Q&A: A COVID-19 vaccine is coming—will it be safe?

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In March, at the start of the COVID-19 pandemic, there was a consensus among health care providers and public health officials that a vaccine that provided complete immunity to SARS-CoV-2, the virus that causes

COVID-19, would effectively end the pandemic.

At the time, experts suggested that the development of a safe and effective COVID-19 vaccine could be accomplished in 12 to 18 months, even though vaccine development typically takes about 10 years. (In fact, the fastest vaccine ever developed—a mumps vaccine—still took four years.)

Yet, because of the urgency created by this global pandemic—and the serious illness and death rates associated with COVID-19—preclinical and clinical trials to test the efficacy and safety of COVID-19 vaccine candidates are happening at a rapid, almost frenetic, pace.

That leaves many Americans concerned about how safe a COVID-19 vaccine will be. According to a survey conducted by the Pew Research Center, the number of Americans who planned to get a COVID-19 vaccine has fallen from 72% in May to just 51% in September. What's more, according to the report, when asked about the pace of the vaccine approval process, 78% say their primary concern "is that it will move too fast, without fully establishing safety and effectiveness."

This fear was stoked in early September, when the Centers for Disease Control and Prevention (CDC) told state officials across the country to prepare for the distribution of a COVID-19 vaccine by November 1, just days before the presidential election. Whether this vaccine would be granted official licensure from the Food and Drug Administration (FDA) or be released by an emergency use authorization (EUA)—a tool by which the FDA can authorize use of medical products, including vaccines, that have not completed clinical trials—is unclear.

Nevertheless, the announcement raised concerns about undue political influence over the release of a COVID-19 vaccine, leading the chief executives of nine pharmaceutical companies to publicly pledge to

"make the safety and well-being of vaccinated individuals" their "top priority," while stating that they would only seek approval of a vaccine if a Phase 3 trial establishes that it is both safe and effective. The pledge aimed to reassure the public that any vaccine that is approved will have passed all safety and efficacy checks.

But many remain skeptical—and confused.

With this in mind, we sat down with Saad Omer, MBBS, Ph.D., MPH, the director of the Yale Institute for Global Health. Dr. Omer leads a World Health Organization (WHO) group that evaluates the safety of COVID-19 vaccines.

He provided answers to our questions about COVID-19 vaccine development.

This interview—taken from three conversations—has been edited for length and clarity.

Q. Why do we need a COVID-19 vaccine?

A. Because it is the end game. If you want to resume the normal activities of life—eat at restaurants, go to theaters, all of the other things that you want to do without taking drastic actions—then you need a "population level" of immunity.

And there are two ways to achieve this. One is to let the whole population—or a large number of people—get infected with COVID-19. This would result in a great deal of mortality, a lot of people dying, which is obviously undesirable. The other way is through vaccination.

Q. Do you know if the vaccine will be similar to the

annual flu vaccine, where we need to get it every year, or if it might provide immunity for life, like with the MMR vaccine?

A. We don't know yet. But, I would be surprised if it's a year-to-year vaccine. I expect the protection to last for at least a few years. Beyond that, we'll have to see.

Q. COVID-19 vaccines are being developed on a compressed timeline. Why won't that compromise safety?

A. Well, so far the speed is being gained due to process efficiencies rather than by cutting corners or eliminating the actual steps from development.

Q. What's an example of a process efficiency in this case?

A. Steps that are usually done sequentially are taken in parallel, while getting to the same end result of having good data. For example, running combined Phase 1 and Phase 2 trials, doing animal studies in parallel with human studies, doing quick target identification. And having vaccine development manufacturing facilities ready even before a vaccine is finalized.

Q. But if you're running combined trial phases, isn't there a greater risk for the people enrolled in a later-phase trial without first knowing the results of the earlier-phase trial?

A. No, there's really just a subtle difference in how the trials are run. If the trials were separate, you would publish the full data, and then recruit a new set of participants. For a combined trial, the data and safety monitoring board would look at the interim data and determine whether it's still worth continuing the trial. So, you're not stopping it and then taking a look. You're taking a look on an ongoing basis.

