Review Article

Evolving Strategies for Respiratory Syncytial Virus (RSV): A Review Article of Preventive Agents and Vaccines for RSV

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Abstract

Objective: The objective was to describe the pharmacology, efficacy, safety, and recommendations for the use of newly approved preventive agents and vaccines for respiratory syncytial virus (RSV) and discuss their uptake during the 2023 to 2024 RSV season. **Data sources:** A literature search of PubMed was performed (January 2020 to February 2024) with the search terms RSV vaccine, preventive antibody, and RSV prevention. Utilization data were collected from TriNetX using the US Collaborative Network (May 2024) using the terms palivizumab, nirsevimab, and RSV prefusion F protein. **Study selection and data extraction:** Relevant English-language studies assessing the use of Food and Drug Administration (FDA)-approved preventive agents and vaccines for RSV in humans were considered. Population-level utilization data were extracted from TriNetX. **Data synthesis:** Nirsevimab was observed to have noninferior efficacy and safety compared with palivizumab with less frequent administration. Nirsevimab is recommended to replace palivizumab for RSV prophylaxis in all eligible infants. Arexvy and Abrysvo are effective at reducing the risk of RSV infection in adults aged ≥60 years, and Arexvy is indicated in adults aged ≥50 years. These vaccines are equally recommended for use in the elderly adult population, but only Abrysvo is indicated and recommended for maternal administration. Most infants only require prophylaxis through either maternal RSV vaccination or nirsevimab administration **Relevance to patient care and clinical practice:** This review compares the indications for use, guideline recommendations, and clinical trial efficacy and safety data for palivizumab, nirsevimab, Abrysvo, and Arexvy to guide clinical decision-making. **Conclusions:** Novel RSV preventive agents, including Abrysvo, Arexvy, and nirsevimab, offer less burdensome dosing and administration compared with palivizumab, show promising efficacy and safety data, and expand the populations eligible for RSV prevention. Updated clinical guidance supports immediate adoption of these agents in practice, and population-level data suggest these agents were used during the 2023 to 2024 RSV season.

Keywords

respiratory infections, preventative medicine, vaccines, infectious disease, immunizations, clinical practice guidelines, clinical pharmacy, evidence-based medicine, prescribing patterns, drug information

Introduction

Respiratory syncytial virus (RSV) is the most common cause of upper and lower respiratory tract infections in infants and young children and is a leading cause of acute respiratory infections worldwide.[1-3] Many infants will experience RSV infection by their second year of life.[4] Although RSV particularly affects infants and young children, older adults and individuals with compromised immune systems are also vulnerable to RSV infections and associated complications. In the United States, RSV is estimated to be responsible for 58 000 to 80 000 hospitalizations and 100 to 300 deaths in children aged <5 years and 60 000 to 160 000 hospitalizations and 6000 to 10 000 deaths in adults aged ≥65 years each year.[5-12]

RSV exhibits a seasonal pattern, with the highest activity occurring during the fall and winter months in temperate climates.[13] In most regions of the United States, the onset and offset of the RSV season are typically from October or November through March or April, with peak disease activity in December or January.[13] In tropical climates such as Florida, seasonal patterns of RSV differ,

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and circulation can occur year-round.[13] Data from polymerase chain reaction (PCR) testing reported to the National Respiratory and Enteric Virus Surveillance System (NREVSS) in the United States is used to track the RSV season each year, with the start and end of the season distinguished by positive PCR test rates crossing above or below 3%.[13] Although social distancing during the COVID-19 pandemic caused deviations in RSV circulation, regional RSV data reported to NREVSS for the current 2023 to 2024 season appear to demonstrate a continued shift back toward typical seasonality.[13,14]

Clinical manifestations of RSV infection range from mild upper respiratory symptoms, such as rhinorrhea and cough, to severe lower respiratory tract disease (LRTD) characterized by wheezing, dyspnea, and respiratory distress.[15] Bronchiolitis is the hallmark manifestation of severe RSV disease in infants and young children and often necessitates hospitalization and supportive care.[15,16] It is common for RSV infection to occur concomitantly with other viruses, and the presence of multiple respiratory viruses has been shown to further increase disease severity.[17,18] RSV infection may also result in long-term respiratory sequelae such as recurrent wheezing and asthma, particularly in children with severe bronchiolitis.[19] Moreover, severe RSV disease can lead to respiratory failure, secondary bacterial infections, and cardiovascular or neurological complications, imposing a substantial clinical and economic burden on affected individuals and health care systems.[19]

