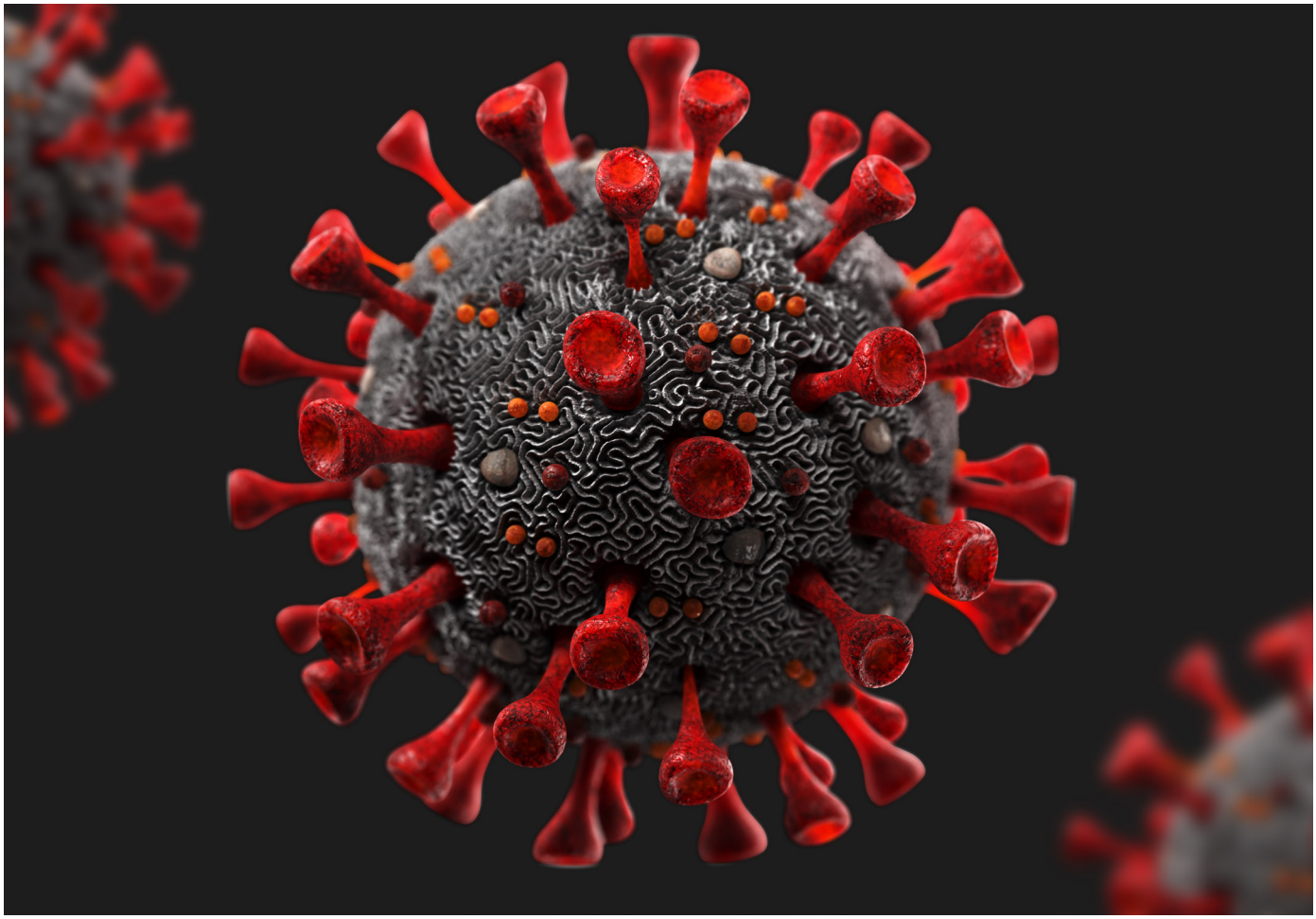
UNTESTED: THE INVESTMENT CASE BEHIND THE RACE FOR A CORONAVIRUS VACCINE

As the candidates hurtle toward the finish line, modelling the long-term profits for one of the most audacious undertakings in the history of science remains a separate challenge.

