Expert Report

Effect of DTP Vaccines on Mortality in Children in Low-Income Countries

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Summary

A WHO systematic review from 2014 assessed the effect of three vaccines on total mortality in infants and children: BCG (Bacille Calmette-Guérin), DTP (diphtheria, tetanus, and pertussis) and measles.

I updated the literature searches and found two highly relevant studies where the researchers had improved on their previous research in response to the criticisms raised in the WHO report. They found that the DTP vaccine doubled mortality, confirming their previous findings. In one of their studies, which represents the best available evidence, they explained that the criticisms raised in the WHO report were either not relevant, or they had taken it into account. They found that all the documented biases favored the vaccinated group, i.e. they had likely underestimated the harmful effect of the DTP vaccine on mortality.

The researchers provided a statistical summary (meta-analysis), of the only three studies of the introduction of DTP in Guinea-Bissau. They found that DTP vaccination was associated with a hazard ratio of 2.14 (1.42 to 3.23) compared with DTP-unvaccinated children. They also found that all studies of DTP, which analyzed existing data sets collected for other purposes, suffered from substantial frailty and survival bias that lead to underestimation of the harms of the vaccine.

There were major problems with the WHO report. Although it found that most studies showed a deleterious effect of DTP, the authors concluded that the results were inconsistent because two studies showed a beneficial effect. However, they did not find a significantly beneficial effect on mortality, and they were so seriously biased that they should not have been taken into account.

The authors did not provide summary estimates because the WHO Working Group had requested that meta-analyses not be done.

This is an unacceptable interference with research by a body that includes people with numerous financial conflicts of interest in relation to vaccines. Furthermore, the reasons offered for not performing meta-analyses were invalid. It is difficult to explain unless one assumes that the WHO did not want to run a risk of receiving a systematic review that suggested that the DTP vaccine increases total mortality.

WHO's experts that advised against using meta-analysis wrote, after having seen the WHO report, that the data suggested that both the BCG vaccine and the measles vaccine reduce all-cause mortality. However, when I did meta-analyses of the randomized trials, I did not find significant reductions in mortality. Therefore, the experts could not conclude that both vaccines reduce total mortality without including also the non-randomized studies in their deliberations. In contrast, for the DTP vaccine they dismissed the non-randomized studies. This is inconsistent and scientifically unacceptable, particularly considering that the results for the cohort studies for the BCG and the measles vaccines varied equally much as those for the DTP vaccine.

The most important principle in medical ethics is: First, do no harm. I believe that the DTP vaccine should not be used unless being one of the interventions in a large randomized trial.

Contents

I. Introduction

I analyzed the strengths and weaknesses of the WHO systematic review from 2014 (1) regarding the effect of the diphtheria, tetanus, and pertussis (DTP) vaccine on total mortality and conducted a review of the literature and analyzed any studies published after the WHO report, which assessed the effect of DTP vaccine on total mortality.

The literature searches for the WHO report were carried out on 27 November 2012 (1). I did a search on PubMed (US National Library of Medicine) from 27 November 2012 till 15 February 2019 using the strategy: *(DTP or Diphtheria-Tetanus-Pertussis) and (mortality or death or deaths or survival)*.

The search identified 155 records, 20 of which had any bearing on the issue. Two of the records were abstracts of research articles, from 2017 (2) and 2018 (3), respectively, which were highly relevant because the researchers, Professor Peter Aaby and colleagues, had improved on their previous research in this area in response to the criticisms raised in the WHO report in 2014. As indicated below, I have obtained additional information from Aaby for my report.

First, I shall describe these two articles because a careful assessment of them makes it easier to understand the shortcomings in the WHO report, which I shall describe next. By the end of my report, I shall briefly mention the remaining 18 records.

II. Peter Aaby's 2017 Study

The study was carried out in Guinea-Bissau (2). The researchers examined the effects of the introduction of the DTP and the oral polio vaccines (OPV) in an urban community in the early 1980s. The child population had been followed with 3-monthly nutritional weighing sessions since 1978. From June 1981, DTP and OPV were offered from 3 months of age at these sessions. Due to the 3-monthly intervals between sessions, the children were allocated by birthday in a 'natural experiment' to receive vaccinations early or late between 3 and 5 months of age.

The researchers included children who were less than 6 months old when vaccinations started and children born until the end of December 1983. There were 1452 children in the total cohort, 1356 of which were followed till 3 months of age. There were 1057 children in the analyses (78% of 1356). Of the children not in the analyses, 220 did not get the scheduled 3-monthly examinations; for 66, the vaccination card was not seen; 4 had inconsistent vaccination information; 5 an unknown vaccination date; and 4 were orphans.

Three groups of children were analyzed according to what happened when they were 3-5 months of age: 662 children were vaccinated, 186 attended weighing sessions but were not vaccinated (the child was sick, the nurse was sick, there were no vaccines or syringes, or other reasons; Aaby, personal communication) and 209 did not attend weighing sessions. The three groups were very similar, e.g. for birth weight and weight-for-age before the first examination.

The three DTP and OPV doses could be given with an interval of one month but since the researchers only arranged weighing every three months, most children had longer intervals between doses. DTP was administered intramuscularly and OPV as an oral drop.

To avoid survival bias, the researchers used a landmark approach where a child's vaccination status was only updated on the day the information was collected (4). This is to avoid the so-called immortal person-time where children are not at risk of dying between date of vaccination and date of visit, whereby the survival bias places immortal person-time in the vaccinated group. Several previous studies of mortality have not avoided this bias, which can be very large. Aaby and colleagues found that the mortality rate ratio between vaccinated (any vaccine) and unvaccinated children changed from 0.74 (95% confidence interval 0.53 to 1.03) in the landmark approach to 0.18 (0.15 to 0.22) in the retrospective updating approach (4).

Due to additional vaccination sessions organized by the nurse some "unvaccinated" children received a vaccine before the weighing session where they changed status to "vaccinated." Of 651 unvaccinated children, 219 received DTP and/or OPV before their first weighing examination (to enter the unvaccinated group, the children should have been seen with a previous examination before 3 months of age. If a child had not been examined before 3 months but came at 4 months, it would be offered vaccination and count as vaccinated but count as unvaccinated between 3 and 4 months of age before being vaccinated; Aaby, personal communication). As a sensitivity analysis, the researchers did an analysis including the additional vaccination sessions as landmarks. in the landmark approach to 0.18

A. Allocation to the Three Groups

The allocation by birthdate meant, for example, that children who were just over 3 months old at the time of the 3-monthly weighing sessions were vaccinated at that age while those who were just below 3 months old would be vaccinated for the first time at almost 6 months of age (2).

As just noted, the allocation to the three analyzed groups depended on more than the birthdate, however. Sick children were not vaccinated. In the main analysis, the researchers censored 'unvaccinated' children who attended a weighing session but did not receive a vaccination. Since this could have introduced bias, they also conducted an intention-to-treat analysis in which the unvaccinated children were included in the DTP group.

Children who travelled and never attended any session were not included in the 'unvaccinated' group.

