COVID-19 Vaccines: What's Next?

Interview with Margaret Hamburg, M.D.
Former Commissioner
U.S. Food and Drug Administration

Margaret Hamburg is a former Commissioner of the U.S. Food and Drug Administration (FDA), having served in this post from 2009-2015. A physician-scientist and public health expert, she recently completed a term as Chair of the Board/President of the American Association for the Advancement of Science (AAAS). HVP Editor Kristen Jill Abboud recently spoke with Hamburg about the regulatory issues concerning the eventual licensure of COVID-19 vaccines. These issues are particularly relevant given recent reports that indicate vaccine candidates being developed by Pfizer/BioNTech and Moderna are highly effective.

An edited version of the conversation appears below.

What do you think about the potential risk of politics influencing the licensure of COVID-19 vaccines?

Developing a vaccine is a very big scientific challenge that requires enormous focus and attention on conducting the right studies, ensuring that they are sufficiently rigorous to determine safety and efficacy, and making sure that they are designed and structured ethically. Those issues are generally taken for granted, but in this highly charged political environment there have been concerns raised about the chance that either there will be corners cut in the effort to accelerate vaccine development, or that political pressure will lead regulators to make decisions without adequate and complete information. In my view, it is essential that all of the stakeholders come together to support a robust vaccine research and development process, and I think that has been happening. I have enormous confidence and faith in the FDA and in the teams of scientists and experts that are reviewing these candidate vaccines. We need to have COVID-19 vaccines, preferably more than one, and we need them to be safe and effective. But we also need people to have trust and confidence in those vaccines. If they don't trust these new vaccines, they won't take them and then they will not serve their intended purpose to help manage, control, and ultimately end this devastating pandemic.

Pfizer/BioNTech and Moderna have both reported that their vaccine candidates are 95% effective against COVID-19. Was this surprising? Do you anticipate that COVID-19 vaccines will far exceed the U.S. FDA's minimum efficacy level of 50%?

This was very encouraging news. We are all eager to see more data, but these announcements suggest that these vaccines will meet criteria for authorization and their administration in priority, high-risk populations may begin soon. The data also suggest that the SARS-CoV-2 Spike protein is an appropriate vaccine target, and this bodes well for many of the other vaccine candidates in development that are using different approaches, but are using the Spike protein as the antigen.

Many vaccines are not as effective as we would ideally want them to be. The FDA was thinking about COVID-19 vaccines with regard to the experience with influenza vaccines, which range from 40-70% efficacy. The FDA guidance indicated a 50% efficacy as the minimum threshold for authorization/approval, so these results are coming in dramatically higher than initially expected for this respiratory virus.

Do you suspect these trials will be sufficient to determine the efficacy of COVID-19 vaccines in specific subpopulations such as the elderly?

Determining efficacy across all relevant populations is a problem for vaccine studies, but we are noticing it more acutely now because there is a very wide range of individuals that will ultimately need to be vaccinated against COVID-19. There has been an effort from the beginning to include elderly individuals in the vaccine studies because we know they are a very important target group because of their elevated risk. Other high-risk groups have been included in the vaccine studies as well, including those with comorbidities, but there will probably need to be expanded studies in some key subpopulations as well. One critical group will be pregnant women, who have not been recruited in a targeted way in the ongoing studies. Another important group is children and youth. A couple of the studies, most notably Pfizer/BioNTech's, have lowered the age cutoff down to include age 12 and up, but we are going to have to do additional work to understand safety and efficacy, as well as appropriate dosing and immunization schedules in younger children, who may not be at the greatest risk of life-threatening disease, but are certainly important in the dynamics of disease transmission. We will want to have COVID vaccines for all of these population groups, and this will require bridging studies to further flesh-out appropriate use of these vaccines in populations that either weren't included or a large part of the initial studies.

It will be important to have ongoing oversight of vaccines, even as they move out of the research context and into broader use, because we always want to monitor for emerging safety concerns and deepen our understanding of efficacy. It will be particularly important that we learn more about the duration of protection and determine if certain vaccines work better in specific subpopulations. We will learn much more about that over time and with expanded use as we go from controlled studies of tens of thousands of people, to millions, or even billions of people receiving vaccines worldwide.

If the first candidate vaccines are found to be effective, will all future vaccine candidates need to be compared to those in head-to-head trials for them to receive licensure?

That is a hugely important question and one that is being debated as we speak. It is unusual to be developing and testing so many different vaccines for the same disease at one time. The good news is that there are lot of potential COVID-19 vaccines, but this does make the testing scenarios much more complicated, both scientifically and ethically. Some of the best scientific minds and most qualified vaccine researchers are discussing these issues and it will be critically important that a clear strategy is developed. For now, it is still very much under discussion.

As data from efficacy trials continues to emerge, what are some of the most pressing issues facing regulators?

