Sandra Fryhofer, MD, discusses the latest on phase 3 vaccines trials

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Featured topic and speakers

In today's COVID-19 update, AMA Chief Experience Officer Todd Unger talks to the AMA liaison of the CDC's Advisory Committee on Immunization Practices about the latest on vaccines for COVID-19, including at least three vaccines that have entered phase 3 trials in the U.S.

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Speakers

- Sandra Fryhofer, MD, physician, AMA liaison, Advisory Committee on Immunization Practices, CDC

Transcript

_Unger_: Hello, this is the American Medical Association's COVID-19 update. Today we're getting an update on vaccines and COVID-19 from Dr. Sandra Fryhofer, an internal medicine physician, adjunct associate professor of medicine at Emory University School of Medicine and an AMA trustee in Atlanta. Dr. Fryhofer is the AMA liaison to the CDC's Advisory Committee on Immunization Practices or ACIP, and serves as the AMAs representative on the COVID-19 vaccine work group. I'm Todd Unger, AMA's chief experience officer in Chicago. Dr. Fryhofer. We see so much in the news about vaccines every day, can you give us the big picture? Realistically, how far along are we?

_Dr. Fryhofer_: Well, there are over 200 COVID vaccines in different stages of development around the world and things are moving fast thanks to Operation Warp Speed. This federal initiative has pledge more than $10 billion to develop and deliver 300 million doses of COVID-19 vaccines. Already, at
least three vaccines have entered phase three trials in the U.S and expect more to enter phase three by the end of this year. The initial OWS goal was to have at least some doses available by January 2021. And when you consider it usually takes 10 to 15 years to develop a vaccine, this is quite an ambitious goal. Until now, the fastest vaccine to come to market was the mumps vaccine back in the 1960s, and that took four years. News reports now suggest COVID vaccine doses may be available even sooner than originally planned, but many experts worry too much could be happening too fast. Are corners being cut? And how could so much be happening so quickly?

Vaccine manufacturers did get a head start, building on previous work for SARS and MERS vaccines. The virus sequence was posted on the web in January 2020. Phase one, two and three trials that usually occur in a stepwise sequence have now been combined. They’ve essentially been overlapping and running at the same time.

**Unger:** Well, Dr. Fryhofer, can we talk a little bit about those phases? Where are we right now? A lot of these vaccines have entered phase three trials, can you give a quick overview of what happens between those particular phases?

**Dr. Fryhofer:** Sure. The very first step is preclinical, which means testing in animals. And after that, human studies begin. In phase one, small groups of people, maybe 20 to 100 at most, receive the vaccine. Phase two include several hundred volunteers. In phase three, the vaccine is given to thousands of people and tested for efficacy and safety. Phase three trials need to be large in order to reveal rare side effects that may have been missed in the smaller studies. The next step, applying for FDA approval.

**Unger:** Dr. Fryhofer, there are a number of different types of vaccines, can you give us an overview of them and how they work from a science perspective?

**Dr. Fryhofer:** COVID-19 is caused by the SARS-CoV-2 coronavirus, which has spikes on its surface that look like a crown. These spike proteins are the main target for vaccine development. Although more than 200 vaccine candidates are under study, there are only four basic platforms used for COVID vaccine development.

The first category includes both live attenuated and an activated virus vaccines. This is traditional technology we’re all familiar with, the kind used for many flu vaccines. Next, viral vector vaccines. You take a weakened version of a virus, which is the viral vector, then genetically engineer it to make coronavirus proteins in the body.

There are two types of viral vector vaccines, replicating and nonreplicating. The AstraZeneca Oxford candidate vaccine, AZD1222, is a nonreplicating viral vector vaccine. Phase three trials of this vaccine were recently paused when a single event of unexplained illness occurred in the UK. News outlet suggest the patient developed transverse myelitis. FDA is still deciding whether or not to allow its phase three trials in the U.S to resume. Janssen, the pharmaceutical arm of Johnson and Johnson
also has a nonreplicating viral vector vaccine candidate, Ad26.CoV-S1, and it's now starting phase three trials.

**Unger:** Which vaccines has ACIP looked at so far?

**Dr. Fryhofer:** Well, there are two more vaccine platforms I'd like to tell you about before we go over that.

**Unger:** Okay, all right.

**Dr. Fryhofer:** The next vaccine platform is protein based, recombinant vaccines. Protein based vaccines induce an immune response using either protein subunits, which are pieces of the virus that focus on the spike proteins or the LPs, virus like particles that mimic the structure of the virus but are just empty shells. The final vaccine platform includes a group of genetic vaccines called nucleic acid vaccines. For licensing, this is uncharted territory. There has never, ever been a vaccine licensed by the FDA which uses a nucleic acid platform.

Nucleic acid vaccines introduce genetic material, either DNA or messenger RNA. Then the body's own cells make the protein antigen, which triggers the immune response. Both the Moderna’s mRNA-1273 and Pfizer BioNTech mRNA-VNT162 are messenger RNA vaccines. Remember, the entire SARS-CoV2 genome sequence was publicly released in January 2020. And once that viral sequence was released, companies making nucleic acid vaccines could get started right away. And that's probably why we started hearing so much about Moderna’s mRNA vaccine so early. But understand this, Moderna has never, ever brought a vaccine to market. This could be their first.

