Doshi public comments at FDA VRBPAC meeting, Oct 22, 2020
3 minutes.

Hello, my name is Peter Doshi. Hopefully you can see my title slide now. 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. A copy of my slides is available on my faculty homepage.

[next slide 2 please] I have reviewed the FDA's guidances on Covid-19 vaccines and the four publicly released phase 3 trial protocols.

My brief presentation today aims to point out that, unless urgent changes are made to the way the trials are designed and evaluated, we could end up with approved vaccines that reduce the risk of a mild infection but do not decrease the risk of hospitalization, ICU use, or deaths—either at all, or by a clinically relevant amount.

The reason for this is that all trials are using a primary endpoint of Covid-19 of essentially any severity, such that even a mildly symptomatic person would qualify. For example, in the Moderna and Pfizer trials, somebody with a mild cough and positive lab test would meet the primary endpoint definition.

[next slide 3 please] Permitting mild Covid cases to be counted as the primary endpoint will allow trials to complete quickly, but doing this will leave us without proof that the vaccine prevents serious complications of Covid. Simply preventing mild cases is not enough and may not justify the risks associated with vaccination.

Additionally, without a definitive assessment of efficacy in the elderly and other subgroups at highest risk, we could be left with an approved vaccine that reduces mild cases in healthy people but does little to protect the most vulnerable. Estimates are that somewhere around half of all deaths are occurring in nursing homes. We need the trials to find out which vaccines can save lives.

[next slide 4 please] I think this issue has flown under the radar because most people assumed severe Covid **was** what we were studying. The NIH in fact even said so in a press release about Moderna's trial.

[next slide 5 please] Finally, please note the FDA and sponsors' definition of "severe Covid-19" also needs revising, because currently mild Covid-19 cases with the added single criterion of a blood oxygen saturation of 93% meets the definition.

The problem is that at least 1 in 20 normal, asymptomatic, older adults have an oxygen saturation of 92% or less. Low blood oxygen levels are arguably an important risk factor for severe disease, but they are not severe disease itself.

[next slide 6 please] Most Americans assume our vaccine development process—in contrast to, say, Russia's—ensures that an approved vaccine can save lives, reduce hospitalizations and ICU

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admissions. But unless we set the right primary endpoint in trials, we won't have hard evidence to know that is the case. **Thank you for listening. I would be happy to take any questions.**