August 2020



KEY TAKEAWAYS

- Its high margins and barriers to entry, low rivalries, and moderate profits over extended periods have historically made vaccine development one of the most appealing pharamaceutical segments for long-term investors.
- Under the urgency of the pandemic, vaccine makers have been asked to compress timelines that in many cases stretched across multiple decades into less than a year.
- A successful coronavirus vaccine could be the proof of concept for new models of discovery and development that shake up the old order of how many infectious diseases are tackled.
- The companies that achieve durable revenue and profit from the current race will most likely be the companies with the safest and most effective products, not necessarily the companies that obtain approval first.

January 11, 2020, the date the genetic sequence of SARS-CoV2 was published, marked the start of the race for a vaccine. On July 31, Dr. Anthony Fauci, the US's top infectious disease official testified before Congress that he was "cautiously optimistic" a vaccine would be ready near the end of this calendar year. As he spoke, there were approximately 200 candidates in the race,[1] and nearly a quarter million Americans had already volunteered to take part in clinical trials. "I don't think it's dreaming," Fauci added.

Perhaps not, but such a pace would be unprecedented. Vaccines have been at least as slow-moving as other major areas of drug development, slowed by the added precautions and safety regulations that apply when developing a drug for a healthy population. It takes on average 10 to 15 years for a novel vaccine to move from initial discovery to market. The fastest time was for the mumps, famously kickstarted at one in the morning when five-year-old Jeryl Lynn woke her father, Merck researcher Dr. Maurice Hilleman, complaining of a swollen jaw. Later that day, using a then-experimental system, Dr. Hilleman inoculated chicken egg embryos with a sample he'd swabbed from his daughter's throat to begin cultivating successive generations of the virus. Ultimately, he hoped, the virus would lose enough of its ability to replicate in humans that it could be used to immunize children. Just four years later he had perfected the Jeryl Lynn Strain vaccine, a record for efficiency that still stands 53 years later. Notably, 90% of today's vaccine production, including for the mumps, measles, and flu, still involves methods nearly identical to the ones Dr. Hilleman helped pioneer.

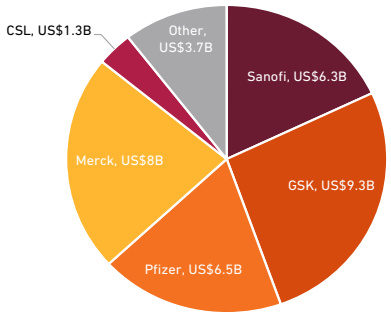
"We're relying on a whole new paradigm," says David Glickman, CFA, health care analyst at Harding Loevner. "Any prediction has to be tempered by the fact that the model is largely untested in large clinical studies."

Suffice it to say, few of those traditional methods have been employed in the breakneck race for a coronavirus vaccine. "In essence, we're relying on a whole new paradigm," says David Glickman, CFA, health care analyst at Harding Loevner, referring to the computer modelling, gene synthesis, and expedited approval processes that characterize the present contest. "The good news is that pieces of the paradigm have been around for a while, but, at this point, any prediction still has to be tempered by the fact that the model is largely untested in large clinical studies."

A CONCENTRATED INDUSTRY

While the US$35-billion-a-year vaccine business[2] is a relatively small part of the US$1.2 trillion pharmaceutical complex,[3] it is a rather attractive one. Once a new vaccine has endured the costly and lengthy development, testing, and manufacturing stages, the economics turn quickly in the manufacturer's favor. In the US, the world's largest and most lucrative vaccine market, the Centers for Disease Control negotiates vaccine prices for patients without insurance, but private insurers and Medicare typically pay 50–100% more. Given the potential for unforeseen problems and consequential blowback from the anti-vaxxer movement, once a vaccine has established a successful track record, the US government has little appetite to shop around for cheaper or incrementally better alternatives. Vaccine manufacturers thus have few marketing expenses and, unlike for most pharmaceuticals, even patent expiration tends to be a non-issue. The result is a highly concentrated industry, with five pharmaceutical companies controlling close to 90% of vaccine sales, functioning as oligopolies or even monopolies with respect to most products.