Certain factors predispose individuals to severe RSV infection, including premature birth, age $<$6 months, bronchopulmonary dysplasia (BPD) or chronic lung disease (CLD), congenital heart disease (CHD), congenital abnormalities of the airway, cystic fibrosis, immunodeficiency, some genetic diseases such as Down's syndrome, and exposure to environmental tobacco smoke.[16] Crowded living conditions, daycare attendance, and inadequate breastfeeding practices also contribute to heightened RSV susceptibility and transmission among vulnerable populations.[16] Infants of American Indian, Alaskan Native, or European heritage have been identified as having an increased likelihood for hospitalization due to RSV infection compared with the general infant population.[20,21] Additional RSV risk factors for adults include those with chronic conditions such as asthma, chronic obstructive pulmonary disease, coronary artery disease, congestive heart failure, diabetes, neurologic or neuromuscular conditions, and those with hematologic, kidney, or liver disorders.[22,23] Hospitalization rates among adults also increase proportionally with age, with the highest rates occurring in those aged $\geq$75 years.[24]

Despite the significant burden RSV has on population health, there are no medications available for its treatment apart from symptomatic management with corticosteroids, diuretics, and supplemental oxygen.[16] Thus, disease prevention plays an extremely significant role in reducing the impact of RSV on vulnerable populations. There continues to be a need for additional strategies to reduce the severity, hospitalizations, morbidity, and mortality associated with RSV, with a particular focus needed on fair global distribution to alleviate the disproportionate impact of RSV in developing countries.[25,26] Prior to 2023, palivizumab was the only prophylactic agent available to patients and is indicated for use in narrow patient populations.[16,27,28] In addition, palivizumab is a costly medication that requires monthly administration by a health care provider during the RSV season and offers limited benefits with no reduction in mortality.[27] Newly available immunoprophylactic agents approved by the Food and Drug Administration (FDA) in 2023, including Arexvy, Abrysvo, and nirsevimab, may address some of these unmet needs.[29-31] This article reviews the pharmacology, clinical efficacy, and safety of these newly approved agents. However, RSV prophylaxis continues to evolve, with recent FDA approval of the mRESVIA RSV vaccine in May 2024.[32] The mRESVIA vaccine is not discussed as part of this review due to the timing of its approval relative to the completion of this review and the lack of uptake data available for comparison.

Data Sources

A literature search was conducted in PubMed (January 2020 to February 2024) with the search terms *RSV vaccine*, *preventive antibody*, and *RSV prevention*. Utilization data were collected from TriNetX using the US Collaborative Network (as of May 2024) with natural language processing using the terms *palivizumab*, *nirsevimab*, and *respiratory syncytial virus prefusion F protein*.

Study Selection and Data Extraction

The literature search included all relevant clinical studies that assessed the efficacy, immunogenicity, and/or safety of preventive treatments for RSV. Limits applied included the following: English language, data from human subjects, FDA-approved therapies, and experimental study design. Utilization data were extracted from TriNetX using the same search terms with results for respiratory syncytial virus prefusion F protein filtered to specify Abrysvo and Arexvy.

Pharmacology

RSV is a negative-sense, single-stranded RNA virus with 2 subtypes, A and B, that are dependent on the reactivity of the F and G surface proteins.[25] Both subtypes are known to cause disease in humans and circulate at varying levels depending on the RSV season.[25]