Time spent as DTP-unvaccinated also came from children who did not turn up at the weighing sessions between 3 and 5 months of age but had been seen before 3 months of age and therefore were part of the community cohort. “Hence, the DTP-vaccinated and DTP-unvaccinated children were all children from the same cohort of children born in Bandim and their allocation depended on the timing of their birth date, the timing of the weighing sessions and their traveling pattern” (1).

B. Statistical Analysis

The authors compared mortality between 3 and 5 months of age of DTP-vaccinated and not-yet-DTP-vaccinated children using Cox proportional hazard models with age as independent variable.

C. Results

Having received DTP (± OPV) was associated with a mortality hazard ratio (HR) of 5.00 (95% confidence interval 1.53 to 16.3) compared with not-yet-DTP-vaccinated children. When vaccinations given on vaccination days without weighing were included in the landmark analysis, DTP (±OPV) compared with unvaccinated children was associated with a HR of 3.90 (1.20 to 12.3). The intention-to-treat analysis gave a similar result, HR 3.92 (1.20 to 12.8).

The harmful effect was particularly strong for children who had received DTP only, without the OPV (HR 10.0; 2.61 to 38.6).

D. Discussion

The authors mentioned that their result may be conservative because the unvaccinated children had slightly worse nutritional status (weight-for-age) before 3 months of age than the children who were subsequently DTP vaccinated (p = 0.09) and because the unvaccinated children travelled more than the DTP vaccinated children (which exposes them, for example, to malaria; the study was performed in an urban community).

The misclassifications caused by the fact that some 'unvaccinated' children had already received a vaccination before coming for a weighing session could not explain the increased mortality in the DTP group. The estimate for DTP-vaccinated (± OPV) compared with DTP-unvaccinated children was a 4-fold higher mortality when these additional landmarks were included in the analysis.

The authors noted that there was only one other study of the introduction of DTP (conducted by themselves and published in 2004 (5), not in an urban community, but in rural Guinea-Bissau). In this study, DTP (± OPV) was associated with a doubling in mortality. They wrote that all studies that documented vaccination status and followed children prospectively have indicated that DTP has harmful effects; in a 2016 meta-analysis of eight studies (6), they found a doubling in mortality for DTP-vaccinated compared with DTP-unvaccinated, mostly BCG-vaccinated children (Bacille Calmette-Guérin, against tuberculosis). The authors also referred to the harmful effect of high-titer measles vaccination in girls, which led to the global withdrawal of this vaccine, and to their finding from 2003 (7,8) that this harm was due to the administration of DTP *after* the measles vaccination (they have demonstrated in several studies that the sequence of live and non-live vaccines may influence their outcome on total mortality).

The harmful effect of DTP was worse in their natural experiment than in previous studies. The authors argued that this is presumably because some of the unvaccinated control children in previous studies were too frail to get vaccinated (e.g. they might have been ill).

The authors referred to several of their previous studies, which suggested that the oral polio vaccine likely decreases total mortality. It is a live vaccine and Aaby's group has published many papers that, in my opinion, when taken together, are quite convincing in terms of providing support to their hypothesis that live vaccines decrease total mortality while non-live vaccines increase total mortality. The authors referred to their own studies when they suggested that the harmful effect of DTP might be because it increases tolerance, i.e. the susceptibility to unrelated infections (a paper about this is under peer review; Aaby, personal communication). This seems a very likely explanation because it is impossible to predict what happens in terms of susceptibility to infections in general, of all types, when the immune system is being stimulated through vaccination, and because by far the most important cause of death in these children is infections.

The authors criticize other studies of DTP, which analyzed existing data sets collected for other purposes, and they have documented that all such studies suffer from frailty and survival bias. These studies have updated follow-up time for DTP-vaccinated children who survived whereas children who died without their vaccination status being documented were classified as "unvaccinated". Such procedures give a misleadingly high mortality rate in the unvaccinated group and introduces substantial bias (4) that makes it difficult to find a possible increase in mortality with DTP.

The authors have worked out a bias index based on this fundamental flaw (6). They found that all studies with prospective follow-up had a bias index below 2.0 and that this index was only 0.41 in their own study. The authors also commented on the WHO 2014 systematic review (1) initiated by the Strategic Advisory Group of Experts (SAGE), which is the principal advisory group to WHO for vaccines and immunization (1,9). In 2012, SAGE requested that WHO review the evidence concerning the possible non-specific effects of routine infant vaccines on mortality. The systematic review performed on behalf of SAGE found that most studies showed a deleterious effect of DTP, but the authors concluded that the results were inconsistent because two studies showed a beneficial effect.

These two studies were from Bangladesh and Papua New Guinea, and the latter actually did not find a significantly beneficial effect on mortality, as the effect was 0.48 (0.22 to 1.09) (1). Aaby and colleagues did not find the results of these two studies surprising because the mortality rate in the unvaccinated group was unnaturally high and the bias index was 3.40 (2.93 to 3.95) and 7.52 (5.15 to 10.97), respectively. I shall come back to these two studies when I assess the WHO systematic review below.

The SAGE working group emphasized that the overall effect remains unclear because DTP had been given in combination with other vaccines and under circumstances where the burden of the target diseases had been reduced to a very low level. Aaby and colleagues also rejected these arguments.

E. Conclusion

The study has some shortcomings as described above but far less so than other studies in this area. Based on my review and survey of the literature relating to DTP and mortality, this study represents the best available evidence on mortality changes caused by the DTP vaccine.

III. Peter Aaby's 2018 Study

In this study (3), the researchers reported on mortality in children older than the 3-5 months at the start of vaccination, also from their health project in Guinea-Bissau. They reported on mortality in children aged 6 to 35 months.

The methods were similar to those used in the researchers' 2017 study, but there was no allocation by birthdate:

"In principle, children above 3 months of age attending the weighing sessions were offered vaccination if vaccines and equipment (syringes, sterilization stove) were available. However, nurses and mothers were reluctant to vaccinate sick or weak children. Other reasons for not being vaccinated were that the children were temporarily traveling, or that they stayed for prolonged periods in the rural areas where access to health

care was limited and child mortality was higher. Thus, apart from the specific disease-protective effect of DTP, inherent biases would lead one to expect that DTP-vaccinated children had better survival than DTP-unvaccinated children."

There were 1276 children in the total cohort, and for 386 of these, the follow-up ended before the introduction, leaving 890 children in the relevant part of the cohort. There were 702 children in the analyses (79% of 890). Of the children not in the analyses, 73 did not get the scheduled 3-monthly examinations; for 107, the vaccination card was not seen in 2015 (and may never have been made because the child did not attend a weighing session (Aaby, personal communication); as this was 34 years after the introduction of the vaccine, the amount of missing data was very low); 2 had an unknown vaccination date; 3 were orphans; and 3 had a "rare vaccination status".

