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Vaccine controversies are not new, but the COVID-19 pandemic has brought them to the forefront, and directed attention to the question of vaccine safety and regulation. This essay explores how vaccines are regulated, and how this applies to COVID-19 vaccines. What I hope to demonstrate is that while no regulatory framework is perfect, we have a strong set of monitoring mechanisms available to oversee vaccine safety.

COVID-19, Vaccines, and COVID-19 Vaccines

Our world is not as it was before 2020. COVID-19, a new and especially tricky virus, changed our reality—legally, economically, and practically. Over the past year and some, more than three million people world-wide, and over half a million people in the United States, died from COVID-19. Millions more were impacted, some by spending weeks in the hospital, some by suffering long-term harm, and some by suffering severe economic consequences (and these categories, of course, overlap).

In response to the pandemic, public health authorities at the local and state level put in place an unprecedented program of restrictions, including stay-at-home orders and mask orders. A year later, not all restrictions have been lifted. The United States experienced several crises where states ran out of ICU capacity. The economic and human effects of the pandemic are staggering.

Our way out of the pandemic is multifaceted, but a large part of it is vaccines. Vaccines are among the most important medical advances in history, responsible for preventing extensive deaths, disability, disease and economic harm. Vaccines are also extremely safe.[1] But those vaccines have been developed over the course of years. In the context of the COVID-19 pandemic, the first vaccines have been brought to market less than a year after the pandemic started. It is reasonable to wonder whether the speed of development—combined with the interests of the pharmaceutical companies to seize the potential market provided by COVID-19—allowed sufficient oversight and whether the end result is as safe as routine vaccines.

This article addresses the process of creating vaccines. It then explains the system in place for monitoring them. Finally, it evaluates the effectiveness of this system in overseeing vaccine safety and identifying problems.

Creating Vaccines

Normally, the process of creating vaccines takes years. Before COVID-19 vaccines, the fastest vaccine to be developed was the mumps vaccine, which took four years in the 1960s—before modern standards. Influenza vaccines are updated annually, but the only thing to be changed for them is the active ingredients—the strain of the virus—while their formula and the facilities to produce them remain the same. During a pandemic, waiting years means loss of life and extensive harm. We may still have had to do that, if the first vaccines had

(Courtesy of NIAID, National Institute of Health, via Flickr CC by 2.0)

A National Institute of Allergy and Infectious Diseases (NIAID) scientist researches the COVID-19 vaccine, January 30, 2020.

not met safety and effectiveness milestones. We got lucky: the first COVID-19 vaccines exceeded expectations.

The usual process for bringing a vaccine to market involves identifying the germ and identifying the target for a vaccine candidate, followed by preclinical studies in animals and three stages of trials in humans—increasing from a small number (tens) of healthy volunteers to large clinical trials of the target population, consisting of thousands or tens of thousands.[2] This process normally takes years. Most vaccines fail the first stage of clinical trials and never make it to market. This could have happened to COVID-19 vaccines, but did not.

The rationale behind the process for vaccines—longer and more demanding than for most products—is that because vaccines are given to healthy individuals, to prevent a disease, they are held to a very high safety standard. Our tolerance for risk is lower for vaccines than for drugs given to address an existing condition. Although the pandemic context complicates the analysis, because the risks of the pandemic are also immediate and glaring, we still are unlikely to accept vaccines that cause harm more than very rarely—as demonstrated in the case of the clots that may (or may not) be caused by the Johnson and Johnson (J&J) vaccines.

Although the speed of production may raise concerns about cutting corners, that is not what happened. We arrived at fast vaccines against SARS-CoV-2, the virus that causes COVID-19, thanks to three things, and some luck. The three important factors were previous developments in areas of research crucial for the creation of these specific vaccines; concentrated attention by many teams of talented scientists on the issue; and the infusion of large amounts of government money that allowed companies to take financial risks they could not otherwise take (without compromising safety). This discussion will focus on the mRNA vaccines produced by Pfizer-BioNtech and Moderna, because addressing all vaccines would take too long. In the discussion of safety monitoring, I will use the Johnson and Johnson vaccine and blood clots to show the surveillance system at work.

The process began with a germ that was already known. Early on, through global surveillance, scientists identified SARS-CoV-2, a new coronavirus, as the culprit behind the new disease; and relatively soon, they narrowed in on the virus's spike protein (a protein on the surface of the virus that allows it to go into cells) as the target for vaccines. Immediately, several companies began working on a variety of vaccine candidates.

