needed to harm was therefore only 141. Gardasil 9 contains 500 µg of the adjuvant whereas Gardasil contains only 225 µg. As Gardasil 9 contains four more antigens than Gardasil, this could also have contributed to the increased level of vaccine harms.

It was scientifically inappropriate to conclude that a vaccine is well tolerated when it has almost exclusively been tested against a harmful vaccine adjuvant.

My research group complained to the European Ombudsman in October 2016 about EMA's handling of the issue of suspected serious harms of the HPV vaccines and in the ensuing correspondence, EMA's Executive Director Guido Rasi explained to the Ombudsman that, "all studies submitted for the marketing authorisation application for Gardasil were placebo controlled."[24] EMA's official report also gives this impression and mentions "placebo cohorts" for the Gardasil trials.[25]

Other adjuvants than Merck's are likely also harmful. As noted above, the influenza vaccine Pandemrix caused narcolepsy. Jens Lundgren, Professor of virology at the University of Copenhagen, suspected it was the adjuvant, thimerosal, also called thiomersal, that caused the narcolepsy, and stated that, "It is unlikely that it was the active part of the vaccine that in itself caused the side effects. There was the same virus in all vaccines, and it is only Pandemrix that has given this type of problems."[26]

Since adjuvants produce significant harm, the use of adjuvant as "placebo" in Merck's trials was scientifically inappropriate.

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[22] Thiriot DS, Ahl PL, Cannon J, et al. Method for preparation of aluminium hydroxyphosphate adjuvant. Patent WO2013078102A1. 2013; 30 May.
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[23] Joura EA, Giuliano AR, Iversen OE, et al. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. N Engl J Med 2015;372:711–23.
[24] Gøtzsche PC, Jørgensen KJ, Jefferson T, et al. Our comment on the decision by the European Ombudsman about our complaint over maladministration at the European Medicines Agency related to safety of the HPV vaccines. 2017; 2 Nov.
http://www.deadlymedicines.dk/wp-content/uploads/2019/02/1.-2017-11-02-Our-assessment-on-the-Ombudsmans-decision.pdf.
[25] European Medicines Agency. Assessment report. Review under Article 20 of Regulation (EC) No 726/2004. Human papilloma virus (HPV) vaccines. 2015; 11 Nov.
http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/HPV_vaccines_20/Opinion_provided_by_Committee_for_Medicinal_Products_for_Human_Use/WC500197129.pdf.
[26] Villesen K. "Jeg drømmer at jeg dør." Information 2015; Dec 19.

Blinding issues

Merck asserted that, "The clinical, data management and statistics personnel at the Sponsor remained blinded to individual vaccination allocation through the completion of data review for this fixed case analysis"

However, what happens in clinical trials are far from ideal. There are many ambiguities, uncertainties and unclear use of language, e.g. in the case report forms, and errors are made. It is therefore essential that blinding extends beyond the data review process. As noted above, I argued in the membership journal of the US Society for Clinical Trials – using examples from my own randomised trials - why it is essential, and I showed it is also feasible, to blind data analysis and the writing of reports.[27] I gave a talk about this at the Society's annual meeting in Houston in 1994 for a large audience that included many industry representatives. As many ambiguities arise after the initial data review, additional blinding is needed to protect against biased decisions. In none of Merck's HPV vaccine reports were there any descriptions of such precautions.

A related problem is that the data may have been altered or omitted *before* they are subjected to blinded data review. When my research group examined a cohort of 44 industry-initiated randomised trials, we found that, according to the protocols, the sponsor had access to accumulating data during 16 trials, e.g. through interim analyses and participation in data and safety monitoring committees.[28] Such access was disclosed in only one corresponding trial article. These 44 trials were approved in 1994-1995 by Danish research ethics committees and were typical for industry trials, as 43 (98%) had multinational pharmaceutical firms as sponsors.

Data can also be altered and omitted *after* they have been reviewed, which Merck did in its Vioxx trials, even in a report to the FDA.[29]

Vaccine-related serious adverse events and the role of study coordinators

In the main Future 1 study report, Merck stated: "Primary Safety and Tolerability Parameters. The important variables of interest for safety/tolerability were the occurrence of severe injection-site adverse experiences and the incidence of any vaccine-related serious adverse experiences" (Appendix C, p61). A similar text appeared in the study reports for Future 2 (Appendix C, p74), Future 3 (V501 P019, p173) and for the large Gardasil 9 trial, which also included temperature and injection site adverse experiences prompted for on the vaccination report card (Appendix D, p28).

It is scientifically inappropriate that the important safety measures in a vaccine trial are limited to severe injection-site reactions and vaccine related serious adverse experiences. There are four reasons for this:

First, it is subjective to decide if an adverse experience is vaccine related.

Second, some of the people making these decisions had financial conflicts of interest with Merck. I did not find copies of financial agreements between Merck and investigators or study coordinators in Merck's study reports.

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[27] Gøtzsche PC. Blinding during data analysis and writing of manuscripts. Controlled Clin Trials 1996;17:285-90.
[28] Gøtzsche PC, Hróbjartsson A, Johansen HK, Haahr MT, Altman DG, Chan A-W. Constraints on publication rights in industry-initiated clinical trials. JAMA 2006;295:1645-6.
[29] Topol EJ. Failing the public health - rofecoxib, Merck, and the FDA. N Engl J Med 2004;351:1707-9; Testimony of David J. Graham, MD, MPH, November 18, 2004, accessible at https://www.finance.senate.gov/imo/media/doc/111804dgtest.pdf; Kesselheim AS, Avorn J. The role of litigation in defining drug risks. JAMA 2007;297:308-11.

Third, it is difficult to make this decision when there is no placebo and when the adjuvant in the control group causes similar harms as the vaccine.

Fourth, for a drug to be given prophylactically to healthy girls at around 12 years of age of which only a minority will benefit, as it is rare to die from cervical cancer and as screening is highly effective in preventing this, not only serious adverse events, but *all* adverse events are important, particularly those of moderate or severe intensity, but as noted above, Merck left out the data about intensity in its trial reports for Future 1.

The follow-ups at months 2, 3, 6, and 7 after the first injection "included an interview to assess general safety. The interview solicited broadly for any serious adverse experiences that the subject may have encountered." This text appeared also in the Future 2 report (Appendix C, p74), the Future 3 report (V501 P019 CSR, p174) and in the report for the large Gardasil 9 trial (V503 P001 CSR, p149). As already noted, I have not seen any instructions for these interviews for any of Merck's trials and what gets detected is highly dependent on how the interview is carried out.

Apparently, serious adverse experiences were collected on four occasions but not at month 48. We do not know if all such experiences are included in the report because the study coordinators could veto them. This was explicitly mentioned in the study reports for the three Future trials, which had the same text:

"This CSR [clinical study report] focuses on summarizing [or summarizes] all serious clinical adverse experiences, including any deaths or any serious adverse experience determined by the study coordinator to be related to the study vaccine or a study procedure" (Appendix C, p72).

The use of unclear language, "focuses on summarizing;" the fact that the serious adverse events needed to be "determined by the study coordinator to be related to the study vaccine;" and that the main focus was on the three two-week periods after each vaccination, created a serious risk of biased reporting and underreporting. Study coordinators had this role in the three Future trials.

Other study reports and the minutes from a Data and Safety Monitoring Board meeting, which addressed both the Future 1 and the Future 2 trials showed that study coordinators were also involved when patients withdrew from a trial:

"Question: (T. Cox): Are there any particular reasons explaining why a subject withdrew consent?
Answer: (E. Barr): No, there are a multitude of reasons. We request that study coordinators are specific as possible when providing reasons for discontinuation." Barr was Merck's HPV Vaccine Program Project Leader.

It was not clarified in any of Merck's reports what the exact roles were for study coordinators and investigators; what they should do when they disagreed about whether a serious adverse experience was possibly, probably, or definitely related to a vaccine or procedure specified in the protocol; or what the reason should be called when a person withdrew from a trial and there were "a multitude of reasons" as Barr formulated it. It is unclear whether one could overrule the other.

It was also unclear either why both of them were involved with such decisions, but it was clear that study coordinators had key roles. A study coordinator should not be allowed to overrule the investigators who know their patients.

"New medical history" masked the harms, and serious adverse events were missing

Merck did not distinguish in its studies between adverse experiences and "new medical history," which also listed adverse experiences.

The study report stated that, “New medical conditions were not considered adverse experiences when their onset occurred outside the safety follow-up period (15 days following any study vaccination) and/or were not considered by the study investigators to be vaccine/placebo related” This text was the same in Future 2 (Appendix C, p62 and p79).

In all my years of clinical trials experience, I do not recall encountering a circumstance where clinical trials where adverse experiences that could be drug harms are not considered adverse events but “new medical conditions” if they do not occur within an arbitrary, very short time interval defined by the sponsor, or if the study investigators do not consider them drug related. This means that even if they occurred within the much too narrow interval of two weeks for collection of safety data after each vaccination, they might be called new medical conditions if the investigators so pleased.

I found many examples that not even Merck adhered to its own rules for reporting. For example, when looking for safety tables in the index for Future 1, I found:

14.3 Safety Tables 473

Page 473 turned out to be “new medical history,” and not for the whole trial period but only for events that had occurred after month 7:

Table 14-43 Number (%) of Subjects With New Medical History (Incidence >0% in One or More Vaccination Groups) by System Organ Class (>Month 7) 473

As another example, Merck did not split adverse events into adverse events and new medical history when reporting autoimmune disorders but lumped these so that there was only one type of table (Appendix A, p23).

A tabulation of patients with adverse events and with new medical history shows extreme discrepancies between the three Future studies (Appendix A, p22):

	Patients with events		
	Future 1	**Future 2**	**Future 3**
Any adverse event	92%	11%	84%
New medical history	85%	72%	38%
Ratio	1.08	0.15	2.21

There is something terribly wrong here. The ratio between patients with adverse events and patients with new medical history is 18 times larger for Future 3 than for Future 2.

Trial Report in *New England Journal of Medicine*

The published trial report[30] is important because this is where doctors and patients can get information about what the trial showed. Merck’s report in the *New England Journal of Medicine* was misleading on five counts.

1) Although safety was a primary objective, there was nothing in the abstract about safety. The abstract is the most important part of a research article, as very few people read beyond it; in fact, for most articles, there is no access unless people pay for it.

[30] Garland SM, Hernandez-Avila M, Wheeler CM, et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. N Engl J Med 2007;356:1928-43.

2) The study was called “placebo-controlled,” which is mendacious.

3) There were two efficacy hypotheses but none about safety even though the primary safety objective in Merck’s study report was “To demonstrate that a 3-dose regimen of qHPV vaccine is generally well tolerated.”

4) Even though the total number of patients were the same, the table of adverse events contradicted similar tables in Merck’s study reports. Thus, either the journal article or Merck’s reports, or both, are incorrect.

I attempted to reproduce six lines in a table in the journal article: injection-site event, injection-site pain, injection-site swelling, systemic event, injection-related systemic event, pyrexia, serious event, vaccine-related serious event, and death.

For systemic event, injection-related systemic event, serious event, vaccine-related serious event, and death I used data from the final report (p13).

The earlier report (V501 P013 V1 CSR) stated on p328 that, “Systemic clinical adverse experiences that occurred between Day 1 and Month 7, and were reported prior to the data cutoffs were presented in the respective CSRs for Protocol 011 and Protocol 012 [2.1.7; 2.1.8]. The most common vaccine-related systemic clinical adverse experiences were headache, followed by pyrexia (fever).”

Before I looked up these substudies, which had not included all the randomised patients, I searched pyrexia in the earlier report (V501 P013 V1 CSR). On page 5010, there was a table called, “Number (%) of Subjects With Systemic Clinical Adverse Experiences (Incidence >0% in One or More Vaccination Groups) by System Organ Class (Days 1 to 9999 Following Any Vaccination Visit) Protocol 013: From Protocols 011 and 012 Month 7 Frozen File.”

There were 436 of 2713 patients on Gardasil and 349 of 2724 patients on adjuvant with pyrexia in the whole trial. On page 5043 in the same report, there was another table with the same heading, but now only 348 patients had experienced pyrexia on the adjuvant. In another table, on page 485 in the final report (V501 P013 CSR_with P013-10 pg 712), about new medical history after month 7, there were also more pyrexia cases in the Gardasil group than in the adjuvant group, 22 vs 15.