A. Statistical Analyses

Analysis 1

"We compared DTP-vaccinated children and those who were not DTP-vaccinated when they came for their first weighing session after the introduction of vaccinations in June 1981. Since not all children were included, the analysis had less power. We followed children from their first weighing session and until they received their next vaccination or they migrated, died, or turned 3 years of age. Thus, children had to be present at a weighing session to be included in this analysis and we could adjust for the weight-for-age z-score (WAZ) obtained at that session."

Analysis 2

Children were considered DTP-vaccinated from the date they received their first DTP vaccination. Children were considered DTP-unvaccinated from the date vaccination was first offered in their sub-district, irrespective of whether they were present at the weighing session, and until they were DTP-vaccinated at a subsequent session, migrated, died, or turned 3 years of age.

"The difference between this analysis and Analysis 1 was that children were considered DTP-unvaccinated if they were age-eligible, irrespective of whether they had attended a weighing session or not, and vaccination status could change during follow-up, so a child could contribute risk time first as DTP-unvaccinated and then as DTP-vaccinated."

Analysis 3

"We compared mortality of children according to their most recent vaccination status; DTP-vaccinated children were compared with children who had received no vaccination or live vaccine only (measles, oral polio vaccine, or both) as their most recent vaccination."

A Cox proportional hazard model was used, adjusting for age. In analysis 1, the analysis was also adjusted for nutritional status (WAZ score). To avoid survival bias, a landmark approach was used in all analyses (4).

The authors did a meta-analysis of the only three existing studies of the introduction of DTP, all their own, from Guinea-Bissau, including the present one (3). They described other unique characteristics of their studies: the nutritional status was worse for children not vaccinated; most dates of vaccination were known because they administered nearly all vaccines; there were no campaigns with other vaccines or micronutrient supplements at the time of the studies; and reporting bias was not an issue because they represented all the data sets available on the introduction of DTP in Guinea-Bissau.

B. Results

Before they reached 3 years of age, 82% and 84% had received at least one dose of the DTP and oral polio vaccines, respectively, the median ages of vaccination being 633 vs 614 days. Only 38% and 49% of the children received all three doses of DTP and OPV, respectively, before 3 years of age. Due to earlier measles vaccine campaigns, 82% had received a measles vaccine at a median age of 348 days.

There were 42 deaths: 14 had fever as the main symptom, 13 had diarrhea or diarrhea and vomiting, 6 died from measles, 1 had respiratory infection, 1 was malnourished, 1 had anemia, 1 did not eat, and 5 had no information, most likely because the mother/family had moved.

In contrast to the 2017 study, the two groups were not comparable at baseline. Compared to children who remained DTP-unvaccinated until at least 3 years of age, the DTP-vaccinated children were far more likely to have attended weighing sessions (2.6 vs 0.9 sessions per year), to have received measles vaccine in the campaigns (71% vs 58%), or to have received DTP at the Mother and Child Clinic before June 1981, i.e. before the project started (6% vs 0).

Analysis 1

At the first weighing session after the vaccinations started in June 1981, the WAZ was much higher for the children who received DTP (WAZ −0.83) than for those children who did not receive DTP (WAZ −1.17). DTP vaccination at the first weighing session was associated with a non-significant HR of 2.22 (95% CI 0.82 to 6.04) adjusted for WAZ. In the unadjusted analysis (only adjusted for age), HR was similar, 2.01 (0.74 to 5.41).

Analysis 2

Including all children in the cohort, following them to 3 years of age and allowing them to change status during follow-up when new information was collected at a weighing session, having received DTP was associated with a non-significant HR of 1.48 (0.72 to 3.06).

Analysis 3

Children who received DTP (with or without OPV) as the most recent vaccination had a HR of 1.77 (0.93 to 3.38) compared with children who had received a live vaccine or no vaccine at all, and the HR was 1.90 (0.92 to 3.94) if compared with children who had received live vaccine only. The authors reported that, in a sensitivity analysis, including also 47 children whose most recent weighing session had been before October 1980, the HR was 1.89 (1.00 to 3.55).

Studies of the introduction of DTP

In the three studies of introduction of DTP in rural and urban Guinea-Bissau, DTP vaccination was associated with a HR of 2.14 (1.42 to 3.23) compared with DTP-unvaccinated children.

The estimate for the current study used in the meta-analysis was the one derived from the sensitivity analysis, HR 1.89 (1.00 to 3.55). The authors should not have used an estimate from a likely non-planned sensitivity analysis but one of the other estimates, which were: 2.22 (0.82 to 6.04), 1.48 (0.72 to 3.06) and 1.77 (0.93 to 3.38). This is not a major problem, however, because, if they had used one of these, their meta-analysis estimate would have been much the same. The original authors were against using the result from the sensitivity analysis in their meta-analysis; this was requested by a peer reviewer (Aaby, personal communication).

C. Discussion

"Although lower mortality was expected for

DTP-vaccinated children compared with the frail unvaccinated children, DTP vaccination was associated with higher mortality."

As the authors pointed out, the inherent biases in the study are clearly in favor of the DTP vaccine. The unvaccinated children were usually children deemed too sick or too weak to be vaccinated, as evidenced by the nurse's notes and by the fact that these children had worse nutritional status. They also attended the weighing sessions far less often and were therefore more likely to be staying for longer periods in the rural areas where the mortality risk was higher (mortality information from these children was obtained because their father and other relatives stayed in the study area).

I find Aaby and colleagues' studies quite convincing. They represent some of the best evidence we have and suggest a doubling in mortality when the DTP vaccine is used in children in a low-income country.

IV. WHO Experts & Committees

WHO experts have argued that the harmful effect of DTP is exaggerated because studies have only been conducted in situations with herd immunity against pertussis where the benefit of preventing pertussis would not be seen. Aaby and colleagues noted that, "However, pertussis was endemic in the 1980s before the roll out of the vaccination program in Guinea-Bissau."

Various WHO committees have previously reviewed the non-specific effects of vaccines and have dismissed the possibility that DTP could have harmful effects and have suggested that the seemingly harmful effect of DTP is likely explained by confounding factors. However, as Aaby and colleagues pointed out, it is important to consider the *direction* of bias and they argued that all the documented biases favored the vaccinated group.

It is important also to consider the four potential biases, which the WHO SAGE review mentioned would favor the unvaccinated group (1), and Aaby and colleagues' responses to them.

First, according to the SAGE review, sick children might come more often to a health center for consultation and, therefore, be more likely to receive DTP, since WHO has recommended vaccination of sick children. "This bias was clearly not relevant in Guinea-Bissau, where neither nurses nor mothers thought that a sick child should be vaccinated." Furthermore, the "data clearly showed that DTP vaccinations were delayed in unhealthy children. Hence, healthier children received DTP first, and DTP-unvaccinated children should, therefore, have had a higher mortality rate."

Second, starting follow-up from a survey sometime after the actual DTP vaccinations had been administered, as would often happen in a setting where vaccination information is collected with intervals, could potentially mean that frail children in the unvaccinated group had already died, and that the DTP-vaccinated children, therefore, had an "unnaturally" high mortality. However, "the one study testing this found no evidence for such a bias." "More importantly, several studies, including all three studies of the introduction of DTP in Guinea-Bissau, started observation at the date of vaccination for almost all children and found strong negative effects. Hence, this bias was not relevant."

