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An infant receives ventilation for respiratory syncytial virus. Infections are often worst in young babies.

THE NEW WAVE OF VACCINES FOR A KILLER RESPIRATORY VIRUS

Respiratory syncytial virus hospitalizes millions of people a year and kills tens of thousands. After decades of failure, four vaccines are now being tested in late-stage trials.

By Kendall Powell

In February 2020, just as a new coronavirus was triggering the global COVID-19 pandemic, structural biologist Jason McLellan and his team published the structure of the key protein it uses to invade human cells[1]. Immediately, scientists began using that protein's structure to develop COVID-19 vaccines.

But that wasn't the first time McLellan, now at the University of Texas at Austin, had solved a structure and spurred on a new wave of vaccines. In 2013, he was focusing on a different killer — respiratory syncytial virus, or RSV[2].

RSV causes a respiratory tract infection that affects 64 million people per year worldwide. It hospitalizes 3 million children under 5 years old and approximately 336,000 older adults annually. The global health-care costs of RSV-associated infections in young children in 2017 were estimated to be US$5.45 billion[3].

Researchers have been trying for decades to develop a vaccine, and have had some particularly devastating failures — including the deaths of two participants in a trial in the 1960s.

Solving the protein structure revived the RSV field. McLellan, then a postdoctoral researcher at the US National Institute of Allergy and Infectious Diseases in Bethesda, Maryland, and his colleagues looked at a protein that the virus uses to fuse with cells and infect them, called the F protein, and found a way to stabilize it in its prefusion form — the shape it adopts when ready to grab on to cells. The structure of the prefusion F protein unveiled the best target for making vaccine-induced antibodies that could prevent the virus from entering human cells.

Now, an effective RSV vaccine is nearly within reach: four candidates and one monoclonal antibody treatment are in late-stage clinical trials.

"It's been 8 years since the prefusion F protein conformation was elucidated and now we're all in phase III trials based on that fundamental discovery," says Christine Shaw, vice-president of early-development programmes in infectious diseases at messenger RNA therapeutics company Moderna in Cambridge, Massachusetts.

The quest for RSV vaccines has not escaped the effects of the COVID-19 pandemic. The pandemic has complicated the trials, but it also helped spur developments that might finally protect against this childhood killer.

Rough start

RSV infects most children by age three, and most adults many times over, but natural immunity to it is not long lasting. Infections are usually most severe in infants under two months old, who are encountering the virus for the first time. A vaccine or treatment would drastically reduce hospital and intensive-care admissions for this most vulnerable group, says Rabia Agha, a paediatric infectious-disease specialist at Maimonides Children's Hospital in New York City. And because of the acute medical need for vaccines and treatments for RSV, regulatory agencies in the United States and Europe are prioritizing them for review.

These candidates have been a long time

coming. In the late 1960s, a series of vaccine trials tested a vaccine made from inactivated RSV in children in the United States. Tragically, the shot did the opposite of what it was meant to – it made disease worse in vaccinated children when they were later naturally infected with RSV. This caused severe lung disease that hospitalized most of the children in the trial and killed two.

Steven Varga, a viral immunologist who studies RSV at the University of Iowa in Iowa City, says that early vaccine was "the culmination of a perfect storm of events": it evoked too few virus-blocking antibodies and simultaneously caused an overactive inflammatory response. Researchers now know more about the science of both RSV infection and vaccinology, and Varga says there is no concern that the current crop of vaccine candidates could provoke a similar response.

Vaccine researchers soldiered on, but were targeting the wrong viral proteins – or the wrong forms of these proteins – for decades. "People have tried to make RSV vaccines since the 1970s, but it had been one failure after another," says Rino Rappuoli, senior vice-president and chief scientist for vaccines at GlaxoSmithKline (GSK) Vaccines, based in Siena, Italy. "Things changed completely when we began to understand the main viral protein, protein F."

In a very similar fashion to SARS-CoV-2 and its spike protein, RSV uses the prefusion form of the F protein (preF) to wedge its way into human cell membranes and fuse with them. Once that happens, the protein undergoes a major conformational shift to its more stable postfusion form (postF). Many of the earlier failed vaccines targeted postF.

By contrast, preF induces potent neutralizing antibodies that have been found to block the virus from entering human cells, Varga says.