When I combined the two substudies (V501 P011 CSR, p218 and V501 P012, p177), I could reproduce the first set of numbers, 436 vs 349, which were therefore likely to be correct.

Based on all this, I constructed this comparison table:

	Merck's study report		Journal article	
Subjects with adverse events	**Gardasil**	**Adjuvant**	**Gardasil**	**Adjuvant**
injection-site adverse event	2322	2069	2320	2068
pain	2283	2014	2281	2014
swelling	697	415	694	413
systemic adverse event	1746	1701	1745	1701
vaccine related	1162	1087	1161	1085
pyrexia	436	349	361	272
serious adverse event	49	45	48	45
vaccine related	1	0	1	0
death	2	2	2	2

There were discrepancies for all the events, with differences of up to 3 patients, apart from pyrexia, where there were large differences of up to 79 patients. In the final study report (V501 P013 CSR with P013-10 pg

712, p13), there were more 12% patients with injection-site events, 2497 vs 2405, than either set of data in the table, with differences of up to 377 patients.

5) There was no mention of new medical history even though it was clear in Merck's study report (albeit not in the protocol) that this was about adverse events. None of the publications of the three Future trials included any mention of new medical history even though most adverse events in these trials were reported under this category (14,853 vs 9,451 that were reported as adverse events).

Nine of the 19 authors of the journal article were current or former employees of Merck and owned stock or held stock options; eight had received fees from Merck; and four of these also received grants from Merck.

The principal investigators also had an agreement with Merck that restricted their rights to discuss or publish trial results after the trial was completed.[31]

The Future 2 study, P015

With 12,167 patients, this trial is the largest one of Gardasil against the adjuvant. Future 2 and Future 3 were designed in the same way as Future 1 and suffered from the same flaws.

There were five reports. The final report was incomplete. Most patient narratives of serious adverse events were only included in an earlier report, e.g. 9 of the 12 deaths. Some reports were mentioned without explaining what they were or where they could be found, e.g. "the First Supplemental BLA Clinical Report."

A substudy under Future 2 compared three manufacturing lots, but data were presented for only 207 (14%) of the 1514 randomised patients (Appendix C, p89). There was no explanation why and the reporting was obscure: "Detailed safety summaries and analyses will appear in the CIN 2/3 Efficacy CSR. However, summaries of clinical adverse experiences, injection-site adverse experiences, systemic clinical adverse experiences and elevated temperatures by consistency lot for the subset of subjects in both the Consistency Lot substudy and the nonserious adverse experience (NSAE) substudy are provided in this CSR."

As it was not clear where the full safety data were located, I searched electronically for "CIN 2/3 Efficacy CSR" in the final report, which yielded only one page, page 3862, which was 1699 pages further ahead in the report after "CIN 2/3 Efficacy CSR" was first mentioned. That page also stated that "Detailed safety summaries and analyses will appear in the CIN 2/3 Efficacy CSR." I eventually discovered that "CIN 2/3 Efficacy CSR" is the main report of Future 2. This term was used at the top of the title page, which was page 2 in the report, and also on page 3. The "CIN 2/3 Efficacy CSR" *was* the main study report.

To write in a 5500+ page main study report that, "Detailed safety summaries and analyses will appear in the CIN 2/3 Efficacy CSR" suggests to the readers that this information is not available in the report but perhaps somewhere else. Where that information is will remain obscure for all readers but the most tenacious ones.

The "placebo" diluent was not the same as in Merck's only placebo-controlled trial

Merck continued to call its adjuvant placebo: "the placebo used in this study will be Merck standard aluminum diluent (225 µg alum) in normal saline, USP (NaCl 0.9%)" (Appendix C, p70). The same text appeared in the Future 1 study report (V501 P013 CSR, p1845) and in the Future 3 study report (V501 P019 CSR, p5). Merck's clinical study reports, its informed consent forms, corresponding journal publications, and the package inserts all used the term placebo even though it contained the adjuvant.

[31] https://clinicaltrials.gov/ct2/show/results/NCT00092521

Except for the adjuvant, the "placebo" in the Future trials was not the same as the one used in Merck's "placebo-controlled" study, which was the carrier solution that moreover, according to the FDA, did not contain saline but water for injection. As Merck did not explain what the "aluminum diluent" was, it was not clear whether some of the components in the carrier solution in the vaccine were also included in the "placebo."

The WHO has stated that using adjuvant or another vaccine as comparator instead of placebo makes it difficult to assess the harms of a vaccine, and that placebo can be used in trials of vaccines against diseases for which there are no existing vaccines,[32] which was the case here.

Inadequate collection and reporting of adverse events

Merck's methods for collecting and reporting adverse events were problematic. Even after I had studied a total of 43,211 pages describing the three Future trials, corresponding to about 200 medium-sized books, I still did not know in sufficient detail how Merck collected data on clinical adverse events and reported on them, not even when they were serious or deadly. The various messages were often contradictory or unclear and the ambiguity left the door wide open to biased reporting, as there were many ways in which possible harms could have been hidden, ignored or left out.

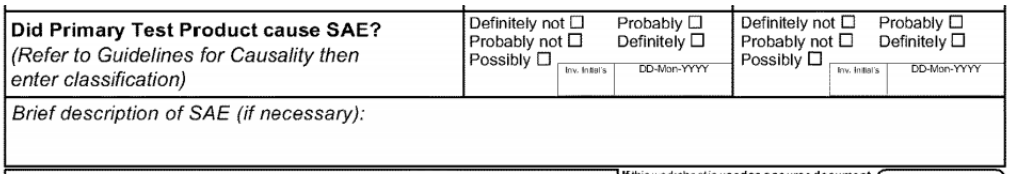
As already noted, it appears the investigators were obliged to report all serious adverse experiences, occurring within 14 days of each vaccination, whether or not related to the vaccine, whereas only events determined by the study coordinator to be related to the vaccine or a study procedure were reported in the clinical study report.

For a vaccine to be given to healthy people, non-serious adverse experiences are also important, but it appears Merck was not keen to get these reported: "The reporting of non-serious adverse experiences while not formally solicited from subjects in this population could be reported based on investigator discretion. Adverse experience reports received from these investigators were only captured if they occurred during the 14 days following each vaccination" (Appendix C, p73).

This provision, which applied to all countries apart from the few patients recruited in United States and the United Kingdom (see below), sends the message that there was no need to report anything unless the patient died, experienced a life-threatening adverse event, went to hospital or experienced a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.

The vaccine was provided in single-dose vials containing a volume of 0.75 mL, but it should be administered as a 0.5-mL dose. Merck defined an overdose as a serious adverse event and in Future 1, many investigators erred and injected the whole vial and not just 0.5 mL, which resulted in many reported such events.

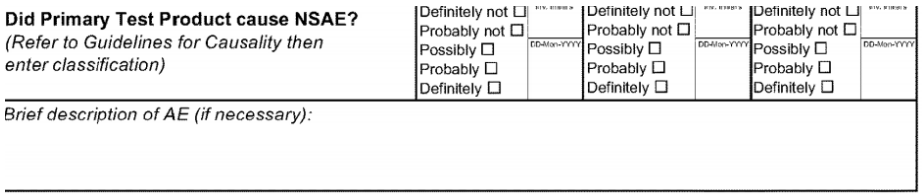
On a two-page form to be used for serious adverse events, only one-third of a page was allotted to the narrative, which is far too little for many serious events. There was another form for serious adverse events, of only one page. I could not find any instructions about when to use which form. On that form, two serious adverse events could be listed, with virtually no space for the narrative:



[32] Expert consultation on the use of placebos in vaccine trials. WHO 2013. https://apps.who.int/iris/bitstream/handle/10665/94056/9789241506250_eng.pdf?sequence=1.

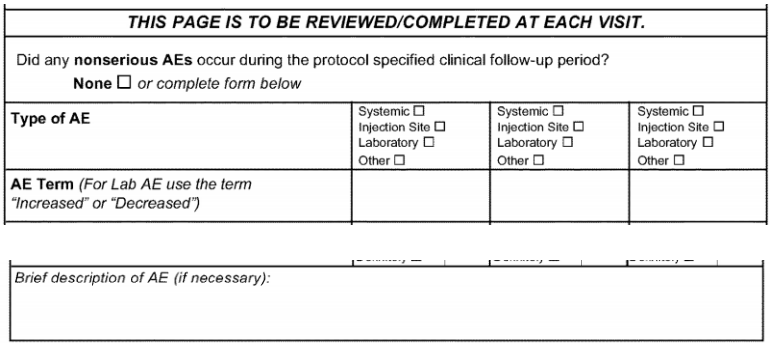
Even serious adverse events were only supposed to be recorded within two weeks: “Brief description of SAE (if necessary).” It is *always* necessary and required to describe serious adverse events.

A third form, for non-serious adverse events, was miniscule but could nonetheless be used for three different events. Again, the tiny space at the bottom for up to three narratives was only to be used “if necessary:”



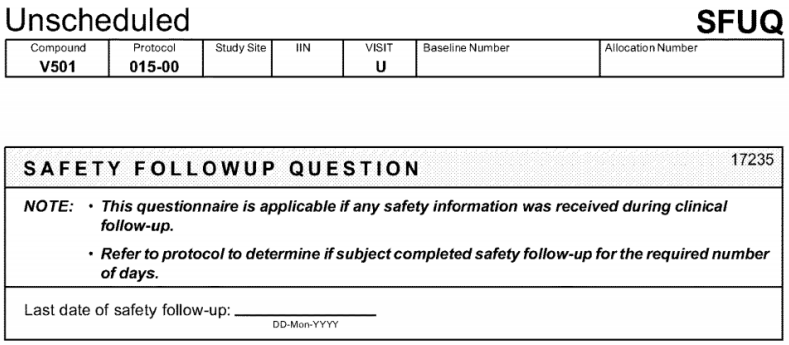
Did Primary Test Product cause NSAE? *(Refer to Guidelines for Causality then enter classification)*	Definitely not ☐ Probably not ☐ Possibly ☐ Probably ☐ Definitely ☐ DD-Mon-YYYY	Definitely not ☐ Probably not ☐ Possibly ☐ Probably ☐ Definitely ☐ DD-Mon-YYYY	Definitely not ☐ Probably not ☐ Possibly ☐ Probably ☐ Definitely ☐ DD-Mon-YYYY
Brief description of AE (if necessary):			

A fourth form, which looked similar to the previous one, was to be used at each visit for non-serious adverse events. Again, the tiny space at the bottom could be for three events, and “Brief description” of the adverse event was only to be filled out “if necessary”:



THIS PAGE IS TO BE REVIEWED/COMPLETED AT EACH VISIT.			
Did any **nonserious AEs** occur during the protocol specified clinical follow-up period? **None** ☐ *or complete form below*			
Type of AE	Systemic ☐ Injection Site ☐ Laboratory ☐ Other ☐	Systemic ☐ Injection Site ☐ Laboratory ☐ Other ☐	Systemic ☐ Injection Site ☐ Laboratory ☐ Other ☐
AE Term *(For Lab AE use the term “Increased” or “Decreased”)*			
Brief description of AE (if necessary):			

A fifth form was similar:



Unscheduled **SFUQ**

Compound	Protocol	Study Site	IIN	VISIT	Baseline Number	Allocation Number
V501	015-00			U		

SAFETY FOLLOWUP QUESTION 17235
NOTE: • ***This questionnaire is applicable if any safety information was received during clinical follow-up.*** • ***Refer to protocol to determine if subject completed safety follow-up for the required number of days.***
Last date of safety follow-up: _____ DD-Mon-YYYY

Accordingly, investigators were not encouraged to ask questions, and there was no guide as to how they should ask if they insisted on asking despite Merck’s apparent disinterest. The fifth form should only be filled out “If any safety information was received.” This is like saying: “Merck does not want you to report anything but if you are desperate to do so, here is your opportunity.”

A US substudy showed how easy it would be to demonstrate vaccine harms, compared to adjuvant, if one takes an interest in studying harms. This substudy had a particular focus on non-serious adverse events and was called “Detailed safety cohort” (Appendix C, p87-8). Even though the study was very small, 119 of 448 patients on Gardasil versus 75 of 447 patients on adjuvant with follow-up had moderate or severe injection-site adverse events in the vaccine group ($p = 0.0005$, Fisher’s exact test, my calculation). Merck did not do a significance test on these severity data.