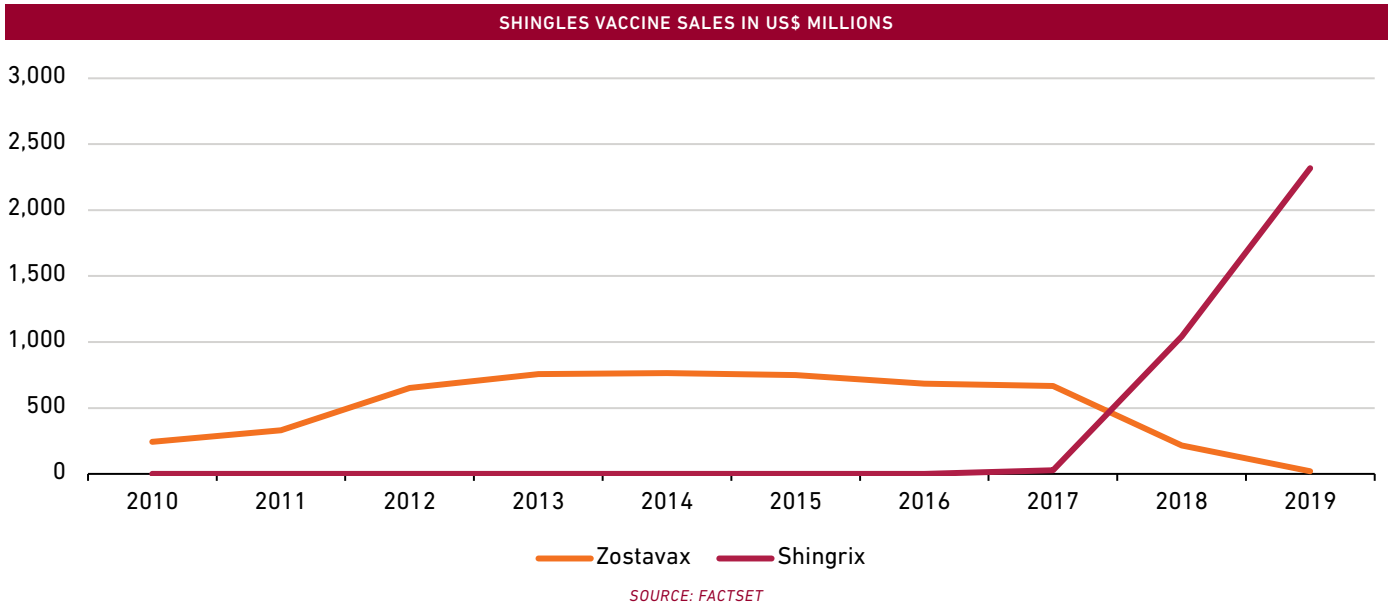
2019 VACCINE REVENUE: MARKET SHARE BY COMPANY



SOURCE: COMPANY REPORTS

When vaccines are less than fully effective, these walls around a vaccine's revenues become more breachable. The essential balancing act of vaccine creation—exposing the immune system to a foreign body that tricks it into raising its defenses, all without causing the disease—has proven easier to achieve for some maladies than others. For the more difficult ones, recombinant vaccine technology has been an important advancement. Genetic material from the targeted pathogen is combined with a stable cell culture such as bacteria or hamster cells to churn out specific virus proteins. Because these proteins are just fragments of the virus, they can be both a truer representation of its composition and potentially safer than an attenuated virus produced using the traditional egg method.

Two of the best-selling vaccines in the world today were produced using recombinant technology: Merck's Gardisal, for the prevention of human papillomavirus (HPV); and GlaxoSmithKlein's Shingrix, for shingles. In 2006, Zostavax, a traditional attenuated virus vaccine (also produced by Merck), was the first shingles vaccine to market. But it had only a 50% effectiveness rate in preventing the most common types of shingles. In 2017, Shingrix made its debut with a 90+% effectiveness rate, and within two years it had seized 98% of the market.



