HEALTH

Your first brush with coronavirus could affect how a fall booster works

As omicron-specific boosters near, scientists debate how ‘original antigenic sin’ will influence immune responses

By Carolyn Y. Johnson

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(Melanie Lee for The Washington Post)

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In the beginning, when the coronavirus was new, the quest for a vaccine was simple. Everyone started out susceptible to the virus. Shots brought spectacular protection.

But the next chapters of life with the virus — and the choice of booster shots for the fall and beyond — will be complicated by the layers of immunity that now ripple through the population, laid down by past infections and vaccinations.

When it comes to viral infections, past is prologue: The version of a virus to which we’re first exposed can dictate how we respond to later variants and, maybe, how well vaccines work.

It’s a phenomenon known by the forbidding name of original antigenic sin, and, in the case of the coronavirus, it prompts a constellation of questions. Are our immune systems stuck still revving up defenses against a version of the virus that has vanished? Will updated booster shots that are designed to thwart variants be much better than the original vaccine? How often will we be reinfected? Is there a better way to broaden immunity?

The answers to those questions will influence our long-term relationship with the coronavirus — and the health of millions of people. But more than two years into the pandemic, the quest to unravel these riddles underscores the seemingly unending complexity of the battle against a new pathogen.

When the virus emerged, no one had encountered SARS-CoV-2 before, so our immune systems started in pretty much the same vulnerable spot — what scientists call “naive.” Now, people have been infected, vaccinated, boosted, reinfected and boosted again — in varying combinations. People’s immune systems are on slightly different learning curves, depending on when they were infected or vaccinated, and with what variants or vaccines.

Should you get a second coronavirus booster? Here's what to know.

“There are no cookie-cutter answers here,” said John P. Moore, a professor of microbiology and immunology at Weill Cornell Medicine. “An omicron infection after vaccination doesn’t mean you’re not going to get another one a bit further down the road. How long is a bit further down the road?”

Coronavirus cases spiked globally in the first weeks of 2022, despite record-high vaccination rates. Here's how the omicron variant took off. (Video: Jackie Lay, John Farrell/The Washington Post)

Scientists are watching in real time as original antigenic sin plays out against the coronavirus — and debating how it will influence future vaccine strategy. Contrary to its biblical thunderclap of a name, the phenomenon is nuanced — more often beneficial or neutral than harmful.

It helps explain why vaccines based on the original virus continue to keep people out of the hospital, despite challenging new variants. But it may also mean that revamped fall boosters have limited benefits, because people's immune memories are dominated by their first experience with the virus.

"We may have gotten about as much advantage out of the vaccine, at this point, as we can get," said Barney Graham, an architect of coronavirus vaccines who now focuses on global health equity at Morehouse School of Medicine in Atlanta. Graham emphasizes that the vaccines are doing exactly what they were designed to do: keep people out of the hospital. Retuning them will have benefits, albeit limited.

"We can tweak it and maybe evolve it to match circulating strains a little better," Graham said. "It will have a very small, incremental effect."

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Echoes of immunity

More than 60 years ago, a virologist named Thomas Francis Jr., observed that influenza infections in childhood had lifelong repercussions. For decades after, people's immune systems carry an imprint from their first flu, activating defenses primarily against the original version of the virus they encountered. He called it "the doctrine of original antigenic sin."

The same thing is happening with the coronavirus. A growing number of studies show that when the omicron variant infects, it causes the immune system to rapidly activate immune memory cells that are already on standby, created by previous vaccinations or infections.

"People are now walking around with different immune-imprinted covid responses, depending on what vaccine schedules they've had — one, two or three doses — and what infections they have had in the past," said Rosemary Boyton, a professor of immunology and respiratory medicine at Imperial College London. "Imprinting is different according to where you live in the world, what vaccines you received — and that's determining the subsequent immune response."