Even though the percentages of patients with systemic adverse events were about the same (60.5% vs 59.5%), there were *fewer* patients with moderate or severe systemic adverse events on vaccine than on adjuvant, 39.7% vs 43.2%. The 3.5% difference could be a chance finding, but one would expect a vaccine plus adjuvant to be *more* harmful than the adjuvant. I therefore looked up "new medical history" to see if some events that should have been included under systemic adverse events in the Gardasil group had ended up there instead. The percentages of patients with a new medical history were 57.1% vs 53.1%. The difference of 4.0% was very similar to the difference of 3.5% in the other direction for moderate and severe intensity of systemic adverse experiences.

Whether these are chance findings, I cannot know, but Merck's splitting of adverse events into two categories, adverse events and new medical history, gives the sponsor an opportunity to conceal important adverse events and their severity, as new medical history events were never assessed as to their maximum intensity (mild, moderate or severe).

The UK substudy was even smaller than the US substudy (104 vs 128 patients with follow-up). In this substudy, the patients did not use a vaccination report card, and only 18% vs 13% patients reported any adverse experiences, in contrast to 91% vs 88% in the US substudy.

In a long-term follow-up substudy of Future 2 based on registers in four Nordic countries, Merck did not attempt to distinguish between adverse events and new medical history but equated safety data with "New Medical Conditions" (Appendix C, p90-1):

14.3 Safety Data

14.3.1 New Medical Conditions

Table 14.3-1
Subject New Medical History Conditions
(Incidence >0% in One or More Vaccination Groups)
During the Long-term Follow-up
(All Subjects as Treated)

There were no tables with adverse experiences, only a long one (30 pages) about "new medical history." There were supposed to be 2750 vs 2097 patients in the substudy, but new medical history was only shown for 2448 vs 1888 patients. Only people who had tolerated three vaccinations with active vaccine and remained in the study were followed up, and "placebo" patients were offered Gardasil. There are many reasons, e.g. selection bias, why adverse experiences cannot be compared in an unbiased way in such follow-up studies.

Merck's own Data and Safety Monitoring Board was critical towards the arbitrary and artificial split between adverse events and new medical history. A Board member found it problematic that Merck's advice when patients in Future 2 had discontinued their participation without giving a reason was to ask them if it was due to an adverse event or a new medical problem.

As already noted for Future 1, there were small indexes scattered around on the thousands of pages in Merck's study reports that were unintelligible, e.g. on p693-4 in the main report for Future 2 (V501 P015 CSR_protocol P005-10 pg 1917):

Appendix		Application Starting Page
16.2.6	**Individual Efficacy Response Data**	NA
16.2.7	**Adverse Experience Listings For All Subjects**	
16.2.7.1	Medium WAES Adverse Experience Reports	5428
16.2.8	**Listings of Individual Laboratory Measurements by Subject**	NA

NA = Not Applicable.

It is obscure what "not applicable" means for "Listings of Individual Laboratory Measurements by Subject." If no laboratory measurements were made, Merck should have said so. If laboratory measurements existed but were not reported, it would have been appropriate to say, "not available in this report."

I went through the entire report again but did not find any laboratory values. Page 262 in the study report stated: "12.3 Clinical Evaluation of Laboratory Safety Tests. No routine laboratory safety tests were conducted within the context of the study." None of the 102 tables in the report were about laboratory values. A "Schedule of Clinical Observations and Laboratory Measurements" on p67 in the report showed a table indicating that no laboratory tests were made whereas Merck tested the girls for pregnancy, gonorrhoea and Chlamydia.

Merck did laboratory tests in some of its animal studies. In its three-month toxicity study in 200 rats, the globulins increased in the three vaccine groups. This was expected, because some of these are vaccine induced immune globulins, but Merck had left out the data for the adjuvant control group. It would have been highly relevant to find out if the adjuvant caused changes in laboratory values related to the immune system, both in animals and humans.

The text and tables about blood pressure and pulse were contradictory. The physical examination on day 1 did not include measurement of blood pressure and pulse, which is unusual for "placebo"-controlled trials of experimental drugs whose harms are unknown. On a case report form for day 1 there were entries for blood pressure and pulse but also the text: "Was exam performed?"

VITAL SIGNS 4074

Was exam performed? **No** ☐ *If **yes**, complete form below.*

Exam performed on visit date ☐ **or** specify date: _____ (DD-Mon-YYYY)

VITAL SIGNS	RESULT		*AE? No	Yes
Weight kg ☐ lb ☐			☐	☐
Temperature °C ☐ °F ☐ *Method:* oral			☐	☐
Blood pressure (mmHg) *Position:* sitting	Systolic	Diastolic	☐	☐
Pulse rate (beats/min) *Position:* sitting			☐	☐
Respiratory rate (breaths/min)			☐	☐

If any "YES" box is checked, complete the appropriate ADVERSE EXPERIENCE (NSAE/SAE) form.

The question, "Was exam performed?" contradicted information elsewhere: "A general physical examination was performed at Day 1. The documented physical examination included height, weight, sitting blood pressure, sitting pulse, respirations, and an oral temperature."

It was well known when Merck planned its studies that vaccinations can lead to changes in blood pressure and pulse, and to fainting and near-fainting. Merck's instructions were ambiguous, it would have been appropriate to ask investigators to measure blood pressure and pulse at each visit and to use a tilt test, if they suspected orthostatic hypotension, which is a decisive test for POTS.

The Data and Safety Monitoring Board (DSMB) meetings illustrate a lack of interest in safety. Although safety is the primary concern for such a board, and a large number of slides were presented at the first DSMB meeting, three months after the Future 2 trial started in June 2002, none of the slides showed any safety monitoring results; they were all about efficacy and principles (Appendix C, p82). Even though a review of the safety data was an objective at the DSMB meeting half a year later, there were only slides about some selected adverse events. There were no systematically collected data on serious adverse events but a few concrete patients with such events were presented, with very little detail.

Fifteen months after the trial started, slides were presented at a DSMB teleconference on serious adverse events, but as they were not divided per treatment group, it would have been difficult for the board to discuss them in any meaningful way. At this meeting, four board members were concerned that the vaccine could cause syncope, convulsions and deaths and asked for more information about two traffic deaths, including the timeframe from vaccination to death. One member noted that, "there could have been other motor accidents we are not aware of which occurred in between visits when subjects are not in contact with the sites." Merck replied: "we are informed of all deaths unless they are in between visits."

Given that the Data and Safety Monitoring Board already this early was concerned about syncope, also if it occurred in the intervals between the vaccinations and were therefore not the result of the needle prick, it is concerning that Merck did not change its procedures to make it more likely that the company detected such possible, serious harms of its vaccine. As noted above, Merck made many protocol amendments during the trial and had ample opportunity to change its procedures for detecting harms of its vaccine.

It is also concerning that Merck did not obtain information about deaths if they occurred between visits but yet again, the information was contradictory. The study report noted that deaths needed only be reported immediately to the sponsor if considered by the investigator to be possibly, probably, or definitely vaccine related, but 692 pages later in the report, there was a statement that, whether or not related to the investigational product, deaths must be reported within 24 hours to one of the people listed on the sponsor contact information page.

In contrast to earlier DSMB meetings, no slides were included for a meeting 3.5 years after the trial started, and both the presentations and the meeting agenda were called confidential. The only information about this was that they were, "Restricted. Confidential, limited access:"

ATTACHMENT 1
MEETING AGENDA
QUADRIVALENT HPV (TYPES 6, 11, 16, 18) L1 VLP VACCINE
PROTOCOLS 011, 012, 015, 019, 020
DATA & SAFETY MONITORING BOARD MEETING
December 6, 2005

A subsequent meeting was also called confidential. Since Merck's study report was written for the FDA and other drug regulators, it makes no sense that the meeting agenda and the slides were not included in the application for marketing approval of Gardasil.

The coding and reporting of possible harms of vaccines and other drugs involve several steps, some of which are automatic or semi-automatic and may involve arbitrary decisions. Merck mentioned some of these issues in its main report: "For all nonserious adverse experience summaries, verbatim terms (i.e. terms used by subjects to report their adverse experiences) are automatically encoded using a logic algorithm to an international standardized dictionary. At this time, none of the auto-encoded terms in the clinical database have been compared with the verbatim terms" (Appendix C, p83).

I have not seen the verbatim terms for any adverse events, as I do not have access to the original reports written by investigators, study coordinators or patients. I only have access to narratives for serious adverse events written by Merck employees.

Misleading trial report in *New England Journal of Medicine*

The published reports of Future 2 are misleading on six counts.[33]

1) Although safety was one of Merck's two primary objectives (V501 P015 CSR_protocol P005-10 pg 1917, p4), there was nothing in the abstract about safety.

2) The control group was said to have received placebo, which was untrue.

3) There was only one hypothesis, related to efficacy, even though the primary safety objective in Merck's study report was "To demonstrate that a 3-dose regimen of quadrivalent human papilloma virus (qHPV) vaccine is generally well tolerated."

4) Although the trial randomised a total of 12,167 people, the table of adverse events was only about the 911 people (7%) who were from the United Stated.

5) There was no mention of new medical history at all even though this is about adverse events; even though Merck put great emphasis on this in its study reports; and even though there were seven times more such events than what Merck categorised as adverse events in this trial.

6) In the Discussion section, the authors wrote that, "no safety concerns among nonpregnant women were identified." However, they only included 7% of the patients in their safety analyses.

Ten of the investigators were current or former employees of Merck and had an equity interest or held stock options; 30 had received fees from Merck; and 19 had received grants from Merck.

[33] FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med 2007;356:1915-27.

Indiana University and Merck had a confidential agreement that paid the university "on the basis of certain landmarks regarding the HPV vaccine" and one of the investigators received "a portion of these structured payments." It is remarkable that only 11% of the patients experienced adverse events in this trial, compared with 92% in Future 1 and 84% in Future 3.

The principal investigators had an agreement with Merck that restricted their rights to discuss or publish trial results after the trial was completed.[34]

The Future 3 study, P019

The design was the same as for Future 1 and Future 2, with four years of follow-up, until month 48, and the study was flawed for the same reasons. There were additional issues.

Inadequate collection and reporting of adverse events

In contrast to Future 1 and 2, there were no listings of numbers of patients experiencing adverse events with MedDRA terms (Medical Dictionary for Regulatory Activities). There was no explanation why this had been left out, in contrast to the usual standard for Merck reports.

Merck wrote in its final report that two new subjects with "nonfatal serious clinical adverse experiences were mistakenly not incorporated into the Clinical Trials Systems (CTS) database but were reported in the worldwide adverse experience system (WAES) database. These adverse experiences will be added into the database. These 2 SAEs are not noted in Table 12-1 or in Table 12-3" (Appendix C, p93-4).

This raises many concerns. As noted on page 6 above, I have not seen an explanation anywhere in the more than 100,000 pages I have read about Merck's trials what Merck's procedures were for including serious adverse experiences in its databases; why at least two databases were used when Merck conducted its trials, the Clinical Trials Systems (CTS) database and the worldwide adverse experience system (WAES) database; how it was decided which one to use; and whether all the data in these two databases were also represented in Merck's study reports. It is clear they were not, as two patients with serious adverse events were not in the tables. This means that the heading for table 12-3 is misleading: "Listing of Subjects With Serious Clinical Adverse Experiences (Entire Study Period) (All Vaccinated Subjects)."

The reports stated in various places that there were narratives for 14 patients, 30 patients, 31 patients, and 32 patients, but I ultimately found out that the correct number was 33. Cases were missing in tables, even of deaths, and one patient was stated to have developed symptoms a year after she died.

I searched electronically for and collected narratives for serious adverse experiences for seven patients. I found six of them in locations not reflected in the study report and found the last narrative on page 5535 in the main report, in a WAES adverse experience report form, not in the text of the report.

Safety data were collected in the same time period as new medical history, from day 1 to month 7, in both Future 2 and Future 3.

Merck presented 186 tables in the main report and started out with selective reporting of new medical history, as events with less than 1% occurrence had been omitted in the first table. As there were over 1900 patients in each group, Merck's selective reporting left out all events that occurred in 19 or fewer patients. This practice excludes many events, as illustrated by "Musculoskeletal and connective tissue disorders," where back pain was the only MedDRA term mentioned although patients with back pain constituted only

[34] https://clinicaltrials.gov/ct2/show/results/NCT00092534

one quarter of all patients with musculoskeletal and connective tissue disorders. There is no indication what the other events were even though pain in extremity is a key symptom for CRPS.

Merck had not yet presented a table with all events before a table of events "Potentially Consistent with Autoimmune Phenomena" popped up.

