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'This Is All Beyond Stupid.' Experts Worry About Russia's Rushed Vaccine

Vaccines are among the safest medical products in the world — but only because of the intense rigor of the clinical trials that test their safety and effectiveness.

By Carl Zimmer

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When Vladimir Putin announced Tuesday that Russia had approved a coronavirus vaccine — with no evidence from large-scale clinical trials — vaccine experts were worried.

"I think it's really scary. It's really risky," said Daniel Salmon, the director of the Institute for Vaccine Safety at Johns Hopkins University.

Dr. Salmon and other experts said that Russia is taking a dangerous step by jumping ahead of so-called Phase 3 trials, which can determine that the vaccine works better than a placebo and doesn't cause harm to some people who get it.

Unlike experimental drugs given to the sick, vaccines are intended to be given to masses of healthy people. So they must clear a high bar of safety standards. If hundreds of millions of people get a vaccine, even a rare side effect could crop up in thousands of people.

Over the course of the past century, researchers have developed increasingly powerful ways to test vaccines for safety and effectiveness. Some of those lessons were learned the hard way, when a new vaccine caused some harm. But vaccines are now among the safest medical products in the world thanks to the intense rigor of the clinical trials tracking their safety and effectiveness.

This testing typically begins before a single person has received a new vaccine, when researchers inject it into mice or monkeys to see how they respond.

If those animal studies turn out well, researchers then enlist a few dozen volunteers for a Phase 1 trial, in which all volunteers get the experimental vaccine.

Doctors typically keep these volunteers under observation to make sure they don't have any immediate negative reactions, and to see whether they make antibodies against a pathogen. It's not uncommon for people to feel achiness in their muscles or even a mild fever, but these mild symptoms typically don't last long.

If Phase 1 trials do not turn up serious safety problems, then researchers usually move to a Phase 2 trial, in which they inject hundreds of people and make more detailed observations.

The first clinical trials on coronavirus vaccines started in March, and now there are 29 underway, with more to launch soon. Companies such as AstraZeneca, Moderna, Novavax and Pfizer are beginning to share optimistic early results: So far, they have only detected mild or moderate symptoms and no severe side effects. Volunteers have also produced antibodies to the coronavirus, in some cases more than are produced by people who have recovered from an infection.

The Binnopharm pharmaceutical factory outside Moscow, which will produce the vaccine. Yuri Kochetkov/EPA, via Shutterstock

But no matter how promising these early results, Phase 3 trials can fail.

The timing of Russia's announcement makes it "very unlikely that they have sufficient data about the efficacy of the product," said Natalie Dean, a biostatistician and infectious disease expert at the University of Florida who has warned against rushing the vaccine-approval process. Dr. Dean noted that even vaccines that have produced promising data from early trials in humans have flopped at later stages.

In a large, randomized control trial, researchers give the vaccine or a placebo to tens of thousands of people, and wait for them to encounter the virus in the real world.

"Then you wait to see, do they get sick or not. Do they die or not?" said Dr. Steven Black, a vaccine expert with the Task Force for Global Health. If a vaccine is effective, fewer vaccinated volunteers will get sick than the ones who received the placebo.

The Russian researchers have not yet begun that crucial test.

In June, the Gamaleya Research Institute of Epidemiology and Microbiology at the Health Ministry of the Russian Federation registered a combined Phase 1 and 2 trial on a vaccine called Gam-COVID-Vac Lyo. The researchers planned to test it on 38 volunteers.

They said that the vaccine was made from an adenovirus — a harmless cold virus — carrying a coronavirus gene, similar to what AstraZeneca and Johnson & Johnson are using in their vaccines. The technology is still relatively new: The first adenovirus vaccine for any disease was approved for Ebola in June.

Since then, Russian officials have claimed that they would be moving the vaccine quickly into manufacturing. Mr. Putin's announcement on Tuesday made it official. Yet the institute has never published its Phase 1 and 2 trial data.

At Mr. Putin's announcement, Russia's Minister of Health, Mikhail Murashko, declared that "all the volunteers developed high titers of antibodies to COVID-19. At the same time, none of them had serious complications of immunization."

