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COVID-19 Vaccine Researchers Mindful of Immune Enhancement

There is no evidence that any of the coronavirus vaccines in development worsen a coronavirus infection rather than confer immunity to it, but the phenomenon is something scientists are closely monitoring.

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Most people who contract the dengue virus, a mosquito-borne RNA virus, experience mild symptoms or none at all. In some cases, it can cause a severe illness known as hemorrhagic fever, with bleeding, abnormal blood clotting, and leaky blood vessels that can sometimes lead to a precipitous drop in blood pressure and circulatory collapse. Curiously, in the 1960s, US army scientists in Thailand noticed this life-threatening condition occurred most frequently in two populations: first-time infected babies born to mothers who were immune to dengue, and children who had once experienced a mild or asymptomatic infection, and later contracted the virus a second time. A scary scenario began to crystalize: a second infection was sometimes worse than the first.

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A series of studies in cells, animals, and people eventually gave rise to a possible explanation: antibodies created during a first-time infection could, under very specific circumstances, end up enhancing the disease rather than protecting against subsequent infections. Researchers called this "antibody-dependent enhancement," or ADE.

ADE is one form of immune enhancement, a poorly understood group of phenomena occurring when components of our immune system that usually protect against viral infections somehow end up backfiring. It's a concern in situations when people are continuously re-infected with particular pathogens, and with vaccines that work by injecting snippets of virus to mimic a first infection. Some immunizations, such as those against respiratory syncytial virus (RSV), have been observed in the past to make disease worse when vaccinated individuals contract the virus.

To date, I haven't seen any clear evidence to support ADE or ERD, but it's something you want to be aware of for sure.

—Dennis Burton, the Scripps Research Institute

As far as researchers know, such cases are exceedingly rare across viruses. For SARS-CoV-2, it's unclear if

any forms of immune enhancement could play a role in infections or vaccines under development, but there is no evidence so far.

"[It's just] a theoretical risk, but people are being extremely careful to make sure that this risk is not becoming a reality," notes Paul-Henri Lambert, an immunologist and vaccinologist retired from the University of Geneva who now advises the university's center of vaccinology and consults for a multinational collaborative project of researchers on safety evaluations of vaccine candidates. "With COVID-19, we have a disease which in eighty percent of people is selectively mild. So what you would not like is to give a vaccine that would not protect well and in a certain percentage of people make the disease worse."

No evidence yet for antibody-dependent enhancement in COVID-19

Dengue remains the best-studied and one of the very few solid examples of ADE. It's thought to occur in communities where there are multiple viral strains of dengue circulating. While antibodies against one dengue strain will typically reliably protect against that strain, things can go awry when the antibodies encounter a different strain of dengue. Instead of neutralizing the virus—that is, binding to and blocking a protein the pathogen needs to enter host cells—the antibodies only bind to the virus without neutralizing it.

That can become a problem when immune cells, such as macrophages, dock onto the tail ends of antibodies using specialized receptors known as Fc receptors—which they often do to clear up antibody-virus debris. Because dengue viruses can use Fc receptors to infect cells, if the antibodies aren't disabling the pathogen, they actually end up helping the virus enter macrophages to infect the cells, Trojan horse–style, explains Dennis Burton, a microbiologist at the Scripps Research Institute in California. This amplifies viral replication, potentially pushing the immune system into over-drive and paving the way for severe disease. "That's the hallmark of ADE, basically . . . you make infection easier, you infect more cells, you get worse disease."

But there are still many questions surrounding ADE and its mechanism. It's not entirely clear, for instance, if the antibodies are the sole effectors of ADE, or if other parts of the immune system also play a role. Nor is it certain whether it's strictly the non-neutralizing characteristic of the antibodies that matters most—it could also be that neutralizing antibodies could also allow viruses to infect macrophages if they're not numerous enough to block all key proteins across a virus's surface.

"It might be that any antibody would enhance if you've got it at a dose that doesn't work," notes James Crowe, an immunologist at Vanderbilt University Medical Center. "This is very hard to study in humans."

Solid evidence for ADE in natural viral infections exists only in dengue virus and some of its relatives. There are a handful of other viruses where ADE has been demonstrated in vitro—in experiments that mix macrophages or similar cells with antibodies and virus and see whether the virus is capable of infecting the cells in spite of the presence of antibodies, Crowe explains. Such experiments have found hints of ADE with viruses including Ebola virus, HIV, and coronaviruses such as SARS and MERS. However, it's still a mystery to what extent this occurs in live organisms in the presence of a functioning

immune system. “The immune system typically modulates things to your benefit. I’m not saying that ADE does not occur in the body—I’m just saying it’s difficult to bridge the results in the test tube to what happens in the body,” Crowe says.

It’s not yet clear if SARS-CoV-2 is capable of infecting macrophages. Although some scientists have reportedly spotted viral protein inside macrophages, whether it actually infects and replicates in macrophages in the body “is something investigators are trying to determine right now,” Crowe says.

Barney Graham, the deputy director of the National Institute of Allergy and Infectious Diseases’s Vaccine Research Center, which is collaborating with the company Moderna on a coronavirus vaccine, told *PNAS* last month that he doubts the dengue mechanism of ADE would apply to SARS-CoV-2 because the coronavirus primarily targets ACE2, not Fc, receptors, and has a very different pathogenesis compared to the dengue family. And even for the original SARS that caused an outbreak in 2003, in vitro experiments suggest that it could infect a human cell line using an Fc receptor, but the virus did not reproduce into infectious particles, Graham writes in a perspective article in *Science*.