Merck continued with "Discussion and Conclusions" before it presented a table of *all* new medical history events.

Even though Merck had not presented the relevant safety data, Merck ended its 15-page discussion of its findings with its usual mantra, that its vaccine "is generally well tolerated."

Finally, after 184 additional tables, came a table with all new medical history events, the penultimate table, but only in the "vaccination period." The 186th and last table was about such events in the "follow-up period."

Splitting the data more than in Future 1 and 2 and omitting data

As noted above, the language Merck used about its various periods for reporting adverse events was obfuscating. "Vaccination period" could be five days, three times two weeks, up to 7 months, or perhaps even beyond, but in this case, it was from day 1 until month 7 (Appendix C, p96). "Follow-up period" can also have multiple meanings because the patients were followed up for injection-site reactions for five days after each vaccination, for systemic adverse events for 15 days, between the vaccine visits, and after month 7. In this case, it was after month 7.

Thus, for Future 3, new medical history was split in two mutually exclusive groups, events recorded before and after month 7. This was new and surprising because I found out when reviewing the Future 1 trial that data from the first type of table (in this case called new medical history ">Day 1") were included in the second type of table (called ">Month 7").

By doing this, Merck made it even more difficult than in Future 1 and Future 2 (that also used the ">Day 1" terminology) to find out which harms its vaccine causes. It is not possible to avoid double counting, as a patient may appear in both sets of tables, even with the same type of event. In Future 3, Merck split adverse events in two ways: Calling them two different things and by splitting the trial period. This is scientifically dubious making it difficult if not impossible for independent researchers to do meta-analyses of all adverse events.

An earlier report on Future 3 stated that a table "displays a summary of clinical adverse experiences reported by subjects at any time during the study through visit cut-off date of 13-Jul-2007" (Appendix C, p99). "Any time during the study through visit cut-off date" is yet another way of mentioning a reporting period, which seemed to be the total length of the trial, which was four years. However, there was no such comprehensive table for new medical history, only for clinical adverse experiences. Furthermore, it was only a summary table showing numbers with adverse events. None of the report's 218 tables showed numbers of patients with MedDRA defined events, as in other Merck trials.

The text in the report about another table was incorrect. The table was not about "any clinical adverse experience by maximum intensity rating within 15 days following any vaccination visit;" it was only about injection-site adverse experiences.

As I could not find a table listing the severity of systemic adverse events going beyond the two-week intervals after each vaccination, I went back to the final report and searched on "Maximum Intensity Rating." There were many entries and tables, but they were all about what happened when all patients, after the

randomised trial phase was over, were offered a dose of the active vaccine. As there were only 104 vs 120 patients in the two groups, these data were not of interest.

Pain in extremity, other significant harms, and an incorrect conclusion about safety

Far more patients had injection-site reactions in the vaccine group than in the adjuvant group, 1443 vs 1210 ($p = 2 \times 10^{-16}$), and far more of the reactions were severe ($p = 0.0005$). There were also far more reactions of severe or moderate intensity ($p = 3 \times 10^{-16}$). Merck did not provide any such significance tests but stated: "Overall Safety Findings. Administration of the qHPV vaccine was generally well tolerated."

With reference to a table that only showed systemic adverse experiences with an incidence of at least 1%, Merck wrote that, "The proportion of subjects who reported pain in the extremity was higher (the lower limit if [sic] the 95% Cl of the difference in percentages was greater than 0.0%) in the qHPV vaccine group than in the placebo group" (Appendix C, p101). This indirect language means that the difference was statistically significant.

This was the first time I saw any mention of pain in extremities, which is a key symptom in CRPS. I calculated that the risk was greater for pain in extremity considered vaccine related than for all pain in extremity events, risk ratio 3.04 vs 2.09. Both differences were highly statistically significant ($p = 8 \times 10^{-6}$ and $p = 5 \times 10^{-5}$, respectively). Merck did not provide any significance tests but showed a confidence interval in a table for all such events, a risk difference of 2.4% (95% confidence interval 1.3% to 3.6%). The number needed to harm for pain in extremity was 42 for all events and 49 for those considered vaccine related.

The table was inconsistent with the declared primary safety endpoint which was the proportion of subjects with vaccine related serious adverse events (Appendix C, p92).

This is called outcome switching. By including non-vaccine related adverse events, the random noise increases, which makes it more difficult to find out the vaccine's harms. Even though the primary endpoint was *serious* vaccine-related adverse events, it was clear in Merck's reports that Merck emphasized those events that the investigators considered vaccine related, whether serious or not.

It is of interest that dizziness and headache occurred together in some patients, as these are key symptoms for POTS that often go together (the total number of nervous system events was 597 but adding the three symptoms, one gets 642):

Nervous System Disorders	**597**	**(31.6)**	**590**	**(31.3)**	**0.30**	**(-2.7 , 3.3)**
Dizziness	79	(4.2)	82	(4.3)	-0.20	(-1.5 , 1.1)
Headache	526	(27.8)	518	(27.5)	0.40	(-2.5 , 3.2)
Migraine	37	(2.0)	40	(2.1)	-0.20	(-1.1 , 0.8)

It is concerning that a table with two serious limitations (at least a 1% incidence and only if reported within two-week intervals after each vaccination) reported that 2249 patients (59.0%) had systemic adverse experiences while another table with no limitations ("Vaccination and Follow-up Periods, Days 1 to 9999") reported only five more patients (0.2% more) (Appendix C, p102).

During only six weeks, 2249 patients had systemic adverse events, and during 4 years, 2254 patients had such events. The study started on 18 June 2004 and the interim report was dated 29 November 2007, 3.5 years later, so even though not all patients had been followed for the full 4-year period when the report was written, this cannot explain that only five more patients had systemic adverse events during all this additional follow-up time. This showed once again that Merck's methods for identifying adverse events were inadequate.

Misleading trial report in *Lancet*

This published report[35] was misleading on nine counts.

1) The study was called "placebo-controlled," which was not true.

2) Even though safety was a primary objective, which the Methods section in the *Lancet* article also stated: "The primary safety objective was to show that a three-dose regimen of quadrivalent HPV vaccine was generally well tolerated," the only mention in the abstract of safety was: "We recorded no vaccine-related serious adverse events." For a vaccine to be given to healthy people, of which very few will experience any benefit, non-serious adverse events are very important. Addressing only vaccine related serious adverse events, which in the large Gardasil 9 trial constituted only 0.05% of all adverse events, is a violation of generally accepted research practices. See also item four below.

3) The statistical analysis section contained nothing about testing for safety.

4) Even though the trial register noted that the time frame for reporting serious adverse events was four years,[36] the Results section only mentioned serious adverse events, and only if they had occurred within the first two weeks after each vaccination. This is inappropriate for a four-year trial and for which 90% of the serious adverse events are expected to occur outside the two-week intervals. It might be defensible to take an interest only in serious adverse events if the patients have life-threatening cancer and are treated with cytotoxic drugs, but not for a vaccine to be given to healthy people.

As the trial ended in April 2009 and was published one month later, there should have been enough time to include the full data set. There cannot have been any need to publish quickly, as two larger trials with the same design, the Future 1 and 2 trials, had been published two years earlier.

Merck reported 3 vs 7 patients with serious adverse events in *Lancet* within the two-week periods after each vaccination, but this was incorrect. In the main study report (V501 P019 CSR), there was a table on page 577 that showed when the serious adverse events had occurred. To be consistent, I used the summary tables for my meta-analyses even when there were contradictory data elsewhere. In this case, there were 14 vs 16 events, both in the summary table and in the table on page 577. But, as noted above, two more serious adverse events, one of Gardasil and one on adjuvant, were described in the text, on page 575, which "were mistakenly not incorporated into the Clinical Trials Systems (CTS) database but were reported in the worldwide adverse experience system (WAES) database." Even when I included these two extra patients, there were only 3 vs 6 patients for which the serious adverse event (the first one, if there were more than one) had occurred within the two-week periods after each vaccination (the other events had occurred from day 44 until day 1059 after a vaccination). Merck reported 14 vs 16 in its summary table in the study report, but also two more cases, and there were also 15 vs 15 in the US trial register. Thus, there were four sets of data for serious adverse events: 15 vs 17, 14 vs 16, 3 vs 7 and 3 vs 6.

5) There was a table of adverse events in the article, which I compared with the data in Merck's study report:

[35] Muñoz N, Manalastas R Jr, Pitisuttithum P, et al. Safety, immunogenicity, and efficacy of quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine in women aged 24-45 years: a randomised, double-blind trial. Lancet 2009;373:1949-57.

[36] https://clinicaltrials.gov/ct2/show/results/NCT00090220?view=results

	Merck's study report		Journal article	
Subjects with adverse events	**Gardasil**	**Adjuvant**	**Gardasil**	**Adjuvant**
adverse events	1645	1535	1642	1532
injection-site adverse events	1450	1213	1450	1212
systemic adverse events	1121	1135	1118	1131
vaccine related adverse events	1565	1391	1565	1389
injection-site adverse events	1449	1213	1449	1212
systemic adverse events	746	697	745	695
serious adverse events	14	16	3	7

There were discrepancies for all the events, with differences of up to 4 patients, apart from the large difference in serious adverse events (see just above).

6) There were no p-values or confidence intervals in the table of adverse events, even though safety was a primary objective, and there were no comments about the large difference in injection-site adverse events ($p = 6 \times 10^{-17}$) or the non-significant difference in systemic adverse events considered vaccine related ($p = 0.11$).

7) There was nothing about safety in the Discussion and no conclusion about safety other than the meaningless sentence in the abstract: “We recorded no vaccine-related serious adverse events” (none of the 3 vs 7 events were considered vaccine related).

8) There was no mention of new medical history at all even though this is about adverse events; even though Merck put great emphasis on this in its study reports; and even though there were 1458 such events (see Appendix C, p98).

9) There was no mention that some patients died. Whether considered drug related or not, deaths must be reported in a clinical trial. Merck’s reporting to the US trial register, which was last updated in 2017, was confusing. The numbers were different to those in Merck’s study report, e.g. there seemed to be no deaths, even though 7 vs 1 died (whereas the numbers of serious adverse events were correct):

All-Cause Mortality

	qHPV Vaccine: Base Study		Placebo: Base Study	
	Affected / at Risk (%)		Affected / at Risk (%)	
Total	--/--		--/--	

Serious Adverse Events

	qHPV Vaccine: Base Study		Placebo: Base Study	
	Affected / at Risk (%)	# Events	Affected / at Risk (%)	
Total	15/1890 (0.79%)		17/1888 (0.90%)	

There were numerous tables, e.g. 26 for primary outcomes, 8 for secondary outcomes and 7 for other prespecified outcomes. I found only one entry where I could see the number of deaths:

4. Primary Outcome

Title	Number of Participants With an SAE Resulting in Death After Vaccine Administration
Description	An adverse event (AE) is any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the study vaccine. Any worsening of a preexisting condition which is temporally associated with the use of the study vaccine is also an adverse event. A serious adverse event (SAE) is an AE that results in death, is life threatening, results in persistent or significant disability or incapacity, results in or prolongs a hospitalization, is a congenital anomaly or birth defect, is a cancer, or is an overdose.
Time Frame	qHPV in Base Study: Up to Month 120; Placebo in Base Study: approximately Month 60 up to Month 120

Outcome Measure Data

Analysis Population Description
Participants who received >=1 qHPV vaccination in the Base Study or EXT1 and had safety follow-up

Arm/Group Title	qHPV in Base Study: All Participants	Base Study: Placebo
Arm/Group Description:	Participants received qHPV vaccination at Day 1, Month 2, and Month 6 in the Base Study	Participants who received placebo or an incomplete qHPV regimen in the Base Study and were offered open-label qHPV vaccine starting at approximately Month 60 in EXT1
Overall Number of Participants Analyzed	1890	1327
Measure Type: Number Unit of Measure: Participants		
	8	4

There seemed to be 8 vs 4 deaths while there were 7 vs 1 deaths in Merck's study report (and none in *Lancet*). The discrepancy between 12 and 8 deaths is unexplained.

Nine of the 18 authors were employees of Merck and potentially owned stock or stock options in Merck; four had received fees from Merck or acted as consultants (which usually salaried); two had received grants from Merck; two had undertaken HPV vaccine studies for Merck; and six were members of the Merck HPV steering committee. Only three authors had not declared any conflicts.

