Doshi public comments at FDA VRBPAC meeting, Dec 10, 2020
3 minutes.

Hello, this is Peter Doshi, thanks for the chance to speak. For identification purposes, I am on the faculty at the University of Maryland and a medical journal editor at The BMJ. I have no relevant conflicts of interest and no one has paid for my attendance.

[slide 2 please] My experience has been that careful review of a large trial takes considerable time and effort. As FDA has already reviewed the data, I would like to know whether FDA is confident in the data collection for the primary endpoint—specifically, that any unofficial unblinding did not affect the results? And that fever and pain medications did not mask symptoms, thus preventing case detection? I didn't find answers to these questions in the FDA's briefing documents.

[slide 3 please] The dramatic difference in rate of side-effects between vaccine and placebo raises questions about how well these trials could be observer-blinded. With a subjective endpoint like symptomatic Covid, blinding is important, but it seems fair to think that people could make reasonable guesses as to which group they were in.

[slide 4 please] In the real world, the mantra has been to "test test test". But this wasn't the case in the trial. The study protocol says in the 7 days after vaccination, do **not** test unless, in the investigator's opinion, the clinical picture suggested Covid rather than vaccine side effects. This amounts to asking investigators to make guesses as to which intervention group patients were in. My question is was this kind of judgment ever applied in the days it could affect the primary endpoint?

[I'd like to skip to slide 6 in the interest of time]

Possible unblinding would matter less if the trials had been designed to directly test the vaccine's ability to reduce deaths, ICU use, and hospitalizations—as most people assumed these trials were set up to do. It's great when the data look encouraging, but trials should be directly testing the endpoints that matter.

Then there is the duration of protection. A vaccine that delivers a 95% relative risk reduction of Covid 2-3 months after vaccination is one thing. But for the many people who lack natural immunity and don't get exposed to the virus soon after vaccination, protection needs to last much longer. After 6 months or a year, would the vaccine still meet FDA's 50% effective requirement? The trials don't have sufficient data to say.

Keeping the trials going with placebo-controlled follow-up will help answer the many crucial questions that remain. For those who do not wish to wait for clear evidence that benefits outweigh risks, an expanded access program can be set up. Access doesn't require authorization.

I want to end by saying that whatever FDA ultimately does, the full trial data must be made publicly available. **Thank you.**