SOURCE: FACTSET

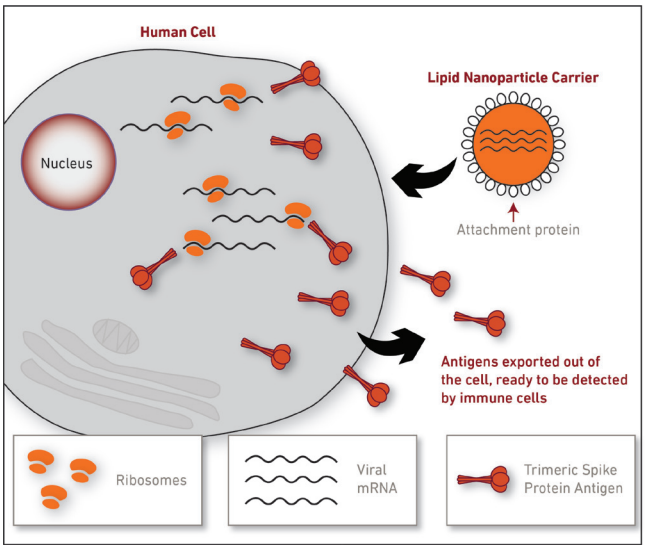
THE NEW MODEL

The vaccines for HPV and shingles were more than 30 years in development. Given the urgent threat of a global pandemic that has already sickened more than 15 million people, the vaccine industry is being asked to compress its time to market into less than a year. That this isn't dreaming is largely a function of other technological breakthroughs that have occurred since Shingrix and Gardisal first made it out of the lab.

Drawing on their experiences with SARS and MERS, two close viral cousins of SARS-CoV2 that flared earlier this century, scientists quickly focused their attention on one protein on the virus's hard outer surface. This protein, shaped like a medieval mace, hooks onto cells lining our lungs, enabling the virus to co-opt the cells' machinery to manufacture copies of itself that can eventually overwhelm our respiratory system. As with SARS and MERS, the clearest path to a vaccine runs through this protein: induce the body's immune system to produce antibodies that interrupt its binding process and beckon other immune cells to the scene to affect the virus's destruction.

One difference between those earlier efforts and the current one is that scientists can perform much of that initial discovery work using computer modelling systems—"in silico," as it's called. Whereas once researchers would have to identify potential antigens from lab observation and grow them in eggs or hamster cells before they could be tested, they can now find them by drawing on vast AI-powered protein libraries. Once they find a promising candidate, faster and more efficient production methods translate the virtual molecule into physical reality. The speed and efficiency comes, in part, from the ability of these "platform" methods to easily and rapidly swap out one antigen for another target. Of the 200 candidates currently in clinical trials, all but 17 are being developed using some variation of such production techniques.[4] For example, Novavax and a Sanofi-Glaxo joint venture both use a high-speed recombinant system involving moth cells to produce antigens. Three other joint ventures, between Moderna and the US National Institutes of Health, AstraZeneca and Oxford University, and Pfizer and the German biotech firm BioNTech, use gene synthesis to produce the genetic sequence that encodes the virus's spike protein. (See the graphic, below.) From the time the SARS-CoV2's genetic code was reported, it took the Moderna group just *42 days* to manufacture a viable prototype using this approach.

INSIDE JOB: THE MODERNA METHOD



SOURCE: MODERNA; "MRNA VACCINES—A NEW ERA IN VACCINOLOGY," NATURE (JANUARY 12, 2018).

In the approach of this Massachussetts-based biotech firm, vaccine manufacturing has been moved inside our own cells. Here, a strand of mRNA that encodes for the coronavirus spike protein is carried by a fat molecule into a lymphatic cell, whereupon it obligingly produces the antigen to trigger the immune response.

What remains to be determined is how well these approaches will actually work. The Moderna, Pfizer, and AstraZeneca efforts are among the eight vaccine candidates that have advanced to Phase 3 clinical trials.[5] Each has been shown to produce an immune response comparable to that seen in actual COVID-19 patients. Assuming those results are confirmed in larger trials, the next step will be to confirm that the response reduces infection risk or severity. A positive side effect of the recent US surge in infections, Glickman points out, is that such preliminary data should be attainable within a few months after the start of the Phase 3 trials. "But will the immunity last for six months? A year? We likely won't know the answer to that for some months or years down the line."

Efficacy and duration are just some of the unknowns that figure into an assessment of the long-term investment opportunity. Among the smaller publicly listed biotech firms in the race, none have any product revenues currently, so they represent highly speculative investments, akin to venture capital. For the larger companies, one can model their hypothetical revenue opportunity and discount it by the likelihood that the company will succeed in bringing its vaccine to market. Take Pfizer as an example. Based on a 49% chance of making it to market (the historical average success rate for a vaccine candidate following an accelerated so-called Phase 2/3 schedule),[6] if the company were to meet its projections of 1.3 billion doses at $20 a dose, that would be worth US$6.37 billion in revenue for Pfizer's half of the joint venture—a not-insignificant boost for a company that, in the absence of a vaccine, is expected to earn US$48 billion in revenue in 2021.

If Pfizer's candidate hits the market with a 50% effectiveness rate, what are the odds that a better vaccine will emerge in a year or two from among the 200 other entries in the race?