The principal investigators had an agreement with Merck that restricted their rights to discuss or publish trial results after the trial was completed.[37]

Other studies

Study P020

This study started three years after Future 1 started but Merck had not heeded the criticisms raised during the running of the Future studies, including those coming from its own Data and Safety Monitoring Board. The design was very similar to that for the Future studies and the scientific problems were the same. The study randomised 4065 men to the vaccine and its adjuvant called "placebo."

The procedures were even more inadequate than those for the Future trials. Merck did some statistical tests, but explicitly noted that no statistical testing was performed for systemic adverse events or for severe injection-site adverse events.

There were 8% more clinical adverse events with the vaccine than with the adjuvant and 12% more injection-site adverse events ($p = 0.001$ and $p = 7 \times 10^{-5}$, respectively). Merck did not provide such p-values but called these differences "slightly higher" and concluded that the vaccine was "generally well-tolerated" and had a "favorable clinical adverse event profile."

Study P023

This study started four years after Future 1, but the procedures were similarly inadequate and there was selective reporting. There were only 117 vs 59 females in the study and 91 vs 42 had adverse experiences on

[37] https://clinicaltrials.gov/ct2/show/results/NCT00090220?view=results

the vaccine and adjuvant, respectively, which were not reported as to their maximum severity, contrary to the trial protocol.

Studies P024 and P025

These were studies where 1791 patients in total were randomised to receive other vaccines or no other vaccines, in addition to Gardasil. They are therefore not relevant for an evaluation of the harms of Gardasil.

Study P027

This was a study from Japan with a design very similar to that of other Merck trials. It randomised 509 and 512 patients to vaccine and adjuvant, respectively.

The incidence of serious adverse experiences after 15 days (i.e. after the two-week follow-up periods after each vaccination) was 35/480 = 7.3% in the vaccine group and 63/468 = 13.5% in the adjuvant group (p = 0.002, my calculation). It is implausible that there can be almost double as many serious adverse events on a "placebo." The explanation was that "The most frequently reported serious adverse experience was cervical dysplasia." As this is what the vaccine is supposed to prevent, this outcome should not be included in serious adverse events. It is a benefit outcome, not a harm outcome.

The reporting of the trial was inadequate in other ways, e.g. only adverse events occurring within two weeks after each vaccination were reported.

Study P028

This was also a Japanese trial and the clinical study report was in Japanese. The study compared the vaccine with adjuvant called "placebo" in 82 vs 25 patients. There were no relevant tables in English.

Study P029

This was an Indian study where all 110 participants received the vaccine. As there was no control group, the study is not relevant for an evaluation of the harms of Gardasil.

Study P030

This was a Chinese study where 302 patients received the vaccine and 298 the adjuvant, called "placebo." There was nothing in the protocol about dividing adverse events into mild, moderate and severe, but there were some tables with such data. These tables showed that not a single patient of the 600 in the study had experienced any redness, swelling or induration at the injection site, nausea, vomiting, headache or "other." The report was contradictory because other tables showed that some patients *did* experience both local and systemic adverse events.

Elsewhere in the report, some data were provided with numbers in severity categories, but only two categories were shown, mild and moderate. It is highly unlikely that none of 600 patients experienced severe induration, pain, redness or swelling at the injection site.

P031

This was a surveillance study from Kaiser Permanent of 189,629 females, published in 2010.

Surveillance, about 190,000 subjects. Kaiser Permanente. See next report just below.

V501 P031-02_Revised Final Report

Surveillance, about 190,000 subjects. Kaiser Permanente. Revised final report.

A Post-Licensure Surveillance Program for the Safety of GARDASIL™ in a Managed Care Organization Setting. Revised Final Report. December 2010.

The study was flawed.

Kaiser did not examine the medical records of all potential cases in either vaccinated or unvaccinated populations. Kaiser did not examine at all the cohort of unvaccinated patients and only did a random sampling of vaccinated cases. For the unvaccinated cohort, Kaiser acted as though the data for the unvaccinated group were missing and estimated a background rate using a non-standard Rubin's multiple imputation model. But the data were not missing, they just were not examined.

Even so, the study did show a statistically significant elevated risk for the autoimmune condition Hashimoto's disease in the vaccinated population.

Both vaccinated and unvaccinated patients' records should have been reviewed equally for a proper analysis.

The study cannot rule out the possibility that Gardasil causes important harm in some people. If such harms are rare, they may easily be overlooked in studies of this type as the signal could be drowned in all the background "noise." Furthermore, it is insufficient to look only at hospital visits within 60 days of each vaccination. For example, it can take years after the vaccinations before POTS, and likely also CRPS, gets diagnosed, if it gets diagnosed at all, as the symptoms are often diffuse.

P033

This was a "Vaccine Impact in Population" study conducted in four Nordic countries based on a combination of registry data and primary data collection that took a series of cross-sectional snap shots at the general female population in various Nordic countries between 2004 and 2012. It is not of any interest in relation to vaccine harms.

P035

In this Chinese study, 40 people were vaccinated: "No severe or serious adverse reaction was observed, tolerance was well."

P041

This study randomised 3006 Chinese women to vaccine or adjuvant. It was similarly designed as the Future studies, including "new medical history," but was carried out much later, starting in 2009.

The study included a "base phase" (until the month 30 visit) and an extension phase whose duration was not defined but all patients were "followed for efficacy evaluation through month 78 visit."

The safety objectives were even more rudimentary and scientifically inappropriate than in the Future trials. Even though it was a randomised study, there was apparently no initial intention of comparing safety outcomes in the vaccine group with those in the adjuvant group:

“Primary Safety Objective: To describe the incidence of vaccine or procedure-related serious adverse experiences and incidence of death in women 20 to 45 years of age who received Quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP Vaccine.”

The conclusion about safety was the usual Merck mantra, “generally well tolerated.”

There was a summary table for adverse events reported in the “Entire Study Period,” which was not explicitly defined but might have been the base phase of 30 months. There were no data on “new medical history” even though such events were collected.

The study report was very short for such a large study.

P046

This was a study from Africa that included only 20 people on “placebo.” It was not of any interest.

P059

This was a surveillance study from Korea with 3605 patients. The focus was on serious adverse events and none were reported. The study was not of interest, as there was no control group.

P070

This was a safety (surveillance) study that the FDA had requested be conducted by Merck after it had approved the use of Gardasil in males in 2009.

The report described a cohort of 106,110 males. Considering that it was a safety study required by the FDA, the methods of collecting possible harms of the vaccine were insufficient, as in all Merck studies. The observation period was only 60 days, and the focus was on serious adverse events; those events that occurred on the day of the vaccination; or were autoimmune disorders diagnosed within six months after the vaccination, which is too short a follow-up period.

The risk of confounding appears significant, as also indicated by Merck. This study cannot be used to “describe the general safety of a first dose of GARDASIL® in males,” as Merck wrote.

P110

This report consisted of 165 pages in Japanese. As there seemed to be only one group, it was not of interest.

P122

This was a study in 1124 Japanese males that started in 2013 and was completed in 2017. Although this was relatively recent, it was designed in the same way as the Future trials including the category, “New Medical History.”

The study ran for 3 years, but the time frame for reporting systemic adverse events was only two weeks after each vaccination. This resulted in a table that described that no one experienced any serious adverse events, even though one patient died outside the two-week interval.

As the study report consisted of 4000+ pages in Japanese, I supplemented it with the published trial report.[38] The published report showed that Merck did not distinguish between adverse experiences and new medical history despite its claims to the contrary: "Tolerability, based on adverse events (AEs), vaccination-related AEs, and new medical conditions, was also assessed as a primary objective." Nowhere in the published trial report was there any account of adverse events that had occurred beyond the two-week periods after each vaccination, and new medical history was not mentioned at all, apart from the Methods section, even though six of its eight authors were from Merck.

The Japanese study report had tables in English that showed how reported adverse events and new medical history should be translated into MedDRA terms, e.g. feeling of weakness was coded as asthenia. Since adverse events and new medical history were coded in the same way with MedDRA terms, this is an additional reason why it makes no sense that Merck operated with both categories in its trials.

The Japanese trial protocol mentioned that "Data generated by this trial will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol." Six of eight authors were employed by Merck.

The frequency threshold for reporting "other adverse events" to the trial register was 5%, which is arbitrary, too high and a violation of Merck's own protocol where the threshold was 1%. The rates were 329/554 (59.4%) on the vaccine vs 303/559 (54.2%) on the adjuvant. In the published trial report, there were 57 more (9% more) patients with adverse events than in the trial register. One would think that this was because there was no 5% threshold for reporting in the journal article. However, the data were the same for systemic adverse events, even though there should be more such events without a threshold. Therefore, the explanation for the discrepancy cannot be the lack of a threshold in the trial publication. This discrepancy between the data in the trial register and the data in the published trial report has not been explained.

The trial publication mentioned in the Discussion that the injection-site adverse events were reported by similar proportions of Japanese men as in earlier trials with males whereas the incidence of systemic adverse events was lower, 14.4% on vaccine vs 15.4% on the adjuvant, as compared to 31.6% vs 31.4% internationally.

This is important information, as it shows that the reporting of different types of adverse events can vary considerably from trial to trial, even when the procedures for collecting adverse events are the same.

Merck restricted its statistical testing of differences in adverse experiences to injection-site reactions and temperature. It is inappropriate not to test for systemic adverse events. Further, Merck did not report to the trial registry whether the adverse events were mild, moderate or severe.

The protocol noted that the investigator or sponsoring institution was paid or received a grant for performing the trial. It was not clear if the physicians were paid privately or if the money went to their institutions. If paid privately, the risk of bias is even greater than if the payment goes to the department.

P125

This was a post marketing surveillance study in India, with no control group. The patients were "under active surveillance for serious adverse events (SAEs) occurring within 30 days after administration of any dose of Gardasil."

No serious adverse events were reported. Non-serious adverse events were reported for one person (0.5%).

[38] Mikamo H, Yamagishi Y, Murata S, et al. Efficacy, safety, and immunogenicity of a quadrivalent HPV vaccine in Japanese men: A randomized, Phase 3, placebo-controlled study. Vaccine 2019;37:1651-8.

In the Future 1 trial, adverse events were reported for 92% of the patients. This illustrates that the reporting of possible harms was insufficient in this study.

P200

The study report was written in Japanese. The study was not of interest, as there was only one group.

Extension safety summaries of five Gardasil trials

A 41-page report summarised "in detail, the serious clinical adverse experiences, pregnancies and pregnancy/infant outcomes that occurred in the Extension Protocols 005-10, 007-20, 013-10, 015-10 and 016-10" (Appendix C, p131-5). It was not formally dated but "06-Oct-2010" appeared in a footnote.

Gardasil was provided to people who: "(1) received placebo in the base study; (2) received monovalent HPV 16 vaccine in the base study; (3) received an incomplete vaccine regimen of qHPV vaccine in the base study; or (4) did not meet the protocol specified criteria for seroconversion (Protocol 016 only)."

There appeared to be 1862 patients in total who were called randomised even though the extension studies were not randomised. There was no information about how many of the originally randomised patients in the studies that were offered participation in the extension studies, or about how many declined and for what reasons. Without this information, the report is uninterpretable.

The report did not describe for how long the patients were followed in the studies. This information was only provided indirectly: "This report includes data for the study extensions for visits conducted through 31-Jul-2009 for P005-10; 14-Sep-2009 for P007-20; 29-Jan-2009 for P011-10, 11-Feb-2009 for P012-10 (sub-study for P013-10); 10-Mar-2008 for P015-10; and 12-Feb-2009 for P016-10." One would therefore need to consult other reports to find out.

Visits were numbered from 1 to 25, all with the label "OB", e.g. 1.0B, 2.0B, which was not explained.

The discontinuation rate was 26%, which is far above the discontinuation rates in Merck's other studies.

The narratives of serious adverse events operated with a new category called "other important medical event." After having read over one 100,000 pages of Merck reports, this was the first time I encountered this category for adverse events. Other reports operated with adverse events and new medical history. We do not know what this third category is about and how it is defined, as there was no definition in the study report. A headache that lasted six months, which the investigator determined was possibly related to the vaccine, was called an "other important medical event."

One woman who had received adjuvant in the base study "experienced a mild allergic reaction" after the first Gardasil dose. After the second dose, she "experienced a classic allergic reaction of severe intensity." "The investigator felt the classic allergic reaction was probably related to the study vaccine and was to be another important medical event."

Case-control study of autoimmunity, protocol GDS03E

This was a report of a case-control study of autoimmunity (Appendix C, p135).

