Peter Doshi: Pfizer and Moderna's "95% effective" vaccines—let's be cautious and first see the full data

November 26, 2020

Only full transparency and rigorous scrutiny of the data will allow for informed decision making, argues Peter Doshi

In the United States, all eyes are on Pfizer and Moderna. The topline efficacy results from their experimental covid-19 vaccine trials are astounding at first glance. Pfizer says it recorded 170 covid-19 cases (in 44,000 volunteers), with a remarkable split: 162 in the placebo group versus 8 in the vaccine group. Meanwhile Moderna says 95 of 30,000 volunteers in its ongoing trial got covid-19: 90 on placebo versus 5 receiving the vaccine, leading both companies to claim around 95% efficacy.

Let's put this in perspective. First, a relative risk reduction is being reported, not absolute risk reduction, which appears to be less than 1%. Second, these results refer to the trials' primary endpoint of covid-19 of essentially any severity, and importantly not the vaccine's ability to save lives, nor the ability to prevent infection, nor the efficacy in important subgroups (e.g. frail elderly). Those still remain unknown. Third, these results reflect a time point relatively soon after vaccination, and we know nothing about vaccine performance at 3, 6, or 12 months, so cannot compare these efficacy numbers against other vaccines like influenza vaccines (which are judged over a season). Fourth, children, adolescents, and immunocompromised individuals were largely excluded from the trials, so we still lack any data on these important populations.

I previously argued that the trials are studying the wrong endpoint, and for an urgent need to correct course and study more important endpoints like prevention of severe disease and transmission in high risk people. Yet, despite the existence of regulatory mechanisms for ensuring vaccine access while keeping the authorization bar high (which would allow placebo-controlled trials to continue long enough to answer the important question), it's hard to avoid the impression that sponsors are claiming victory and wrapping up their trials (Pfizer has already sent trial participants a letter discussing "crossing over" from placebo to vaccine), and the FDA will now be under enormous pressure to rapidly authorize the vaccines.

But as conversation shifts to vaccine distribution, let's not lose sight of the evidence. Independent scrutiny of the underlying trial data will increase trust and credibility of the results. There also might be important limitations to the trial findings we need to be aware of.

Most crucially, we need data-driven assurances that the studies were not inadvertently unblinded, by which I mean investigators or volunteers could make reasonable guesses as to which group they were in. Blinding is most important when measuring subjective endpoints like symptomatic covid-19, and differences in post-injection side-effects between vaccine and placebo might have allowed for educated guessing. Past placebo-controlled trials of influenza vaccine were not able to fully maintain blinding of vaccine status, and the recent "half dose" mishap in the Oxford covid-19 vaccine trial was apparently only noticed because of milder-than-expected side-effects. (And that is just one of many concerns with the Oxford trial.)

In contrast to a normal saline placebo, early phase trials suggested that systemic and local adverse events are common in those receiving vaccine. In one Pfizer trial, for example, more than half of the vaccinated participants experienced headache, muscle pain and chills—but the early phase trials were small, with large margins of error around the data. Few details from the large phase 3 studies have been released thus far. Moderna's press release states that 9% experienced grade 3 myalgia and 10% grade 3 fatigue; Pfizer's statement reported 3.8% experienced grade 3 fatigue and 2% grade 3 headache. Grade 3 adverse events are considered severe, defined as preventing daily activity. Mild and moderate severity reactions are bound to be far more common.

One way the trial's raw data could facilitate an informed judgment as to whether any potential unblinding might have affected the results is by analyzing how often people with symptoms of covid-19 were referred for confirmatory SARS-CoV-2 testing. Without a referral for testing, a suspected covid-19 case could not become a confirmed covid-19 case, and thus is a crucial step in order to be counted as a primary event: lab-confirmed, symptomatic covid-19. Because some of the adverse reactions to the vaccine are themselves also symptoms of covid-19 (e.g. fever, muscle pain), one might expect a far larger proportion of people receiving vaccine to have been swabbed and tested for SARS-CoV-2 than those receiving placebo.

This assumes all people with symptoms would be tested, as one might expect would be the case. However the trial protocols for Moderna and Pfizer's studies contain explicit language instructing investigators to use their clinical judgment to decide whether to refer people for testing. Moderna puts it this way:

"*It is important to note that some of the symptoms of COVID-19 overlap with solicited systemic ARs that are expected after vaccination with mRNA-1273 (eg, myalgia, headache, fever, and chills). During the first 7 days after vaccination, when these solicited ARs are common, Investigators should use their clinical judgement to decide if an NP swab should be collected.*"

This amounts to asking investigators to make guesses as to which intervention group patients were in. But when the disease and the vaccine side-effects overlap, how is a clinician to judge the cause without a test? And why were they asked, anyway?

Importantly, the instructions only refer to the first seven days following vaccination, leaving unclear what role clinician judgment could play in the key days afterward, when cases of covid-19 could begin counting towards the primary endpoint. (For Pfizer, 7 days after the 2nd dose. For Moderna, 14 days.)