That means that whenever their Phase 1 and 2 trials are combined, for example, independent data review committees monitor the safety data in a blinded fashion. And these committees are appointed—usually, they are professors or other experts who are not related to the trial. They work directly with study statisticians, and the principal investigators of the study are not privy to those meetings. So, the committee monitors the trial on an ongoing basis. If they see concerning trends in the data, they can stop or pause the trial and then re-evaluate it, as necessary.

Q. Which is what happened with the AstraZeneca and Johnson & Johnson trials recently.

A. Yes.

Q. Many people are concerned about the shortened timeline of the Phase 3 trials. If those typically last 6 to 8 months, for example, but a vaccine is approved by November—in only a few months—how can we be confident that we're not missing data on side effects and efficacy?

A. The efficacy part is easier to answer. Essentially, there are two ways of running the trials: You can follow up with trial participants for a longer period of time, or you can have what are called "event-driven

trials," where you enroll a ton of people so you can get events [people getting sick with COVID-19] from a large number of people. The event-driven trials are one way to find efficiency.

Q. How does that translate into an efficiency?

A. With these trials, the statistical information rather than the sample size is set in advance. In this case, this means that the trial enrollment size depends on the rate of events that have to occur to ensure the vaccine has an efficacy rate of at least 50%.

So, if you need 130 or 150 events to happen to confirm the vaccine's efficacy rate, you might enroll 30,000 participants. But, sometimes your events are accrued faster—if there's more disease in the community, as there would be in a pandemic, or if the vaccine isn't working as well, or a combination of both. The faster accruals mean you reach your events faster, which can save a significant amount of time.

Q. What about safety?

A. Safety comes down to oversight and transparency. Because this is a public health emergency, independent committees would be looking at the data earlier on in the process. That's where two committees, a trial DSMB [data and safety monitoring board] and what is called a VRBPAC [Vaccines and Related Biological Products Advisory Committee]—a standard committee that looks at the data before approval authorization licensure—come into play. The FDA commissioner has announced that they're going to have a meeting at the end of October—and that it will be open, meaning they recognize that transparency is important.

What's more, the FDA recently said that they're going to need to see at least two months of median follow-up safety data from vaccine

manufacturers before they would even consider an EUA, and that's a good thing; it's more stringent criteria.

And there are other independent safeguards in place. Professional organizations like the American Academy of Pediatrics can issue or withhold their endorsement statements. If the data are not sufficient, they would point to that.

Also, from a data perspective, there is a process called post-marketing surveillance, where vaccines are followed carefully to see if there are early signals of adverse events. But even before that, there is some basic follow up that a large number of people will have to have to give us confidence in the safety of the vaccine. So, we as public health experts will want access to that data.

Q. Circling back to the condensed timeline question, is it fair to say that if there are no adverse events seen in these Phase 3 trials—however shortened they may be—we can assume there will likely be no long-term negative effects?

A. Well, we know that most of the adverse events that happen tend to cluster early on, usually within the first couple of months, so yes. And the idea is to be preemptive—to make sure that you're ready to detect any signals and mitigate and modify your recommendations.

So, you follow trial participants for anything that looks like disease or other things that are of concern, like autoimmune reactions, among others. If the committee thinks that there are no minimal or serious adverse events, it is reassuring.

But another consideration is that enough follow up has occurred so that

we can say with confidence that it is okay to start vaccinating people. It's a risk–benefit situation, and the benefits should substantially outweigh the risks. Because it's a pandemic, we don't have the luxury of waiting years and years.

Q. We're testing new platforms that have not been used for approved vaccines before. You mentioned that, for traditional vaccines, the adverse events cluster in the first couple of months, which would alleviate fears about a compressed timeline. Do we know the same to be true for these new platforms?

A. We don't know, but they are new platforms, not new biology. They're using nature's own mechanisms to induce immunity. And we have experience from the early-phase trials. It's also important to recognize the distinction between serious adverse events and a subcategory of early events that are not serious and are fairly common for vaccines—things like injection pain or fever, which happen within one or two days of receiving the vaccine and then resolve. Those aren't typically related to serious events.

Q. Is it possible to know which vaccine candidates are more promising over the others?

A. No, not at this point. We have a broad category of the things that are in advanced stages. They all show promise, but which one of them would be more successful or more advanced and more efficacious remains to be seen.

