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"What Worries Me Is That People Do Trust Vaccines"

Interview with Paul A. Offit, M.D.
Professor at the University of Pennsylvania
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Paul Offit is a widely recognized expert on vaccines and immunology. He is a co-inventor of the rotavirus vaccine known as RotaTeq, manufactured by Merck & Co., and now sits on the US National Institutes of Health's (NIH) public-private committee known as Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV), which is advising on the clinical trials of COVID-19 vaccine candidates.

We asked for his thoughts on the clinical trials of COVID-19 vaccine candidates prioritized by Operation Warp Speed. A slightly edited version of our conversation appears below.

Are the vaccines that are being prioritized by Operation Warp Speed in the US the most likely to work or just the fastest to produce?

I think they're just the fastest to be produced because for the most part they are all genetic vaccines; mRNA or replication-defective simian or human adenoviruses where you can just sort of plug and play. You know the gene you're interested in—it's the gene that codes for the SARS-CoV-2 surface protein, the Spike protein—so you just plug it in. It's much easier to make than an inactivated viral vaccine, a live-attenuated viral vaccine, or a purified protein vaccine. There is nothing that says these vaccines will be more likely to be safe or effective than existing vaccine strategies.

I don't know how the decision was made to prioritize these candidates. I'm on the NIH ACTIV group but we weren't involved in picking those vaccines.

Is there a potential trade-off between speed and safety/efficacy in the race to develop vaccines for SARS-CoV-2?

I'll tell you eight months from now. The Phase III trials will tell all, assuming that we do the Phase III trials that we've been asking to do, which will involve at least 20,000 vaccine recipients and 10,000 placebo recipients. If we at least do that, we'll see.

We have no experience with those strategies. There are no mRNA vaccines or replication-defective simian or human adenovirus vaccines on the market. They don't exist. With messenger RNA, the mRNA itself is a very labile molecule that is rapidly degraded, so that doesn't worry me. But do you know how many particles are given when you give a replication defective virus vaccine? Roughly 100 billion particles. Might that invoke some aberrant immune response? It's possible. That's why you have to enroll at least 20,000 volunteers in the vaccine arm to rule out an uncommon side effect. You're not going to be able to rule out rare side effects until you put the vaccine in 20 million people.

Are there plans now to test any of these COVID-19 vaccine candidates in children?

Not initially. When the vaccine rolls out, then children will be part of those studies. For children, you have to hold this vaccine to an especially high standard of safety because although there is this post-infection Kawasaki-like disease, it's still the rare child that dies of this virus. When you consider that there 114,000 people who have died in the US from COVID-19, how many have been children? It has to be fewer than 20, whereas 160 children died from flu this year.

Does releasing a vaccine so quickly risk increasing the distrust of vaccines, particularly among certain groups?

The true anti-vaccine activists, which is to say the conspiracy theorists, will still find some reason to hate this vaccine no matter how safe or effective it is, even though those reasons won't be valid.

I think the focus by the media has been wrong to some extent. When people say there's a distrust of vaccines, I don't think that's true. What worries me is that people do trust vaccines. Very much so. Parents in this country are asked to give children 14 different vaccines in the first years of life—that can be as many as 27 inoculations during that time period and as many as five shots at one time—to prevent diseases most parents have never seen, using biological fluids most parents don't understand. They do trust us. I think we risk that trust if we rush this along and don't do the type of Phase III testing that we need to do for this vaccine.

We also need to manage expectations when we do release a vaccine to say that we don't know if it causes rare side effects, but we're looking, and we don't know how long the duration of immunity will be because we'll learn as we go. You will never, ever convince the anti-vaccine people because data doesn't convince them.

When vaccines are available, what percentage of the population will likely need to be vaccinated to establish herd immunity?

It's a guess. It is a combination of two factors: the contagiousness of the virus and the effectiveness of the vaccine. With measles, for example, you have a very, very contagious virus—the most contagious of the vaccine-preventable diseases—but you have an extraordinarily effective vaccine, so you need to have just over 90 percent of the population vaccinated. With polio, we started to see a decrease in the spread of polio when we started to get to 40-50 percent immunization rates. With rotavirus, by the time you got to 60-70 percent immunization rates, the disease dramatically declined. I think if you get to 70-80 percent with a COVID-19 vaccine you'll see a dramatic reduction in the incidence of this disease, as a guess.

What keeps you up at night given all of this?