In a proper trial, all cases of covid-19 should have been recorded, no matter which arm of the trial the case occurred in. (In epidemiology terms, there should be no ascertainment bias, or differential measurement error). It's even become common sense in the Covid era: "test, test, test." But if referrals for testing were not provided to all individuals with symptoms of covid-19—for example because an assumption was made that the symptoms were due to side-effects of the vaccine—cases could go uncounted.

Data on pain and fever reducing medicines also deserve scrutiny. Symptoms resulting from a SARS-CoV-2 infection (e.g. fever or body aches) can be suppressed by pain and fever reducing medicines. If people in the vaccine arm took such medicines prophylactically, more often, or for a longer duration of time than those in the placebo arm, this could have led to greater suppression of covid-19 symptoms following SARS-CoV-2 infection in the vaccine arm, translating into a reduced likelihood of being suspected for covid-19, reduced likelihood of testing, and therefore reduced likelihood of meeting the primary endpoint. But in such a scenario, the effect was driven by the medicines, not the vaccine.

Neither Moderna nor Pfizer have released any samples of written materials provided to patients, so it is unclear what, if any, instructions patients were given regarding the use of medicines to treat side effects following vaccination, but the informed consent form for Johnson and Johnson's vaccine trial provides such a recommendation:

"Following administration of Ad26.COV2.S, fever, muscle aches and headache appear to be more common in younger adults and can be severe. For this reason, we recommend you take a fever reducer or pain reliever if symptoms appear after receiving the vaccination, or upon your study doctor's recommendation."

There may be much more complexity to the "95% effective" announcement than meets the eye—or perhaps not. Only full transparency and rigorous scrutiny of the data will allow for informed decision making. The data must be made public.

***Peter Doshi**, associate editor,* The BMJ.

Competing interests: *I have been pursuing the public release of vaccine trial protocols, and have co-signed open letters calling for independence and transparency in covid-19 vaccine related decision making.*

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Lisa Mair · 10 days ago
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Zekria Ibrahimi · 7 days ago
Science can't work without scepticism.

Each vaccine trials looks like a cohort study- which is usually a very long-term thing. As Mister Doshi seems to point out, the trials have lasted only a few months, alas. So we can't know what the vaccine's impact will be over the difficult years to come, in terms of side effects or (limited?) efficacy.

Someone has asked on this forum about NNT (Number Needed to Treat). The author has observed that the absolute risk reduction is much less than the relative one in this trial.

We could have Big Pharma playing statistical games- again.

You have to be unfortunately suspicious (again) when Big Pharma doesn't choose to give the full data.

Covid-19 disrupts the immune system. The immune system overreacts, to produce an autoimmune response that can be fatal. WHO appears to be recommending steroids treatment, which undermines the immune system.

I would ask- why wasn't even a tenth of the resources put into a vaccine not deployed into steroids and other autoimmune drugs instead?

Because steroids are old generic drugs that won't give the profit and prestige of a new vaccine?

Science can't work without scepticism...
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Havinga · 10 days ago
With reference to caution, safety and open access to all the data, the biopharmaceutical vaccine developing companies should provide information regarding the problems they have encountered with the type of vaccine currently developed for COVID19 which they studied in previous trials.

For example, the Oxford team addressed the concern that if people already have immunity to the human adenovirus, the bioengineered human adenovirus vaccine is less likely to be clinically effective, because the vaccine's adenovirus will be neutralised by the body's immune system before it can infect cells and instruct body cells to produce the spike protein. That is why the Oxford team changed to use a monkey (simian) adenovirus as few people will be immune to that.

The following Lancet correspondence advises against using a human adenovirus as a non-replicating viral vector. (Non-replicating, because the coding for the chimpanzee adenovirus to replicate has been inactivated and each modified virus should theoretically infect only one body cell.)
https://www.thelancet.com/j...

However, the Janssen (Johnson) and the CanSino (Chinese) and Sputnik V (Russian) vaccines still use a human genetically modified adenovirus to instruct body cells to produce the COVID19 spike protein.

Governments need to inform the public about that concern when the public is offered the human adenovirus type of non-replicating vector virus vaccines.
Doctors need this information when enabling shared decision making (SDM) when discussing taking a covid19 vaccine.

Another aspect that needs to be clarified with using viral vectors, are the "impurities", the "contaminants" that might end up in the content of the vaccine syringe.

These can be viruses
https://www.the-scientist.c...
but also bacterial and human genetic material.
For example, the poliovirus vaccine was contaminated with simian virus 40 (SV40).
https://www.nature.com/arti...