To solve the structure of preF in a way that would make it useful for vaccine design, McLellan's team made a version of it in which the protein was fixed in a particular shape, so that its vulnerabilities were on display. To stabilize the protein in this shape, the team added a crucial chemical bond that acted like double-sided tape, keeping the protein folded in the preF shape, with its key antibody-target sites exposed. Vaccines that use this stabilized form prompt a much stronger antibody response from the immune system. All the current RSV vaccine candidates involve this stabilized form of preF, and healthy adults produce high levels of neutralizing antibodies against it.

Vaccines work by presenting the immune system with key bits of a pathogen, which induce the production of antibodies and immune cells that can recognize and fight the whole pathogen when the person is re-exposed to it. Many RSV vaccines use a similar array of technologies to those in development or use for COVID. Of the four RSV vaccines in phase III trials, two, from GSK and Pfizer, contain the stabilized preF protein itself. Another, from Janssen, uses a modified adenovirus that produces preF after delivery into the body, plus a dose of the pure protein, in the same shot. The fourth, from Moderna, delivers modified mRNA that produces preF once the RNA is inside cells.

Promising trials

Once approved, an RSV vaccine will be most useful for the very young and the very old. But to simplify clinical trials, all four companies in the race are initially testing their shots in people older than 60.

So far, early-stage data from phase II trials, some in older adults and some in younger adults, suggest that the vaccines will be safe and effective. Both Janssen and Pfizer have run small-scale challenge trials, exposing vaccinated younger adults to RSV, and have shown that their vaccines protect against infection.

> **"Things changed completely when we began to understand the main viral protein."**

The Janssen, Moderna and GSK vaccines increased levels of neutralizing antibodies 9–15-fold.

GSK, Janssen, Moderna and Pfizer now each have global phase III trials under way in tens of thousands of older adults. GSK leads the pack, and Rappuoli says he expects to have interim results in early 2022.

Newborn babies' immature immune systems present a more complicated challenge. They don't respond robustly to many vaccines, which is why most childhood vaccinations are given after two months of age – just outside a critical window for the most severe RSV infections in infants. Instead, babies can be immunized while still in the womb. A few months before birth, a pregnant person is given the vaccine; their body makes antibodies and these are transferred through the placenta, and later through breast milk, to their newborn.

GSK and Pfizer are running phase III trials of their vaccines in pregnant people and following their babies to test for antibody levels at birth and for efficacy at preventing RSV infections during their first year.

In a good sign that this immunization strategy works, infants in Pfizer's phase II trial had higher antibody titres than their birth parent and the vaccine showed 85% efficacy at protecting babies against RSV infections requiring medical attention, says Alejandra Gurtman, vice-president of clinical research and development at Pfizer in Pearl River, New York.

A second way to protect newborns is by injecting them with antibodies that target the virus. AstraZeneca and Sanofi have partnered to test a monoclonal antibody called nirsevimab directed against stabilized preF, which has proved effective at reducing RSV infections in a phase III trial in healthy premature and full-term term infants.

Varga predicts that because older adults, pregnant people and the very young require different vaccine strategies, the vaccine race will not be winner takes all. "More than one of these RSV products will gain approval in each of these spaces," he says.

Pandemic help and hindrance

Running clinical trials for an RSV vaccine during a pandemic caused by a different respiratory virus has brought both challenges and opportunities, vaccine developers say. One problem is that lockdowns and social distancing enacted to stop the spread of COVID-19 caused the RSV season – typically the winter – to shift considerably during 2020–21. Agha and her colleagues at the Maimonides Children's Hospital closely tracked cases of verified RSV, and found that they dropped to nearly zero in April 2020, staying that low throughout the Northern Hemisphere winter and then peaking the following summer[4]. Such an unpredictable season makes it hard for health-care institutions to be properly prepared, and might mean it takes longer for participants in RSV vaccine trials to be exposed to the virus, which is needed to test the effectiveness of their jab. Whether the RSV season will return to normal remains to be seen, says Agha.

Nevertheless, the success and speed of the COVID-19 vaccines' development was a boon. "That success created awareness at every level, renewed interest to participate in clinical trials, and brought new platforms like mRNA vaccines that might be more efficient ways to stimulate the immune system," says Gurtman.

Moderna's mRNA-based RSV vaccine was in development before SARS-CoV-2 appeared, giving the technology a head start. "The COVID vaccine benefited from the RSV programme, and then it flipped," with the RSV programme benefiting from efficiencies gained from the COVID-19 programme, says Shaw.

Agha says the COVID-19 vaccines exemplified how quickly an effective vaccine can now be made against a respiratory virus. "As infectious disease experts, we're always excited when there is hope in the pipeline to make RSV a preventable disease in the future."

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