Arexvy and Abrysvo

Arexvy consists of recombinant RSVPreF3 antigen with $AS01_E$ adjuvant, administered as a single dose.[33] The RSV fusion protein is derived from the RSV fusion (F) surface glycoprotein of an RSV-A strain and stabilized in the prefusion trimeric conformation (RSVPreF3) of the naturally occurring F protein (120 μg).[33] Abrysvo is a bivalent recombinant stabilized prefusion F protein subunit vaccine (RSVpreF).[33] It consists of equal amounts of prefusion F antigens from the 2 major RSV subgroups: RSV-A prefusion F (60 μg) and RSV-B prefusion F (60 μg).[33] In adults aged ≥60 years, each of the subunit vaccines, Abrysvo and Arexvy, function via active immunization by eliciting an immune response that helps prevent RSV-associated LRTD.[29,30] Abrysvo has also been shown to provide passive immunization of infants and neonates following administration to the pregnant mother.[29] The immune response to RSV subunit vaccines has been measured by assessing the increase in the geometric mean titer of RSV-A and RSV-B neutralizing antibodies (nAbs). Both RSV subunit vaccines, Abrysvo and Arexvy, have been shown to increase antibody levels and CD4+ T levels compared to prevaccination with limited CD8+ T-cell response in adults.[34,35] In expecting mothers, at day 31 postvaccination with Abrysvo, nAb titers increased 12.7-fold and 14.9-fold against RSV-A and 10.6-fold and 13.2-fold against RSV-B in the 60 and 120 μg RSVPreF3 groups, respectively.[34] In both mothers and infants, nAb titers at day 43 postdelivery remained 8.9-fold to 10.0-fold over prevaccination levels.[36]

Nirsevimab

Nirsevimab is a recombinant human immunoglobulin (Ig) G1 monoclonal antibody that binds to the RSV fusion protein and locks the RSV fusion protein in the prefusion conformation to block entry into host cells.[37] Nirsevimab can be administered to children up to 24 months of age, and in clinical trials, serum concentrations have been shown to decrease linearly over time.[31] Mean half-life of nirsevimab has been determined to be approximately 71 days.[31] At day 151 in clinical trials, mean nirsevimab concentrations remained above the targeted 90% effective concentration threshold of 6.8 μg per milliliter.[38,39]

Clinical Trials/Clinical Efficacy

Table 1 summarizes the results of relevant clinical efficacy trials of Abrysvo, Arexvy, and nirsevimab. Abrysvo has been studied in adults aged ≥60 years and in maternal vaccine recipients. Arexvy has only been studied in adults aged ≥60 years, and nirsevimab has only been studied in infants and neonates ≤2 years of age. There are no published studies on the comparative effectiveness of nirsevimab and Abrysvo in preventing RSV-related LRTD in infants or published studies on the comparative effectiveness of Arexvy and Abrysvo in preventing RSV-related LRTD in adults aged ≥60 years. No conclusions should be drawn on superior effectiveness between the newly approved agents.

Phase 3 Study of Abrysvo in Adults Aged ≤60 Years (RENOIR; NCT05035212)[29,40]

A phase 3, randomized, multicenter, placebo-controlled trial was conducted in adults aged ≥60 years (Table 1). Participants received either an intramuscular (IM) injection of Abrysvo at a dose of 120 μg (RSV subgroups A and B; 60 μg each) or placebo (Table 1). Relevant endpoints are included within Table 1. Demographics were similar across both treatment arms, with the median age of participants being 67 years. In the RSVpreF vaccine group, 51.1% were male, 59.9% of participants were in the United States, and 51.5% had a prespecified high-risk condition (tobacco use, diabetes, lung disease, heart disease, liver disease, or renal disease) compared with 50.4%, 59.7%, and 51.7%, respectively, in the placebo arm. Abrysvo successfully met both primary endpoints (Table 1), and the trial demonstrated that Abrysvo is effective at preventing RSV-associated LRTD in adults aged ≥60 years compared with placebo. Some limitations from this study included low representation of adults aged ≥80 years (5.6% across all participants), and no representation of immunocompromised patients who have increased susceptibility to severe RSV-related LRTD.

Phase 3 Study of Abrysvo in Pregnant Women (MATISSE; NCT04424316)[29,41]

Another phase 3, double-blind, randomized, placebo-controlled trial was conducted in pregnant women at 24 through 36 weeks gestation to receive a single IM injection of Abrysvo at a dose of 120 μg or placebo. The 2 primary efficacy endpoints are included within Table 1. Baseline characteristics were similar across both groups. The median age of women enrolled in the study was 29 years, and the median gestation was 31.3 weeks. Most of the women enrolled in the study were non-Hispanic/Latinx (70.3%) and white (64.5%). In total, 94% of the infants in the study were born at term (37 to <42 weeks), and 51% were male. The statistical success criterion of the lower boundary of the confidence interval (CI) >20% was met for each primary endpoint except for MA RSV-associated LRTD within 90 days (vaccine efficacy = 57.1%; 99.5% CI = 14.7 to 79.8) (Table 1). Through 180 days, the trial demonstrated that maternal vaccination with Abrysvo was effective at reducing severe RSV-associated LRTD at all time points within 180 days but failed to show efficacy at reducing LRTD due to RSV. However, vaccine efficacy at reducing LRTD due

Table 1. Summary of Clinical Trial Findings.

