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The Next Frontier in RSV Prevention—A Vaccine for Young Children

The journey toward an RSV vaccine for children has been wrought with tragedy and setbacks. But six decades after scientists embarked on that path, they are nearing the finish line

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Scientists have made monumental strides in their quest to protect vulnerable babies from respiratory syncytial virus (RSV): in just the past few years, monoclonal antibody injections for infants and a maternal vaccine that delivers protection through the placenta have substantially reduced infant hospitalizations and deaths.

But researchers still are grasping at a broader goal: to make a vaccine available for toddlers and preschoolers, who are also vulnerable to severe RSV disease.

That breakthrough, medical researchers say, could be right around the corner.

The most promising candidate is a two-dose vaccine administered as a nasal spray. Should it prove safe and effective in clinical trials, which are currently underway, it could help prevent severe RSV disease in children over the first several years of their lives—not just the first months.

"Where we're heading next is the possibility of having true vaccines, not monoclonal antibodies, for kids after their first birthday," says James Campbell, an infectious disease pediatrician at the University of Maryland.

Before the arrival in 2023 of Pfizer's maternal vaccine and a preventive monoclonal antibody drug called nirsevimab, developed by Sanofi and AstraZeneca, RSV brought an annual scourge upon children's hospitals. Historically, it has been the number one cause of infant hospitalization; about 2 to 3 percent of infants in their first year of life are hospitalized with RSV each year in the U.S.

During the fall and early winter, RSV "fills up our hospitals with sick children and may potentially have long-term ramifications in terms of a higher likelihood of wheezing," says Jennifer Nayak, an infectious disease pediatrician at the University of Rochester Medical Center. "The fact that there are prevention strategies out there ... has actually moved the landscape quite far in this area."

A second monoclonal antibody, Merck's clesrovimab, was approved for use in infants this year.

The monoclonal antibodies and maternal vaccination both protect babies through passive immunization, which means the infants are given antibodies. For RSV, the antibodies are either directly injected as nirsevimab or clesrovimab, or passed through the placenta after the vaccine is given during pregnancy. Those antibodies are ready to fight the disease, but they eventually wear off. Because infants do not receive a vaccine that prompts their immune systems to make their own antibodies—known as active immunity—they aren't primed to fight RSV after the passively received antibodies have waned.

"Unlike active immunization, where you establish immune memory, passive immunization doesn't do that," Nayak says.

And while RSV is the most dangerous to babies, it's far from harmless in older kids.

A Centers for Disease Control and Prevention analysis of data from two different groups of children in the U.S. revealed this stark reality. In it, scientists found that RSV-related hospitalization rates among infants seven months and younger decreased by about 28 and 43 percent, respectively, during the peak of the 2024–2025 RSV season, when both preventatives were

available, compared with pre-COVID-pandemic RSV seasons from 2018 to 2020.

Those same statistics also underscored the ongoing vulnerability of older children: While RSV-related hospitalizations declined in infants, they increased in older kids. For children aged eight months to 19 months, hospitalization rates from RSV were 26 and 34 percent higher in the two groups, respectively, in the 2024–2025 season than they were in 2018–2020. In one of the cohorts, the hospitalization rate rose from five per 1,000 children to nearly seven. Hospitalization rates for 20- to 59-month-olds in the two groups were 1.7 and 2.5 per 1,000 children, 55 and 67 percent higher than they were in those prepandemic seasons.

The existing passive immunization products are reducing the impact on infants, but "what we want to do for them after that is going to be the question," Campbell says. "We all know that in the second and third season, there is still a burden in two-year-olds and three-year-olds."

The disease is even more deadly in low- and middle-income countries that don't have the resources to provide supportive care to children with severe infections. Worldwide, RSV is responsible for more than 3.6 million hospitalizations and about 100,000 deaths in children under age five each year, according to the World Health Organization.

In a separate global estimate, a little more than half of pediatric deaths in hospitals from RSV were in children older than six months.

Researchers say this points to the need to have products to protect children once the passive immunity from monoclonal antibodies or maternal immunization wears off.

“An active immunization strategy would allow us to really protect those infants going forward—both infants in their second RSV season, who may not have been exposed to RSV and now remain at high risk, as well as kids with other risk factors, such as prematurity and chronic lung disease,” Nayak says.

Attempts to develop an RSV vaccine for young children date back to the 1960s, less than a decade after scientists first identified the virus. But unexpected tragedy quickly stopped development in its tracks: During clinical trials for a vaccine that contained an inactivated form of RSV, 80 percent of the vaccinated toddlers were hospitalized when they became naturally infected with the virus, and two died from the disease. No deaths occurred among the children who received the placebo, and hospitalizations among children in the placebo group were also much lower when they encountered the virus naturally.

It took decades to understand what had gone wrong, but scientists eventually figured out that the vaccinated children developed such severe disease because of a phenomenon called antibody-dep endent enhancement. The antibodies their immune systems made in response to the vaccine did not attack the virus adequately and actually made their disease worse.

