HEALTH

A Truly Amazing Vaccine Breakthrough Is Hiding in Plain Sight

The COVID shots—and new ones for RSV—herald a new era for designing vaccines.

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Every fall, when the air turns chilly and the leaves red, pediatric ICUs begin preparing for the onslaught of the virus known as RSV. Not flu, not COVID, but RSV, or respiratory syncytial virus, is the No. 1 reason babies are hospitalized, year after year. Their tiny airways can become inflamed, and the sickest ones struggle to breathe. RSV is deadly on the other end of the age spectrum too, killing 6,000 to 10,000 elderly Americans every year.

For decades though, there was no way to stop the virus's seasonal tide. The quest for a vaccine always came up short. And then suddenly, the vaccines started working.

This year, doctors have not just one but multiple new shots to prevent RSV. Three gained FDA approval in rapid succession in recent months: an antibody shot for infants called nirsevimab, a form of passive immunization for babies too young to get proper vaccines; a vaccine from Pfizer for both adults over 60 and pregnant mothers, who can pass the immunity on to their babies; and finally, a vaccine from GlaxoSmithKline also aimed at adults older than 60. Together, these herald a new era for RSV.

That these three new RSV shots are coming out at once is no coincidence. They succeed where others failed because they all target a specific weak spot in the virus, first identified in 2013. This strategy of finding a virus's most vulnerable points applies to other pathogens too, and experts say it can revolutionize the design of vaccines for other diseases. In fact, it was quietly used to make the COVID vaccines from Pfizer and Moderna. Scientists had originally perfected the idea with RSV, only to repurpose it for the COVID vaccine, which raced ahead, given the urgency of the pandemic. This year, though, the shots are coming for RSV.

"We're in a really good position, finally, after more than 65 years," says Asunción Mejías, an infectious-diseases doctor at St. Jude Children's Research Hospital.

The first attempts to make an RSV vaccine began not long after the virus’s discovery, in 1956, but an early trial ended so catastrophically that it had a chilling effect for decades.

It had started off with promise. The early vaccine was modeled after a successful one for polio, in which the virus is inactivated with a chemical called formalin. But when infants given the early RSV vaccine later caught the virus, a whopping 80 percent had to be hospitalized—compared with only 5 percent in the control group. Two of the babies died, their lungs ravaged. The vaccine did worse than offer no protection; it made the disease more severe. “It was such a disaster,” says Ann Falsey, an infectious-diseases doctor at the University of Rochester. Scientists spent years piecing together why—the vaccine riled up the wrong part of the immune system in very young babies—but they got no closer to making a vaccine that worked. The field was stuck.

Then, in 2008, a serendipitous meeting led to an eventual breakthrough. A young, freshly minted Ph.D. named Jason McLellan, who studies the structure of proteins, began a new job at the National Institutes of Health to work on HIV vaccines. The lab he had joined, on the fourth floor, had run out of room, though, so he got put in

another, on the second. There, he ran into Barney Graham, a virologist who had been trying to solve the puzzle of RSV since the 1980s. He convinced McLellan that this virus was worth a look too.

By then, scientists had at least homed in on a plausible vaccine target. Much as COVID uses spike protein to infect cells, RSV uses a protein—called F for "fusion"—to physically fuse the virus particle to a human cell. F comes in two forms, though: an extremely unstable prefusion state and a far more stable postfusion state. And once it switches to the postfusion state—which can also happen spontaneously— "it can't come back," McLellan told me.

When RSV vaccines are manufactured, all the F protein eventually switches to the postfusion state. But the antibodies against postfusion F weren't very effective. McLellan soon figured out why. He found that extremely potent neutralizing antibodies bind to a specific site—the very tip of the prefusion F—that is lost when the protein rearranges into its postfusion form. With that, Graham told me, "you lose ten- to 1,000-fold potency." An effective RSV vaccine would need to target the prefusion F.

The team knew what to do, but had a practical dilemma: How to stabilize F in its prefusion form, so the team could put it in a vaccine? McLellan rejiggered the protein slightly, adding molecular "staples" and filling a hole in the protein structure. These changes froze F in its prefusion shape. When the team tested this version of the vaccine in mice, the results could not have been clearer. The vaccine induced the highest levels of neutralizing antibodies Graham had ever seen in his three decades of studying RSV. "This is it," McLellan remembers thinking.

Soon, pharmaceutical companies came calling, and the race was on. (The experts in this article—like nearly everyone who works on RSV vaccines—have all received research grants, consulted for, or worked in some other way with one or more of the companies developing shots for RSV.) Today, Pfizer's and GlaxoSmithKline's newly approved RSV vaccines target the prefusion F protein, as does nirsevimab, the antibody shot for infants from AstraZeneca and Sanofi. Both the vaccines and the antibody shot trigger immunity against RSV: Vaccines stimulate the immune system to make its own antibodies, and nirsevimab is a direct infusion of antibodies.

Trials for all three shots were already under way when the coronavirus pandemic hit. But because RSV nearly disappeared during social distancing, the trials got delayed. Meanwhile, McLellan and Graham devised a similar molecular trick to stabilize COVID's spike protein, which Pfizer and Moderna later used in their vaccines. (The stabilization wasn't make-or-break for COVID, as it was for RSV, though—

AstraZeneca's COVID vaccine was effective despite not having this modification.) But unstable fusion proteins are found in many different classes of viruses beyond RSV. McLellan, now at the University of Texas at Austin, is working on shots against the prefusion structure of other stubborn viruses such as cytomegalovirus and Crimean-Congo hemorrhagic fever. (Graham is now a professor at Morehouse School of Medicine.) This approach—called structure-based vaccine design—could unlock new ways of targeting once-elusive viruses.

For RSV, this fall and winter will be a test of how well the shots fare in the real world. As the adage goes, vaccines don't save lives; vaccinations do. Falsey, the University of Rochester doctor, specializes in studying RSV in the elderly, and she worries that too few Americans over 60 will get the new vaccines this year. A CDC advisory panel decided that elderly Americans can get the vaccines through "shared clinical decision-making" with their doctors but did not go as far as to fully recommend vaccination, which would have triggered private insurers to cover the shots under the Affordable Care Act. Out of pocket, they can cost more than $300. The shots are poised to have a bigger impact for infants though. The same CDC panel today endorsed Pfizer's vaccine for pregnant women, and it had already previously recommended the antibody shot, nirsevimab, for newborns. (Most babies will need just one or the other.)

Nirsevimab replaces an existing RSV-antibody shot called palivizumab, which is not widely used. Palivizumab targets a less potent site that is on both the pre- and postfusion F, and it needs to be administered up to five times a season (compared with once for nirsevimab), at a cost of some $1,500 a dose. For these reasons, it's been reserved for the highest-risk babies, such as preemies with underdeveloped lungs. But most babies who end up hospitalized were healthy to begin with, says St. Jude's Mejías, so the older shot didn't put much of a dent in overall hospitalizations. Nirsevimab is meant to be more widely used: The shot is approved for all infants in their first RSV season. "It's going to change the way we manage and treat RSV,"

Mejías told me. It should be available for babies starting in October. And if all goes according to plan, pediatric ICUs could be a little quieter this winter.