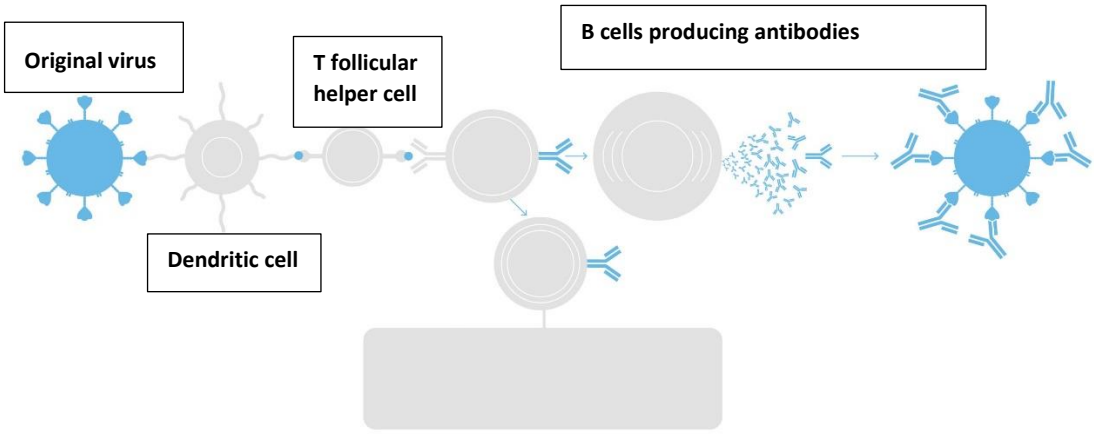
In flu, the immunological echoes of original antigenic sin have real consequences: When flu strains are similar to the ones encountered in childhood, people are better protected against severe illness. The 1918 flu pandemic was caused by an H1N1 strain, which continued to circulate for decades afterward. When the 2009 H1N1 pandemic occurred, older people who were exposed to H1N1 in childhood had stronger immune responses than younger people who had been infected with other strains. When a flu strain is a more distant relative of that initial exposure, people may be more susceptible.

There's not a consensus on how original antigenic sin plays out with the coronavirus — and it's a touchy subject among immunologists. Many quarrel about whether "sin" is the appropriate word for a phenomenon that undergirds our immune system's ability to provide partial protection against changing viruses.

But time is of the essence: Companies are already manufacturing fall boosters based on a new recipe. Many scientists think that, in the absence of certainty, moving forward with retuned boosters is the best strategy — even if they may offer short-term protection, mostly against severe illness.

When you have covid, here's how you know when you're no longer contagious

"Maybe 10 to 15 years from now, we live in a world where the vaccine is birth-year specific or make strain selection decisions that take into account different immune histories in the population," said Katelyn Gostic, a researcher at the University of Chicago. "I think we need and are actively developing better technologies and better techniques to try to work at the science fiction frontier here, of figuring out these imprinting questions."



How the immune system learns to recognize a virus

After a virus invades, **dendritic cells** grab pieces of virus.

The dendritic cells then look for helper **T cells** that match features of the viral pieces.

The activated B cells turn into **plasma cells** that churn out virus-blocking **antibodies** to fight the infection. Some become memory B cells.

Once matched, an activated helper T cell then locates

B cells that also match the virus's distinct features.

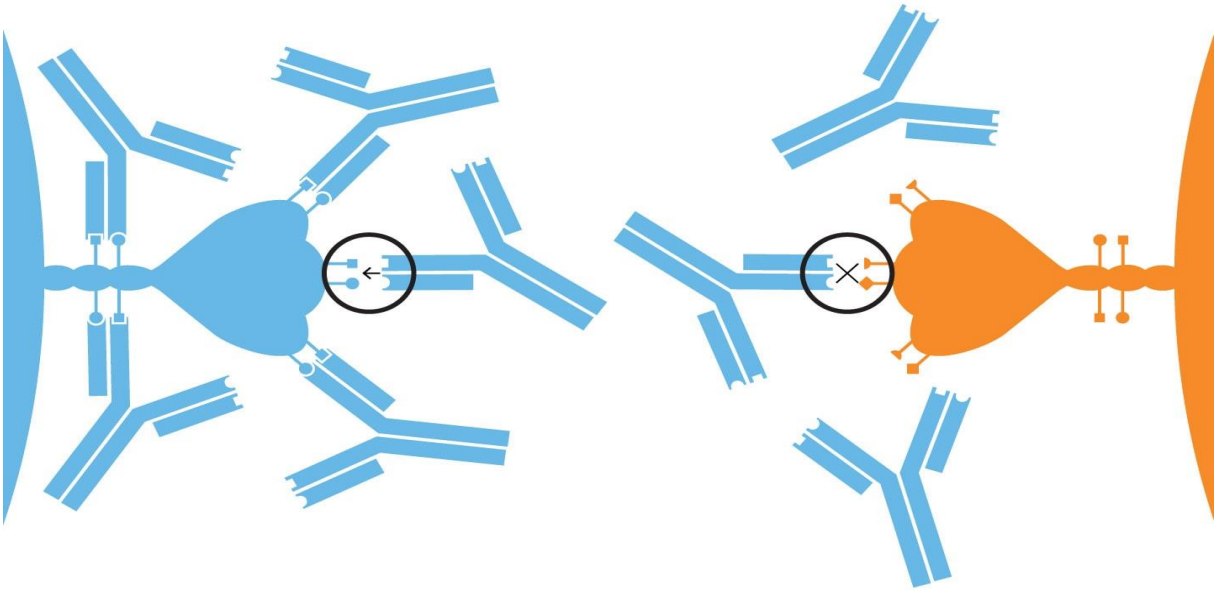
Antibodies flood the body and latch on to the virus to block it from infecting more cells.