Author/year	Study design	Intervention	Relevant endpoints	Vaccine efficacy[a] (95% CI)
Walsh 2023 *RENOIR*	Phase 3, multicenter, double-blind, randomized, placebo-controlled trial in adults aged ≥60 years	RSVpreF vaccine (n = 16306) vs placebo (n = 16308)	1. First episode of RSV-associated LRTD with ≥2 symptoms[b] 2. First episode of RSV-associated LRTD with ≥3 symptoms[b] 3. RSV-associated acute respiratory illness[c]	1. 66.7 (28.8 to 85.8) 2. 85.7 (32.0 to 98.7) 3. 62.1 (37.1 to 77.9)
Kampman 2023 *MATISSE*	Phase 3, double-blinded, randomized, placebo-controlled trial in pregnant women at 24-36 weeks gestation	RSVpreF vaccine (n = 3682) vs placebo (n = 3676)	1. Medically attended severe RSV-associated LRTD in infants within 90, 120, 150, and 180 days after birth[d] 2. MA RSV-associated LRTD in infants within 90, 120, 150, and 180 days after birth[d]	1. 90 days after birth: 81.8 (40.6 to 96.3) 120 days after birth: 73.9 (45.6 to 88.8) 150 days after birth: 70.9 (44.5 to 85.9) 180 days after birth: 69.4 (44.3 to 84.1) 2. 90 days after birth: 57.1 (14.7 to 79.8) 120 days after birth: 56.8 (31.2 to 73.5) 150 days after birth: 52.5 (28.7 to 68.9) 180 days after birth: 51.3 (29.4 to 66.8)
Papi 2023 *AReSVi-006*	Phase 3, randomized, placebo-controlled, multicenter trial in adults aged ≥60 years	RSVPreF3 vaccine (n = 12466) vs placebo (n = 12466)	1. RSV-related LRTD 2. According to RSV subtype	1. Overall: 82.6 (57.9 to 94.1) Severe: 94.1 (62.4 to 99.9)[e] 2. RSV A: 84.6 (32.1 to 98.3) RSV B: 80.9 (49.4 to 94.3)[e]
Hammitt 2022 *MELODY*	Phase 3, randomized, double-blind, placebo-controlled trial in infants ≥35 weeks gestational age	Nirsevimab (n = 994) vs placebo (n = 496)	1. MA RSV-associated LRTD 2. Hospitalization for RSV-associated LRTD	1. 74.5 (49.6 to 87.1) 2. 62.1 (−8.6 to 86.8)
Griffin 2020	Phase 2b, randomized, double-blind, placebo-controlled trial in healthy, preterm infants born ≥29 weeks to ≤34 weeks	Nirsevimab (n = 969) vs placebo (n = 484)	1. MA RSV-associated LRTD 2. Hospitalization for RSV-associated LRTD	1. 70.1 (52.3 to 81.2) 2. 78.4 (51.9 to 90.3)

[a]Vaccine efficacy is defined as the relative risk reduction of the endpoint in the vaccine group compared with the placebo group.
[b]Signs or symptoms of RSV included cough, sputum production, wheezing, shortness of breath, and/or tachypnea.
[c]Defined as ≥1 symptom of an acute respiratory illness (sore throat, cough, nasal congestion or discharge, wheezing, sputum production, or shortness of breath, any of which were new or increased in intensity).
[d]99.5% CI at 90 days; 97.58% CI at later intervals.
[e]96.95% CI for the population overall ≥60 years and 95% CI for all subgroup analyses.
Abbreviations: CI, confidence interval; LRTD, lower respiratory tract disease; MA, medically attended; RSV, respiratory syncytial virus.

to RSV was shown from 90 days through 180 days after birth. A limitation of this study is the exclusion of women with high-risk pregnancies, whose infants may be at a higher risk of RSV-associated LRTD. In addition, the trial was not powered appropriately to assess differences in RSV antigen subgroups.