Third, censoring follow-up at subsequent measles vaccination would remove some of the best children from the DTP-vaccinated group

and cause higher mortality in the DTP group. "The studies that have tested this potential bias have not found evidence for such a bias." "More importantly, several studies - like the present one - did not censor for measles vaccination and found equally strong negative effects for DTP."

Fourth, it has been discussed whether a bias in reporting could have played a role. "We have now reported all the possible data sets from when DTP was introduced in both urban and rural areas of Guinea-Bissau … all showed a negative effect of DTP vaccination. Hence, reporting bias is not relevant in relation to the studies of the introduction of DTP from Guinea-Bissau."

I agree with Aaby and colleagues that the various biases suggested by the WHO experts cannot explain their findings of a harmful effect of the DTP vaccine; in fact, the biases are likely to have underestimated this harm. We do not yet know how to explain the phenomenon demonstrated in many studies that live vaccines seem to decrease total mortality while non-live vaccines increase total mortality. It has been suggested that live vaccines (e.g. BCG against tuberculosis and vaccinia against smallpox) induce innate immune training producing stronger proinflammatory responses which may lead to protection against unrelated infections; and that non-live vaccine may induce tolerance which could enhance the susceptibility to unrelated infections (3).

V. The WHO 2014 Systematic Review

As already noted, in 2012, SAGE requested that WHO review the evidence concerning the possible non-specific effects of routine infant vaccines on mortality (9).

The SAGE report describes the results of a systematic review of the evidence concerning the effects of the BCG vaccine, DTP vaccine and measles vaccine on total mortality when routinely administered to infants and children (1). The review was not limited to low-income countries, but all included DTP studies were from such countries.

When possible, the authors reported on mortality at age 5 years. Children who had received medium or high titer measles vaccine were excluded. (Epidemiological studies have found that the high titer measles vaccine increases mortality compared to standard titer vaccines (7,8,10)).

To avoid double counting, information about overlap of studies, i.e. when some children had been included in more than one paper, was obtained from study authors.

A. Assessment of the Risk of Bias in the Studies

The authors used the Cochrane Collaboration tool for assessing the risk of bias in randomized trials (11). For non-randomized studies, also called observational studies, they used a version of a tool under development by the same team that developed the randomized trials tool, considering methodological issues specific to the vaccine research area.

The authors appeared to have assessed the risk of bias in the studies carefully. For example, they considered these issues:

(i) Were the methods of assessment of vaccination status comparable for participants with different outcomes?
(ii) Was the approach to analysis 'landmark' or 'retrospective'?
(iii) If a retrospective approach was used, is it

unlikely that substantial numbers of dead children have been assigned to the wrong vaccination status?

"A very high risk of bias would arise if follow-up started somewhat after vaccines were administered in such a way that vaccines had potential to affect mortality rates before the start of follow-up" (1).

For each of the three vaccines, the authors summarized the overall risk of bias, considering all the studies together, using the GRADE approach recommended for all WHO reviews. The authors did not describe this tool in their report or provided a reference for it, but just showed their results. Since all three authors on the WHO report do work for the Cochrane Collaboration, I downloaded the Cochrane description of the GRADE tool (12).

The GRADE tool was developed for assessing the quality of randomized trials. I find it problematic that the authors used a version of this tool under development for observational studies, and I am also concerned about the way they used it. The authors described their approach this way: "Because in each case a large majority of the included evidence is from non-randomized studies, the starting point for each assessment is a score of 2 (equivalent to the interpretation 'Our confidence in the estimate of the effect on the health outcome is limited'). The score can be decreased or increased according to specific factors. In no instance did we regard it appropriate to increase the score, and in most instances, we had less confidence so assigned a score of 1 (equivalent to the interpretation 'We have very little confidence in the estimate of the effect on the health outcome')."

In terms of the GRADE tool, as it is currently being used by authors of Cochrane reviews, this approach means that if a study was not randomized, the quality of the evidence was automatically called "low," and if there was just one additional limitation with the research, the quality dropped to "very low" and could not drop any further. I shall discuss below what this means for the authors' conclusion about the possible harmful effect of the DTP vaccine, which I find they dismiss far too easily by their cook-book approach.

B. Statistics

The authors provided a number of traditional graphs of the mortality estimates for the individual studies that we are used to seeing in meta-analyses, but surprisingly, there were no meta-analysis summary estimates showing the overall effects of the vaccines on mortality, not even for the subset of studies for the BCG and measles vaccines that were randomized. This omission was not explained when the graphs were presented, which was very confusing, but much later in the paper: "Statistical synthesis: the Working Group requested that meta-analyses not be done, so none of the statistical syntheses are included in the report."

I consider this an unacceptable interference with research by a body that includes people with numerous financial conflicts of interest in relation to vaccines (see below). I have worked with meta-analyses for over 30 years and was the first person in the world to defend a Doctor of Medical Science thesis on meta-analyses in healthcare (13), but I have never seen a systematic review where the authors abstained from doing the obvious – combining the results in a meta-analysis – unless they were so heterogenous that it made no sense to do it. This was not the case for the randomized trials in the SAGE review (see below; I did such meta-analyses based on the SAGE data).

To prohibit the researchers before they even start doing their work to do meta-analyses on their collected data is difficult to explain unless one assumes that the WHO did not want to run a risk of receiving a systematic review that suggested that the DTP vaccine increases total

mortality. Researchers should *never* accept such *a priori* limitation on their research; they should abstain from doing the research.

In another document, I found out how SAGE had reasoned when they prohibited the researchers from doing meta-analyses (14):

"The Cochrane Handbook for Systematic Reviews stipulates that the use of single summary statistics from non-randomized studies should be discouraged. Another central issue is that sampling error can be very much smaller than uncertainties due to bias, selection, missing data, reporting so that even the use of 99% confidence intervals could be misleading. In addition to issues of statistical heterogeneity, and different levels of target diseases between populations (thus different specific-effect contributions to all-cause mortality), there is another fundamental reason to question the appropriateness of meta-analysis in this context. The hypothesis of non-specific effects implies protection against "other causes of mortality" than a vaccine's target disease. We do not know what these may be, precisely, but it is not unreasonable to suppose that they be different – and/or be present to different degrees or frequencies - in different populations. We should thus expect, *a priori*, that non-specific effects would be heterogeneous, and differ considerably between populations. This expectation fits the data to date. It has repeatedly been pointed out that much of the evidence to date comes from specific poor West African populations with high child mortality risks - risks which probably reflect particular infection conditions of these populations."

I reject these arguments, which I find reveal a substantial bias in the way SAGE argues. Their statements show that this expert group is far from being impartial.