**Unger:** Well, which vaccines has ACIP looked at so far?

**Dr. Fryhofer:** At our August ACIP meeting, ACIP reviewed phase one safety and immunogenicity data for both Moderna and the Pfizer BioNTech's mRNA vaccines. Phase one data for both vaccines showed induction of neutralizing antibodies seven days after the second dose that exceeded levels in convalescent sera. Both vaccines induced a TH1-biased CD4 T cell response. Both vaccines also caused transient local and systemic reactions, pain at the injection sites and fever, chills, headache, fatigue, muscle and joint aches. ACIPs review supported advancing both vaccines to large phase three clinical trials to evaluate safety and efficacy. And those phase three trials are currently enrolling.

**Unger:** Well obviously, to say there are challenges, it would be an understatement, but let's talk about some of the biggest challenges to vaccine development and beyond.

**Dr. Fryhofer:** Well, the biggest hurdle for these two mRNA vaccines is cold chain storage and distribution requirements. The Moderna vaccine has to be stored really cold at negative 20 degrees centigrade. The Pfizer BioNTech vaccine has to be stored ultra cold at negative 70 degrees centigrade. So these cold chain requirements would make it very difficult for community clinics and
pharmacies and doctor's offices to store and administer vaccines under these conditions. For vaccine development, work group discussions have stressed the importance of enrolling diverse populations. There needs to be sufficient time after the second dose to evaluate safety signals. Maternal and fetal outcomes for women who become pregnant during the clinical trials needs to be reported and reviewed. We also need data on co-administration with other vaccines, especially flu vaccine and data on used in pregnant women and children.

**Unger:** You mentioned equity in terms of the research side and making sure that we have a diverse population being tested with these vaccines. So in addition to storage, how do we, on the distribution side, ensure equitable distribution once we have a vaccine?

**Dr. Fryhofer:** Well, initially there will be limited doses available. And administration of COVID-19 vaccine will initially require a phased approach. Our work group has discussed this extensively. Many groups have gone on record and weighed in including the National Academy of Medicine, the John Hopkins Center for Health Security and the World Health Organization. AMA also shared a document for allocating limited supplies of vaccine based on our AMA Code of Medical Ethics. All groups agree that healthcare personnel should be included in the first phase of vaccine recipients. But what are the groups should also be a part of phase one? Essential workers, adults with high risk medical conditions, adults 65 and older? It's hard to say who should be first?

We still have so many information gaps, and there are multiple vaccines under study with different profiles so we don't know vaccine efficacy for younger versus older adults. Some vaccines may work better in certain groups than others. We need data on vaccine performance, including the magnitude of benefit and potential risk for younger versus older patients. There are many unanswered questions that need to be answered before responsible decisions can be made. More information is needed.

**Unger:** So much continue the need for more data and learning, it's just been really a consistent theme throughout this. And transparency is another big thing that you spoke to earlier in this. Some people might be surprised at the level of transparency that you spoke about. Not long ago, the AMA released a statement urging the FDA to ensure transparency in vaccine development. What are your thoughts on that and how do we do it?
Dr. Fryhofer: Well with COVID vaccine development moving at such a rapid pace, physicians need to feel confident in the safety and efficacy of COVID vaccine candidates. The AMA has urged FDA to work more closely with the physician community to develop a plan for further education and transparency surrounding COVID vaccine candidates. It’s important to start this process now to help physicians promote vaccine confidence among their patients and the general public. The release of FDA’s guidance document for evaluation of vaccine efficacy was a step in the right direction. However, we still need more transparency from the FDA on standards used to develop vaccine safety and to evaluate vaccine safety. In an effort to earn the trust of the public and the scientific community, both Moderna and Pfizer have released protocols for their trials.

Unger: Well last question, you spoke about vaccine confidence. Every year, we try to get people to get their flu shots and we’re facing what some people have called a twindemic coming up this fall. What can you tell us about the flu vaccine for the fall, and its importance in light of COVID?

Dr. Fryhofer: Flu season is right around the corner, and there’s no crystal ball for how bad this year’s flu season will be. This year, as you mentioned, we’re at risk of a double whammy, both flu and COVID. The symptoms are similar so we need to get flu off the table by getting vaccinated. Everyone six months and older needs flu vaccination, especially this year. The community’s hit hardest by COVID are the same as those where severe flu outbreaks are likely to occur. And although the flu season has been mild in the Southern hemisphere, that’s no guarantee for us in the Northern hemisphere. So please, take advantage of any available opportunity to get vaccinated. Flu vaccination is not 100% effective, but we do have flu antiviral medications that can help treat it if you happen to get sick.

Unger: And there are a number of variations on that flu vaccine, correct?

Dr. Fryhofer: Well, this year’s flu vaccine composition has had a makeover. Components for three strains, two flu As, and one flu B have been updated. Most vaccine available this year is quadrivalent, meaning it covers four rather than three strains of flu. And here’s some other reminders, egg allergy is no longer a contraindication for flu vaccination. The high dose shot and the adjuvanted vaccine are specially designed for those 65 and older to improve immune response. The nasal flu vaccine is back as an option for healthy persons age two to 49, as long as you’re not pregnant. Pregnant women need flu vaccination, but they should get the inactivated shot. The nasal flu vaccine is a live attenuated influenza vaccine and won’t work if given at the same time you’re taking antiviral medications. Remember, everyone six months and older needs flu vaccination, but we also must continue to be diligent about wearing a mask, staying physically distanced from others and sanitizing our hands.

Unger: Well, thank you so much Dr. Fryhofer. With so much information out there about vaccines, it’s really incredible to hear your perspective and thoughtful responses to these questions. And I hope that it clarifies a lot of the issues around vaccine development for our audience out there. That

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