Phase 3 Study of Arexvy in Adults Aged ≥60 Years (AReSVi-006; NCT04886596)[30,42]

A phase 3, randomized, international, placebo-controlled trial was conducted in adults aged ≥60 years. Participants received either an IM injection of Arexvy or placebo before the RSV season. The primary endpoint is included within Table 1. To meet the primary endpoint, a lower limit of the CI around the efficacy estimates of more than 20% was established. The mean age of all study participants was 69.5 years, and baseline characteristics were similar across both groups. In the Arexvy group, 52% were female and 39.6% had a pre-existing condition known to cause an increased risk of RSV. In the placebo arm of the trial, 51.4% were female, and 38.9% had a pre-existing condition known to cause an increased risk of RSV. The primary endpoint was met (Table 1), and this indicated that Arexvy was efficacious at preventing RSV infection in adults aged≥60 years. The trial demonstrated that Arexvy prevented RSV-related LRTD and severe RSV-related LRTD in adults aged ≥60 years (Table 1), regardless of RSV subtype. A limitation of the trial is the limited number of participants aged >80 years, who only represented 8.2% of the trial population.

Phase 3 Study of Nirsevimab in Infants (MELODY; NCT03979313)[31,38]

A phase 3, randomized, placebo-controlled trial was conducted in healthy infants aged ≤1 year entering their first RSV season and born at a gestational age of ≥35 weeks. Participants were excluded if they met criteria to receive palivizumab, had any fever or acute illness within 7 days before randomization, or had previous RSV infection. Participants were assigned in a 2:1 ratio to receive an IM injection of nirsevimab or placebo. The primary efficacy endpoint and secondary efficacy endpoint are included within Table 1. Baseline characteristics were similar across groups, and infants were stratified based on hemisphere of residence. In the nirsevimab arm, 58% of infants were ≤3 months old, 86.7% had gestational age ≥37 weeks, 46.8% were female, and 69% resided in the northern hemisphere compared with 57.5% of infants who were ≤3 months old, 84.6% were ≥37 weeks in gestational age, 51.8% were female, and 69% resided in the northern hemisphere in the placebo arm. This trial indicated that nirsevimab is effective in providing protection against MA RSV-associated LRTD when given to infants before an RSV season (Table 1), and the findings were consistent with the previously conducted phase 2b trial showing that nirsevimab prophylaxis led to a 70.1% lower incidence (95% CI = 52.3 to 81.2) of MA RSV-associated LRTD (Table 1).

Safety and Tolerability

Abrysvo, Arexvy, and nirsevimab are contraindicated in patients who have a history of severe allergic reaction to any component of each product. Like most vaccines, Arexvy and Abrysvo have precautions for use in persons experiencing moderate or severe acute illness with or without fever. Local reactions were reported more frequently by Abrysvo vaccine recipients than by placebo recipients (12% vs 7%), but systemic events were similar between both groups (27% and 26%, respectively).[29,40] The most reported local reaction for Abrysvo recipients was injection-site pain (10.5%), and the most common systemic reactions for Abrysvo recipients were fatigue, headache, and muscle pain (15.5%, 12.8%, and 10.1%, respectively).[29,40] In total, 2.3% of vaccine recipients and 2.3% of placebo recipients reported a serious adverse event (SAE) at the data cutoff date. The most common local reaction reported by maternal vaccine recipients of Abrysvo was injection-site pain (40.6%), and the most common systemic reactions reported were muscle pain (26.5%) and headache (31%).[29,41] The rate of maternal participants (13.8%) with any reported AEs was similar to the placebo group (13.1%).[29,41] Among maternal participants, the incidence of SAEs was similar in vaccine recipients (16.2%) and the placebo group (15.2%), and most occurred after the 1-month period following vaccination.[29,41] Preterm births were more common among recipients of Abrysvo, with preterm birth events occurring in 5.7% (202 of 3568; 95% CI = 4.9 to 6.5) in the Abrysvo group and 4.7% (169 of 3558; 95% CI = 4.1 to 5.5) in the placebo group, but the data were not sufficient to establish a causal relationship to vaccination with Abrysvo.[29,41] No SAEs in infants were attributed to the vaccine.[29,41]