First, I founded the Cochrane Methods Group on Non-Randomized Studies many years ago, which was based at my centre, the Nordic Cochrane Centre in Copenhagen. I therefore know how Cochrane experts have reasoned over the years about non-randomized studies. It was *never* the intention to say that one could never combine non-randomized studies in a meta-analysis. Accordingly, the Cochrane Handbook *does not* recommend against combining non-randomized studies in a meta-analysis. What it says is (11):

"13.6.2.2 Combining studies
Estimated intervention effects for different study designs can be expected to be influenced to varying degrees by different sources of bias (see Section 13.5). Results from different study designs should be expected to differ systematically, resulting in increased heterogeneity. Therefore, we recommend that NRS [non-randomized studies] which used different study designs (or which have different design features), or randomized trials and NRS, should not be combined in a meta-analysis."

This means that one may meta-analyze results from studies with similar research designs, for example a sample of cohort studies, and there are examples of this in Cochrane reviews (15). Furthermore, the introduction to the chapter about non-randomized studies (Chapter 13) mentions that, "For some Cochrane reviews, the question of interest cannot be answered by randomized trials," and that "Meta-analyses of non-randomized studies must consider how potential confounders are addressed." Section 13.1.2.2 notes that one of the most important roles for reviews of non-randomized studies is to assess potential unexpected or rare harms of interventions, and that, "A review should also try to quantify the harms of an intervention."

As randomized trials are rarely useful for identifying lethal harms of drugs and vaccines because they lack the power to demonstrate this, observational studies are of utmost importance, as a supplement to trials, and so are meta-analyses of observational studies.

Second, expected heterogeneity *is not* a reason to abstain from meta-analysis. On the contrary, as

I have argued (16), it is a good reason for doing meta-analyses, which may help to find out why there is heterogeneity and what it means if outliers are excluded from the meta-analysis.

Third, if a meta-analysis is not carried out, the investigators are prone to use less reliable methods to get an overview of the research question. This was exactly what happened. The authors of the WHO systematic review used vote counting, which is a method recommended against in the Cochrane Handbook! (see their faulty reasoning below.)

Fourth, the SAGE is biased when saying that, "The hypothesis of non-specific effects implies protection against 'other causes of mortality' than a vaccine's target disease" (14) It is remarkable that they say this when the concerns about non-specific effects are not about additional benefits but about increased mortality.

Fifth, as the argument just above exemplifies, the WHO seems to be inconsistent and biased towards positive effects of vaccines. When a result pleases the WHO, it can be accepted, but not when a result does not please the WHO. The same SAGE group that advised against using meta-analysis wrote, after having seen the report I am currently discussing (1) that, "The available data suggest that the current WHO recommended schedule for BCG vaccine has a beneficial effect on all-cause mortality and this should be emphasized" and that, "The available data suggest that the current WHO recommended schedule for current standard titer measles-containing vaccine has a beneficial effect on all-cause mortality in children" (9).

Although these conclusions were derived without meta-analysis, SAGE looked at the data and drew conclusions. It is clearly much better to combine the data formally, in a meta-analysis. I did two meta-analyses of the effect of the BCG and the measles vaccines. I only included the randomized trials. Based on the point estimates and the 95% confidence intervals in the authors' report (1), I calculated the natural logarithms of the estimates and of the standard errors and did an inverse variance meta-analysis with a random effects model using the Cochrane meta-analysis software, Review Manager (11). I checked that my calculations gave the correct estimates and confidence intervals for each study and arrived at these results:

For BCG, there were 5 randomized trials. The effect estimate for mortality was 0.70 (0.49 to 1.01, p = 0.06, I square = 33%). This means that there was a reduction in mortality that was not statistically significant, with acceptable heterogeneity, i.e. with minor differences between the mortality estimates in the five trials.

For the measles vaccine, there were 4 randomized trials. The effect estimate for mortality was 0.74 (0.51 to 1.07, p = 0.11, and I square = 0). This means that there was a reduction in mortality that was not statistically significant, with no heterogeneity.

It seems to me that in order for SAGE to arrive at the conclusion that both vaccines reduce total mortality, they would need to also include the non-randomized studies in their deliberations, as none of the estimates were statistically significant. They are therefore in the same situation as for the DTP vaccine where they, in contrast, decided to dismiss the evidence derived from the non-randomized studies. This is inconsistent, and it is unacceptable to argue in this way, particularly considering that the results for the cohort studies for the BCG and the measles vaccines varied equally much as those for the DTP vaccine (1): For BCG, there were 8 cohort studies, and 2 confidence intervals did not overlap with a third. For the measles vaccine, there were 16 studies, and 5 confidence intervals did not overlap with a sixth interval.

C. Results

For the DTP vaccine, there were no randomized trials. Fifteen cohort studies and one

case-control study were identified; six results from the cohort studies were considered to be at very high risk of bias and were presented separately at the bottom of the graph (which I have inserted at the end of my report). Oral polio vaccine (OPV) was administered concomitantly with DTP in most of the studies.

I find that the way the authors described their results demonstrated that they had a bias against the hypothesis that DTP increases total mortality. They seemed to try to avoid confirming this hypothesis. They wrote, for example:

"Excluding the results considered to be at very high risk of bias, the results of the 10 studies (all considered nevertheless to be at high risk of bias) produced diverse results, ranging from a halving of mortality risk after DTP administration to a four-fold increase in mortality risk after DTP administration."

The first author of the WHO review, Julian Higgins, is a statistician, and he is also the first author of the Cochrane Handbook for Systematic Reviews of Interventions (11), which is full of valuable statistical guidance for review authors. He knows that it is highly misleading to describe variations in research results by mentioning only their point estimates and not their confidence intervals (i.e. the uncertainly around the point estimate). Estimates can vary ten-fold and still be compatible with each other if the confidence intervals are very broad and overlap.

The four-fold increase in mortality the author mentioned is this one, from Guinea-Bissau: 4.33 (95% confidence interval 1.54 to 12.19). The large confidence interval shows that there were few deaths in the study and that the point estimate of 4 is rather imprecise. The halving of the mortality risk was seen in two studies, from Bangladesh and Papua New Guinea, respectively, and the estimates were 0.52 (0.31 to 0.87) and 0.48 (0.22 to 1.09). These confidence intervals do not overlap with that from Guinea-Bissau, but Aaby and colleagues have explained why these two studies are highly unreliable and biased in favor of the vaccine (2). Further, it appears misleading to use 0.52 (0.31 to 0.87) for the Bangladesh study (see below). As already noted, the mortality rate in the unvaccinated group was unnaturally high and the bias index was also very high, 3.40 (2.93 to 3.95) and 7.52 (5.15 to 10.97), respectively. Therefore, the finding that study results vary is not surprising. This can be explained and should not be used to dismiss the whole sample of studies.

There are additional, serious problems with the way the authors argued. They wrote that most of studies indicated a deleterious effect of DTP on mortality. Three of these, which were all undertaken in Guinea-Bissau, had 95% confidence intervals that excluded no effect. Three of the other results were from the Guinea-Bissau investigators (Bangladesh, Malawi, Senegal), two of which were re-analyses of studies undertaken by other teams (Bangladesh and Malawi). Two of these suggested possible deleterious effects. The three studies from different investigator teams produced more equivocal results, with one suggesting a beneficial effect of DTP (Papua New Guinea), one providing rate ratios in the region of 1 (Burkina Faso) and two suggesting deleterious effects (Benin and India).