One of the critical regulatory issues is whether COVID-19 vaccines will receive an Emergency Use Authorization (EUA) or a full approval. I think it's pretty safe to say that the first candidate vaccines will most likely be authorized using an EUA and that their use will be targeted to a well-defined set of priority groups for vaccination. The EUA allows more flexibility to move a vaccine out in the context of a massive public health crisis. The process of getting a full licensure is a longer one with more specific data and administrative aspects. My guess is that companies that seek an initial EUA will move quickly to a full licensure application, but that the FDA might ask them to collect additional information before full licensure is granted.

One of the regulatory issues related to actually moving vaccines out into larger and larger populations involves the continued need for "pharmacovigilance" as touched on earlier, which is the ongoing monitoring/oversight to detect any emerging safety concerns and to learn more about levels of efficacy and duration across various subpopulations. Another key regulatory focus will concern vaccine scale up and manufacturing. There has been a great deal of attention paid to this early in the development process of COVID-19 vaccines, which is atypical. Because of the urgency of this situation, decisions were made to "manufacture at risk" before the candidate vaccines are authorized or approved. That will significantly speed the ability to get the vaccine out to people who need it, but there will still be a need for robust regulatory oversight of the scale up and manufacturing process to compare different lots of vaccine as it gets manufactured in larger and larger volumes.

From the beginning of this crisis, regulators around the world have tried very hard to work together and I think have done so in important ways, including collaborative activities to look at the science of developing COVID vaccines and accelerating both the research and development efforts and the regulatory process for reviewing these candidates globally.

What other issues do you think we will face as vaccines become available?

One of the important issues is understanding what having a vaccine will mean. Early on, vaccines will be a huge step forward, but we will still need to follow many of the non-pharmaceutical public health interventions we have come to know so well—wearing masks, social distancing, washing hands, and avoiding large groups. We have to realize that even though there has been a huge push to scale up the manufacturing of vaccines even before authorization or approval, there are still going to be limited quantities in the beginning, and so it could be a while until everyone who wants the vaccines are going to be able to get them. Many of the vaccines that may be available early on are going to require two doses so that limits the supply, and also means it will take longer until you reach your desired level of protection.

Vaccines differ, and some may reduce the seriousness of the symptoms of disease or the length of the course of disease, but they may not always prevent infection per se, so people can still get sick. And if you can get sick, most likely you can still transmit the virus, so we're going to have to be mindful of all of that as we move into a world where vaccines are available.

We need to be careful not to convey the message that vaccines are going to be the magic bullet that will turn the COVID crisis around overnight and we can go right back to our normal lives. On the other hand, we need to work much more aggressively to help the public understand why vaccines matter and to encourage use of the vaccines once they are available. It's been distressing to see the decreasing number of people who are expressing the conviction that they will take the vaccine. We have to ensure that the right message about the safety and efficacy of the vaccines is getting out so that people trust the vaccines. That message shouldn't just come from the government or companies. We also need to engage a network of communities—and trusted community leaders—to do outreach to help people understand the use of these vaccines and their potential benefits in a way that is meaningful to them. The great tragedy will be if we have vaccines that work and are safe and nobody wants to take them.

Interview by Kristen Jill Abboud

Spotlight

Following Final Efficacy Analysis, Pfizer/BioNTech Vaccine Heads for Review

Yesterday, Pfizer and BioNTech reported their vaccine candidate was 95% effective against COVID-19, based on the final efficacy analysis of the ongoing Phase III trial involving more than 43,000 volunteers. The candidate, known as BNT 162b2, uses mRNA to deliver the Spike or S protein of SARS-CoV-2. This news comes just more than a week after preliminary efficacy data for this vaccine candidate were released, suggesting infections are accruing rapidly as the pandemic continues to surge in many places around the globe (see COVID in Numbers, below).

The companies report that among the 170 confirmed COVID-19 cases that have occurred so far, 162 were in the placebo group and 8 were in vaccine recipients. The efficacy was consistent across different age, gender, race, and ethnic groups, according to the press release, which also notes that efficacy in adults over age 65 was over 94%. This last finding is particularly important given older adults are at the highest risk of experiencing severe disease, hospitalization, or even death as a result of COVID-19. Of the 10 severe cases of COVID-19 disease observed in the Phase III trial, nine were among placebo recipients and only one was in a vaccinated volunteer.

So far, no serious safety concerns have arisen in the Phase III trial of BNT 162b2. According to the latest release from Pfizer and BioNTech, fatigue and headache are the most significant side effects observed to date. Based on this, the companies plan to submit their data and manufacturing information to the U.S. Food and Drug Administration, as well as other regulatory agencies around the world, as part of an application for an Emergency Use Authorization for this vaccine.