The most common local reaction reported by both Arexvy recipients and placebo recipients was pain (60.9% and 9.3%, respectively).[30,42] The most common solicited systemic reaction reported was fatigue (33.6% in Arexvy recipients and 16.1% in placebo recipients).[30,42] Headache, myalgia, and arthralgia were also more commonly reported by Arexvy recipients (27.2%, 28.9%, and 18.1%, respectively).[30,42] Similar rates of SAEs were reported between participants who received Arexvy (4.2%) and participants who received placebo (4.0%).[30,42]

Across both trials of nirsevimab, the types and frequencies of AEs were similar in the 2 groups, and most AEs were grade 1 or 2 in severity.[31,38,39] In the phase 3 trial assessing nirsevimab, SAEs were reported in 6.8% of nirsevimab recipients and 7.3% of placebo recipients, and none of the SAEs or deaths recorded during the trial period

were deemed to be related to nirsevimab or placebo.[31,38,39] In a pooled safety population from each trial cohort, the most commonly reported AEs in the nirsevimab group that were higher than placebo included rash (0.9% and 0.6%, respectively) and injection-site reactions (0.3% and 0%, respectively).[9]

Relevance to Patient Care and Clinical Practice

Comparison of Newly Approved and Previously Available Preventive Agents

Pharmacologic activity is similar among the 2 monoclonal antibody products and the 2 RSVpreF vaccines. Although palivizumab and nirsevimab share the same mechanism of action, the much longer half-life of nirsevimab allows for dosing once per RSV season as opposed to monthly dosing during the RSV season with palivizumab.[28,31] This alleviates a considerable burden to patients given that these agents must be administered by a health care provider. Nirsevimab dosing is also easier for health care providers due to its use of a weight-based threshold to select from one of 2 available strengths, whereas palivizumab often requires dose adjustments throughout the RSV season with changes in patient weight.[28,31] Both Abrysvo and Arexvy are only recommended for 1-time administration based on current data, providing additional low-burden preventive options for patients requiring RSV prophylaxis.[29,30]

These 4 agents start to differentiate themselves more when examining the indications for use, with each of the 3 new agents expanding the patient populations eligible for prophylaxis. The target population for RSV prophylaxis with palivizumab is limited to infants aged ≤6 months with a history of premature birth, or those aged ≤24 months with conditions that would predispose them to serious LRTD caused by RSV including BPD or CHD.[28] Nirsevimab is also indicated for use in children aged ≤24 months, but is labeled more broadly to include all neonates or infants entering their first RSV season and for any children who remain vulnerable to severe RSV disease in their second RSV season.[31] Abrysvo and Arexvy further expand the patients eligible for prophylaxis to adults aged ≥60 years, with Arexvy additionally indicated for prevention in adults aged 50 to 59 years at an increased risk for LRTD caused by RSV. Older adults had no previous prophylactic options, despite the potential for severe RSV infection and associated morbidity and mortality in this population.[29,30] Abrysvo was additionally approved for prevention of LRTD caused by RSV in infants aged ≤6 months, but unlike monoclonal antibody products, it is administered to the pregnant mother at 32 to 36 weeks gestational age to provide coverage via passive immunization.[29]

Limited comparative studies have been completed assessing the efficacy or safety of RSV agents, but some indirect comparisons may be made between agents that were studied in similar patient populations. This would include efficacy and safety comparisons between Arexvy and Abrysvo in adults aged ≥60 years and efficacy comparisons between Abrysvo and nirsevimab in healthy infants entering their first RSV season. Indirect comparisons should be interpreted with caution given the impact that differing mechanisms of action, study methodologies, and patient demographics may have on the observed results.

