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FDA urged to publish follow-up studies on covid-19 vaccine safety signals

The FDA has been criticised for taking more than a year to follow up a potential increase in serious adverse events in elderly people receiving Pfizer's covid-19 vaccine, Maryanne Demasi reports

Maryanne Demasi *investigative journalist*

In July 2021 the US Food and Drug Administration (FDA) quietly disclosed findings of a potential increase in four types of serious adverse events in elderly people who had had Pfizer's covid-19 vaccine: acute myocardial infarction, disseminated intravascular coagulation, immune thrombocytopenia, and pulmonary embolism.[1] Little detail was provided, such as the magnitude of the increased potential risk, and no press release or other alert was sent to doctors or the public. The FDA promised it would "share further updates and information with the public as they become available."

Eighteen days later, the FDA published a study planning document (or protocol) outlining a follow-up epidemiological study intended to investigate the matter more thoroughly.[2] This recondite technical document disclosed the unadjusted relative risk ratio estimates originally found for the four serious adverse events, which ranged from 42% to 91% increased risk. (Neither absolute risk increases nor confidence intervals were provided.) More than a year later, however, the status and results of the follow-up study are unknown. The agency has not published a press release, or notified doctors, or published the findings by preprint or the scientific literature or updated the vaccine's product label.

The BMJ has also learnt that the FDA has not publicly warned of similar signals detected in a separate observational cohort study it conducted of the third dose (first booster dose) in the elderly[3]; nor has the agency publicly acknowledged other published observational studies or clinical trial reanalyses reporting compatible results. Experts spoke to *The BMJ* about their concerns about the data and have called on the FDA to notify the public immediately.

"To keep this information from the scientific community and prevent us from analysing it ourselves, is irresponsible. It presumes that these organisations are perfect and cannot benefit from independent scrutiny," says Joseph Fraiman, an emergency medicine physician in New Orleans, who recently carried out a reanalysis of serious adverse events in Pfizer's and Moderna's randomised trials.[4]

Unearthing safety data

The FDA's July 2021 findings came from a "near real time surveillance" system called Rapid Cycle Analysis (RCA) that the agency has in place to monitor a list of 14 adverse events of special interest. The RCA study is not capable of establishing a causal relation but rather is intended to detect potential safety signals rapidly. The agency said the associations were not identified for the other two covid-19 vaccines authorised in the US made by Moderna and Janssen (Johnson & Johnson). The July 2021 follow-up study protocol states that there is a "manuscript in preparation" for the original RCA study, but to date nothing has been published for either study.[2]

"The fact that the FDA found these four safety signals means they should have followed up on the results and I don't understand why we haven't had more information since then. It has been over a year," says Tracy Høeg, epidemiologist and physician currently conducting covid-19 vaccine research with the Florida Department of Health and California's Marin County Department of Health and Human Services.

In 2022 details regarding the results of a separate (third) safety study were disclosed inside another study protocol for evaluating boosters. Buried within that protocol the FDA stated, "In a cohort study of the third dose safety in the Medicare population where historical controls were used, we detected a statistically significant risk for immune thrombocytopenia (incidence rate ratio 1.66, confidence interval 1.17 to 2.29) and acute myocardial infarction (IRR 1.15, CI 1.02 to 1.29) among people with prior covid-19 diagnosis as well as an increased risk of Bell's palsy (IRR 1.11, CI 1.03 to 1.19) and pulmonary embolism (IRR 1.05, CI 1.0001 to 1.100) in general."[3]

Again, the FDA has made no public statement regarding these results. "It's disturbing that they have not released any of these data. If the FDA is stating publicly that they're collecting it, then they should be publicly reporting it. They shouldn't be burying the results in protocols as they've done. It's sneaky," said Fraiman.

"The protocols say that they're looking into these data further, but I'd like to know the results now, it's been long enough. They need to view this from a public health perspective, they need to consider a person's right to informed consent. As physicians, we recommend medical therapies and we need to explain the full risks and benefits to the patient. This is not happening," adds Fraiman.

Dick Bijl, physician epidemiologist in the Netherlands, says, "The FDA managed to determine the efficacy of the vaccines in a short period of time, but they have not analysed the pharmacovigilance data with the same speed. If they found signals in July 2021, they should have been analysed and published within months."

As president of the International Society of Drug Bulletins, Bijl has campaigned for years to have drug safety data communicated to doctors in a timely manner. He credits his organisation for prompting the World Health Organization to begin publishing regular updates about drug safety signals. These are possible safety problems that circulated only in pharmacovigilance centres and have been incorporated in the WHO Pharmaceuticals Newsletter since 2012, so that all doctors can take note of them.

"The FDA should have informed doctors about any early safety signals from the vaccines," says Bijl. "Most doctors are not trained to, nor are they focused on, recognising side effects, especially because vaccines are generally regarded as quite safe. It's important that doctors are told what to look out for."