As shown by the wide confidence intervals, the case-control study was far too small to rule out associations between autoimmune diseases and Gardasil, e.g. for type 1 diabetes mellitus, the matched adjusted odds

ratio was 1.21 (95% CI 0.38 to 3.58). The authors concluded themselves that their study "lacked the power to conclude on individual disorders."

Since it is difficult to perform reliable case-control studies, it is important to know who the researchers are. There were five authors on the report that had two names in common with four people on the research team and four names in common with people on the scientific committee; thus, there were 11 names altogether. Later in the report, there were other numbers; seven members of the research team and six of the scientific committee.

Four of the six members of the scientific committee and four of the seven members of the research team had signed the report. One of the authors of the report was not a member of the research team and had not signed the report, and three members of the research team - all statisticians, it seemed - were not authors. The reason for this is unexplained.

The address for the five authors of the report was "LA-SER 10 Place de Catalogne" in Paris but a search on this address yielded nothing about the company.

A search of the email address, contact@la-ser.com and "la-ser paris" also led nowhere. Further into the report, it was noted that, "The system and the data collected belong to LA-SER, a private corporation."

The report also noted that SPMSD (Sanofi Pasteur MSD) "which commercialises Gardasil" had subscribed to the data.

Placebo-controlled study of Gardasil 9 (P006)

This is the only placebo-controlled study of Merck's two HPV vaccines where the control group did not receive adjuvant or the carrier solution but just saline.

The study was flawed by recruiting people who had tolerated Gardasil

Safety was a primary objective, but the study was flawed, as all patients had received three doses of Gardasil previously. Thus, those who had not received all three doses previously, e.g. because they had experienced harms, were not included in the trial. Furthermore, those who had not tolerated the three doses well were also unlikely to have been included. It is therefore likely that the trial underestimated the harms of Gardasil 9.

A secondary objective was to see if vaccination with five more antigens than the four in Gardasil would provide acceptable immunity to each of the additional antigens.

Unequal randomisation and very small sample size

Like in the carrier solution-controlled trial of Gardasil (P018), Merck randomised the participants in a 2:1 ratio, 618 vs 306 females, which reduces the chance of detecting any harms of the vaccine, compared to the usual 1:1 ratio. This fact, and the very small sample size, and considering that Merck had already randomised about 30,000 people in its HPV vaccine trials to vaccine and adjuvant when this trial started, illustrated yet again Merck's lack of interest in finding out what harms its vaccines cause.

Inadequate testing of safety

The study was similarly designed as Merck's other studies and suffered from the same flaws. Although the only primary objective was safety, "The important variables of interest for safety/tolerability were the occurrence of injection site adverse experiences prompted for on the VRC [vaccination report card] (such as

redness, swelling, and pain/tenderness/soreness occurring Day 1 through Day 5 following any vaccination) and elevated temperature (≥100.0°F [≥37.8°C]), from Day 1 to Day 5 following any vaccination"

"Other important variables of interest included severe injection-site adverse experiences and the incidence of any vaccine-related serious adverse experiences ... Follow-up at Months 2, 6, and 7 after the first injection included an interview to assess general safety. The interview solicited broadly for any serious adverse experiences that the subject may have encountered."

This was not an appropriate way to study safety of a vaccine in the only genuinely placebo-controlled study Merck ever carried out. Systemic adverse experiences were not even mentioned, apart from those extremely few that are serious and which the investigators consider vaccine related. As I show in my meta-analyses (Appendix A), the investigators in Merck's studies considered that only 1% of the serious adverse events were vaccine related and as there were a total of only 14 such events in trials including 48,962 patients, this is an incidence rate of 0.03%. Thus, in the placebo-controlled trial of only 924 females, one would not expect to find a single person with vaccine related serious adverse events (as 0.03% of 924 is 0.3).

Merck had already assembled data from tens of thousands of patients in other vaccine trials before they started the placebo-controlled trial in February 2010. Merck therefore *knew* that they would not expect to find a single person with vaccine related serious adverse events in this trial.

In case the investigators should report any non-serious systemic adverse events, Merck had ensured that this was unlikely to detract from its mantra that the vaccine was "well tolerated" because "the analysis of safety parameters" was limited to "*specific* [my emphasis] systemic adverse experiences within 14 days following any vaccination occurring in ≥1% of subjects in any vaccination group."

Misleading conclusions and interpretations

Merck's conclusion was misleading. As in its other studies, Merck concluded that Gardasil 9 was "generally well tolerated" despite the fact that 91% of the patients experienced injection site adverse events on Gardasil 9 versus only 44% on placebo. I calculated that $p = 1 \times 10^{-52}$ for this huge difference. The likelihood that it had occurred by chance is the same as the likelihood that a person can guess this number with 52 digits correctly: 5074573868335562843078316354228395742053952447378508.

The injection site reactions were not trivial either: 24 vs 1 experienced severe reactions (p = 0.0008) (which means incapacitating with inability to work or do usual activity), and 240 (39%) vs 12 (4%) experienced moderate or severe reactions ($p = 6 \times 10^{-36}$) (moderate means discomfort enough to cause interference with usual activities). Merck did not provide any such calculations.

Merck's standard conclusion, that its vaccine is well tolerated, is written before the trials are undertaken, and it doesn't matter what Merck finds in its trials; the foregone conclusion remains unaltered.

Merck wrote in the text that the incidence of 91% for injection-site adverse experiences in the vaccine group "was numerically higher" than the 44% incidence in the placebo group without saying that the difference was statistically significant, with an extremely small p-value. "Numerically higher" is an expression researchers use if the numbers are higher, without being statistically significantly higher. Merck therefore seriously misled the readers of its report.

Merck claimed that the "overall safety and tolerability profile" of its vaccine "was acceptable" and that the findings were "generally consistent" with what Merck had found previously for Gardasil. None of this was true. Moreover, Merck's findings were not consistent with earlier findings but highly inconsistent, which I show in my meta-analyses.

Selective Reporting and Missing Data

There was selective reporting *within* Merck's study report. Merck described that, after 7 months, all patients who had received placebo were eligible to receive the vaccine under a study extension, but there were no data from this extension in the study report.

Merck noted that, "Adverse experience data for the entire study period is presented in Appendix [16.4]." This appendix 16.4 was also missing. It was mentioned again on the very last page of the study report:

16. LIST OF APPENDICES (CONT.)

Appendix		Application Starting Page
16.3:	CASE REPORT FORMS	
	Individual subject case report forms are not provided within the clinical study report.	
16.4:	INDIVIDUAL SUBJECT DATA LISTINGS	
	The Data Definition File page contains a list of the individual case report tabulations.	

When I compared two adverse events tables, I found that, during two weeks after each vaccination, 806 patients experienced adverse events, whereas there were only 6 more patients when the whole trial period was included. (See Appendix D, p10.) For systemic events (called non-injection-site events), the numbers were 533 vs 551, or only 18 (3%) more patients. As noted above, similar data can be found in Merck's other trials and they illustrate that the registration and reporting of adverse events was grossly insufficient.

Lack of blinding

The vaccine was a whitish, semi-translucent suspension and the placebo was a clear colourless liquid. To blind the study, Merck used highly elaborate procedures, which carried a great risk of unblinding: "The blinded study personnel waited outside the examination room while the unblinded personnel administered the vaccine/placebo and entered the examination room only when the unblinded personnel completed their responsibilities"

It is unclear why the vials were not produced centrally by Merck. They were stored in a refrigerator at the study site and I can therefore see no reason why they were prepared locally. Something could have been added to the placebo that made it look like the vaccine or the vials could have been blinded in other ways that did not involve a great risk of unblinding the investigators, e.g. by enclosing the syringe in a wrapping.

On top of this, Merck used additional unblinded personnel, which seemed totally unnecessary. As I have not seen such detailed revelations in Merck's other studies, I quote them here:

"9.4.5.5 Roles of Unblinded Sponsor Clinical Personnel: Unblinded Clinical Scientist, Unblinded Clinical Research Associate, and Unblinded Project Manager

Because the vaccine and placebo used in this study were visually distinguishable, the vaccine/placebo was prepared and administered by unblinded study personnel not otherwise involved in subject management. An unblinded CRA [Clinical Research Associate] was assigned to the study to monitor study procedures that involved the administration and accountability of the vaccine/placebo. An unblinded PM [Project Manager] was assigned to review all monitoring visit reports (MVR), track all unblinded MVRs and collate site issues

provided by the unblinded CS [Clinical Scientist] and unblinded CRA. In addition, an in-house unblinded CS was assigned to the study to ensure that no in-house Merck personnel directly involved in the conduct of the study were accidentally unblinded based on the appearance of the vaccine/placebo when communicating with the study sites."

New medical condition

As usual, reporting of "new medical conditions" was unclear. It was not made clear, for example, when dizziness was an adverse event and when it was a new medical condition: "new medical conditions not present at baseline and not reported as an adverse experience were to be collected throughout the study."

Dizziness, POTS and fever

Since Merck has only performed two small placebo-controlled trials, both with serious shortcomings, I looked at dizziness reported as an adverse event because it is a key symptom for POTS, often the one that lands patients in hospital. When I combined the two placebo-controlled trials in a meta-analysis, I found an increased risk for dizziness, which was statistically highly significant ($p < 0.00001$; risk ratio 1.69; 95% confidence interval 1.42 to 2.01). The number needed to harm was only 56.

There were three serious adverse events in each group. One patient reported syncope of moderate intensity with an onset 14 days after the second vaccination with Gardasil 9, lasting three days. The tilt test was positive, and the patient was diagnosed with dysautonomia. This patient is the one that came closest to a diagnosis of POTS that I have seen in Merck's study reports, but this diagnosis was not made by her cardiologist despite a positive tilt test and Merck did not use the word POTS in its study report. I searched POTS in the report but did not find anything. When I searched on postural, I found the curriculum vitae for Jesper Mehlsen, the head of the Danish Syncope Unit, because five of his publications contained the word "postural."

Merck found that significantly more patients had fever on Gardasil 9 than on placebo and reported the p-value in a table ($p = 0.026$), but Merck dismissed this finding: "The proportion of subjects who reported a fever during the 5 days following any vaccination was low in both vaccination groups and within the range reported in previous qHPV vaccine studies" This gave the impression that the vaccine *does not* cause fever.

Misleading trial report in *Vaccine*

As doctors and patients do not have access to Merck's study reports but only to the published medical literature, I looked at the published trial report.

The abstract of the article mentioned the huge difference in injection site reactions but provided no p-value and concluded, like Merck's internal report, that the vaccine was "generally well tolerated."[39] Four of the ten authors were from Merck and three other authors had received honoraria from Merck. As few people read beyond the abstract, it is less important what is in the rest of the article, but I read the whole paper.

The paper stated that, "Saline placebo was used as the control which allowed an overall assessment of the safety/tolerability profile of all vaccine components, including antigenic proteins and adjuvant," and it explained the increased occurrence of injection-site adverse events in the vaccine group this way: "given that a saline placebo was used, this difference represents the local reactions due to the antigen and adjuvant in the 9vHPV vaccine."

[39] Garland SM, Cheung TH, McNeill S, et al. Safety and immunogenicity of a 9-valent HPV vaccine in females 12-26 years of age who previously received the quadrivalent HPV vaccine. Vaccine 2015;33:6855-64.

This is the only time I have seen Merck coming close to admitting that it was inappropriate to use adjuvant as control in its trials, incorrect to call it a placebo, and wrong to give people the impression that the adjuvant is harmless.

"At each vaccination visit, most injection-site AEs [adverse experiences] were mild to moderate in intensity. The most common (incidence ≥2%) vaccine-related systemic AEs among subjects who received 9vHPV vaccine were headache, pyrexia, nausea, and dizziness (Table 2A). Few participants had a fever (≥37.8 °C) (Table 2B)."

This was scientifically inappropriate for three reasons.

First, it is misleading to write that most injection-site reactions were mild to moderate in intensity when $p = 1 \times 10^{-52}$ for the difference in occurrence, $p = 0.0008$ for severe reactions and $p = 6 \times 10^{-36}$ for moderate or severe reactions (see just above).

Second, Merck violated its own trial protocol that operated with a cut-off for reporting systemic adverse events of ≥1% (see V503 P006 CSR , p79) whereas ≥2% was the cut-off in the article.

Third, it is misleading to write that few participants had a fever when Merck had shown that significantly more patients had a fever on the vaccine than on placebo.