This latest news on Pfizer's/BioNTech's vaccine candidate comes just days after the biotech company Moderna reported their mRNA vaccine candidate was nearly 95% effective against COVID-19 based on their preliminary efficacy analysis. Together, these results, which many experts say are even better than expected, are spurring optimism for these and other COVID-19 vaccines in development, as well as for the use of mRNA as a platform that may be applicable to other vaccines for both infectious and non-communicable diseases.

To see how leading vaccine and public health experts are reacting to the latest COVID-19 vaccine news, see recent special issues of the COVID Report. As more data emerges, the COVID Report will continue to provide updated analysis, commentary, and perspective on the quest to develop biological interventions that are critical to ending the pandemic.

Must Read

While researchers and public health officials are buoyed by the interim efficacy reported for both Pfizer/BioNTech's and Moderna's COVID-19 vaccine candidates, there are still many questions about how well these and other vaccines may work in different populations around the world. Recently published research addresses some of these lingering questions.

- Recent research published in *Science* investigates why certain populations have largely been spared the consequences of the COVID-19 pandemic. One study shows that approximately 4% of Kenyans have antibodies against SARS-CoV-2, suggesting prior infection, however, the death rate due to COVID-19 has been very low in Kenya and elsewhere in Africa. In a second study, approximately 60% of children ages 6-16 compared with only about 5% of adults had antibodies that recognize SARS-CoV-2.
- This review article discusses the prospects for the development of COVID-19 vaccines for use in elderly populations.
- Another review published in *The Lancet Infectious Diseases* examines the challenges with continuing to assess the clinical efficacy of different COVID-19 vaccines.
- This review article outlines which assays and animal models can be used to understand the correlates of protection for COVID-19 vaccines that are found to be effective.
- Based on information from official government and department of health webpages from 45 countries, this study published in *Nature* confirms that children around the world are less susceptible to COVID-19, whereas adults older than 65 have the highest mortality rates from the disease.
- In this preprint publication researchers detail the kinetics of antibody, memory B-cell, and CD4+ and CD8+ T-cell memory responses to SARS-CoV-2 in infected individuals, some of whom were infected more than six months ago. This analysis indicates that immune memory may last years following infection.

COVID-19 in Numbers

Global COVID-19 Hotspots

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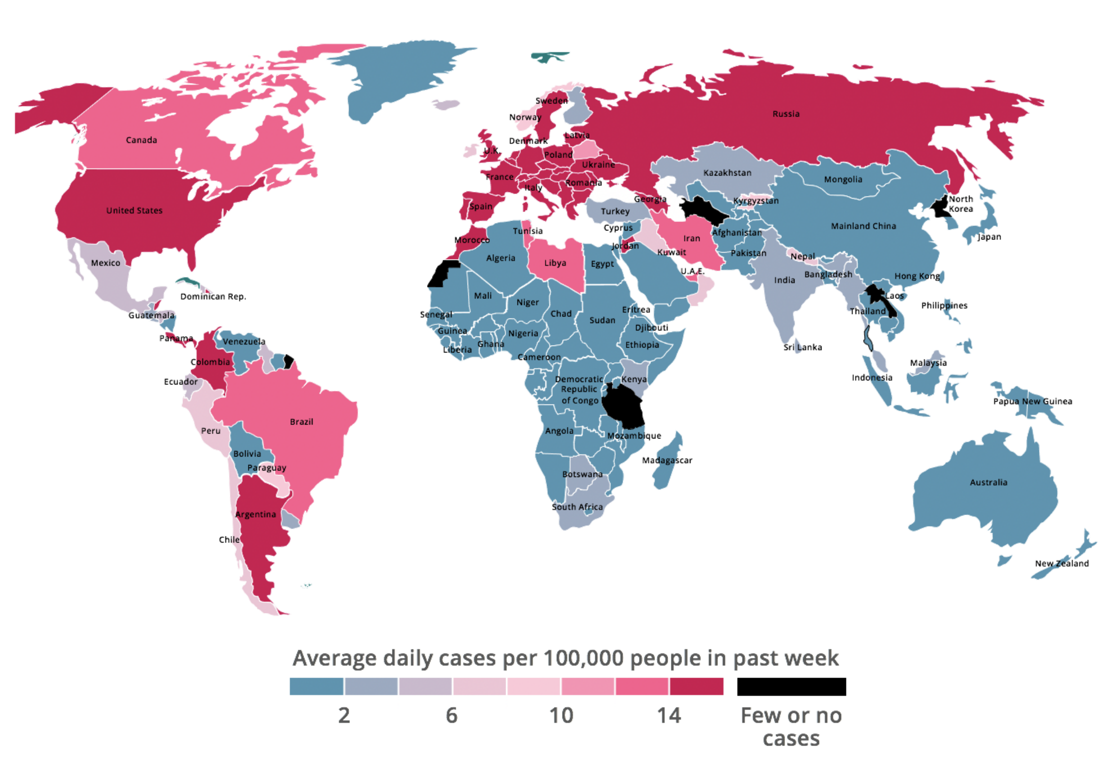

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