Memory B cells remain in the body after the first infection is cleared. They can then quickly reactivate to produce more antibodies if the same virus is encountered again.

‘A dog’s dinner’

The most gloomy interpretation of original antigenic sin holds that the immune system is stuck fighting an old war. Each new infection leaves behind no useful immune memory, instead summoning defenses against antiquated versions of the virus.

“Your coronavirus immunity repertoire is such a dog’s dinner it might actually enhance immunity to past variants a little bit, in ways that aren’t useful anymore,” said Danny Altmann, an immunologist at Imperial College London.



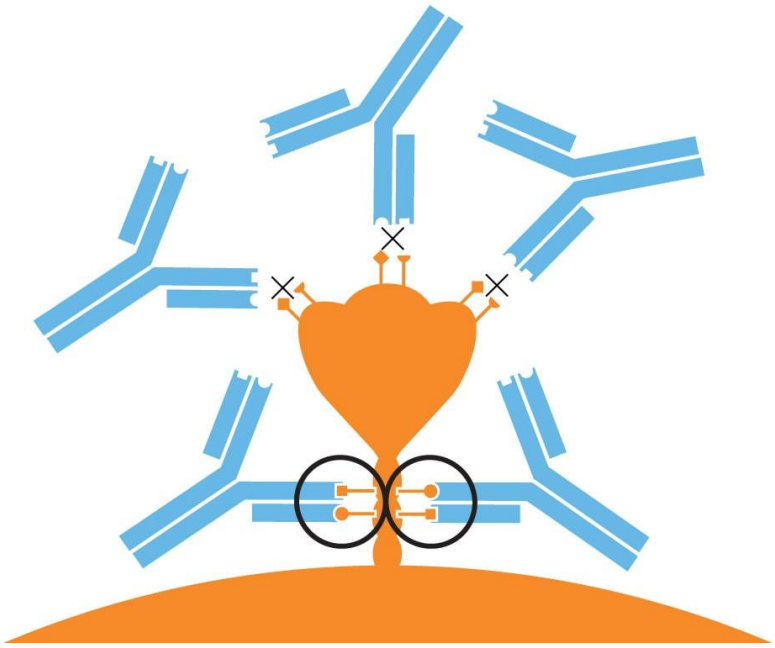
Antibodies match and latch on to the original virus. (left)
But the older antibodies are not a good match for newer variants. (right)

He and Boyton published a Science paper in June that suggested people who were infected with the original version of the coronavirus and later vaccinated and reinfected with omicron mustered subpar immune responses to omicron. Their interpretation: **People’s immune systems were locked into a fight against older iterations of the virus.**

Not so fast, say others, who think there may be explanations other than original antigenic sin.

An essential element of how the immune system works is memory, the ability to recall viruses that have infected people before. Although virus-fighting antibodies naturally drop over time, memory B cells kick into action and churn them out on demand when a virus intrudes.

When viruses evolve, as is happening with the coronavirus variants, this memory can still be quite useful. Viruses typically swap out only bits of their costume. Parts of the spike protein of omicron look very different, but other bits look the same.



Antibodies to the original virus may still be able to attach to some parts of a newer variant that have not changed.

Mismatch

Match

“What our immune system likes to do best is recognize things it already has seen. It responds very quickly to these parts of the virus that haven’t changed,” said Matthew S. Miller, a viral immunologist at McMaster University. “The vaccines are still doing an exceptionally good job in preventing us from getting severe illness. The reason is that is, essentially, original antigenic sin.”