The Discussion section in the article was misleading. The vaccine was claimed to be "generally well tolerated" and it was repeated that "Injection-site AEs were mostly mild or moderate in intensity."

In contrast to the study report, the published article did not mention anything about new medical conditions.

The published article showed the following data for vaccine related systemic events:

Systemic event[c]	363	(59.7)	170	(55.7)
Vaccine-related[d] systemic event	186	(30.6)	79	(25.9)
Headache	119	(19.6)	55	(18.0)
Pyrexia	31	(5.1)	5	(1.6)
Nausea	24	(3.9)	6	(2.0)
Dizziness	18	(3.0)	5	(1.6)

I found the same numbers in a table showing such events in the study report ("Days 1 to 15 Following Any Vaccination Visit") (p415). However, there was also a table of new medical history conditions after day 1 (p426) that showed these numbers:

Headache: 9 vs 5
Pyrexia: 4 vs 1
Nausea: 1 vs 2
Dizziness: 1 vs 0.

The time periods for registering systemic adverse events and new medical history events overlapped and some of the patients in the two types of tables could have been the same. At any rate, it is scientifically inappropriate to register adverse events as new medical history events and then say nothing about them in the published trial report.

Two tables in the published article were contradictory. Table 2A, which was a summary of adverse events, listed 316 patients with mild injection site pain for the whole trial period ("Days 1-5 following any vaccination") whereas table 3 listed 368 such patients already after the first vaccine dose, also within the first 5 days. This is a mathematical impossibility. I found a table in the study report that showed that 368 patients had mild pain "post-vaccination 1" (p370) but in another table, 473 patients had mild pain "post-vaccination 1," listed under the subheading "General disorders and administration site conditions" (p325). As the table

header was “Subjects With Injection Site Adverse Events (Incidence >0% in One or More Vaccination Groups) (Days 1 to 5 Postvaccination 1) (All Vaccinated Subjects),” it is curious that there were now 473 patients and not 368.

Merck’s many tables in its study reports, 102 tables in this case, show that what Merck has reported in its clinical study reports cannot be trusted, neither in its study reports, nor in its published trial reports.

The large Gardasil 9 versus Gardasil study, P001

This trial, which included 14,215 patients, started six years after the Future 1 trial, but the procedures and the reporting were even more inadequate. The voluminous study report of 8000+ pages was written in such a way that obfuscated and downplayed the harms of Gardasil.

This study had two primary objectives:

“(1) Objective: To evaluate the tolerability of the 9-valent HPV L1 VLP vaccine when administered to 16- to 26-year-old women. Hypothesis: 9-valent HPV L1 VLP vaccine administered to 16- to 26-year-old women is generally well-tolerated.

(2) Objective: To demonstrate that administration of 9-valent HPV L1 VLP vaccine will reduce the combined incidence of HPV 31-, 33-, 45-, 52-, and 58-related high-grade cervical abnormalities (CIN 2/3), Adenocarcinoma In Situ (AIS), invasive cervical carcinoma, high-grade Vulvar Intraepithelial Neoplasia (VIN 2/3), high-grade Vaginal Intraepithelial Neoplasia (ValN 2/3), vulvar cancer, or vaginal cancer, compared with GARDASIL™ in 16- to 26-year-old adolescent and young adult women who are seronegative at Day 1 and PCR negative Day 1 through Month 7 to the relevant HPV type.”

Because of its sheer size, this is a pivotal study.

After six months, serious adverse events were only collected if someone (not specified by whom) determined them to be vaccine related or related to a study procedure, although it was a primary objective to evaluate the tolerability of Gardasil 9.

P-values were only computed for those adverse experiences that were prompted on the vaccination report card (two-week periods only) and for fever. Risk differences and 95% confidence intervals were computed for injection site adverse experiences, “specific systemic adverse events,” severe injection-site adverse events, serious adverse events, and fever.

When safety was first described, there was nothing about events the investigators considered vaccine related, in contrast to the Future trials. However, there were data on this in tables and it was described 128 pages later that this judgment was to be made in relation to the two-week registration periods only. It was also applied to serious adverse events, 90% of which occurred outside the two-week intervals after each vaccination. There was nothing about whether the systemic adverse events were mild, moderate or severe, but there were data on this.

Since serious adverse events are a subgroup of all adverse events, the difference in events when the three two-week periods are compared to the whole trial period should be exactly the same for serious adverse events as for all adverse events. This difference was 386 for serious adverse events but only 46 for all adverse events. This is an unexplained mathematical impossibility.

Merck claimed that the proportion of subjects with serious adverse experiences was “low and comparable” between the two groups. This was not accurate for several reasons.

1) The incidence of serious adverse events was not low; and the difference, 283 (3.3%) vs 183 (2.6%), was statistically significant, p = 0.01 (my calculation); and the number needed to harm was only 143. This was low and therefore alarming for a vaccine, which was not even compared with placebo but with another vaccine, because serious adverse events include deaths, life threatening events, persistent or significant disability, and hospitalization.

2) Merck violated its own protocol. The statistical analysis plan, and the three updates of this plan, all showed that a p-value would be computed for vaccine related serious adverse events for the whole trial period. Merck provided no such p-value.

3) The statistical analysis plan had glaring inconsistencies. Serious adverse events were only analysed if they occurred within the three two-week periods after each vaccination whereas serious adverse events considered vaccine related by the investigators were NOT analysed for this restricted period, only for the whole trial period. Whether considered vaccine related or not, serious adverse events must be analysed the same way, but Merck failed to analyse ALL events for the WHOLE trial period.

I have not seen any explanation for this approach to statistical analysis of potentially very important harms, only a statement that the approach was "commonly used by the SPONSOR when conducting safety assessments," which is not reassuring.

To only pay attention to serious adverse events that occurred outside three arbitrary two-week periods in a 3.5-year trial if the investigators, many of whom had financial conflicts of interest, considered them vaccine related increases the risk of biased conclusions.

4) Among Merck's 388 tables, I found only two with confidence intervals for serious adverse events. The large difference in serious adverse events, 233 vs 183 was totally gone. Instead, readers were presented with very small numbers, in an inconsistent fashion. The first table had 25 vs 17 events, which were ALL events in the three two-week periods (not only those considered vaccine related). The second table had 2 vs 2 events for the whole 3.5-year trial period, which were ONLY those events considered vaccine related. This was selective and inconsistent reporting to the extreme.

5) Merck tried to explain away the difference of 233 vs 183 serious adverse events by saying that most of them were related to pregnancy, e.g. elective and spontaneous abortion. However, in a randomised trial, one will expect pregnancy outcomes to be similarly distributed in the two compared groups, which Merck confirmed was the case: "In both vaccination groups, the most common serious adverse experiences were infections and pregnancy-related events. These events occurred at generally comparable frequencies among both vaccination groups."

The reporting of adverse events was insufficient. A total of 8009 patients reported one or more systemic clinical adverse experiences, but there were only 178 more patients when the registration period was increased from six weeks to 3.5 years. For events considered vaccine related, there were only 3 more patients.

Merck concluded that, "The proportion of subjects who reported systemic clinical adverse experiences was generally comparable in the 2 vaccine groups." However, more patients reported such events on Gardasil 9 than on Gardasil (p = 0.10) and the difference was significant for vaccine related events (p = 0.003), which Merck considered more important than all events.

More patients on Gardasil 9 than on Gardasil experienced nervous system disorders (p = 0.01), headache (p = 0.02) and dizziness (this difference was not statistically significant, p = 0.12, but when events are subdivided, a

true signal might not be statistically significant). The number needed to harm for nervous system disorders was only 50. The corresponding table for new medical history also showed that more patients on Gardasil 9 than on Gardasil had nervous system disorders, 515 vs 481.

Merck did not mention anything about this important and significant harm on the nervous system, but only drew attention to headache. In another table, about new medical history, three more patients experienced dizziness on Gardasil 9 than on Gardasil and three more patients had postural dizziness, which is a key symptom for POTS. This demonstrates that, by splitting adverse events arbitrarily into two categories, Merck made it more difficult to detect vaccine harms.

OTHER ISSUES:

The number of randomised trial participants unclear in Merck's tables

According to good scientific practice, tables should be self-explanatory so that readers will not need to read the main text to understand them. Conversely, the main text should be clear so that readers will not need to consult the tables to understand the findings. Merck's report did not live up to this universal standard for scientific reports.

The dose-ranging substudy was small and had four groups: three different doses of Gardasil 9 and one of Gardasil. The main study was called the efficacy substudy. It used data from only one of the three Gardasil 9 doses, the mid-dose, and data from the comparator group, the Gardasil group. It was difficult to find out exactly how many women had been randomised and how many had been included in which analyses, as the explanations were scattered around in various places in the large study report.

The report described that incorrectly randomised females were excluded from efficacy analyses, but it was not clear if they were also excluded from safety analyses or what happened to other protocol violators, even though it was stated that "All subjects who received at least one dose of 9vHPV vaccine or qHPV vaccine were followed for safety."

There was no flow chart of in- and excluded patients, with reasons, neither in this report nor in any other of Merck's reports, even though this has been the scientific standard for reporting randomised trials since 1996, nine years before Merck's trial started.[40] [41]

I did various calculations and arrived at a total number of randomised people of 14,840. This number was confirmed by looking up the trial in the EU trial register, which also stated that 14,840 people had been randomised.[42]

Misleading conclusions and contradictory data about safety

There were two tables of adverse events in the efficacy substudy, one for those noted in the three two-week periods after each vaccination and one for the whole trial period. (Appendix D, p 29-30):

[40] Begg C, Cho M, Eastwood S, et al. Improving the quality of reporting of randomized controlled trials. The CONSORT statement JAMA 1996;276:637-9.
[41] Altman DG, Schulz KF, Moher D, et al. The revised CONSORT statement for reporting randomized trials: Explanation and elaboration. Ann Intern Med 2001;134:663 94.
[42] https://www.clinicaltrialsregister.eu/ctr-search/trial/2007-003528-39/results#moreInformationSection

	Days 1 to 15		Whole trial period	
	Gardasil 9	Gardasil	Gardasil 9	Gardasil
with one or more adverse events	6640	6419	6661	6444
injection-site	6423	6023	6423	6024
non-injection-site	3948	3883	4052	3957
with vaccine-related' adverse events	6519	6200	6519	6202
injection-site	6422	6023	6422	6024
non-injection-site	2086	1929	2088	1930
with serious adverse events	25	17	233	183
with serious vaccine-related adverse events	2	1	2	2

Combining the Gardasil 9 and Gardasil groups, 42 patients experienced serious adverse events during the three two-week periods, which increased to 416 for the whole trial period. Thus, 90% of all serious adverse events occurred outside the two-week intervals after each vaccination.

Since serious adverse events are a subgroup of all adverse events, the difference between 416 and 42, which is 386, should also be the difference in all adverse events. This was not the case. There were 13,105 patients with adverse experiences in the whole trial period and 13,059 in the three two-week periods, a difference of only 46 patients. Merck did not describe this discrepancy and did not offer any explanation for it. Since the discrepancy should not exist – it is a mathematical impossibility; there are no assumptions at all – this shows yet again that the numbers in Merck's reports about adverse events are unreliable.

Misleading trial report in *New England Journal of Medicine*

The published trial report[43] is of overriding importance because this is where doctors and patients can get information about what the trial showed.

This article was misleading on eight counts.

1) The article stated that 14,215 women had been randomised, which was incorrect; the correct number was 14,840. Contrary to the usual scientific standard, there was no flow chart of patients, which would have revealed that the information on the number of randomised women was incorrect;

2) The only mention of adverse events in the abstract was: "Adverse events related to injection site were more common in the 9vHPV group than in the qHPV group." This downplayed the differences between the two vaccines. There were statistically significant differences in adverse events related to the injection site with extremely low p-values (my calculations; Merck did not provide any such calculations in its study report or in the published trial report);

3) The Background section noted that, "Analyses of clinical trial and post-licensure safety data have not identified safety concerns associated with HPV vaccination." There were eight references to this statement, but none to the most relevant trial, the placebo-controlled trial of Gardasil published 8 years earlier.[44] And none to one or more of the large and pivotal Future trials.

[43] Joura EA, Giuliano AR, Iversen O-E, et al. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. N Engl J Med 2015;372:711-23.

