What RSV interventions are in the research pipeline?

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Reduced immunity in the wake of the COVID-19 pandemic has contributed to large surges in respiratory syncytial virus (RSV) infections this year, overwhelming pediatric hospitals.

While RSV mostly causes mild, cold-like symptoms in older children and adults, it causes serious illness requiring hospitalization in roughly one in 56 otherwise healthy infants, according to European data published in *Lancet Respiratory Medicine*. The risk of severe disease is highest among premature infants and those with heart and lung disease. Severe illness can also occur in older adults and those with weakened immune systems or underlying heart and lung conditions.

Yet, interventions against RSV remain limited, and treatment is mostly supportive.

Palivizumab, a monoclonal antibody, is the only intervention to prevent RSV currently available in Canada. Although thought to prevent 40%–80% of RSV hospitalizations in infants, palivizumab is expensive and must be given via monthly injections, and its use is limited to infants and children at highest risk of severe illness.

However, several new interventions are in the works that could potentially come to market in Canada by the next RSV season.

Long-acting monoclonal antibodies

Nirsevimab is a longer-acting monoclonal antibody developed by AstraZeneca and Sanofi to protect infants during their first RSV season with a single dose.

Like palivizumab, nirsevimab binds to the fusion protein on the surface of the virus, blocking it from being able to attach to cells. Unlike palivizumab, a single treatment with nirsevimab has been shown in phase 3 trials to reduce the risk of RSV requiring medical attention or hospitalization for up to 150 days — long enough to last through an entire season.

Immunization advisory committees will likely be considering use of nirsevimab in all infants, "including the vast majority who are not eligible for palivizumab," said Pascal Lavoie of the BC RSV Immunoprophylaxis Program.

It's not clear how much the intervention will cost, and negotiations over its rollout in Canada are ongoing, Lavoie said. However, "that's probably going to happen soon."

With a reported efficacy of 74.5%, it's estimated that universal immunization of infants with nirsevimab during their first RSV season could prevent nearly 25 000 hospitalizations and save US$612 million in the United States alone.

According to Lavoie, a longer window of protection for a wider number of children could make a major difference in years when RSV season hits early. Typically, the season starts in early November, give or take a few weeks. However, last year, it started in August, with five times as many cases as usual, Lavoie said.

"We're not used to running palivizumab prevention programs in the summer, so I think that's where the long-acting monoclonal [nirsevimab] might be advantageous," he says. "Because you don't need to give it every month during the peak season. You only give it once and it lasts for several months."

Maternal vaccination

Maternal vaccinations are likely the next preventive intervention coming after long-acting monoclonal antibodies. Given during the third trimester of pregnancy, maternal vaccination works by inducing antibodies in the pregnant parent that are transferred to the fetus via the placenta.

In November, Pfizer shared preliminary results from a phase 3 trial for its RSV vaccine candidate — currently the only one in the approval pipeline for use in both pregnant people and older adults.

According to Pfizer, the vaccine candidate's efficacy against medically attended illness due to RSV was 81.8% in newborns whose mothers received the shots during pregnancy, with "no safety concerns for both vaccinated individuals and their newborns."

Based on these results, Pfizer plans to submit the vaccine candidate for approval in the United States by the end of 2022, and to other regulatory authorities in the coming months.

Full peer-reviewed results haven't been published yet, however. "We're all waiting to see the data and what the price will be," Lavoie said.

One-time maternal vaccinations could provide an alternative for parents who may be wary of monoclonal antibody shots for their children "if it's only going to prevent the infection for one season," Lavoie said.

"The caveat to this is whether [maternal vaccination] will work as well with premature babies, for example, who don't get [maternal] antibodies transferred at the same rate because that happens late in pregnancy," Lavoie said.

Joan Robinson, a professor in the department of pediatrics at the University of Alberta, said a combination of interventions will likely be required to maximize protection.

"I don't think we'll decide between the monoclonal antibody or maternal vaccine and use only one or the other," says Robinson. "One could imagine the

vaccine being used in pregnant women, and then maybe nirsevimab being given to infants who were born before we would think they had enough antibodies that have crossed the placenta… or it might be given to infants whose mothers chose not to be vaccinated."

Other vaccines

Other vaccines are still a few years away from meeting the bar for approval, though Lavoie said a few are in the works which appear to "generate good immunogenicity," at least in preclinical studies.

Moderna is developing several mRNA vaccines for RSV, including a three-in-one combined shot against RSV, COVID-19 and influenza that has triggered a "very strong immune response" in preclinical studies, according to the company.

Moderna plans to submit the three-in-one vaccine candidate to Health Canada for regulatory approval within a year, but it's not clear who specifically the vaccine is for.

Moderna has also started a phase 3 trial of an RSV vaccine for adults over age 60.

GSK recently announced preliminary phase 3 trial results for its RSV vaccine candidate for people over 60, showing an overall efficacy of 82.6% against RSV lower respiratory tract disease, and 94.1% against severe disease. The company submitted the vaccine candidate to Health Canada for regulatory approval in November.

Such announcements should be taken with a grain of salt, however, until the full peer-reviewed trial data become available.

Early promotion of vaccine candidates has raised concerns among some experts about "science by press release," particularly as some pharmaceutical stock prices have flagged recently alongside declining uptake of COVID-19 vaccines.

Meanwhile, "it's still not clear exactly the extent of the burden of RSV in the elderly," said Jesse Papenburg, a pediatric infectious disease physician at the Montreal Children's Hospital and assistant professor at McGill University. "It's not as high as influenza, I don't think, but it is up there."

Why are interventions for RSV so limited?

Part of the reason why it's been so difficult to develop interventions to treat RSV is that infants at the highest risk of severe disease don't respond as well to vaccinations as older children and adults, Papenburg said. Hence, the focus has been on "indirect methods" of protecting infants via vaccination of expecting parents or passive immunization with monoclonal antibodies.

A disastrous first attempt at testing an RSV vaccine in infants in the 1960s "set back RSV vaccine development in infants for decades," Papenburg explained.

That vaccine candidate not only failed to induce an immune response sufficient to neutralize the virus but also provoked a "very fulminant inflammatory response," Papenburg said.

Pinning down RSV's shapeshifting fusion proteins may prove a game-changer. Before these fusion proteins bind to a host cell, they exist in a form containing a major "antigenic site" or target for the body's neutralizing antibodies, but once the proteins bind to a host cell that target is lost, eliciting a different immune response.

Older RSV vaccine candidates likely targeted the "postfusion" form of these proteins, which may be why they failed to neutralize the virus. But newer vaccines and antibody treatments in the research pipeline target the prefusion form.

The price of new interventions is another unknown that could have a major impact on their use, especially when it comes to monoclonal antibodies.

"How [monoclonal antibodies] will be used is still a big question mark," Papenburg said. "There are modelling studies trying to [evaluate] whether it's more cost-effective to use in a targeted manner only during or preceding RSV season for a certain amount of time to optimize [protection for infants] during their highest risk period, particularly during those first six months of life."

Papenburg also noted that the economic calculus may be different for rich countries like Canada, where deaths from RSV are relatively infrequent because of access to supportive care, versus poorer countries where RSV remains a leading cause of death in young children.

"These vaccines could potentially be hugely impactful from a global health perspective," he said. "In Canada, we're talking about reductions of hospitalizations and reductions of medically-attended lower respiratory tract infections, bronchitis, and pneumonia. But in low- and middle-income countries, we'd anticipate a reduction in childhood mortality."

Diana Duong, *CMAJ*

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