That is the sort of result you'd expect from a Phase 1 trial. It doesn't tell you if the vaccine actually works.

"This is all beyond stupid," said John Moore, a virologist at Weill Cornell Medical College in New York City. "Putin doesn't have a vaccine, he's just making a political statement."

President Vladimir Putin of Russia meeting with the minister of health, Mikhail Murashko, in January. Sputnik, via Reuters

On Tuesday, the Russian institute put up a website claiming that a Phase 3 trial would begin the next day involving more than 2,000 people in Russia as well as the United Arab Emirates, Saudi Arabia, Brazil and Mexico.

All other Phase 3 trials of coronavirus vaccines currently underway are more than ten times larger than that, with 30,000 volunteers apiece.

Dr. Nicole Lurie, a former assistant secretary for preparedness and response at the U.S. Department of Health and Human Services and currently an adviser at the Coalition for Epidemic Preparedness Innovations, said the lesson that the U.S. government should draw from Mr. Putin's announcement is clear.

"This is exactly the situation that Americans expect our government to avoid," she said.

A faster process

Along with determining whether the vaccine protects people, Phase 3 trials can reveal uncommon side effects that may not have shown up in the comparatively small number of volunteers who enrolled in the earlier phases.

Just because someone gets sick or dies after getting a vaccine, however, doesn't necessarily show that the vaccine was the culprit. By comparing large groups of people who received the vaccine versus the placebo, researchers can identify unusual clusters of cases in the vaccinated participants.

Along the way, vaccine developers share these results in reports to government regulators and in peer-reviewed papers for scientific journals. Outside experts then evaluate the data from Phase 3 trials and give their recommendation to the F.D.A., which then decides whether to approve a vaccine for widespread use.

"It's not enough for me to say I have a great product," said Dr. Salmon. "Before you use it, you need other people to really look at the data and be convinced that the benefits outweigh the risks."

And even after a vaccine is licensed, researchers still keep an eye on it to make sure it's safe. As millions of people get a vaccine, even rarer side effects may emerge over time. It's also possible that certain groups of people, such as children or the elderly, turn out to face risks from a vaccine that weren't immediately clear from the Phase 3 trials.

Regulators can then make adjustments to the vaccine — changing the dose, for example — to make it safer.

In July, a team of researchers at Tel Aviv University reviewed licensed vaccines in the United States over the past 20 years and concluded they were "safe, with no important post-approval safety issues."

Elena Smolyarchuk, left, a chief researcher at Sechenov University, with volunteers in the vaccine study in Moscow last month. Yuri Kochetkov/EPA, via Shutterstock

Putting in safeguards slows the development of vaccines. In recent years, new outbreaks such as Ebola, SARS and pandemic flu strains have spurred vaccine makers to look for ways to speed the process without sacrificing safety.

Now, in the midst of the Covid-19 pandemic, they're putting those ideas into practice.

One way to safely accelerate vaccine trials is for regulators to prepare in advance to analyze each batch of data, so that they can cut down the time between trials. Vaccine manufacturers have already been demonstrating to regulators that they can make coronavirus vaccines safely on an industrial scale, long before the vaccines themselves have made it through clinical trials.

But researchers are still figuring out how SARS-CoV-2, the name of the virus that causes Covid-19, makes us sick and evades the immune system.

Adding to the complexity, vaccine makers are testing out just about every technology they can for a Covid-19 vaccine. Some of the experimental vaccines are based on old designs, but others have never been approved for use in humans for any disease.

Dr. Black and his colleagues have been working with CEPI, a nonprofit organization that is accelerating the development of vaccines, on a new set of safety procedures for some Covid-19 vaccines, including those developed by AstraZeneca, CureVac and Novavax.

The researchers have come up with a set of potential medical complications that vaccine trials should pay particular attention to. They have addressed the possibility that the vaccine could actually make people prone to worse cases of Covid-19, for example. Fortunately, the research so far shows no sign that this is happening.

CEPI is coordinating the sharing of data among vaccine developers. By pooling the safety data from different vaccine developers, Dr. Black said, CEPI will be able to detect rare side effects that they might not have even considered as possible risks.

Andrew Kramer and Katherine J. Wu contributed reporting.