[44] Reisinger KS, Block SL, Lazcano-Ponce E, et al. Safety and persistent immunogenicity of a quadrivalent human papillomavirus types 6, 11, 16, 18 L1 virus-like particle vaccine in preadolescents and adolescents: a randomized controlled trial. Pediatr Infect Dis J 2007;26:201-9.

Not a single one of Merck's previous trials was quoted. All eight references were to observational studies or reviews. The most relevant one was a review[45] that stated in the abstract that it described five clinical trials, with a total of 21,480 participants, who had received qHPV (Gardasil) or placebo. But this was false. Only one of the five trials had used a placebo; the other four trials had used adjuvant as control. Two of the other trials reviewed were Future 1 and Future 2; Future 3 was not included (the study report was dated 17 November 2009, three months before the review was published). It was also incorrect when the abstract stated that, **"**All serious and non-serious adverse experiences (AEs) and new medical conditions were recorded for the entire study period(s)," as non-serious adverse experiences were only recorded for the three two-week periods after each vaccination. The review had 12 authors of which 7 were employees of Merck and held stock or stock options; the remaining 5 had all received personal financial support from Merck and four of them had received research grants from Merck. The author team could therefore not claim that they did not know better.

4) The 277-word long section in *New England Journal of Medicine*, "Primary hypotheses and end points," contained nothing about safety even though safety was one of the two primary objectives for the trial (see above). It was all about efficacy.

5) The 657-word long section "Statistical analysis" contained nothing about safety analyses even though safety was one of the two primary objectives for the trial. It was all about efficacy.

6) The reporting of adverse events was misleading, as it violated Merck's own protocol on several counts. There were no p-values and no confidence intervals and the cut-off for reporting was 2% and not 1%. About injection-site events, it was noted that "Events of severe intensity were more common in the 9vHPV group" (I found $p = 10^{-8}$ for this difference). There was nothing about serious adverse events in the text: "All the serious adverse events are listed according to system organ class in Tables S6 and S7 in the Supplementary Appendix."

There was a table of adverse events, listed for each group separately but without a single p-value or confidence interval. This table shows a line with "Serious adverse event," with 233 (3.3%) versus 183 (2.6%), but as it has 34 lines, this line can easily be overlooked, P = 0.01 for this difference (my calculation).

7) There was no mention of new medical history at all even though this is about adverse events; even though Merck put great emphasis on this in its study reports; and even though there were over 10,000 such events (see Appendix A, p21-3).

8) The Discussion section only mentioned that "Most adverse events related to the injection site were mild or moderate in intensity. Few participants discontinued study vaccination because of a vaccine-related adverse event." This was misleading. There was no information about the number needed to harm.

This article was published in one of the world's most prestigious journals, yet it contained numerous falsehoods on which countless doctors and patients relied. It cannot be said often enough that safety is more important than efficacy for a vaccine given to healthy children and young people for a risk that is rare.

Seven of the 27 authors were current or former employees of Merck and held stock or stock options in Merck; nine had received personal honoraria or other financial support from Merck; two had received a grant from GlaxoSmithKline, another HPV vaccine manufacturer; and one also personal honoraria. Only eight authors had

[45] Block SL, Brown DR, Chatterjee A, et al. Clinical trial and post-licensure safety profile of a prophylactic human papillomavirus (types 6, 11, 16, and 18) l1 virus-like particle vaccine. Pediatr Infect Dis J 2010;29:95-101.

not reported any conflicts of interest. The principal investigators had an agreement with Merck that restricted their rights to discuss or publish trial results after the trial was completed.[46]

Other Gardasil 9 studies

Study P002

The study is not of interest, as there was no randomisation to vaccine and placebo or another vaccine.

Study P003

The study is not of interest, as there was no randomisation to vaccine and placebo or another vaccine.

Study P005

The study is not of interest, as there was no randomisation to vaccine and placebo or another vaccine. Merck studied if Gardasil 9 could be administered simultaneously with a meningococcal vaccine and a vaccine against tetanus, diphtheria and pertussis. The usual mantras were applied: “generally well tolerated” and “favorable safety profile.”

Study P007

The study is not of interest, as there was no randomisation to vaccine and placebo or another vaccine. Merck studied if Gardasil 9 could be administered simultaneously with a vaccine against tetanus, diphtheria, pertussis and polio. The vaccine was “generally well tolerated,” but on this occasion, the safety profile was only “acceptable.”

Study P009

This study compared Gardasil 9 with Gardasil in 600 girls.

The summary table of clinical adverse events raises serious concerns. Although the heading states that the table summarizes clinical adverse events from day 1 to month 7, systemic adverse events are limited to days 1 to 15. There was no table in the report of systemic adverse events through month 7.

[46] https://www.clinicaltrials.gov/ct2/show/results/NCT00543543

Table 7. Clinical Adverse Event Summary
(Day 1 Through Month 7 Following Any Vaccination) - Safety Set

	9vHPV Vaccine (N=299)	qHPV Vaccine (N=300)
Number of subjects with	**N subj (%)**	**N subj (%)**
No adverse event	12 (4.0%)	19 (6.3%)
One or more adverse event	287 (96.0%)	281 (93.7%)
with one or more vaccine-related adverse event	279 (93.3%)	271 (90.3%)
Injection-site adverse reaction from Days1 to 5	274 (91.6%)	265 (88.3%)
Solicited injection-site adverse reaction	274 (91.6%)	265 (88.3%)
Injection site erythema	102 (34.1%)	88 (29.3%)
Injection site pain	267 (89.3%)	265 (88.3%)
Injection site swelling	143 (47.8%)	108 (36.0%)
Other injection-site adverse reaction	35 (11.7%)	42 (14.0%)
Systemic adverse event from Days 1 to 15	142 (47.5%)	156 (52.0%)
Vaccine-related systemic adverse event	62 (20.7%)	73 (24.3%)
Serious adverse event at any time	1 (0.3%)	2 (0.7%)
Serious vaccine-related adverse reaction	-	-
Death	-	-
Withdrawn due to an adverse event at any time	1 (0.3%)	1 (0.3%)
Withdrawn due to a vaccine-related adverse reaction	-	-
Withdrawn due to a serious adverse event	1 (0.3%)	1 (0.3%)

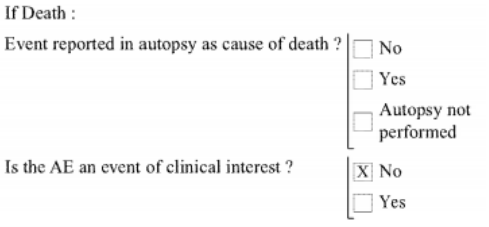
Merck operated with a “Condition of Particular Attention” and with “the Sanofi Pasteur MSD Specification 005261 List of Adverse Event of Special Interest (AESIs).” It is not clear what these are and where these conditions and events have been defined.

Even though the study was very small, more girls had a rise in temperature after Gardasil 9 than after Gardasil ($p = 0.059$).

Merck also found that more girls developed swelling after Gardasil 9 than after Gardasil and reported $p < 0.05$ in the text; the exact p-value is 0.004, my calculation), but Merck tried to dismiss this finding: “The significance of the finding of higher incidence of swelling in subjects administered 9vHPV vaccine vs. subjects administered qHPV vaccine is uncertain. It could be either due to lack of multiplicity adjustment (i.e. false positive finding) or possibly related to the higher amount of VLPs [virus like particles, i.e. antigens] and adjuvant contained in the 9vHPV vaccine compared to qHPV vaccine.”

However, not only was the p-value low, but Merck’s other trials clearly showed that the increased incidence of swelling could not be a chance finding. I showed that $p = 3 \times 10^{-45}$ for the difference in swelling between Gardasil 9 than after Gardasil in the largest trial that has compared the two vaccines.

In contrast to all Merck’s other study reports, this one included case report forms as filled out by the investigators. Even though only three of the 600 patients developed serious adverse events, there were 2094 pages with case report forms. They were revealing, but somewhat confusing. When I tried to find the girl with epilepsy, I discovered that there were three different identifiers for that person: AN 51128, baseline number 0603-00017, and case reference number E2011-02911. Most curiously, although the event was serious for two reasons: the patient was hospitalised, and it was “Persistent or significant disability/ incapacity,” the investigator did not consider the epilepsy of clinical interest:



This patient also had headache and throat pain. Many pages later, there was a more comprehensive narrative than the one in the main text of the study report:

ADVERSE EVENT REPORT

Sanofi Pasteur MSD (Europe)
8 rue Jonas Salk
LYON Cedex 07
69367
FRANCE

AER NO: E2011-02911()
?

REPORT TYPE : Serious
INITIAL RECEIVED DATE: 09/MAY/2011
PROVINCE/COUNTRY: SWEDEN
OTHER ID NOS:

FROM:
LATEST RECEIVED DATE: 02/APR/2012

PATIENT ID	DOB	AGE	AGE GROUP	SEX
UNKNOWN	REDA... 1996	14 Years	Adolescent	Female

This narrative described in much more detail the precursor events and also showed that she had two other seizure episodes while she was hospitalized. The narrative did not have as identifier the AN 51128 (as in the main text), or the baseline number 0603-00017 (as in the case report forms), but the case reference number E2011-02911.

This illustrates that it can be difficult to follow individual patients in Merck's reports. All in all, the case report forms for this patient took up 140 pages (some were blank, e.g. those related to pregnancy).

It is laborious for clinical investigators to report serious adverse events. One would therefore expect such events to be considerably underreported in Merck's trials. It is also clear that much more comprehensive narratives of serious adverse events exist than those Merck provided in most of its clinical study reports.

Study P010

The study is not of interest, as there was no randomisation to vaccine and placebo or another vaccine. The study compared the vaccine with itself: two doses versus thee doses of Gardasil 9 in 1518 people, and it was not blinded.

The design of the study was inappropriate, as the age groups were not comparable. Those who received two doses were girls and boys, 9 to 14 years of age, while those receiving three doses were young women, 16 to 26 years of age.

Merck found that more patients reported adverse events on three doses than on two, which they explained was for the apparent reason that the former patients had one more "vaccination episode around which adverse events can occur."

As always, the vaccine was "generally well tolerated."

Study P020

This study compared Gardasil 9 with Gardasil. The design and reporting were very similar to that for P009, but in this study, boys and young men were randomised, 249 vs 251.

The summary table of clinical adverse events from day 1 to month 7 was equally misleading as in study P009, as systemic adverse events were limited to days 1 to 15. There was no table in the report of systemic adverse events through month 7.

Merck claimed that numbers were "comparable." There were 17 more patients with injection-site reactions on Gardasil 9 than on Gardasil ($p = 0.09$, my calculation). It is inappropriate to claim events were comparable in a study that is too small to likely find differences, and when large studies have clearly shown that Gardasil 9

causes far more injection-site reactions than Gardasil, which Merck knew because their report for study P020 was from December 2015.

Another sign of increased harm with Gardasil 9 was that lymphadenopathy was reported for 6 patients, all from the Gardasil 9 group. This difference is statistically significant (p = 0.03, my calculation). Merck also reported that there was a significant difference: Merck called it a risk difference of 2.4, with a 95% confidence interval of 0.7 to 5.2, but forgot the percentage sign. The correct result is a risk difference of 2.4%. Thus, the number needed to harm was 41.

Merck tried to explain away this finding of harm by questioning that all 6 cases of lymphadenopathy had been considered vaccine related by the investigator, even though Merck otherwise put great emphasis on whether or not the investigators considered events vaccine related. Merck considered the relationship with the injection questionable for two of the patients because the adverse event began on the same day as the injection whereas it began between four and six days for the other four patients.

In this study Merck compared systemic adverse events only if they occurred "in at least 4 subjects in either group." This meant that events with an incidence below 1.6% did not count. In Merck's other studies, the standard criterion for non-reporting was 1%. Merck did not explain why they introduced this new, odd rule of 4 patients. This was yet another demonstration that Merck's approach to reporting adverse events is highly flexible.

V503 P021-01_Stat Report

This was an interim analysis of a 10-year follow-up of those females who were from Denmark, Norway and Sweden. Although it was a register-based study, it only included data reported before 2016 and there were no additional reports.

The blurred distinction between adverse events and new medical history was absolute in this report, as safety was the same as new medical history:

"4.4 Safety
Table 4-17 displays the number and percentage of subjects with new medical history …"

The main study report mentioned that this follow-up study "will also assess antibody persistence and selected new medical history events." To pick and choose "selected" new medical history events is scientifically inappropriate, particularly considering that, "An important goal of the study was to evaluate the safety and tolerability of the 9vHPV vaccine."