Elation or caution over COVID-19 vaccines? The evidence so far.

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Many have been hoping that science will deliver a safe and effective coronavirus vaccine so that we may restore some sense of 'normality' to our daily lives. Over the past month, several vaccine manufacturers have made public announcements about the huge success of their vaccine trials and the media has responded in kind.

Headlines boasted "blockbuster" results, celebrating "a great day for humanity," and medical experts joined the chorus suggesting "nothing should limit our relief." It was a boon for the vaccine manufacturers, with companies like Pfizer seeing its share price jump nearly 20% the day after its announcement.

Russia has started mass vaccination in Moscow with its Sputnik V vaccine, despite final trials yet to be completed. The UK drug regulator, which granted emergency use authorisation (EUA) for the novel Pfizer/BioNTech mRNA vaccine, has also commenced vaccinating Britons. Following closely is the US, where FDA advisers voted yesterday to recommend that the US agency also grants EUA for Pfizer's vaccine, some suggesting that it could be rolled out within days.

Now as countries prepare to vaccinate millions of citizens with coronavirus vaccines that have been developed faster than any other in history, what does the evidence tell us so far?

Science by press release

Much of what we initially learned about coronavirus vaccine safety and efficacy data came from drug company press releases.

In response to the frenzied media coverage, Dr Richard Horton, editor-in-chief of *The Lancet* commented on Twitter; "Publishing interim results through a press release is neither good scientific practice nor does it help to build public trust in vaccines. An announcement should come with full publication of a peer-reviewed research paper in a scientific journal."

Fiona Godlee, editor-in-chief of the BMJ also commented; "Science by press release is just one of many flaws in the way new treatments are evaluated," she wrote, pointing to previous fiascos involving anti-viral drugs such as remdesivir and Tamiflu.

Vaccine manufacturers took an important step towards transparency by publishing the protocols for the trials - documents that describe the design, methods and statistical aspects of the trial.

But the questions everyone wants answered are: Will the vaccines prevent people from getting seriously ill and hospitalised from COVID-19 and will the vaccines prevent deaths?

According to a BMJ article, the trials have not been designed to answer those questions, which has sparked criticism that vaccine manufacturers have set themselves a low bar for success. That's because trials conducted by Pfizer, Moderna and AstraZeneca only require that their vaccine prevents moderate symptoms of COVID-19 which may be as mild as cough, or headache.

What is the evidence for the Pfizer vaccine?

On 2 Dec, a 10-page regulatory document was released for UK healthcare professionals regarding Pfizer's mRNA vaccine. The documents reveal that trials have shown the vaccine prevents one mild case in every 119 people who have been vaccinated. Thus, 118 vaccinated people receive no benefit, and some will likely suffer with adverse effects.

Put another way, the absolute reduction in risk to an individual taking the vaccine is 0.84%, humbling when compared to the impressive figures quoted in the media. A summary of the Pfizer data is outlined at nogracias.org.

The trials also found no clinically meaningful differences in overall vaccine efficacy in participants who were at high risk of severe COVID-19 disease, i.e. those with one or more pre-existing conditions like diabetes, obesity and asthma.

There are also some outstanding unknowns. How long will immunity last? Is the vaccine safe and efficacious for children under 16 years of age, or for the elderly (the group with the highest fatality risk)? And will the vaccine prevent community transmission of the virus?

Those with antibodies to SARS-CoV-2 were excluded from participating in the trial. It is not understood, therefore, how the vaccine might affect people who have already been exposed to COVID-19, which could be substantial.

The documents also indicate that the vaccine is not recommended during pregnancy since it is unknown whether elements of the vaccine are excreted in human milk and a risk to the newborns/infants could not be excluded. Studies looking at the "reproductive toxicity" of laboratory animals administered with the vaccine have not yet been completed.

Over a month after Pfizer announced its trial results by press release, the New England Journal of Medicine finally published the data with a linking editorial describing the results as "impressive" and a "triumph".

The authors reported the efficacy of the Pfizer vaccine was 52% after the first shot, which increased to 91% after the second shot. It also found that among 10 cases of severe Covid-19, nine occurred in placebo recipients and one in vaccine recipients.

What about harms?

In an interview with the BBC, Bill Gates was asked whether we might have to "compromise" with some of the safety measures during testing because time is so crucial. He responded

saying, “Of course. If you want to wait and see if a side effect turns up two years later, then that’s going to take two years”.

As noted by the BMJ however, history has many examples of where vaccines have been rushed to market and have resulted in serious adverse events. In the 50s, there were contaminated polio vaccines, in the mid-70s, cases of Guillain-Barré syndrome were seen in recipients of flu vaccines and in the 2009 Swine flu pandemic, narcolepsy was linked to the Pandemrix vaccine.

The data for the Pfizer vaccine suggests that the benefits outweighs its harms, but this is still short-term data (only two months). On the first day of rolling out the Pfizer vaccine in the UK, two NHS workers experienced an “anaphylactoid reaction” shortly after receiving the jab, causing the UK regulator to issue a warning that people with a history of allergic reactions should not be vaccinated.

It’s not surprising; people with a history of severe allergic reactions such as anaphylaxis, were excluded from the original studies, a common problem when trials do not recruit participants that reflect “real world” populations.

The UK drug regulator will continue surveillance of adverse reactions for the coronavirus vaccine. Recently it posted a tender request for the development of an artificial intelligence software tool that can process “the expected high volume of Covid-19 vaccine Adverse Drug Reaction (ADRs)” since its current system is not able to “handle the volume of ADRs that will be generated by a Covid-19 vaccine.”

