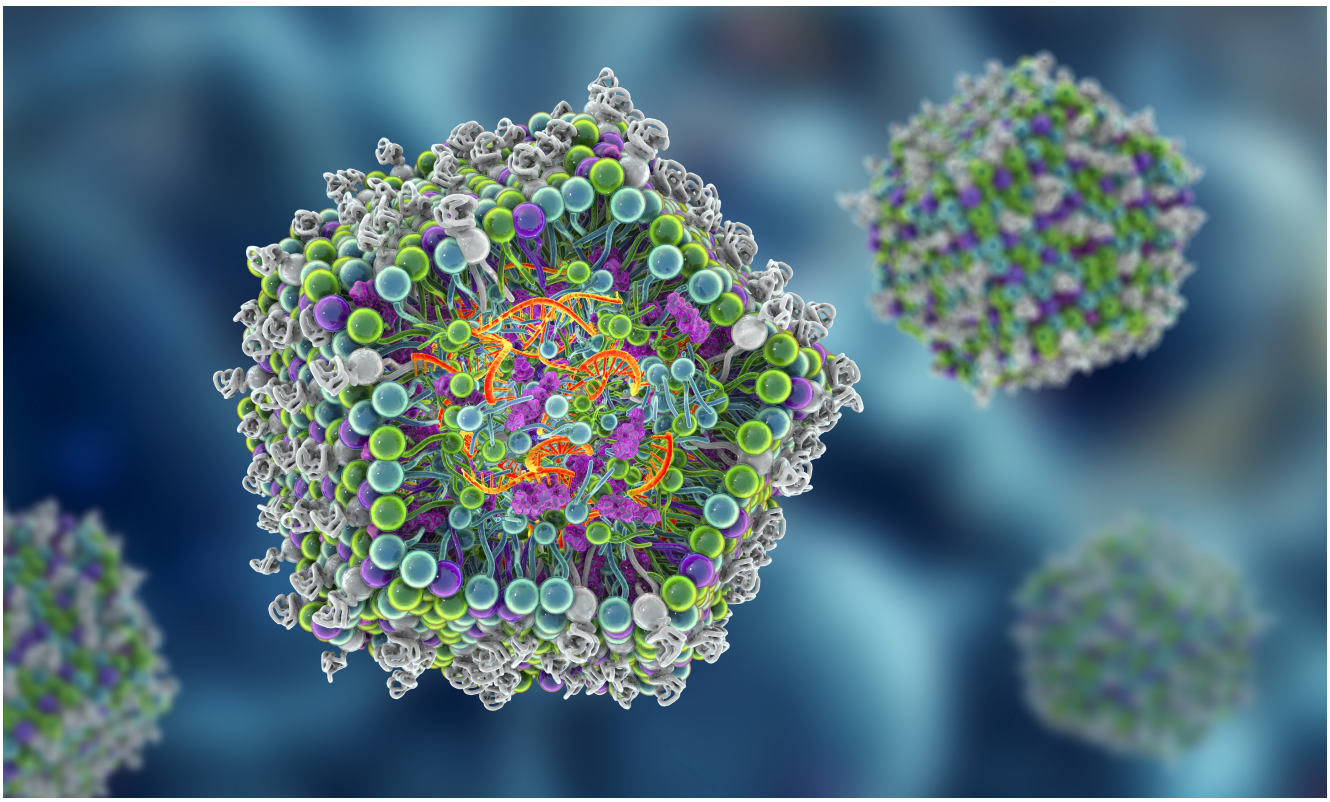
RSV POSES SERIOUS RISKS, BUT NEW VACCINE OPTIONS ARE EMERGING

mRNA technology shows promise for creating long-sought vaccines for RSV, as well as COMBINATION VACCINES THAT TARGET THREE RESPIRATORY VIRUSES—RSV, influenza, and SARS-CoV-2—at once.



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▲ mRNA vaccines deliver lipid nanoparticles containing genetic information that instructs host cells to make the viral antigen. It should be possible to create combination vaccines by mixing together different types of mRNA.

As a paediatrician in training, Jacqueline Miller was struck by how, every winter, she saw a steep rise in the numbers of patients with two conditions: respiratory syncytial virus (RSV) and rotavirus. The hospital was absolutely full to bursting," she recalls. When a rotavirus vaccine was introduced, she saw the number of cases of rotavirus drop dramatically. "But for RSV, there was really nothing," says Miller, now senior vice president and head of development for infectious diseases at Moderna.