I have three concerns about this paragraph:

First, the authors use vote counting, which is a method Higgins warns against using in the Cochrane Handbook (11): "Occasionally meta-analyses use 'vote counting' to compare the number of positive studies with the number of negative studies ... vote counting … should be avoided whenever possible."

Second, the authors seem to have a bias against the researchers from Guinea-Bissau, as also evidenced by another of their comments: "There was limited evidence on alternatives to the WHO-recommended ordering of vaccinations. Three observational studies

provided a suggestion that simultaneous administration of BCG and DTP may be preferable to the recommended schedule of BCG before DTP; and there was suggestion that mortality risk may be higher when DTP is given with, or after, measles vaccine compared with when it is given before measles vaccine (from five, and three, observational studies, respectively). These results are consistent with hypotheses that DTP vaccine may have detrimental effects on mortality, although a majority of the evidence was generated by a group centered in Guinea-Bissau who have often written in defence of such a hypothesis." It is unacceptable and unscientific to suggest that results that show that the DTP vaccine increases mortality should be ignored because most of the evidence was generated by a research group that "have often written in defence of such a hypothesis." If you do good research, and most other researchers don't, which is the case here, you will of course do what you can to defend what you have done!

Third, the authors' estimate for the Bangladesh study, 0.76 (0.67 to 0.88), described in a footnote, is different to the one they show in their graph, 0.52 (0.31 to 0.87), and this difference is not explained. Both estimates were ascribed to the original investigators, but the 0.52 estimate came from the re-analysis by the Guinea-Bissau investigators (17). The Bangladesh study seems to be so unreliable that it is better to ignore it, but if used, there are several estimates to choose from, e.g. also 1.94 (1.42 to 2.63), or an *increase* in mortality, which is the estimate for giving DTP after BCG, as the WHO recommends, rather than giving BCG and the first dose of DTP at the same time.

In their GRADE assessment, the authors wrote about the 10 observational studies they included: "We have very little confidence in the evidence about the effect of DTP vaccine on all-cause mortality." They decreased their starting score of 2 to 1 (the lowest possible score) because there were "very serious" inconsistencies in the direction of the effects.

I do not accept this explanation. First, it is similarly wrong to look at the direction of the effects as to look at the point estimates. We need to look at the confidence intervals (see the figure at the end of my report). Some of these do not overlap, which is a sign of considerable heterogeneity in the results. When that happens, it is the duty of the meta-analyst to try to explain the heterogeneity, and we already know that the only two studies that reported a beneficial effect (from Bangladesh and Papua New Guinea) were seriously flawed. The authors did not undertake such an assessment and they also did not undertake formal sensitivity analyses where these two studies were excluded, which they were prohibited from doing because the WHO Working Group had told them not to do meta-analyses.

Based on the data in the authors' report (1), I did two meta-analyses in the same way as described above for the BCG and measles vaccines. If the three most outlying studies of the ten observational studies are excluded (those from Bangladesh and Papua New Guinea which reported beneficial effects, and the one from Guinea-Bissau reporting a four-fold increase in mortality), the meta-analysis yields an estimate of 1.58 (1.24 to 2.01; p = 0.0002 and I square = 0, i.e. a significant effect with no heterogeneity). If these three studies are retained in the analysis, the estimate is 1.38 (0.92 to 2.08; p = 0.12 and I square = 71%, i.e. a non-significant effect with substantial heterogeneity). I would not recommend including all ten studies in a meta-analysis and therefore find the former estimate much more reliable.

D. The Authors' Comments on Study Methodology and Bias

"All of the results from observational studies were judged to be at high risk of bias or very high risk of bias, so all the findings above should be interpreted with caution."

"Although most results were adjusted for some confounding factors, only one study addressed a measure from each of our four pre-specified domains of confounding (health of the child, socio-economic status, age and gender), and this was achieved in part by matching children in a case-control design." This was a study from Benin, which reported an effect of 2.20 (0.93 to 5.22), i.e. a doubling of mortality that was not statistically significant.

"Different biases were considered likely to operate in different directions. Baseline confounding, if ignored, would tend to lead to bias towards a beneficial effect of the vaccine, because children with a worse prognosis generally tended to be vaccinated later or not vaccinated at all (sometimes described as 'frailty bias'). Some selection biases were expected to operate in the opposite direction: if children are recruited sometime after vaccination then early deaths among unvaccinated children – that might have been prevented had they been vaccinated – are not counted and the bias works against the vaccine and can switch the direction of effect. Misclassification of vaccinated children as unvaccinated would lead to bias towards the null (no effect), as occurs when a 'landmark' approach is taken to the analysis. Previous receipt, co-administration and subsequent administration of other vaccines … would lead to biases that depend on the effects of these vaccines and combinations, which we cannot infer in the context of this review. Therefore, we do not predict the direction of bias for individual studies or for the accumulated body of evidence. A further potential source of bias, which is very difficult to assess, is the selective reporting (and non-reporting) of results, both through mechanisms that lead papers to be written and published, and through decisions about what results to present in papers. There is not a single approach to design and analysis of studies in this research area, leaving open the possibility that investigators may have tried multiple ways to select and analyze the data, thereby putting the accessible literature as a whole at risk of bias."

These considerations are reasonable. However, the SAGE systematic review is not only biased against finding a detrimental effect of the DTP vaccine, it is also outdated because Aaby and his team have taken these criticisms into account in their most recent studies (2,3).

E. Conflicts of Interest

There were no conflicts of interest statements in the WHO report (1), which is otherwise the standard for research articles, particularly for systematic reviews of commercially available products.

In April 2014, a month after the WHO systematic review was finalized, it was discussed by SAGE (9). Eight of the 14 experts in SAGE had relevant conflicts of interest in relation to companies producing vaccines, but the WHO saw it differently: "Eight members reported relevant interests, which were assessed not to constitute a conflict of interest" (18). I consider this interpretation bizarre. Three SAGE members even had ties to GlaxoSmithKline, which produces the DTP vaccine Adacel®.

Such blanket statements are meaningless because research has overwhelmingly demonstrated that people become influenced when they have financial ties to drug companies, even when these ties are not directly related to the drugs or vaccines in question (19). There are several reasons for this. Obviously, if experts are too critical when exercising their expert function, they might not be chosen by other companies to conduct research for those companies in the future. It is a matter of not biting the hand that feeds you, whether directly or indirectly, and companies talk to each other. A critical expert can therefore quickly become blacklisted by all companies.

A related issue has to do with human psychology. The psychological research literature has convincingly shown that when human

beings have made up their minds about something, they are almost impossible to sway, even when they were in serious doubt before they chose one of two options. In fact, the stronger the counter evidence they are presented with, the more stubbornly will they defend the position they took initially. It is very odd, but unfortunately, this is how we are (20).