There is a system, which I trust, that has been in place since the 1950s to make sure that the vaccines that are brought into this country are tested as much as is reasonable to mitigate risks regarding safety and efficacy. This system involves the NIH, the CDC [US Centers for Disease Control and Prevention], and the FDA [US Food and Drug Administration]. As long as that system stays in place, I'm good. What worries me is that this system could be perturbed by an administration that perturbs the science. This is an administration that took the words climate change off the EPA's [US Environmental Protection Agency's] website. This is an administration that pushed hydroxychloroquine [as a COVID-19 treatment] and got the FDA to approve it—a product that had never been shown to work, was known to have a certain level of toxicity, and that ended up doing more harm than good. That was the FDA at its worst. They let themselves be pushed around and if that happens here, that would be a problem.

For more information on Prof. Paul Offit's views, see his recent op-ed in the New York Times.

Interview by Kristen Jill Abboud

Spotlight

Two mRNA Vaccine Platforms are Prioritized in US

By Kristen Jill Abboud
Editor at the Human Vaccines Project

With scientists across the globe racing to develop and test COVID-19 vaccine candidates, It may not be surprising how many of the more than 140 SARS-CoV-2 vaccine candidates in development utilize nucleic acid technology: DNA, messenger RNA (mRNA), or self-amplifying RNA approaches.

The development and manufacturing process for these genetic vaccines is much faster than for traditional approaches, which typically rely on using an attenuated or killed virus or a viral protein to trigger an immune response. As noted recently in the *New England Journal of Medicine*: "From their earliest conception, nucleic acid vaccines were recognized as a possible solution for a rapid pandemic response."

Two of the five vaccine candidates that were reported to be among the priority candidates for Operation Warp Speed—a partnership of US government entities that aims to deliver 300 million doses of a safe and effective vaccine against SARS-CoV-2 by January of next year—utilize mRNA to try to induce a protective immune response against the virus.

Prior to SARS-CoV-2, mRNA was already being explored for a variety of infectious diseases, including Zika, Ebola, influenza, and HIV, as well as cancer and genetic diseases. But the mRNA strategy remains unproven—none of the licensed vaccines utilize this approach.

Moderna's SARS-CoV-2 mRNA vaccine candidate mRNA-1273, which is being developed in partnership with the US National Institute of Allergy and Infectious Diseases (NIAID) and is one of those prioritized by Operation Warp Speed, was the first SARS-CoV-2 vaccine candidate to enter clinical trials. The Phase I trial started in mid-March, just 60 days after the genetic sequence of the novel coronavirus was released, and the first volunteers were enrolled in a Phase II study by the end of May.

Interim data on the development of neutralizing antibody responses in eight volunteers from the Phase I trial were reported in a press release in mid-May, but no data from the trial have been published yet. Immunogenicity data in mice were recently reported for a prime-boost mRNA-1273 vaccine regimen similar to that being tested in humans.

Moderna and NIAID plan to conduct a Phase III trial involving 30,000 subjects (evenly split between vaccine and placebo arms) as early as July. Zaks said he expects efficacy data from this trial by late fall/winter of this year. "We've been working closely with the NIH [US National Institutes of Health] and Operation Warp Speed to accelerate not only the development, but down the road the eventual deployment" of a vaccine, said Tal Zaks, Moderna's Chief Medical Officer, who spoke recently at The New York Academy of Sciences' (NYAS) webinar, *COVID-19: When Will a Vaccine Be Ready?*

The other mRNA platform prioritized by Operation Warp Speed is being developed through a collaboration between Pfizer and the German company BioNTech. Their Phase I/II trial, which started in Germany in April and in the US in early May, is evaluating four different RNA vaccine candidates at three different doses. Three of the candidates use either uridine-containing (unmodified) mRNA or nucleoside-modified mRNA, and the fourth candidate uses a self-amplifying RNA approach.

Kathrin Jansen, senior vice president and head of vaccine research and development at Pfizer who also participated in the NYAS webinar, said that the companies would advance the best candidate from these trials into a Phase III, global study involving 20,000-30,000 volunteers (randomized 1:1 vaccine to placebo) as early as July.

"The fastest way to the finish line is taking advantage of the RNA platform," Jansen said. "RNA has a lot of advantages. The footprint is small to produce a large number of doses and you don't have to worry about impurities or purification processes. Assuming success, we really think we have a chance to have vaccine available in October."