However, at this point, we don't know how effective Pfizer's candidate will be. Regulators have suggested the bar for effectiveness could be low because of the need to get a start, even if a slow one, on halting the virus's spread. If Pfizer's candidate hits the market with a 50% effectiveness rate, what are the odds that a better vaccine will emerge in a year or two from among the 200 other entries in the race? We also don't know how the market for SARS-CoV2 vaccines will form and evolve. Will the price for subsequent phases stay around the US$20 a dose that Pfizer agreed to initially? Or, succumbing to social and political pressure, could it settle somewhat closer to the €2.50 (US$2.80) per dose that the AstraZeneca-Oxford joint venture has agreed to with a bloc of four European nations?

"All of the factors that have traditionally made the vaccine industry such an attractive long-term investment—moderate growth rates over long periods of time, high-margin products, low rivalries, high barriers to entry, buying power that while concentrated has not typically been exercised—are not materializing in the race for the coronavirus vaccine, at least not where we stand today. Far from it," Glickman says.

For this reason, Glickman says it may make more sense to look for investments beyond the companies furthest along in their development efforts. He cites the example of Shionogi, the largest vaccine manufacturer in Japan. Shionogi has a vaccine candidate soon starting clinical trials that employs an approach similar to Sanofi-Glaxo's recombinant moth cell model. While governments, including Japan, have been busy tying up deals with frontrunners in the race, the likelihood is that, once approved, any vaccine not already spoken for will go first to the country where it's been developed and manufactured. Thus, in addition to inking a 120-million-dose agreement with Pfizer-BioNTech (at two doses per vaccination course, enough to immunize roughly half the Japanese population), for national security reasons Japan has also awarded Shionogi ¥37 billion (US$350 million), by far the most given to any Japanese vaccine maker. Given the country's limited vaccine production capability, these factors would seem to both improve the odds of a speedy approval process for Shionogi and provide confidence in maintaining a long-term market, assuming its vaccine proves successful. The prospect of selling up to 50 million doses a year for several years would materially move the needle for Shionogi, a mid-sized company.

Of course, if any of the vaccine candidates make it to market within the next six months, it will be a monumental human achievement, perhaps one of the greatest in the history of science. It could also usher in a new era of vaccine development in which many infectious diseases are tackled by the new modalities and platform production techniques. The flu, for example, would seem to be low-hanging fruit. Given the flu's high mutability and the time currently needed to produce a new vaccine every year, scientists must decide during one flu season which strains to immunize against in the next, based on predictions about which ones will then be in circulation. It is easy to imagine how, by allowing such decisions to be postponed, a faster platform approach could improve on flu vaccines' effectiveness rates, which range from around 50% to as low as 20%. Another area ripe for improvement is the respiratory ailment RSV, among the last of the major childhood viruses to have eluded a successful vaccine. Then there is the whole category of future novel pathogens, the *next* MERS or SARS-CoV-2, which require a hyper-compressed R&D timeline.[7] Whether a vaccine discovery and development platform will confer a durable competitive advantage for a company, or instead prove easy to legally mimic, will only become more apparent over time. "In the meantime, as investors," Glickman says, "we're taking it one step at a time."

CONTRIBUTORS

Analyst David Glickman, CFA contributed research and viewpoints to this piece.

ENDNOTES

[1]Milken Institute COVID-19 Treatment and Vaccine Tracker.

[2]Alliance Bernstein, "Vaccines: The Robinhood of Therapeutics" (April 2020).

[3]IQVIA Institute for Human Data Science, "The Global Use of Medicine in 2019 and Outlook to 2023" (January 2019; figure cited as of 2018), 4.

[4]Milken Institute COVID-19 Treatment and Vaccine Tracker.

[5]The New York Times Coronavirus Vaccine Tracker, as of August 17, 2020.

[6]Chi Heem Wong, Kien Wei Siah, Andrew W. Lo, "Estimation of clinical trial success rates and related parmeters," Biostatistics (April 2019), 273-286.

[7]Johns Hopkins Center for Health Security, "Vaccine Platforms: State of the Field and Looming Challenges" (2019).

DISCLOSURES

READ MORE ***FUNDAMENTAL THINKING***:
hardingloevner.com/fundamental-thinking

400 CROSSING BLVD, FOURTH FLOOR • BRIDGEWATER, NJ 08807
T (908)218-7900 • F (908)218-1915 • HARDINGLOEVNER.COM