This work benefited from two lines of research already in existence. Before, but especially since, the emergence of deadly outbreaks caused by other coronaviruses that target humans (the SARS outbreak in 2002–2003 and the MERS outbreak in 2012), teams of researchers have spent years or decades studying coronaviruses. Although SARS-CoV-2 can and did surprise us in many ways, by the time of the pandemic there was a body of knowledge about coronaviruses, and a body of work that looked at creating vaccines against them, though no vaccines had yet been made.[3] So the work on creating vaccines for the pandemic did not start from scratch; in fact, the focus on the spike protein was the result of previous work. Another line of previous work that helped was the development, over years, of RNA (ribonucleic acid) vaccines. These vaccines have not yet been market-ready, but they have been the focus of work of several scientists and companies over previous years.[4] The vaccines themselves have initially gone through animal studies, though the first stage studies in human volunteers (with a small number of healthy volunteers) started before the end of the animal studies. However, the vaccines did not move forward to large clinical trials until strong data came out of both sets: animal studies, and first stage human studies.

During spring 2020, the federal government stepped in. The government offered hundreds of millions of dollars to the companies making the vaccines. Normally, companies do not start stage III trials until they have very strong data from stage I and II. That is because stage III trials are very expensive. But government money changed the equation: companies could move on to stage III with more limited data, with no financial risk to themselves.

The process combined stage II and stage III trials. That sometimes happens, but not always. In July 2020, both Moderna and Pfizer-BioNTech started clinical trials. The trials included over 30,000 participants for Moderna, over 40,000 for Pfizer-BioNTech, half in the control group, half in the placebo group. In late November, Pfizer submitted results to the Food and Drug Administration (FDA), and Moderna did so shortly after. The FDA experts reviewed the data and found it to justify granting an Emergency Use Authorization (EUA). FDA then convened its external expert committee (the Vaccines and Related Biological Products Advisory Committee, VRBPAC), which in a lengthy public meeting reviewed the data and supported granting an EUA for both vaccines.

The data was extremely strong. Both mRNA vaccines were over 90% effective against symptomatic COVID-19—a very high rate of vaccine effectiveness. They were also both highly effective at preventing severe diseases. The FDA said it would want to see over 50% effectiveness to grant an EUA; these far exceeded it. There were also no safety signals in the trials: while large numbers of people who got the vaccines had temporary unpleasant side effects (a day of fever, fatigue, pains at the injection site), there were no indication of serious harms from the vaccines.

The authorization was followed by additional review by the Centers for Disease Control's (CDC) expert advisory committee (the Advisory Committee on Immunization Practices), which recommends vaccines for the appropriate populations—and engages in another review of the data. The Committee includes

experts in relevant fields, as well as a consumer representative.

The clinical trials were as large or larger than those for routine vaccines, and the data were stronger than is the case for most vaccines. The EUA had a very strong basis behind it, as strong as many licenses, even if the duration of time for which data had been available was shorter. There remained open questions: would the vaccines prevent infection? How long would immunity last? But the bottom line is still that the vaccines went through large clinical trials, were presented to the FDA with very strong data behind them, and earned the authorization. A second review was undertaken by a separate independent expert committee, which confirmed the result.

Post Marketing Approval

Vaccine monitoring continues after a vaccine is licensed, even in routine times, and the CDC prepared to provide additional monitoring to the usual systems for COVID-19 vaccines. The reason for that is that clinical trials are too small to identify a very rare side effect. Even large clinical trials that consist of tens of thousands of people would not catch a one in a hundred thousand or one in a million side effect. But we want to know of such a risk. Among other things, it may mean that some populations should not be vaccinated—if a type of individual is at higher risk, that individual may be protected by herd immunity. Second, it can help doctors and vaccinators identify a problem after a vaccine and treat it appropriately, reducing or preventing harm. For example, knowing that mRNA vaccines have a higher rate of allergic reactions among people with previous allergies to certain things led to those people being asked to wait 30 minutes at a vaccination site rather than 15, so they can be treated if a reaction occurs.