Because the causes of antibody-dependent enhancement vary dep ending on the disease, it took more time to discover why it occurred with RSV. Solving that mystery took many years and led to the successful development of today’s monoclonal antibodies and RSV vaccines for pregnant and older adults. But the chilling effect on pediatric RSV vaccine development following the 1960s disaster has never fully dissipated.

“There’s just a lot of caution around moving these products forward and making sure that doesn’t happen again,” says Coleen Cunningham, a

pediatrician at the University of California, Irvine, and Rady Children's Health.

Concerns about severe disease halted development of a recent mRNA vaccine against RSV last year. In babies aged five to eight months who developed symptomatic RSV, 26 percent of those who had received a low dose of the vaccine developed a severe case of RSV, compared with 8 percent of those who received the placebo. Effectiveness was also an issue in that study: the children who had received nirsevimab more than six months before getting the vaccine did not have as strong an immune response to the vaccine as those who had never received the monoclonal antibody.

So any vaccine for older children needs to be effective even for those who have received protection from the maternal vaccine or monoclonal antibodies earlier in life.

"You really want to target getting some other form of protection that will be more long-lasting by the time that monoclonal antibody has worn off," Cunningham says. "Antibodies aren't perfect protection for RSV. You've had RSV dozens of times, and you'll still get RSV again next winter when it goes through the community. We know this isn't like measles or chicken pox, where once you have the antibody, you really aren't going to get it."

Given the past challenges with inactivated and mRNA vaccines, researchers have largely focused on live, attenuated vaccines against RSV. In this kind of RSV vaccine, the virus has been weakened so much that it cannot cause disease. Yet it still prompts the immune system to make antibodies against it.

"With the live, attenuated vaccines, the immune response is more like the immune response you get to a natural infection," Cunningham says. So far,

several studies on these live, attenuated RSV vaccines haven't shown even a hint of related severe disease, she adds.

To improve their chances of creating a successful vaccine, scientists have also changed the type of immunity they are targeting. The immune system has different ways of fending off attacks from pathogens. Most people are familiar with the one used by most existing vaccines, called systemic immunity. With systemic immunity, the immune system makes antibodies in response to a vaccine and sends them throughout the body in the blood.

But another type of immune response, called mucosal immunity, occurs only at points of entry into the body. Mucous membranes—also called mucosa—are the moist tissue that line openings into the body, and are present in the nose, mouth, ears and eyes. A mucosal response involves a different type of antibody that mostly remains within the mucosa. The idea is to neutralize the virus just as it is trying to enter the body.

The pathway to the digestive system from the mouth contains mucosal surfaces all the way into the gut, and some of the few approved vaccines that target mucosal immunity are live vaccines against gastrointestinal diseases, such as the rotavirus vaccine and the oral polio vaccine.

But only one vaccine targeting mucosal immunity has been develop ed against a respiratory disease, the intranasal flu vaccine, which triggers the same mucosal response in the nose as an influenza virus does when it enters the body in that way.

That's the goal of a live intranasal RSV vaccine.

When the weakened virus enters the nose, it will multiply and trigger an immune response, just like when someone becomes infected with RSV

naturally, Cunningham says. “It’s going to replicate in the nasal mucosa, and if you’re using an attenuated vaccine, you want it to replicate,” Cunningham says. Nasal vaccines come with another big advantage: kids and parents often prefer them because they’re easier to administer and less painful than shots.

While there are a handful of RSV vaccine candidates for children in phase 1 and 2 studies, only one has reached phase 3—a live, attenuated nasal vaccine, administered in two doses eight weeks apart, that was developed by Sanofi and based on research from teams that included Cunningham and National Institutes of Health scientists.

An early trial tested the safety and the immune system response of the vaccine in 180 children aged six to 18 months in the U.S., Chile and Honduras. One third of the participants received a low dose of the intranasal vaccine, one third received a high dose of the vaccine and one third received a placebo.

The adverse events that occurred after both a first dose and a second dose were similar to those of other vaccines, including the intranasal flu vaccine, according to results published in August in *NEJM Evidence*. Side effects included nasal congestion, fever, tiredness, loss of appetite and irritability. The researchers also measured the antibodies produced in response to the vaccine and found that, after the second dose, approximately two thirds of the vaccinated patients had four times as many antibodies against RSV as they did before the RSV vaccine.

Those findings don’t yet prove that the vaccine will prevent severe disease from RSV. The next step will be to test the vaccine’s ability to prevent hospitalizations and possibly deaths in a trial involving hundreds or thousands of children.

As Peter Wright, a pediatrician at Dartmouth College, mentions in an editorial also published in *NEJM Evidence*, researchers need to make sure the vaccine is safe in larger groups of children and to determine the most appropriate age for children to receive the vaccine. They also need to find out how long immunity lasts.

Even with these outstanding questions, the results represent "one more step in a long line of steps toward that answer" of whether a live nasal vaccine can prevent severe RSV disease in toddlers, Wright explained in the editorial. And that's further than almost any other RSV vaccine has gotten since those fateful clinical trials six decades ago.

"The advances we have had in the last three years have been astronomical, and I think those advances are going to fuel energy behind finding an active vaccine," Nayak says. "We're learning from what we knew before, from what's failed in the past, and hopefully we'll have a path forward."

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