The approvals of Abrysvo and Arexvy for the prevention of LRTD caused by RSV in adults were supported by the results of the phase 3 RENOIR and AReSVi-006 trials, respectively.[40,42] Differences to note when comparing the enrolled patient populations of these trials include a higher proportion of patients 70 to 79 years of age (36.0% vs 31.9%) and ≥80 years (8.2% vs 5.6%) in the AReSVi-006 trial, more patients located in the southern hemisphere (24.2% vs 7.8%) in the RENOIR trial, and more patients with ≥1 high-risk condition (51.5% vs 39.6%) in the RENOIR trial.[40,42] There were a total of 35 971 participants enrolled in the RENOIR trial and 26 664 participants in the AReSVi-006 trial, and each trial followed patients for approximately 7 months on average after vaccine administration.[40,42] Efficacy results observed in these trials are summarized in Table 1. Vaccine efficacy appeared to be higher with Arexvy compared with Abrysvo for all RSV-associated LRTD (82.6% vs 66.7%) and against severe RSV-associated LRTD (94.1% vs 85.7%).[40,42] Among the safety populations of 7169 participants in the RENOIR trial and 1799 participants in the AReSVi-006 trial, fatigue was the most common systemic adverse reaction (16% vs 33.6%), and injection-site pain was the most common local reaction (11% vs 60.9%).[40,42] Serious and/or fatal AEs were observed in similar proportions of participants in each trial compared with their respective placebo groups.[40,42] Indirect comparison appears to suggest not only slightly higher efficacy but also an increased potential for adverse reactions with Arexvy compared to Abrysvo in the population aged ≥60 years.

The approvals of Abrysvo and nirsevimab for the prevention of RSV-associated LRTD in neonates and infants were respectively supported by the results of the phase 3 MATISSE and MELODY trials.[38,41] Results were assessed in participants entering their first RSV season, with MATISSE following individuals through 6 months of age and MELODY enrolling participants up to 1 year of age at the time of randomization.[38,41] The gestational age of enrolled patient populations was similar between the MATISSE and MELODY trials (≥34 weeks vs ≥35 weeks).[38,41] Racial distribution of enrolled patients was similar apart from a higher proportion of Asian participants in the MATISSE trial (12.3% vs 3.6%) and American Indian

or Alaskan Native participants in the MELODY trial (5.8% vs 1.0%).[38,41] Participants with high-risk conditions were excluded from the MELODY trial, but approximately 10.1% of the study participants in the MATISSE trial were noted to have a congenital malformation or other neonatal problems.[38,41] The efficacy population receiving active treatment was 3495 infants in the MATISSE trial and 994 infants in the MELODY trial.[38,41] Efficacy results for these trials are summarized in Table 1. The efficacy rate based on MA severe RSV-associated LRTD observed with Abrysvo within 180 days after birth appears to be similar to the efficacy rate observed with nirsevimab within 150 postadministration (69.4% vs 74.5%), and this was also true with efficacy results based on RSV-associated hospitalization (56.8% vs 62.1%).[38,41] Subgroup analyses in the MELODY trial identified reduced estimates of efficacy among infants aged ≤3 months at the time of randomization or approximately aged ≤8 months by the end of the 150-day follow-up period.[38] Therefore, the slightly higher efficacy results observed with nirsevimab may be explained by a difference in participant age compared with younger infants enrolled in the MATISSE trial.

The double-blind, randomized, phase 2/3 MEDLEY trial assessed the efficacy and safety of nirsevimab with palivizumab as an active comparator.[31,43] This study enrolled preterm infants in alignment with populations eligible to receive palivizumab according to national and local guidelines.[31,43] Participants were randomized 2:1 to receive either nirsevimab or palivizumab and divided into 2 cohorts for patients with CHD/CLD and patients born preterm.[31,43] Re-randomization of treatment in the CHD/CLD cohort occurred between the first and second seasons for applicable subjects.[31,43] Efficacy was assessed as a secondary endpoint in the MEDLEY trial because it was not powered sufficiently for primary analysis.[31,43] In the first RSV season of the MEDLEY trial, the incidence of MA RSV-associated LRTD through 150 days postadministration was 0.6% in the nirsevimab group and 1.0% in the palivizumab group.[31,43] No cases of MA RSV-associated LRTD were observed in any subjects in the second season of the MEDLEY trial following re-randomization of treatment.[31,43] The occurrence of treatment-emergent AEs, AEs of special interest, and new-onset chronic disease were similar across treatment groups in both RSV seasons.[31,43] No statistical analyses were available for the efficacy or safety results of this study at this time of this review. However, these findings appear to suggest similar efficacy and safety between nirsevimab and palivizumab, despite the differences in dosing and administration.