Global COVID Lab Meeting

Join us for the next Global COVID Lab Meeting on July 2nd at 10:00 am EDT when Prof. Shane Crotty of the La Jolla Institute for Immunology will discuss T cell-responses to SARS-CoV-2 and the implications for vaccine development. His team was involved in a recent study that shows SARS-CoV-2-infected people harbor T cells that target the virus—and may help them recover. Register for the webinar here.

Must Read

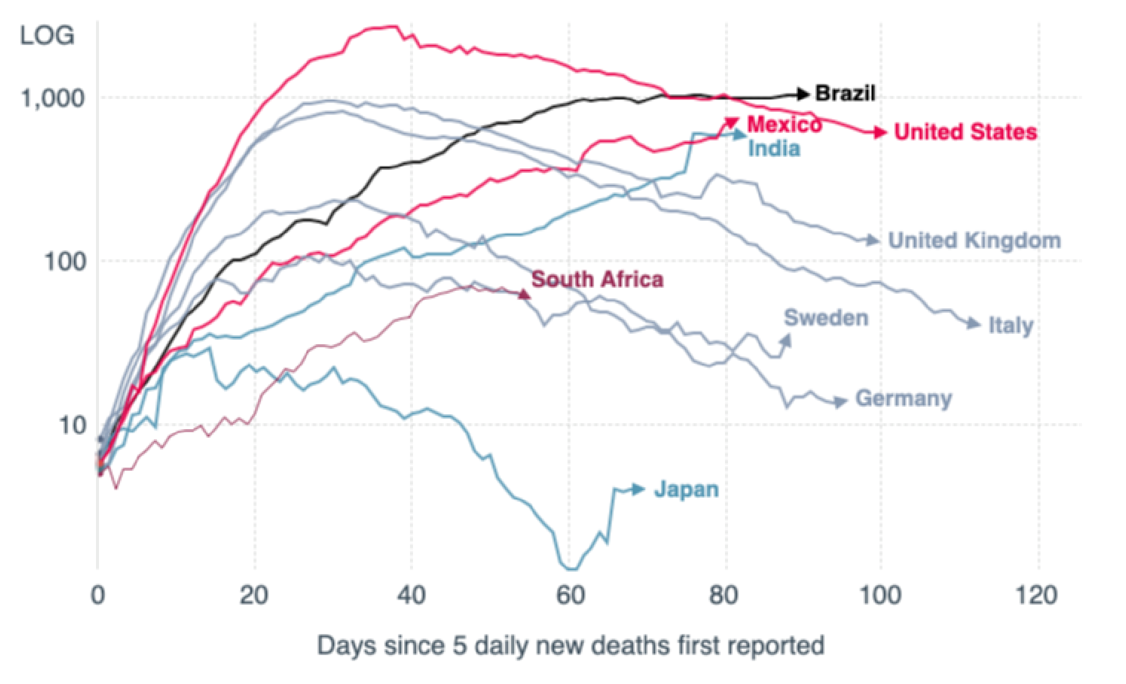
Recent publications highlight animal data for an mRNA vaccine candidate, the development of mouse models of SARS-CoV-2 infection, and the need for a unified global commitment to eventual vaccine access.

- In two related papers published in *Cell*, researchers manipulated murine cells to express the human ACE-2 receptor to allow permissive infection by SARS-CoV-2. The first paper by researchers at the University of Washington demonstrates that neutralizing antibodies can protect from SARS-CoV-2 infection. The second paper by researchers from Guangzhou, China, focuses on validation of a mouse model for evaluating COVID-19 pathogenesis, vaccination, and treatment.
- Two studies published in *Nature* show that lockdowns and other distancing measures may have prevented three million deaths in Europe and averted 500 million infections in China, the US, and four other countries.
- In this preprint publication, scientists report that Moderna's mRNA-1273 vaccine candidate prevented viral replication in mice for more than three months following a prime-boost regimen similar to that being tested in a Phase II human clinical trial.
- An editorial published in the *Lancet* emphasizes the need for global cooperation in the development, production, and equitable distribution of COVID-19 vaccines.

COVID-19 in Numbers

Daily New Confirmed COVID-19 Deaths

Januar 25 - June 23



Source: European Centre for Disease Prevention and Control – Situation Update Worldwide – Data last updated 23rd Jun, 10:33 (GMT-04:00)