A week after the UK became the first western country to grant EUA for Pfizer’s vaccine, the US FDA released a 53-page public report, showing the vaccine has high efficacy (~90%), noting that six deaths had occurred during the trials, although, they say none were linked to the vaccine.

If granted an EUA by the US drug regulator (as expected), Pfizer has indicated that it would offer the coronavirus vaccine to the placebo subjects, effectively ‘unblinding’ the ongoing trials. If too many subjects cross over to the vaccine group, it will hamper efforts to establish whether the vaccine has long-term harms.

Oxford/AstraZeneca vaccine hits a snag

The ChAdOx1 nCoV-19 vaccine manufactured by the University of Oxford in collaboration with AstraZeneca was considered the front runner several months ago but has hit a snag according to results published in *The Lancet* this week.

The results consisted of pooled trial data from 23,700 participants in the UK, Brazil and South Africa. However, some participants received a lower dose (90% efficacy) compared to those who received the standard dose (62% efficacy). The authors averaged the results to reach 70% efficacy overall.

Notably, however, the group which received the lower dose did not include adults over the age of 55 years. Therefore, it is not possible to infer efficacy in older adults, who are the group at greatest risk of severe COVID-19 outcomes.

Because of this, unfortunately, the results from the Oxford/AstraZeneca vaccine are convoluted. Cases of severe disease and hospitalisation were monitored from 21 days after the first dose and there were 10 participants hospitalised for COVID-19, all in the control arm of the trial; two were classified as severe, including one death.

The vaccine was found to be safe - only three out of 23,745 participants experienced a serious adverse event - one in the vaccine arm, one in the control arm, and one in a participant who remains masked to group allocation.

Of note, not included in these three trials, is the trial underway in India with the Oxford/AstraZeneca vaccine, known as "Covishield". A participant developed acute neuro-encephalopathy ten days after receiving a single shot of vaccine (not the placebo), and later sought compensation for his injuries.

The company manufacturing the vaccine (Serum Institute of India, SII) said the claim was "malicious and misconceived," and has threatened to sue the trial participant for damages. The company has powered on, just announcing that it has applied for emergency use approval of the Covishield vaccine.

Serious adverse events are rare, and we do not know if they were caused by the vaccine, but it has raised the alarm with those who are hesitant about the safety of the vaccine.

The advantage of the Oxford/AstraZeneca vaccine is that it is cheaper and easier to distribute, thus, is advantageous for application in developing countries.

Government indemnity

To encourage uptake of the COVID-19 vaccine, it is recommended that compensation schemes should be in place in case of a rare but serious event resulting from the vaccines.

The UK government has granted Pfizer a legal indemnity protecting the drug company from being sued by patients in the event of any complications. Instead, people are able to claim a "Vaccine Damage Payment", as stated on its website:

"If you're severely disabled as a result of a vaccination against certain diseases, you could get a one-off tax-free payment of £120,000." It goes on to explain that the payment could affect entitlements to other benefits such as income support, housing benefits and employment / support allowance.

The UK's Independent newspaper reported that Pfizer's UK managing director refused to explain why the company needed an indemnity, saying, "We're not actually disclosing any of

the details around any of the aspects of that agreement and specifically around the liability clauses."

In the US, there is already a law, the National Childhood Vaccine Injury Act of 1986, which was created as a no-fault compensation program. The purpose of the Act was to eliminate the potential financial liability of vaccine manufacturers in the event of vaccine injury claims.

The Australian government has committed to indemnifying two COVID-19 vaccine manufacturers (AstraZeneca and Commonwealth Serum Laboratories) against any potential lawsuits, but is mostly silent on the details, except to say, that it will cover the cost of "certain liabilities".

Public trust

For a successful vaccination program to roll out, the vaccines not only have to be safe and effective, there has to be widespread uptake in the community. National drug regulators will play a significant role in keeping the population safe and fostering public trust.

In some areas, uptake of the vaccine is expected to be lower than desired. A survey taken in October by the US Department of Heath reportedly shows "significant concerns" about receiving the vaccination, as only 47% of nurses and 66% of doctors said they would "definitely or probably" take it.

A cross-sectional survey of healthcare workers of the University of California, Los Angeles (UCLA) Health System found 47% of respondents reported an unwillingness to participate in a coronavirus vaccine trial, and most (67%) intend to delay vaccination.

In Australia, a recent survey of over 3,000 adults found that 59% of adults said that they would definitely get the vaccine and a further 29% were 'likely' to get the vaccine but were not certain, data that was collected before the announcement of positive trial results.

In the UK, a survey of 1500 adults found that 64% would be receptive and likely to receive a vaccine, 27% were unsure if they would have the vaccination and 9% reported that they were unlikely to be vaccinated.

It will not be constructive to ignore the current gaps in our knowledge about the COVID-19 vaccines, or to label people with concerns as 'anti-vaxxers'. People's trust in science and government officials has already been compromised by the Tamiflu and remdesivir fiascos, so the same must not occur for coronavirus vaccines.

'Mandatory vaccination' is one debate that seems to fuel distrust in vaccines. Most political leaders have reassured the public that the vaccine will be voluntary, but there are other ways that may motivate or coerce people to be vaccinated. Governments and airlines, for example, may require travellers to be immunised and prove it with a new form of digital documentation called a 'vaccine passport'.

Qantas Airways has recently announced that a COVID-19 vaccine will be 'mandatory' for all Australians flying overseas once international air travel returns in 2021. Air New Zealand has echoed a similar position.

The economy will not suddenly surge now that the first injections have been administered, but at least the new vaccines have offered some hope that, sometime down the road, our lives can return to normal.