This hair-trigger immune response isn’t fine-tuned to block the new virus; people can still get infected. But a suboptimal response that’s ready to go, many scientists think, is better than waiting for the body to create one from scratch.

“Essentially, original antigenic sin is often a very good thing,” said Laura Walker, chief scientific officer of Adagio Therapeutics, a biotechnology company focused on developing monoclonal antibody drugs. Walker recently published a paper showing that vaccinated people who came down with an omicron infection had an initial immune response driven by the immune cells created by their original vaccination.

This burst of antibodies capable of recognizing a new variant is not surprising to experts. It’s Immunology 101. And in the case of the coronavirus, it helps.

“It’s not a sin. It’s a natural progression of our immune response,” said Ali Ellebedy, an immunologist at Washington University School of Medicine in St. Louis. “We should not think of it as a glitch.”

How the lucky few to never get coronavirus could teach us more about it

New memories

What scientists don't know yet is what happens in the weeks and months after an infection or new vaccine.

One possibility: The immune system creates a new memory of the new variant. The next time a descendant of omicron comes along, the body can draw from an expanded memory bank to mount its next defense.

Another, more worrisome scenario: The fast-draw immune response interferes with the creation of new memories. The next time a version of the virus comes along, the body simply reactivates the existing response — and eventually, a variant comes along that is so changed it is unrecognizable.

"**The question is: Is that memory pool going to get broadened, or is it going to get fixated?" said Wayne A. Marasco, an immunologist at Dana-Farber Cancer Institute**.

The Food and Drug Administration asked companies in June to update coronavirus boosters for the fall, to a shot that includes two components: one that targets the original strain; and the other tailored to fight the most recent variants, BA.4 and BA.5. Companies showed preliminary data that vaccines containing those versions of the virus can trigger stronger immune responses in the weeks after vaccination. But the **advantage of a switch was modest, and long-term effects of those vaccines will depend in part on whether they help create new memories**. If they simply provide a short-term boost of the existing memory response, many scientists are debating a change in vaccine strategy.

"This is not in my mind going to be the dramatic change to limit symptomatic omicron infection," said Robert Seder, chief of the Cellular Immunology Section at the National Institute of Allergy and Infectious Diseases. Seder showed in a primate study this year that an omicron booster did no better than an additional shot of the original vaccine. He has focused his efforts on a change in tactics, such as a nasal vaccine that could help block infections and spread of the virus.

Even though a revamped vaccine is unlikely to be a game changer, many scientists favor an update. Rafi Ahmed, an immunologist at Emory University, argues that an omicron-based booster is urgently needed.

"There is no point continuing to vaccinate someone with a strain that is not circulating," Ahmed said. Even if a new omicron-specific memory does not coalesce, the variant-specific vaccine will recruit and rev the part of the memory response capable of recognizing omicron.

Some scientists think a new memory response will also develop over time. Others think it might take an additional shot. Ahmed's work on influenza showed that while a first shot against the H5N1 strain primarily activated an existing memory response, a second shot recruited new B cells targeting the strain.

But not all "sin" is created equal. For a virus like dengue, original antigenic sin can be harmful. For flu, it may help in some scenarios and hinder immunity in others. The limited data has left experts in a familiar place during this pandemic: watching what happens next.

“I’m struggling to say: Is this a good thing or a bad thing?” said Christian Gaebler, an assistant professor of clinical investigation at the Rockefeller University. “If someone says they fully understood this, they would be lying.”

Graphics by Aaron Steckelberg.

Coronavirus: What you need to know

The latest: The CDC has loosened many of its recommendations for battling the coronavirus, a strategic shift that puts more of the onus on individuals, rather than on schools, businesses and other institutions, to limit viral spread.

Variants: BA.5 is the most recent omicron subvariant, and it’s quickly become the dominant strain in the U.S. Here’s what to know about it, and why vaccines may only offer limited protection.

Vaccines: For people under 50, second booster doses are on hold while the Biden administration works to roll out shots specifically targeting the omicron subvariants this fall. Immunizations for children under 5 became available this summer. Here’s what to know about how vaccine efficacy could be affected by your prior infections and booster history.

Guidance: CDC guidelines have been confusing — if you get covid, here’s how to tell when you’re no longer contagious. We’ve also created a guide to help you decide when to keep wearing face coverings.

Where do things stand? See the latest coronavirus numbers in the U.S. and across the world. The omicron variant is behind much of the recent spread.

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Gift Article

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