[music]

**Speaker:** The *BioWorld Insider Podcast*.

**Lynn Yoffee:** This is the *BioWorld Insider Podcast*, and I'm Lynn Yoffee, BioWorld's publisher. The COVID 19 pandemic is so all-encompassing and complex with dramatic details shifting almost hourly. It can be easy to lose track of the big picture and there are so many questions. Has industry pushed out vaccines too fast? Was there adequate testing? Did they take shortcuts? Why were governments pushing for boosters before the scientific data was available, and so on?

We've asked Mari Serebrov, BioWorld's regulatory editor, who has covered the pandemic since the beginning, to help put it all into perspective. She has strong insights into COVID 19 vaccine development and into the few winners and quite a few failures in the more than 1,000 vaccines and therapeutics in development. She has a deep understanding of how industry has pushed out vaccines and drugs in this turbocharged timeline. Today, Mari will deliver a reality check in a conversation with BioWorld's staff writer, Lee Landenberger, over to you, Lee.

**Lee Landenberger:** Thanks, Lynn. It's great to sit with my colleague, Mari Serebrov. I'm lucky enough to get the benefit of her insight every morning when the staff gets together to plan the list of daily stories that we'll cover. In addition to reporting on biotech, Mari's worked in academia and in state government, she has a deep understanding of process and government regulations and has a knack for making it understandable and interesting.

Mari, we can't get this pandemic under control until more people are vaccinated, and one of the biggest concerns for those who are hesitant to get a vaccine is that the technology is either too new or it's not well-tested or understood, so how do we counter that?

**Mari Serebrov:** We need to provide some historic context. I think what's forgotten too often is that while the COVID vaccines that have been authorized or approved around the world were developed in record time, they didn't start at ground zero last year, they built off of previous coronavirus research in which scientists were testing various vaccine technologies against a number of coronaviruses, including SARS-CoV starting in 2003 and also MERS in 2013 and Ebola.

That research over the past two decades has included numerous animal tests, which provided important safety and efficacy data, pointing to the vaccine technologies that could best trigger an immune response against a coronavirus. Since SARS‑CoV‑2, the coronavirus responsible for COVID has a lot in common with the SARS-CoV virus of 2003 and 2004. The lessons learned from those trials provided insight into understanding the current threat and how best to respond to it.

Something else that gets ignored is that scientists today have many more tools and a better grasp of how specific drugs or vaccines actually work in the body. When it comes to the COVID vaccines, the sponsors have explained in great detail how their vaccine technology works, what it targets, and what it does. That's a huge advance from where we were just 10 to 15 years ago when drug developers were developing products without always understanding their mechanism of action.

They knew that a particular drug produced the desired results, but they didn't always know why. When I first started covering this industry, I was amazed at how often the FDA stated in its briefing documents for an Advisory Committee meeting that the mechanism of action of a drug was unknown. That wasn't a concern at the time as the focus was on the safety efficacy data, but in today's briefing documents, the mechanism of action is clearly explained for vaccines as well as novel drugs and biologics. Obviously, knowing that mechanism of action is going to help speed development.

**Lee:** Mari, many of those who are hesitant have expressed concerns that too many shortcuts in R&D have been taken, and you alluded to that just now, the short amount of time that all this has taken. What is the reality?

**Mari:** Okay. The time timeline was compressed due, in part, to that previous coronavirus research. That handled a lot of the preclinical work but also by scaling up manufacturing, alongside the development of the vaccines instead of waiting until they were authorized and getting real-time feedback from regulators and submitting and rolling applications all helped speed up the timeline. That allowed regulators to start their reviews as the data was coming in.

That meant that these products could be authorized or approved much quicker. However, no shortcuts were taken. Let's look at the Pfizer-BioNTech vaccine as an example. The FDA granted the vaccine an EUA, an emergency use authorization, last December, based on the safety and efficacy data it had received from an ongoing Phase III randomized, double-blinded, and placebo-controlled trial.

That's the gold standard of clinical trials, and that trial was enrolling 44,000 people. At the time of the December 10th Ad Comm on the vaccine, the FDA had safety data for 38,000 participants who had been randomized one-to-one in the trial with a median follow-up of two months following the second dose. According to the NIH, the average enrollment for a Phase III trial ranges from a few hundred to 3,000 participants.

A clinical trial that meets the gold standard and enrolls 44,000 people is hardly a shortcut. Now, let's go back to the development timeframe. Recruiting sites, investigators, and participants can be a time-consuming process for any clinical trial, with some trials taking years to enroll a few thousand participants, but given the global scope of the pandemic, the pressure of lockdowns, and the demand for a vaccine, sites and participants were lining up for the COVID vaccine trials. That helped really shorten the timeframe because developers didn't have to spend as much time recruiting.

**Lee:** Normally, it takes about 10 years and more than $1 billion dollars to develop new drugs or vaccines. The vast majority of them fail along the way. How is it that companies have been able to produce these vaccines in such a record time?

**Mari:** Aside from all the coronavirus research that started more than 15 years ago, COVID-19 vaccine sponsors have been helped by decades of research into next-generation vaccine technologies. Look at the mRNA vaccines, for instance, they may be the first mRNA vaccines to make it to the finish line, but the technology has been in the works since the late 1990s.