Even in regular times, four monitoring systems exist to cover vaccine safety.[5] The first is the Vaccine Adverse Events Reporting System (VAERS), which is a passive reporting system to which anyone can submit a report of something that happened after a vaccine. By its nature, VAERS accepts any report; so the existence of a report does not confirm the veracity of an event—and certainly does not prove a link to the vaccine. In spite of that, anti-vaccine activists have been misusing VAERS reports to try and create fear and doubt about COVID-19 vaccines—whether by pointing to the number of unverified reports as if it shows the risks of the vaccines, or by taking individual reports and presenting them as fact and as evidence of vaccine harm—a highly problematic practice, given the unverified nature of these reports.[6] VAERS have an important role to play in catching safety signals. Reports can lead to investigations that can show problems. But treating raw reports as evidence of vaccine harms is simply incorrect.

A second monitoring system is the Vaccine Safety Datalink. This is a collaboration between the CDC and healthcare organizations throughout the country, covering over nine million people. This is an active monitoring system: it uses computerized programs to actively look for signals, and allows researchers to conduct studies on questions that come up. A third, the Post-Licensure Rapid Immunization Safety Monitoring System (PRISM) is part of the FDA Sentinel system, a system for monitoring medical products by tracking health insurance claims, using a much larger database and also actively monitoring. Fourth is the Clinical Immunization Safety Assessment Project (CISA), where providers can ask questions about unusual cases, including whether something is a contraindication, or whether a medical problem may be vaccine related. The CISA project also conducts research on specific issues and special populations (like HIV patients).

In addition to these systems, in preparation for the COVID-19 vaccines rollout, the CDC set out the Vaccine

Safety Assessment for Essential Workers, V-SAFE. Under the program, people sign up with their cellphone number after being vaccinated, and receive a text from CDC with a link to fill a short health report—daily for the first week, weekly afterwards for six weeks. If a problem is found, the program involves providing assistance to the recipient to file a VAERS report.

At every meeting of the Advisory Committee on Immunization Practices (ACIP) since the beginning of the vaccines' rollout, CDC officials present a detailed description of the safety data. Multiple studies have also looked at specific safety issues, like the safety of the vaccines in pregnancy, at this point.

An example of how these systems work is the recent discussion of rare blood clots after the J&J vaccine. During the early months of 2021, reports in Europe pointed to rare blood clots happening after the AstraZeneca COVID-19 vaccine. That vaccine was not yet authorized in the United States. But in early April, United States agencies took note of six cases of a rare type of blood clot—cerebral venous sinus thrombosis (CVST)—reported to VAERS among the 6.8 million doses of J&J vaccines distributed at that point. The reaction was immediate. On April 13, 2021, CDC and FDA issued a joint statement pausing administration of the J&J vaccine "out of an abundance of caution."[7] The concern was not just that there might be a link between the vaccine and a rare and serious disorder (two of the people involved were hospitalized, and one died), but that the treatment needed to be different than the usual treatment of blood clots (administering heparin, an anticoagulant drug usually used for clots, could, in these cases, make things worse).

The CDC convened ACIP on April 14, 2021, and the committee met for five hours to look at the different cases and consider them. ACIP concluded that it did not have enough data, and, therefore, did not lift the pause. The decision (like the earlier decision to declare a pause) was controversial. Some experts pointed out that in the context of the pandemic, pausing the distribution of a vaccine (the only vaccine we have that is one dose and does not require high levels of cold storage) costs lives, and that even if there is a causal link, the events are very rare. Others emphasized the need to be especially cautious with COVID-19 vaccines, since people are watching them closely and trust in them is crucial to reaching sufficient uptake in a pandemic. ACIP met again on April 23, 2021, and after over six hours of discussion decided to lift the pause, concluding, by majority vote, that the benefits outweighed the risk. The four dissenters agreed that the vaccine should be unpaused, but would have sent a clearer message to providers and more information to recipients on the risk. While the risks may not be as rare as one in a million (there is a chance the reports did not capture all the events), they do appear, at this point, to be very rare.[8] There may also be a causal connection.

This event teaches us several lessons. First, it teaches us that the systems we have have the ability to detect events when the signal is as rare as one per million. Second, it teaches us that when a signal is detected, it is taken seriously—and regulators react (and according to some observers, overreact). Third, it teaches us that such events are publicly and transparently discussed. While we may be tempted to think this is unique to the charged context of COVID-19, when an early rotavirus vaccine was taken off the market because of a serious side effect in one per ten thousand babies, that, too, received media attention.[9]

The takeaway is that we have very robust systems to oversee vaccine safety, and they have the capacity to identify even rare problems. Vaccine safety is taken seriously by regulators and observers, and the process to address problems is transparent, deliberative (though not necessarily fast), and in-depth.

This combination is what makes vaccines in the United States so safe, with such low risks.

Notes

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