It’s theoretically possible that infections caused by other coronaviruses could generate antibodies in people’s blood and cause ADE upon infection with SARS-CoV-2, but there’s little evidence for this so far, Crowe notes. And in principle, some COVID-19 patients could develop antibodies that don’t neutralize, or produce neutralizing ones at insufficient concentrations, and then develop severe symptoms once they’re infected a second time. But a handful of reported SARS-CoV-2 re-infections have been found to be due to flawed tests. And two preprints appeared last week suggesting that in US patients who received antibody-containing blood plasma transfusions from COVID-19 survivors, the treatment did not make the disease worse, supporting the argument against ADE.

ADE’s role in vaccine development

Nevertheless, ADE is a possibility that vaccine scientists are keeping a watchful eye on, in part due to experiences with other vaccines. When researchers in the 1990s tested vaccines against feline infectious peritonitis, a rare and typically fatal coronavirus disease in cats, vaccinated kittens died much sooner than unvaccinated ones after being exposed to the virus.

Such concerns have pushed some scientists to reconsider vaccine design. One explanation for why some of the early cat coronavirus vaccines caused ADE weren’t using the right vaccine targets, or the targets weren’t specific enough. This could have produced antibodies that target parts of the virus without blocking the specific site on its spike protein which it uses to infect cells—the receptor-binding domain (RBD).

This is one reason why some investigators, including microbiologist and vaccinologist Maria Bottazzi of the Baylor College of Medicine in Houston, specifically pursue the RBD as a vaccine target--to avoid the possibility of generating non-neutralizing antibodies. “If you’re just giving the immune system

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the only choice of making an antibody to the receptor binding domain, then you drastically limit the possibility of inducing ADE," explains her colleague, immunologist David Corry.

some of its relatives.

Burton says vaccine tests in animal models will help researchers understand the likelihood of ADE occurring in a COVID-19 vaccine, although that won't be conclusive proof until clinical tests in humans are conducted. Encouragingly, some recent preliminary vaccine studies found no evidence of ADE. In an April preprint, a team of researchers from the US and China showed that injecting rats with the SARS-CoV-2 RBD protein triggered a burst of neutralizing antibodies, which did not cause ADE when mixed with virus and Fc-expressing cells in vitro. In addition, even a whole inactivated virus vaccine recently tested by Chinese researchers in four macaques protected against exposure to SARS-CoV-2, and the researchers found no evidence of ADE.

As long as it's a good vaccine with a specific target that induces a strong neutralizing antibody response, it's unlikely we'll see ADE, "certainly not commonly," Crowe says. "It's only when you have an ineffective vaccine or antibody that you might see [ADE]. And no one wants to move those [candidates] forward anyway, so that's why I'm optimistic."

Other mechanisms of immune enhancement in vaccines

Bottazzi says she thinks processes involving other components of the immune system may be more relevant for SARS-CoV-2 vaccine concerns than ADE. Different routes to immune enhancement came to the foreground in the 1960s during clinical trials where young children were immunized with whole-inactivated virus vaccines against respiratory syncytial virus (RSV). When the children contracted RSV naturally a few months after the vaccinations, those who were immunized got a lot sicker than those who weren't. In fact, in one trial, 80 percent of children in the youngest cohort had to be hospitalized, and two died.

The syndrome those hospitalized kids developed is called vaccine-associated enhanced respiratory disease (ERD), and is linked with two immunological phenomena, Graham explains in the *Science* article. The first is a high concentration of binding antibodies that don't neutralize the virus and result in the formation of antibody-virus complexes that get stuck in the small airways of the lungs, obstructing these spaces and driving inflammation—a mechanism considered different from ADE, Burton explains.

Researchers also unexpectedly found large numbers of certain white blood cells in the lungs of the children who died, including a proinflammatory kind of cell called an eosinophil, usually associated with allergic reactions. This raised concerns that the vaccine could have somehow primed the immune system to trigger an inappropriate cellular immune response. Normally, vaccines or viral infections trigger a particular group of T helper (Th) cells—known as Th1 cells—to mediate a cascade of reactions involving various infection-fighting immune cells.

But in several studies in animals that received a similar RSV vaccine, challenge with the RSV virus seemed to trigger certain cytokines that mobilized a very different subpopulation of T helper cells, known as Th2

cells. The lungs of inoculated mice were also packed with inflammatory cells, eosinophils in particular. Researchers hypothesized that the vaccine was inducing a response by Th2 cells, which then attracted eosinophils and somehow induced "a kind of allergic reaction," Lambert explains.

A similar phenomenon was seen in animals that received coronavirus vaccines in the past—making researchers such as Bottazzi wary of such forms of immune enhancement. For instance, when researchers administered an inactivated SARS vaccine into mice, and then challenged them with the live virus, they also found eosinophils and other blood cells in the animals' lungs and livers—a possible sign of Th2-type immune responses. Despite these signs of immune enhancement, that SARS vaccine did a good job in producing neutralizing responses, and vaccinated animals survived.

Bottazzi cautions against extrapolating from animal studies to humans. It's possible cellular immune enhancement is an artifact of the animal models or the experimental system.

Of nearly 140 different COVID-19 vaccine candidates, 15 are already in human trials. "To date, I haven't seen any clear evidence to support ADE or ERD, but it's something you want to be aware of for sure," Burton says. "It may be that the vaccines that are already out there—Moderna, Janssen, and so on—they may turn out to be perfectly great, we just don't know at this point. I think it's good to have a plan B, where if there are some problems, you can start working it out quickly what they are, and re-engineering your vaccines based on knowledge about what's wrong."

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