Most children contract RSV before age two, according to the CDC, and reinfection is common. RSV typically causes mild, cold-like symptoms, but in vulnerable people it can cause severe disease. According to infectious disease specialist Ann Falsey, a professor at the University of Rochester School of Medicine, "those who are at highest risk of getting very sick with RSV are young babies, typically under six months, people with chronic cardiopulmonary conditions or underlying immune problems, and the elderly". In the US, RSV hospitalizes 60,000–160,000 adults over 65 each year and a further 58,000–80,000 children under 5.

In young children, RSV infection can be severe, because their immunity and many of their systems are still developing. "Our lungs, for example, continue to branch until age seven," Miller says. "RSV infections in early childhood are associated with long-term reactive airway disease and the development of asthma," she notes. A vaccine against RSV will therefore potentially do more than just prevent the initial hospitalization. "It might be keeping a child's lungs healthier throughout their childhood."

In older adults, declining immune function and a higher burden of pulmonary or circulatory conditions make RSV dangerous. Falsey says, "Initially, it's a very snotty, wheezy, phlegmy virus." It begins as a cold but can worsen after a few days; patients' airways can become inflamed and their oxygen levels may plummet. "A certain percentage of people will end up in the hospital." COVID-19 and the flu pose similar risks to these same groups.

Protecting against RSV is difficult. A vaccine was tested in the 1960s, but instead of generating immunity, it caused a higher rate of serious

illness among the vaccinated children. Two recipients died of complications following RSV infection[1], and RSV vaccine development has been approached with great caution ever since.

Options are becoming available. Non-mRNA adult RSV vaccines developed by Pfizer and GSK gained FDA approval in May; for children, a monoclonal antibody and a maternal vaccine have recently become available. However, the paediatric options do not provide complete protection and the monoclonal antibodies, in particular, may have very limited availability outside developed nations. RSV-related childhood mortality is highest in developing countries, says Falsey. More treatment measures are needed, especially paediatric options. In July, Moderna submitted to US, European and Australian agencies for approval of an mRNA RSV vaccine for adults over 60, and they are working on a paediatric mRNA vaccine. Developing mRNA options for RSV may make a combination vaccine against respiratory viruses achievable.

▲ RSV resembles a cold at first, but can worsen after a few days — particularly in older patients.

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THE CASE FOR COMBINATION

COVID-19 changed many things, including the seasonal respiratory virus landscape. Measures such as masking reduced exposure. "When everything went into lockdown the other viruses just disappeared," says Falsey. However, the resulting immunity gap caused a surge of RSV cases in Autumn 2022, coinciding with an early, intense influenza season.

RSV, COVID-19 and the flu have several commonalities. All three are most dangerous for the young and the elderly. All are respiratory viruses. And immunity, even after natural infection, is not lifelong[2]. If more RSV vaccines can be realized, perhaps a combination vaccine could follow. As Andrea Carfi, chief scientific officer, infectious disease, at Moderna, points out "the schedule of vaccination is getting more and more complex". People currently need to get separate RSV, influenza and COVID vaccines. "Being able to combine them in one shot has advantages both for compliance and for offering maximum protection for this population through the winter season," he adds

THE mRNA ADVANTAGE

mRNA vaccines differ from conventional vaccines because they deliver, not the immunity-inducing antigen itself, but instructions for cells to produce the antigen then display it on their surface. All mRNA vaccines, regardless of which pathogen they target, are made of the same material — mRNA encased in a lipid nanoparticle. According to Carfi, "you can just assemble a combination vaccine by mixing the mRNAs."

This offers manufacturing advantages, as well. Conventional vaccine production involves growing cells or viruses; the process differs for every pathogen and usually requires separate facilities for each vaccine. With mRNA vaccines, the process is the same for every pathogen. "What changes is simply the sequence of the mRNA. That allows you to standardize and speed up those processes, because you don't have to reinvent the wheel," Carfi explains. This simplicity could enable building manufacturing facilities in more regions around the world, enabling wider vaccine availability.