Other studies

Other research groups, including Fraiman's, have produced results that are compatible with the FDA's surveillance data.[4] An observational study from three Nordic countries—Denmark, Finland, and Norway—found statistically significant increases in thromboembolic and thrombocytopenic outcomes following both Pfizer and Moderna mRNA vaccines.[5]

"Nordic countries have very good, nationalised health systems so they have good medical records of these events," said Høeg, who was not involved in the study. "What stood out to me with the mRNA vaccines was the risk ratios of intracranial haemorrhage for Pfizer and for Moderna. It was 2.2 for Moderna, and it's statistically significant. I've heard that people have seen it clinically but a robust analysis like this is much more convincing than anecdote."

Christine Stabell Benn, a vaccinologist and professor in global health at the University of Southern Denmark, highlights two studies that analysed the data from the phase 3 randomised controlled trials of covid-19 vaccines—one by Fraiman and colleagues[4] and the other a preprint[6] by her own research group. "The safety signal seems to be gathering around cardiovascular and cerebral vascular events, things to do with circulation and our larger organs, and these are the same signals that appear to be popping up in the FDA surveillance data as well," says Stabell Benn.

According to Stabell Benn, the underlying problem with documenting adverse events is that the covid-19 vaccines "were not tested properly." She says, "The phase 3 trials offered vaccines to the control groups just a few months after the randomisation, so it doesn't allow for assessment of the long term adverse events—but it's the best evidence we have so far, since no phase 4 trials were carried out. Now, we largely have to rely on poorer quality data and studies."

Adding to the difficulty is the type of adverse events being documented. "Myocardial infarction and thrombosis are events that occur often in the elderly and so doctors are less likely to report them as potentially linked to the vaccine, unlike vaccine induced immune thrombotic thrombocytopenia which is so dramatic and rare and also affected younger age groups, so it was easier to pick up," says Stabell Benn.

To disclose or not to disclose?

Tom Frieden, former US Centres for Disease Control and Prevention (CDC) director, says it's a challenge for public health agencies to balance the release of contentious information. "There's a valid concern that reports of adverse events will be misinterpreted as causal when they're not causal to the treatment or vaccine given, and another concern is if you don't present the information, you may be seen as hiding something, which is also problematic. So, this is not an easy area," says Frieden.

He believes that the FDA and CDC have done a good job at publicly communicating the safety signals of covid-19 vaccines, pointing to the decision to pause the Johnson & Johnson vaccine after six reported cases of cerebral venous sinus thrombosis.[7] "That was exactly the right decision at the time, it was just kind of 'stop, look, and listen,' and then come to a conclusion. Frankly, it was a judgment call whether to reintroduce the Johnson & Johnson vaccine at all. I think they were shared promptly. They were shared openly. I don't see a lot to criticise in how they were shared. The reality is that it's a very difficult thing to do—to share information well, in a way that will lead to people making the right conclusions."

Earlier this year, the CDC admitted to withholding deliberately critical data on boosters and hospital admissions. Kristen Nordlund, CDC spokesperson, told the *New York Times* that the agency had been slow to release data to the public on breakthrough infections "because they might be misinterpreted as the vaccines being ineffective."[8]

In addition, CDC director Rochelle Walensky acknowledged that the agency had not conducted a disproportionality analysis that the agency had indicated it would conduct in 2021 to analyse spontaneous adverse event reports.[9] When asked about his thoughts on Walensky's admission, Frieden said, "I don't know what the reality is. I can't comment."

Cody Meissner, a paediatrician and member of the FDA's Vaccines and Related Biological Products Advisory Committee, said he did not think that the FDA was "deliberately" withholding data from the public but did agree that sharing data is key to establishing trust. "I fully concur that transparency is key, and everyone should know all the information that is available. One of the great tragedies of this pandemic is likely to be the loss of confidence in public health authorities. One of the great problems was the suppression of opposing voices to various recommendations and that's going to cause extraordinary harm," says Meissner. "Everyone is aware that there are going to be side effects from any vaccine and as time goes by, we're going to find out more and more about those side effects. Whether it's an association with myocarditis or association with a pulmonary embolus, it's going to take time," he adds.

The Pfizer and Moderna clinical trial reanalysis by Fraiman and colleagues indicated the mRNA vaccines were associated with an additional serious adverse event for every 800 people vaccinated,[4] far more than the 1-2 for each million reported for vaccines in general.[10] Fraiman says he and his colleagues asked the FDA to warn the public based on their reanalysis, and replicate their study, but this has not happened.

"It seems to me that doctors have a much higher tolerance for covid vaccine side effects because there's been this sense that if you don't take the vaccine, you die. Obviously, that is completely the wrong way to think about it," says Stabell Benn.

"We don't want to create a lot of unnecessary anxiety and we can't say there is now proof that the vaccines cause these events because the data are of poor quality, but we can say there is a danger signal, and the medical profession needs to be alerted to this," she adds.

The BMJ has learnt that the FDA's medical record review and statistical analyses have recently been completed, and the overall study results are currently under internal review. "The findings to date from the fully adjusted epidemiologic study on the primary series vaccinations do not provide strong support for an association between the vaccine and any of the four outcomes described in the

posting to the FDA website. Additional analyses, including evaluation of booster doses, are still being conducted. Release of the study findings is expected later this fall," said the FDA.

Peter Doshi, a senior editor at *The BMJ*, is co-author with Fraiman of a recent reanalysis of serious adverse events in Pfizer's and Moderna's randomised trials, published in *Vaccine*.[4]

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