The sequence of vaccine production from the chimpanzee's or a human nose swab to the syringe has several steps where problems can occur:
• When taking a nose swab you can imagine that a swab will contain an innumerable amount of genomic material from a multitude of viruses and bacteria and body cells.
• The cell lines used to culture the genetically modified virus are human embryonic kidney cells. These cells have been replicated in growth-media since the 1970s. How many impurities have entered these cell lines over the decades?
• By using a Chimpanzee adenovirus is a zoonosis iatrogenically introduced?
• What impurities will accumulate in the laboratory during all the steps to genetically modify the chimpanzee adenovirus or human adenovirus as these need to be cultured in cells?
• And eventually when producing a vaccine, a bunch of cells are incubated in many "bioreactors" (vessels the size of 2000 L) and a solution is added which hopefully contains only the genetically modified chimp or human adenovirus. Considering the content of the chimpanzee's and human nose swab, how can the technician make sure it only contains (simian) adenovirus? There is a good chance that if the contamination virus is unknown, it won't be found, only after it shows in the population.
• The embryonic kidney cells in the incubator will also ooze the spike protein as instructed by the modified vector virus and there are lots of other proteins in the cell brewery. Can the spike protein and the other proteins be totally separated from what goes into the syringe? The concern with injected spike protein is that it could cause serious side effects like ADE or CIP.
https://www.nature.com/arti...
This information should also be part of informed consent when the vaccine is offered?

Wouter Havinga, retired family doctor UK
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Lobkowitz → Havinga · 6 days ago
You have raised some very alarming concerns over these cov-19 vaccines. I made a FOI request to MHRA for the submitted data, was fobbed off with excuses like "not in the public interest". Am asking ICO to look into my requests. These novel mRNA vaccines have no historical approval it is very much in the public interest to have the data to examine and scrutinise, so far all we get are Pfizer press releases and a phase II study from Oxford. The whole vaccine issue has been shrouded in mystery. Given that the UK government made a shambles of controlling the pandemic from the start in March, the PPE fiasco and test track and trace, why should anyone trust them on these novel vaccines. I shall not be having any vector ones, sub unit protein ones might be a safer bet. Until we have a substantial bank of data a 7 year moratorium should be placed on these vaccines to check for ADRs, unintended effects such as immune enhancement. At present the trials are not designed to show these vaccines save lives or improve outcomes as recent BMJ articles highlight. The trials exclude elderly subjects with underlying conditions, so are not representative of the general population, I doubt the efficacy claims of 90% will be achieved.

Vaccines are only one means of addressing the cov-19 pandemic, without effective public health test, track and tracing it will not work. Alas UK government keeps outsourcing.
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John Stone → Havinga · 10 days ago
Wouter

Thank you very much for these fascinating insights.
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Lobkowitz · 6 days ago
Will we ever see any real data? They seem to be planning approval by New Year. Complete madness.
3 · Reply · Share ›

Mike van Loon → Lobkowitz · 5 days ago
UK approved the Pfizer Biontech vaccine but I cannot find the trial data. Is it available?
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Lobkowitz → Mike van Loon · 4 days ago
MHRA have approved it without any peer reviewed publications at all, I put in an FOI for the submitted data and was refused under clauses 41 & 43, not in the public interest and commercial sensitive!! I shall not be rushing for a jab anytime near the next century!
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Lobkowitz · 4 days ago
Can anyone say any cov-19 vaccine is 100% safe? No. They are making a bad situation worse, mRNA vaccines who knows long term effects, unknown, viral vector vaccines, what about carcinogenicity problems, anyone know what Vectors might do. Immune enhancement? This planned roll out is plain madness, they are effectively doing a phase IV trial with Joe Public. I am not having it at all. I never got cov-19 and I am happy with a mask for life!
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Anton Fokler · 3 days ago
So the biggest misgiving in the trial is that the "95% effective" stat is taken from the natural infection rate (0.5 - 1% say) which is only 200 people or so possible in each arm. The vaccine makes you feel like you have flu for a while, maybe worse - so you lay low for a good time and don't do things you'd normally do. So that changes your exposure and the infection rate is lower. You also take meds to get over the symptoms of the vaccine - Lemsip, VitC etc.. same as you do for a cold (they were even told to in the trial leaflet) which affects your immune system and so the infection rate is lower too.
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Rich Austin · 3 days ago
Thank heavens some media are standing up and saying "Hang on a minute!". In the UK the Government have prevented the mainstream news from reporting anything that criticises Government policy. This is more akin to a third world dictatorship. In Parliament MP's have been side lined from democracy and Government denies them access to the data.
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Zekria Ibrahimi · 3 days ago
The author reports an absolute risk difference for the vaccines (treatment versus placebo) of 1%.

The Number Needed To Treat (NNT) is, by definition, the inverse of the absolute risk difference.

So the NNT is 100.

That is, 100 people would have to be on placebo before one extra person would be 'protected' on the vaccine.

This is a very poor NNT.

The Oxford trial was so rushed that it couldn't even get the dosages right.

A bad vaccine- equivalently with a bad test for covid-19- is worse than no vaccine at all.
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Ian Pende · 4 days ago
To take advantage of the indemnity afforded by government agencies, it is in the vaccine developers interest to do the minimum in safety studies. If it can be shown the developer knew before any injury that they were aware the insult was likely to occur they lose this government protection.
1 · Reply · Share ›

JohnDStone · 9 days ago
Discussion of the side effects of Pfizer and Moderna vaccines

https://www.cnbc.com/2020/1...

How mny will be needed to save a single life? Can we even calculate?
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Stirling Smith · 3 days ago
I don't understand the rush to a vaccine when this virus has a survival rate of over 95%.
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