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# Perspectives on preventing RSV disease

**T**he COVID-19 pandemic taught the world a few lessons. First, even in this modern age, new viruses can arise, cause widespread illness, and disrupt society. And second, vaccines are critically important in not only preventing disease in individuals but also in building herd immunity, reducing the transmission of the virus within communities, and thereby promoting global health.

We ought to heed these lessons as we face other respiratory viruses, in particular respiratory syncytial virus (RSV), the focus of this issue of *Cleveland Clinic Journal of Medicine*.

## ■ IN THIS ISSUE... EMERGING RESPIRATORY DISEASES

COVID-19 vaccines were developed in record time and prevented millions of hospitalizations and deaths. For this we can thank scientific and technological advances such as mRNA vaccines.<sup>1</sup> The Nobel Prize in Medicine in 2023 was awarded to Katalin Karikó and Drew Weissman for their discoveries concerning nucleoside base modifications that enabled the development of effective mRNA vaccines against COVID-19,<sup>2</sup> and, potentially, other infectious diseases, accelerating progress in the field of vaccinology. These advances will be handy when (not if) new viral diseases come along, some of which we will talk about in this issue.

## ■ RESPIRATORY VACCINES FOR THE CLINICIAN

Vaccination for respiratory viruses is one of the most important interventions for preventing infection and disease. Influenza and COVID-19 can result in severe disease, especially among unvaccinated persons. Infants, older adults, pregnant people, and people with certain underlying medical conditions are at higher risk of severe COVID-19 and influenza. The influenza and COVID-19 vaccines reduce the risk of severe disease, including pneumonia, hospitalization, and death. Vaccination for COVID-19

can also reduce the risk of multisystem inflammatory syndrome in children and post-COVID conditions. Vaccination against both COVID-19 and influenza is recommended for all people 6 months of age and older, including those who are pregnant.

## ■ RSV IN THE YOUNG AND OLD

RSV is a common respiratory pathogen that can cause severe illness, particularly in infants, older adults, and those with weakened immune systems. It affects millions of people worldwide every year and causes up to 80,000 hospitalizations in young children in the United States and 10,000 deaths in American adults age 65 and older.<sup>3</sup> RSV is the leading cause of infant hospitalization in the United States and causes significant morbidity even among infants born at term.<sup>4</sup> These data demonstrate the critical need for preventive treatments.

## ■ NEW RSV VACCINES

Two strategies for preventing RSV were introduced in 2023: active immunization with RSV prefusion F vaccines and passive immunization with a long-acting RSV monoclonal antibody. They are important advancements for protecting vulnerable populations. At this time, RSV immunizations (active or passive) are recommended to protect those at highest risk for medically attended illness: elderly adults, infants, and young children.

Effective RSV vaccines were made possible by the discovery and crystallization of a surface glycoprotein of the RSV virion, specifically, the prefusion conformation of RSV-F, which is the primary antigenic component of the 2 newly approved subunit vaccines: RSVpreF3 (Arexvy; GSK) and RSVpreF (Abrysvo; Pfizer). Both vaccines are licensed by the US Food and Drug Administration (FDA) and recommended by the US Centers for Disease Control and Prevention (CDC) for adults age 60 and older.<sup>5</sup>

But vaccination needs to be a shared decision, based

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on a discussion between the healthcare provider and the patient. It may be informed by the patient's risk of severe RSV disease and their characteristics, values, and preferences; the healthcare provider's clinical discretion; and the characteristics of the vaccine.

RSVpreF is the only RSV vaccine approved by the FDA for use in pregnant women to protect their unborn infants from RSV via transplacental transfer of antibodies. Passive immunization is another strategy that can be used to protect infants and young children from RSV. The first RSV-specific monoclonal antibody, palivizumab (Synagis; Sobi), was approved in 1998. However, its use was limited to infants and young children at the highest risk of RSV-related hospitalization, due to its high cost and need for monthly intramuscular injections throughout the RSV season.<sup>6</sup> In 2023, nirsevimab-alip (Beyfortus; Sanofi) was approved for use in infants and children 0 to 19 months of age. Compared with palivizumab, nirsevimab-alip is longer-acting, and a single dose provides protection for the duration of the RSV season.

Maternal immunization with RSVpreF and infant immunization with nirsevimab-alip have both been shown to be safe and highly effective in preventing RSV medically attended lower respiratory tract infections in the first year of life. The CDC recommends a 2-pronged approach to RSV prevention in infants using these 2 strategies. Seasonal administration (September through January) of the RSVpreF vaccine is recommended for pregnant people at 32 to 36 weeks gestation.<sup>7</sup> Infants 0 to 8 months of age born to unvaccinated mothers should receive 1 dose of nirsevimab-alip during or before entering their first RSV season.<sup>8</sup> Most infants do not need to receive both active maternal immunization and passive infant immunization. Detailed information about the efficacy, safety, use, and timing of infant RSV prevention strategies will be provided within this supplement.