Faster development also makes it easier to keep pace with rapidly evolving pathogens like COVID-19 and influenza. "We have shown repeatedly with COVID that in 60 to 90 days, we can have a new vaccine against a specific variant in a clinical study," says Carfi. "In the context of flu, that would allow us to update the vaccine closer to the winter season, and therefore have a better way to predict the circulating virus."

In addition to practical advantages, mRNA vaccines have biology-based benefits. Because they provide a viral protein blueprint, not the protein itself, mRNA vaccines induce an immune response that more closely resembles the response to a natural infection, explains Miller. Because the viral antigen is displayed on the cell surface, mRNA vaccines generate a very potent immune response, inducing both B cells, which generate neutralizing antibodies that bind the pathogen and block its ability to infect cells, and T cells, which attack invading cells directly. This may, Miller says, help to induce better and longer-lasting immunity.

THE F PROTEIN PROBLEM

These advantages of mRNA technology are also what helped Moderna finally solve the RSV vaccine problem. Viruses cause disease by hijacking the cellular machinery to replicate themselves. First, they must enter the host cells, which RSV does using its fusion (F) protein.

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▲ Respiratory syncytial virus can cause severe symptoms in young children, whose immune systems are still developing.

Vaccines induce antibodies that bind to pathogens. Neutralizing antibodies bind to crucial sites, such as part of the F protein, blocking the pathogen from infecting cells; antibodies that bind to non-crucial sites are less effective. By analogy, if you want to immobilize a car, placing the immobilization clamp on the wheel will have a better result than placing it on the windshield wiper. Of course, if the car tends to fold up when it parks, tucking its wheels inside, you have a different problem. This, to extend the analogy, is what the F protein does.

The surface of RSV bristles with F proteins, and when they encounter a potential host cell, they transform from their pre-fusion shape, rapidly and irreversibly unfurling into their elongated post-fusion shape.

Along with its shape, the protein's surface changes, too. "There are some neutralizing sites that are present in both the post- and pre-fusion states," says Carfi. "However, one of. the most important ones is site zero. It is the main target for the most potent neutralizing antibodies, and is present only on the pre-fusion form." Site zero disappears, like the wheels folding into the car, when the protein transforms.

The 1960s RSV vaccine failed because it used formalin-inactivated virus. Although standard, this method can alter the shape of viral surface proteins. A 2016 study showed that after formalin inactivation, RSV surface proteins are predominantly in the post-fusion conformation[1]. Vaccination induced high titers of weak antibodies, and when patients encountered RSV, their immune systems overreacted, resulting in rampant inflammation and enhanced disease. To generate strong neutralizing antibodies, and therefore good immunity, a vaccine must present the pre-fusion protein.

There is a final layer to the challenge: the pre-fusion F conformation is very unstable — it's poised, after all, to launch its attack. But mRNA vaccine technology offers a solution. Similar to work done on the COVID-19 spike protein[3,4], researchers slightly altered the mRNA sequence of the F-protein to produce a stable pre-fusion shape[5].

This evanescent but critical antigen-binding site made RSV vaccine development difficult. However, mRNA technology allows "more hypothesis-driven complex vaccine design", says Carfi, enabling the generation of stable antigens when the wild-type antigens are unstable.

BUILDING BETTER OPTIONS

The team at Moderna is leveraging mRNA technology to work towards a paediatric vaccine for RSV, where Miller and Carfi think need is greatest. Moderna is also trialling several mRNA flu vaccines, as well as new COVID vaccines. If these mRNA vaccines could be combined as a COVID-RSV-flu vaccine, those most at risk for these three common respiratory diseases could benefit from greater protection.

Challenges remain. Although flu and RSV are winter viruses, it's not yet clear whether COVID will share their seasonality, and whether that will matter, says Falsey. Another potential issue is whether, with combination vaccines, a stronger immune response to one pathogen might dampen the response to the others. "It's complex," she notes.

At a job interview around 20 years ago, early in her career within the pharmaceutical industry, Miller was asked which vaccine she would design, given her pick of pathogens. When she said RSV, her interviewer called her "crazy". That moment stayed with her a long time, even causing her to wonder whether it would ever be possible to develop vaccines for paediatric RSV. Now, Miller says, "It's really with this technology that I feel we finally have a chance." ■

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