Therefore, expert committees that give advice on immunization programs should not be involved with their re-assessment when research has demonstrated that a vaccine might increase total mortality. A completely different group of experts should assess such findings, and no one should be allowed to have financial conflicts of interest in relation to the pharmaceutical industry.

This is not the case for WHO committees and it is not the case for drug agencies, although it has been repeatedly criticized that those people who approve a drug for marketing are also those who decide whether it should be removed because of the serious harms it causes, which are usually not known at the time of drug approval. This is not likely to happen, which is an important reason why several independent studies have shown that our prescription drugs are the third leading cause of death, after heart disease and cancer (19).

VI. Other Records Identified During Literature Review

Of the remaining 18 records I identified, one was a parallel publication of the WHO report (1) in a medical journal (21); one an erratum to that article (22); two were studies already quoted above (6,17); one was a study looking at the effect of the sequence of administration of vaccines (23); four were studies of gender-differential effects (24-27); one was a study about both sequence and gender effects (28); one was an analysis of risk factors (29); two were studies of vaccine coverage (30,31); one was a case-control study from Burkina Faso of several vaccines (32).

One was a study from Guinea-Bissau showing increased mortality when live vaccines against measles and yellow fever were combined with a pentavalent vaccine with DTP, Haemophilus influenzae type B and hepatitis B, adjusted mortality rate ratio 7.73 (1.79-33.4) (33). Another study from Guinea-Bissau showed higher mortality with the DTP vaccine than with the measles vaccine (34).

All these studies were from low-income countries. An ecological study, which is a very weak research design with numerous possibilities for bias, from the United States, suggested that the DTP vaccine lowered the incidence of sudden infant death syndrome (35).

Finally, a register-based cohort study from Denmark showed an increase in lower respiratory tract infections, adjusted incidence rate ratio 1.27 (1.13-1.42), when the measles, mumps and rubella (MMR) vaccine was combined with a pentavalent vaccine against DTP, polio and Haemophilus influenzae type b than when the MMR vaccine was given alone (36).

VII. Final Remarks and Conclusions

The most important principle in medical ethics is: First, do no harm. When drugs are being used prophylactically, to healthy people, the requirement that we must have demonstrated that they do more good than harm is much greater than when drugs are being used to treat diseases. For vaccines, few people of all those who are vaccinated are expected to benefit, which means that rare harms can be important, as they may outweigh the benefits.

It is the duty of a manufacturer of a drug or vaccine to demonstrate in randomized trials that it works and has a positive benefit to harm balance. This has not been done for the DTP vaccine. Not a single randomized trial has been carried out, but the vaccine is nonetheless on the market. This has created the odd situation that the burden of proof has been reversed. The WHO recommends the use of this vaccine and seems to require very convincing evidence that it increases mortality before any action will possibly be taken.

I find this approach problematic. We base our decisions on the best available evidence, and this evidence tells us that it is likely that the DTP vaccine increases total mortality in low-income countries. I therefore believe no one should be offered this vaccine without full informed consent that includes information that the vaccine is likely to increase total mortality.

I also believe that the vaccine should not be recommended and that, if anyone wants to use it, it must be as part of a large randomized trial. I consider the need for randomized trials an urgent ethical imperative.

Aaby and colleagues have pointed out that the WHO uses the DTP vaccine as a marker for good coverage of vaccination in general (3). The WHO has operated with reaching a "milestone of 90% national coverage with 3 doses of diphtheria-tetanus-pertussis vaccine (DTP3) in all countries by 2015" (9). This should not happen. Program performance indicators should be those which are known to be positively associated with better child survival (3).

VIII. Credentials

I have no conflicts of interest in relation to the drug industry or vaccines. I have worked at the Department of Infectious Diseases at Rigshospitalet, the main hospital in Denmark, and have passed a three-month course in tropical medicine. I consider vaccines in the same way as all other interventions in healthcare: Depending on the setting and the way they are being used, some produce more good than harm, some are equivocal, and some produce more harm than good.

I graduated as a Master of Science in biology and chemistry in 1974 and as a physician 1984. I am a specialist in internal medicine; worked with clinical trials and regulatory affairs in the drug industry 1975-1983, and at hospitals in Copenhagen 1984-95. With about 80 others, I co-founded the Cochrane Collaboration in 1993 and established the Nordic Cochrane Centre the same year. I became professor of Clinical Research Design and Analysis in 2010 at the University of Copenhagen and have been a member of the Cochrane Governing Board twice.

As the only Dane, I have published more than 70 papers in "the big five" (BMJ, Lancet, JAMA, Annals of Internal Medicine and New England

Journal of Medicine) and my scientific works have been cited over 40,000 times (my H-index is 67 according to Web of Science, September 2018, which means that 67 papers have been cited at least 67 times). I am author of several books. The most recent ones in English are:

- Death of a whistleblower and Cochrane's moral downfall (February 2019)
- Survival in an overmedicated world: Find the evidence yourself (to appear in March 2019; will appear in at least 7 languages)
- Deadly psychiatry and organised denial (2015) (has appeared in 9 languages).
- Deadly medicines and organised crime: How big pharma has corrupted health care (2013) (Winner, British Medical Association's Annual Book Award in the category Basis of Medicine in 2014; has appeared in 16 languages).
- Mammography screening: truth, lies and controversy (2012) (Winner of the Prescrire Prize 2012).
- Rational diagnosis and treatment: evidence-based clinical decision-making (2007).

I have given numerous interviews. One, about organized crime in the drug industry, has been seen about 300,000 times on YouTube: https://www.youtube.com/watch?v=dozpAshvtsA. I was in The Daily Show in New York on 16 September 2014 where I played the role of Deep Throat revealing secrets about big pharma. A documentary film about my reform work in psychiatry, Diagnosing Psychiatry, appeared in 2017.

I have an interest in statistics and research methodology. I am a member of several groups publishing guidelines for good reporting of research and have co-authored CONSORT for randomised trials (www.consort-statement.org), STROBE for observational studies (www.strobe-statement.org), PRISMA for systematic reviews and meta-analyses (www.prisma-statement.org), and SPIRIT for trial protocols (www.spirit-statement.org). I was one of the editors of the Cochrane Methodology Review Group 1997-2014.