### ■ TESTING FOR RESPIRATORY VIRUSES

The role of the microbiology laboratory in guiding the clinician in selecting appropriate testing for respiratory viruses will also be addressed in the supplement. At the bedside it is very difficult to distinguish between upper respiratory tract infections caused by influenza, SARS CoV-2, RSV, or other respiratory viruses. Identifying the pathogen in a timely fashion can help with the decision to use antivirals to treat influenza and COVID-19, as well as with infection prevention practices. In the 2023, Cleveland Clinic started routine outpatient testing for adults for RSV, influenza, and SARS CoV-2 for the respiratory season.

Notably, wastewater surveillance, ie, systematically checking for infectious agents in the sewer system, provided a valuable tool for monitoring SARS-CoV-2 circulation during the COVID-19 pandemic; surveillance has expanded from 20 to 53 jurisdictions across the United States, with increasing capacity to test for more respiratory pathogens.<sup>9</sup> Wastewater surveillance is passive and can sample the populations regardless of access to medical care, and is useful for detecting an acceleration of virus spread—not for how much virus is circulating. This information helps local health departments and has been used to provide tailored metrics and messaging to communities, providers, and healthcare systems to improve awareness and preparedness.

### ■ VACCINE HESITANCY

Another important topic addressed in this supplement is vaccine hesitancy and resistance. Vaccine hesitancy is a state of indecision and uncertainty about whether to be vaccinated, before a patient decides yes or no.<sup>10</sup>

Vaccine hesitancy, powered by digital media platforms, spiked globally during the COVID-19 pandemic. This coincided with increased public distrust of the government and of expert guidance from healthcare providers. Although immunization is one of the most successful public health interventions, worldwide vaccine coverage had reached a plateau in the decade before COVID-19 and declined during the pandemic, but seems to be recovering now.<sup>11</sup> Misconceptions about vaccines and novel vaccine platforms may have contributed to vaccine hesitancy.

Vaccination rates for the updated 2023–24 COVID-19 vaccine remain low. As of December 2, 2023, only 17.2% of adults older than 18 years, including 36% of adults age 65 and older and 9.6% of pregnant adults, had received the updated COVID-19 dose.<sup>12</sup> Similarly, uptake of the RSV vaccine among adults older than 60 years remains low. As of December 2, 2023, only 15.9% of US adults age 60 and older reported receiving an RSV vaccine.<sup>12</sup> As of January 24, 2024, only 16.2% of pregnant women elected to receive the RSVpreF vaccine.<sup>13</sup> Meanwhile, 40.5% of eligible infants received nirsevimab-alip, suggesting decreased hesitancy with passive versus active immunization strategies.<sup>14</sup> Key reasons for low uptake of influenza, COVID-19, and RSV vaccines based on survey results include lack of provider recommendation, concerns or issues about unknown serious side effects, occurrence of mild side effects, and lack of time or forgetting.

## ■ UNANSWERED QUESTIONS

Many considerations and potential unanswered questions that are relevant to the new RSV immunizations will be addressed in this supplement, including the duration of effectiveness, the optimal process for shared decision-making between clinician and patient, real-world effectiveness and postmarketing safety surveillance, and vaccine hesitancy and resistance.

One of the key concerns is how long the RSVpreF and RSVpreF3 vaccines will provide immunity or protection against infection. We still do not know whether the vaccine provides long-term immunity or if booster shots will be required.

## ■ COMMUNICATION IS IMPORTANT

Shared decision-making involves engaging patients in discussions about their healthcare and jointly deciding on the best course of action. For RSV vaccines, healthcare workers may face challenges in conveying complex information to patients, especially regarding potential side effects. Monitoring the vaccine's performance in real-world settings is crucial to understand how well it works outside of clinical trials. Additionally, ongoing surveillance for any unexpected side effects or safety concerns is essential. Understanding and addressing public concerns, misinformation, and vaccine hesitancy are critical for successful vaccine implementation.

Healthcare workers may need effective communication strategies to build trust and encourage vaccine acceptance. Messaging and trust are important tools to combat vaccine hesitancy. Clearly the most effective way for the government to protect citizens is by convincing, not mandating, them to choose measures to protect themselves. Healthcare providers will continue to have an important role—safe and effective vaccines will be of limited impact if not accepted.<sup>15</sup>

## ■ DISCLOSURES

Dr. Gordon reports no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest. Dr. Rivard has disclosed being an advisor or review panel participant for Pfizer.

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