New Study Questions Safety of mRNA COVID-19 Vaccines

A new scientific study entitled "*Serious adverse events of special interest following mRNA vaccination in randomized trials*" provides the best evidence yet concerning the safety of the mRNA Covid vaccines. For most vaccines in common use, benefits far outweigh risks, but that may not be the case for the mRNA covid vaccines, according to this study by Joseph Fraiman and his colleagues. It depends on your age and medical history.

The randomized controlled clinical trial is the gold standard of scientific evidence. When regulators approved the Pfizer and Moderna mRNA vaccines for emergency use in December 2020, two randomized trials showed that the vaccines reduced symptomatic covid infection by over 90% during the first few months after the second dose.

Pfizer and Moderna did not design the trials to evaluate long-term efficacy or the more important outcomes of preventing hospitalization, death, or transmission.

The randomized trials did collect adverse event data, including the presence of mild symptoms (such as fever) and more serious events requiring hospitalization or leading to death. Most vaccines generate some mild adverse reactions in some people, and there were considerably more adverse such reactions after the mRNA vaccines compared to the placebo.

That is annoying but not a major issue. We care about severe health outcomes. The key question is whether the vaccine's efficacy outweighs the risks of severe adverse reactions.

The Fraiman study uses data from the same Pfizer and Moderna-sponsored randomized trials presented to the FDA for vaccine approval, but with two innovations that provide additional information.

First, the study pools data from both mRNA vaccines to increase the sample size, which decreases the confidence intervals' size and the uncertainty about the estimated harms.

Second, the study focuses only on the severe adverse events plausibly due to the vaccines. Serious adverse events such as gunshot wounds, suicide, animal bites, foot fractures, and back injury are unlikely to be due to a vaccine, and cancer is unlikely to be due to a vaccine within a few months after vaccination. By removing such random noise, the ability (statistical power) to detect genuine problems increases. If there is no excess risk, shorter confidence intervals bolster confidence in the safety of the vaccines.

Classifying adverse events into the two groups is not a trivial task, but Fraiman et al. do an excellent job to avoid bias. They rely on the pre-defined Brighton Collaboration definitions of adverse events of special interest (AESI). Founded in 2000, the Brighton Collaboration has two decades of experience using rigorous science to define clinical outcomes for vaccine safety studies.

Moreover, Fraiman and colleagues blinded the process where they classified the clinical events as AESIs. Adjudicators did not know whether the individual had received the vaccine or the placebo. Hence, any criticism of so-called p-hacking is unwarranted.

So, what are the results? There were 139 AESIs among the 33,986 people vaccinated, one for every 244 people. That may sound bad, but those numbers mean nothing without comparison against a control group. There were 97 AESIs among the 33,951 people who received a placebo. Combining these numbers implies 12.5 vaccine-induced AESIs for every 10,000 people vaccinated, with a 95% confidence interval of 2.1 to 22.9 per 10,000 people. To phrase it differently, there is one additional AESI for every 800 people vaccinated (95% CI: 437-4762).

That is very high for a vaccine. No other vaccine on the market comes close.

The numbers for the Pfizer and Moderna vaccines are 10 and 15 additional events per 10,000 people, respectively, so both vaccines contributed to the finding. The numbers are similar enough that we cannot confidently say that one is safer than the other. Most excess AESIs were coagulation disorders. For the Pfizer vaccine, there was also an excess of cardiovascular AESIs.

While these safety results are concerning, we must not forget the other side of the equation. Unfortunately, the study does not calculate composite estimates that also included the reduction in serious covid infections, but we have such estimates for mortality.

Dr. Christine Benn and her colleagues calculated a combined estimate of the effect of vaccination on all-cause mortality using the same randomized trial data as Fraiman et al. They did not find a mortality reduction for the mRNA vaccines (relative risk 1.03, 95% CI: 0.63-1.71).

One important limitation of both Fraiman's and Benn's studies is that they do not distinguish the adverse reactions by age, comorbidities, or medical history. That is not their fault. Pfizer and Moderna have not released that information, so outside researchers do not have access.

We know that the vaccine benefits are not equally distributed among people since covid mortality is more than a thousand times higher among the old. Thus, risk-benefit calculations must be done separately for different groups: with and without prior covid infection, by age, and for the first two doses versus boosters.

1. Covid-recovered people have natural immunity that is stronger than vaccine-induced immunity. So, the benefit of vaccination is – at best – minimal. If the risk of adverse reactions is the same as in the randomized trials, there is a negative risk-benefit difference. Why are we mandating people in this group to be vaccinated? It is both unethical and damaging to public health.
2. While everyone can get infected, children have a minuscule risk of covid mortality. There is very limited safety data from the trials on children. If the risk of adverse reactions is the same as for adults, the harms outweigh the risks. Children should not receive these vaccines.
3. Older people above 70 have a much higher risk of covid mortality than the population in the Fraiman study. If their risk of adverse reaction is the same, then the benefits outweigh the harms. Hence, older people who have never had covid and are not yet vaccinated may benefit from these vaccines. However, we do not know if they are better than the Johnson & Johnson and Astra-Zeneca vaccines.
4. It is unclear from the clinical trial data whether the benefits outweigh the risks for working-age adults who

have not been vaccinated and who have not already had covid. This is true both historically, for the original covid variants, and currently for the newer ones.
5. The Fraiman study analyzes data after the first and second doses. Both risks and benefits may differ for booster shots, but no randomized trial has properly evaluated the trade-off.

These results concern only the Pfizer and Moderna mRNA vaccines. Fraiman et al. did not analyze data on the adenovirus-vector vaccines marketed by Johnson & Johnson and Astra-Zeneca. Benn et al. found that they reduced all-cause mortality (RR=0.37, 95% CI:0.19-0.70), but nobody has used trial data to analyze AESIs for these vaccines.

Critically, the Fraiman and Benn studies had a follow-up of only a few months after the second dose because Pfizer and Moderna, unfortunately, terminated their randomized trials a few months after receiving emergency use authorization. Of course, a longer-term benefit can provide a basis to tolerate negative or neutral short-term risk-benefit differences. However, that is unlikely since we know from observational studies that mRNA vaccine efficacy deteriorates a few months after the second dose.

There may also be long-term adverse reactions to the vaccine regarding which we do not yet know. Since the randomized trials ended early, we must look at observational data to answer that question. The publicly available data from the Vaccine Adverse Event Reporting System is of low quality, with both under- and over-reporting. The best observational data is from CDCs Vaccine Safety Datalink (VSD) and FDA's Biologics and Effectiveness Safety System (BEST), but there have only been limited reports from these systems.

Fraiman and colleagues have produced the best evidence yet regarding the overall safety of the mRNA vaccines. The results are concerning. It is the responsibility of the manufacturers

and FDA to ensure that benefits outweigh harms. They have failed to do so.

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