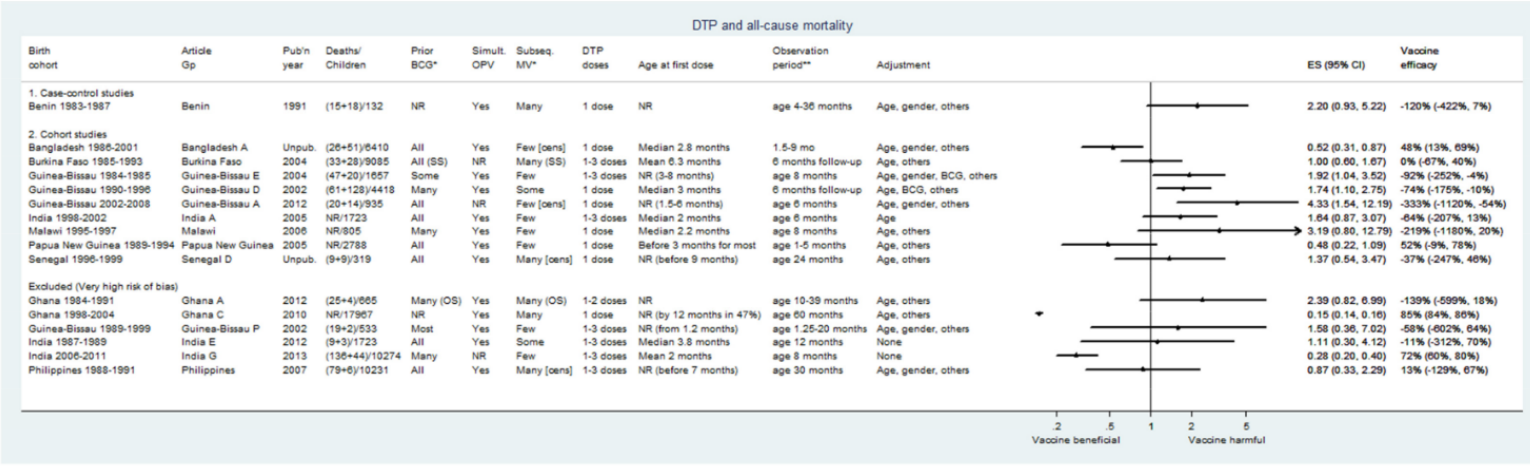
I am Protector for the Hearing Voices Network in Denmark. In March 2019, I shall found the Institute for Scientific Freedom.

My websites: deadlymedicines.dk and scientificfreedom.dk.

Peter C Gøtzsche
Professor, Director, MD, DrMedSci, MSc

Table

Figure 7. DTP and all-cause mortality.



Birth cohort	Article Gp	Pub'n year	Deaths/ Children	Prior BCG*	Simult. OPV	Subseq. MV*	DTP doses	Age at first dose	Observation period**	Adjustment	ES (95% CI)	Vaccine efficacy
1. Case-control studies												
Benin 1983-1987	Benin	1991	(15+18)/132	NR	Yes	Many	1 dose	NR	age 4-36 months	Age, gender, others	2.20 (0.93, 5.22)	-120% (-422%, 7%)
2. Cohort studies												
Bangladesh 1986-2001	Bangladesh A	Unpub.	(26+51)/6410	All	Yes	Few [cens]	1 dose	Median 2.8 months	1.5-9 mo	Age, gender, others	0.52 (0.31, 0.87)	48% (13%, 69%)
Burkina Faso 1985-1993	Burkina Faso	2004	(33+28)/9085	All (SS)	NR	Many (SS)	1-3 doses	Mean 6.3 months	6 months follow-up	Age, others	1.00 (0.60, 1.67)	0% (-67%, 40%)
Guinea-Bissau 1984-1985	Guinea-Bissau E	2004	(47+20)/1657	Some	Yes	Few	1-3 doses	NR (3-8 months)	age 8 months	Age, gender, BCG, others	1.92 (1.04, 3.52)	-92% (-252%, -4%)
Guinea-Bissau 1990-1996	Guinea-Bissau D	2002	(61+128)/4418	Many	Yes	Some	1 dose	Median 3 months	6 months follow-up	Age, BCG, others	1.74 (1.10, 2.75)	-74% (-175%, -10%)
Guinea-Bissau 2002-2008	Guinea-Bissau A	2012	(20+14)/935	All	NR	Few [cens]	1 dose	NR (1.5-6 months)	age 6 months	Age, gender, others	4.33 (1.54, 12.19)	-333% (-1120%, -54%)
India 1998-2002	India A	2005	NR/1723	All	Yes	Few	1-3 doses	Median 2 months	age 6 months	Age	1.64 (0.87, 3.07)	-64% (-207%, 13%)
Malawi 1995-1997	Malawi	2006	NR/805	Many	Yes	Few	1 dose	Median 2.2 months	age 8 months	Age, others	3.19 (0.80, 12.79)	-219% (-1180%, 20%)
Papua New Guinea 1989-1994	Papua New Guinea	2005	NR/2788	All	Yes	Few	1 dose	Before 3 months for most	age 1-5 months	Age, others	0.48 (0.22, 1.09)	52% (-9%, 78%)
Senegal 1996-1999	Senegal D	Unpub.	(9+9)/319	All	Yes	Many [cens]	1 dose	NR (before 9 months)	age 24 months	Age, others	1.37 (0.54, 3.47)	-37% (-247%, 46%)
Excluded (Very high risk of bias)												
Ghana 1984-1991	Ghana A	2012	(25+4)/665	Many (OS)	Yes	Many (OS)	1-2 doses	NR	age 10-39 months	Age, others	2.39 (0.82, 6.99)	-139% (-599%, 18%)
Ghana 1998-2004	Ghana C	2010	NR/17967	NR	Yes	Many	1 dose	NR (by 12 months in 47%)	age 60 months	Age, others	0.15 (0.14, 0.16)	85% (84%, 86%)
Guinea-Bissau 1989-1999	Guinea-Bissau P	2002	(19+2)/533	Most	Yes	Few	1-3 doses	NR (from 1.2 months)	age 1.25-20 months	Age, gender, others	1.58 (0.36, 7.02)	-58% (-602%, 64%)
India 1987-1989	India E	2012	(9+3)/1723	All	Yes	Some	1-3 doses	Median 3.8 months	age 12 months	None	1.11 (0.30, 4.12)	-11% (-312%, 70%)
India 2006-2011	India G	2013	(136+44)/10274	Many	NR	Few	1-3 doses	Mean 2 months	age 8 months	None	0.28 (0.20, 0.40)	72% (60%, 80%)
Philippines 1988-1991	Philippines	2007	(79+6)/10231	All	Yes	Many [cens]	1-3 doses	NR (before 7 months)	age 30 months	Age, gender, others	0.87 (0.33, 2.29)	13% (-129%, 67%)

ES = effect size (hazard ratio, rate ratio or risk ratio; odds ratio for the case-control study)
Deaths/Children = (DTP deaths + Non-DTP deaths)/Total children or Total deaths/Total children
All studies are cohort studies.
In the two studies with 'None' as adjustment for confounding, we computed unadjusted rate ratios from rates presented in the paper.
Vaccine efficacy is computed as (1 – ES) × 100%. A non-negative number describes the proportion of deaths prevented by the vaccine. A negative number reflects a higher death rate among the vaccinated. For example, if vaccine efficacy = -100%, then an *additional* 100% of the deaths that would have occurred without vaccine would occur with the vaccine.
*Prior BCG: whether children studied had received BCG. Subseq. MCV: what proportion of children were likely to receive measles vaccine during the period of observation [*cens* means this event was censored in the analysis].
SS = sometimes given simultaneously with DTP; OS = often given simultaneously with DTP.
**This is the period of observation applicable to the result presented in the forest plot, aiming to capture the effect of DTP with minimal impact of subsequent measles vaccination. The full study may have had a longer period of follow up.

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