There have been failures along the way, but each of those failures pointed to better ways of delivering the mRNA transcript into the targeted cells, and the current COVID mRNA vaccines are taking advantage of that. Also, the conversation tends to focus on the vaccines that have succeeded. Currently, 13 are recognized or pending recognition by the World Health Organization, but there are 232 other vaccine candidates that have been tested or are in the process of being studied.

Some of them went into early-stage development at the same time or even before those that have been authorized, and at least eight of those programs have been discontinued, either because the vaccine failed or it wasn't as effective as the vaccines already available. The same is true of potential COVID therapies. In other words, we have seen failures as well as successes, but we're focusing on the successes, not the failures.

Altogether, though, these efforts represent billions and billions of dollars of both public and private investment and countless investment of human resources, facilities, and opportunity costs.

**Lee:** There is still a lot of tension over boosters, even though regulators in the US and in the EU have signed off on them. Many leading scientists say boosters are not needed, and the World Health Organization has asked for a moratorium on their use through the end of this year. What's this debate all about?

**Mari:** The debate centers around three issues. The first is what the vaccines should be protecting against. Is it severe disease, meaning hospitalizations and deaths, or is it milder infections and even transmissibility? In the recent discussions before the FDA and CDC Advisory Committees, agency officials suggested the goal should be reducing transmissibility and protecting against mild or breakthrough infections while many of the members of the committees saw the goal as protecting against severe infections.

People on both sides agreed that the vaccines were still quite effective against severe disease although their protection against asymptomatic and mild infections appear to wane over time, especially against emerging variants, such as Delta. Part of that discussion is the recognition that COVID infections are coming in waves that ebb and flow. For instance, last week with 57% of the population fully vaccinated and about 3% of Americans having a booster, COVID infections dropped 15% in the US and hospitalizations dropped 10%.

This is the bottom side of the wave. A second issue around boosters is how immunity is measured. Regulators and policymakers have focused on a decline over time in the level of neutralizing antibodies, but many scientists don't agree with that as the best test of immunity. At the CDC's ACIP meetings, several members have consistently pushed for the development of a more accurate immune correlate that looks at T-cell response and immune memory.

They claim that would be a more effective way of determining whether immunity is waning both in those who have been vaccinated and those with natural immunity from having had an infection. The third issue is equitable global access. Given that the demand for the vaccine is expected to continue to exceed the supply for the rest of this year, should healthy people in the EU, Israel, Canada, the US, and other wealthy countries be getting boosters when poor countries can't get enough vaccines to even protect healthcare workers and their most vulnerable populations?

While the US and European countries are clearing the way for boosters or vaccines for kids this year, many other countries likely won't get promised vaccine donations until next year.

**Lee:** That brings us back to the beginning of our conversation when we noted the need to get more people vaccinated to bring the pandemic under control. The wealthier countries are focused on increasing their vaccination levels to control COVID within their borders. Is that enough?

**Mari:** Not in a world that's so interconnected. As long as there are populations of people anywhere in the world with no protection, there will be a breeding ground for new COVID variants that could be more transmissible or resistant to the current vaccines and therapies. Those variants will travel just as the wild-type virus did last year and the Delta variant did this year. Consequently, ignoring the need or delaying vaccines to other countries will continue to put everyone at risk.

**Lee:** What are the long-term consequences of delaying vaccines in poorer countries?

**Mari:** Besides allowing for the emergence of new variants, delaying the delivery of vaccines to any country could have serious health consequences as it will lead to unnecessary deaths in those countries, increase health disparities and economic problems, put those countries further behind in education, and make them more dependent on wealthier nations and less able to respond to future health threats and natural disasters.

Here are a few statistics to show the disparities. As of October 22nd, 40 countries had full vaccination rates of at least 60%. The US wasn't one of those. As I mentioned before, only 57% of Americans were fully vaccinated by that date. In addition, at least 5% of the population in nine countries had received a third dose or a booster. I believe in Israel, 43% had received a booster.

Meanwhile, at the other end of the scale, 36 countries had a full vaccination rate of 5% or less. Fewer than 1% of the people in 13 nations were fully vaccinated. Countries in Africa seem to be the hardest hit when it comes to vaccine access, but it's not just Africa. As of October 22nd, just 0.3% of the population of Haiti had been fully vaccinated. Think about that and what it can mean for the US, Mexico, parts of Central and South America as tens of thousands of Haitian refugees flee their country and make for the US border, staying in makeshift migrant camps where COVID infections could spread.

I guess the moral is that even if wealthier countries want to put their own citizens first when it comes to vaccines, it is in their best interest to ensure a timely global response to the pandemic.

**Lee:** Terrific, Mari. Many thanks for the insights.

**Mari:** Well, thanks for having me. I think this is an important topic that we really do need to explore from various perspectives.

**Speaker:** Yes, I think you're absolutely right. Lynn, back to you.

**Lynn:** Clearly, this is a news story that is not going away anytime soon, and this kind of insight is critical. Thank you, Mari, for joining, and Lee. As always, BioWorld will continue to keep you informed of all the most important scientific, clinical, and business updates in the field. That's our show for today. If you need to track the development of drugs, turn to bioworld.com. Follow us on Twitter or email us at newsdesk@bioworld.com. If you're enjoying the podcast, don't forget to subscribe. Thanks for joining.

**Speaker:** BioWorld, published by Clarivate is a subscription-based news service, but all of our COVID-19 content, more than 5,000 articles, and data entries since the start of the pandemic are freely accessible.

**[00:16:36] [END OF AUDIO]**