Q. Why is representation of minorities—who have

been disproportionately affected by COVID-19—in vaccine trials important? People with risk factors like obesity or advanced age might react differently to a vaccine, but it seems like we don't yet know if there is a genetic or biological link between these groups and severe cases of COVID-19.

A. We don't know about the genetic part of it. But we do know that there's a huge racial component to it. You need generalizable safety and efficacy data in all populations, but especially in the ones that are disproportionately impacted, because of biological, as well as social reasons—a vaccine's impact can vary. So, I couldn't overemphasize the importance of enrolling the populations that are most impacted by the outbreak; they should be reasonably well-represented.

Q. The FDA has said that if a COVID-19 vaccine has an efficacy rate of at least 50%, they will approve it. 50% is also the minimum efficacy rate on the WHO target product profile, although they believe 70% is ideal. Can you reconcile that difference?

A. It speaks to why there are independent processes so that different bodies like the WHO or the U.S. government can arrive at their desired percentage—and often they will converge. But, the WHO is dealing with a larger population, where they need a more efficacious vaccine to provide broader immunity. I think it's reasonable for the U.S. to say that 50% is not ideal, but it's good enough.

Q. Would 50% be good enough to give us herd immunity?

A. It depends on the immunization rates and who gets vaccinated. People tend to think of herd immunity as binary—yes or no. But in these kinds of situations, even with a vaccine that is 50% effective, you start to see what are called "indirect effects" where you slow down the outbreak without extinguishing it.

Q. So we would still need to take precautions, like wear masks, wash our hands, and practice social distancing.

A. Yes. But it's important to remember that 50% is the floor that the FDA has set—the minimum. If there is an approved vaccine that is more effective than 50%, then there's more flexibility in terms of easing up restrictions. So, we shouldn't assume that it will be a 50% effective vaccine just because that's the FDA's minimum requirement for approval.

Q. Is there a risk, then, that if we have a vaccine that's at or around 50% effective, it will slow the development of a vaccine that is 100% effective?

A. Well, if you have a 50% effective vaccine that is widely used, then it becomes what's called the "standard of care." So, for ethical reasons, rather than giving a placebo to trial participants in the control arm, you have to give them the 50% effective vaccine.

Ultimately, it might impact future trial sizes—depending on if you're looking for efficacy and disease events (they would be larger) or instead for the type and level of immune response associated with protection (they might be smaller)—and recruitment efforts. But I don't see it as a concern.

Q. So, if a vaccine that is 50% effective doesn't completely prevent infection, could it offer protection against severe illness?

A. Yes, that's the main end point. The trials are not designed to measure the impact of the vaccine on transmission; they are designed to look at disease outcomes. So, it may very well happen that this is not stopping or reducing transmission, but instead reducing disease.

Q. Will people who have been infected with and recovered from the coronavirus need to get a vaccine?

A. I'm hoping to study that question myself, but at this point we don't know yet.

Q. In September, the FDA said it may approve a vaccine before Phase 3 trials are complete. This came on the heels of what some considered a questionable decision regarding the agency's EUA on convalescent plasma and its claims about it (which the agency eventually walked back). What do you make of these events, and what can we do to protect ourselves?

A. That's a really good question. In terms of convalescent plasma, experts raised their concerns vociferously. There was a lot of pushback. Most experts were okay with the EUA; they were uncomfortable with the over-interpretation of the data.

Recently, the FDA has insulated itself; they've sent good signals about following the accepted, mainstream process. The kinds of evidence they

would expect to make decisions on are very encouraging. The signs are good that despite any political pressure, the career folks at the FDA are likely to follow the by-the-book procedures.

But, basically, the general public doesn't have to interpret this data on their own. Look at the people who have been studying this problem—and not through a Google search—look at the actual original researchers who have served on government advisory panels. See what they're saying. Similarly, watch for how the data is shared, how they're presented, and look for transparency.

Q. Is there a hopeful note you'd like to leave on?

A. The initial studies have shown that there could be a reasonable vaccine for this virus. I haven't seen any major dead ends in vaccine development so far. The animal studies and the data from humans in early trials are encouraging, though not definitive in terms of protection.

In other words—it's like we're going to be taking a long trip, and we're finding reasonable weather in the first part of the journey.

Provided by Yale University

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