Current Place in Therapy for Respiratory Syncytial Virus Prophylactic Agents

Clinical consensus guidelines addressing currently available agents for RSV prophylaxis are available from several professional organizations.[22,23,44-52] Recommendations from these agencies are largely consistent regarding the patient populations advised to receive prophylactic agents and implementation of these treatments into clinical practice.[22,23,44-46,48,49] The National Perinatal Association (NPA) guidelines have not been updated since the approval of nirsevimab or either RSV vaccine product and therefore do not address the use of these agents.[50] The rapid evidence review from the American Academy of Family Physicians (AAFP) only briefly discusses the newly approved agents and does not make recommendations for their use.[47]

Palivizumab is most strongly recommended for use in patients born before 32 weeks and 0 days gestational age and those diagnosed with CLD, CHD, or hemodynamically significant heart disease.[27] Patients with other risk factors for severe RSV infection, such as cystic fibrosis or a congenital abnormality or neuromuscular disease that affects respiratory function, should receive palivizumab based on shared clinical decision-making between the patient and the provider.[27] Guidelines from the AAFP and NPA align with recommendations in the 2014 American Academy of Pediatrics (AAP) guidance on palivizumab use.[47,50] However, a technical report published by the AAP in 2023 suggests that palivizumab use during the second year of life should likely be limited to patients with CLD who continue to require medical therapy and patients with cardiac transplantation during the RSV season. These updates are based on limited available efficacy and safety data supporting palivizumab use in the second year of life and the decline of hospitalization rates associated with RSV for all children during their second RSV season.[51] Updated recommendations from the AAP, Advisory Committee on Immunization Practice (ACIP), and the American College of Obstetrics and Gynecologists (ACOG) now recommend nirsevimab instead of palivizumab in eligible patients unless nirsevimab is unavailable or cannot be administered.[22,23,44,45,48,49] This includes patients who already started prophylaxis with palivizumab but have not received 5 doses and patients who received palivizumab in a previous RSV season.[22,23,44,45,48,49]

Updated guidance from AAP, ACIP, and ACOG in 2023 and 2024 supports the adoption of nirsevimab for RSV prophylaxis in patients previously recommended to receive palivizumab per AAP guidance on palivizumab use.[22,23,27,44,45,48,49] These organizations additionally recommend nirsevimab use in infants aged <8 of age entering their first RSV season if they are not covered by maternal administration of the RSV vaccine during pregnancy, infants 8 to 19 months of age at an increased risk of severe RSV disease, and in infants born <34 weeks gestational age or <14 days after maternal administration of the RSV vaccine.[22,23,44,45,48,49] Infants born ≥14 days following maternal administration of an RSV vaccine may still be considered for prophylactic treatment with nirsevimab if the parent or infant may not have developed

an immune response to the vaccination, the infant may have lost the acquired antibody due to a medical procedure such as cardiopulmonary bypass, or the infant is at an increased risk for severe RSV disease indicated by the presence of hemodynamically significant CHD per AAP and ACOG.[22,23,44,45,48,49]

Updated guidelines also encourage the use of the RSV vaccine in populations who were not previously recommended to receive palivizumab, including pregnant patients and adults aged ≥60 of age. Administration during pregnancy is recommended by ACIP and ACOG between 32 and 36 weeks gestational age in accordance with FDA labeling.[22,23,29,44,49] The ACIP suggests that administration should ideally occur approximately 1 to 2 months prior to the anticipated start of the RSV season through 2 to 3 months after the anticipated end of the RSV season.[22,23,44] Both ACIP and ACOG state that most infants will only require RSV prophylaxis through either maternal RSV vaccine administration or nirsevimab; thus, patient preference and feasibility of each option should be used to guide the choice of prophylactic therapy.[22,23,44,49] More data are needed to establish guidance on whether revaccination is warranted during future pregnancies.[22,23,29,44,45]

The use of an RSV vaccine in adults aged ≥60 years is only addressed in recommendations from ACIP.[22,23,46] It is recommended that all patients aged ≥75 years and patients aged 60 to 74 years at an increased risk of severe RSV disease receive a single dose of RSV vaccine.[22,23,46] Risk factors suggested by ACIP include cardiovascular disease, diabetes with end-organ damage, frailty, hematologic disorders, immunosuppression, advanced chronic kidney disease, lung disease, liver disorders, neurologic or neuromuscular conditions, severe obesity, and residency in a nursing home or other long-term care facility.[22,23,46] Current data do not support revaccination for patients in this age group, regardless of risk factors present.[22,23,46] Patients aged 60 to 74 years who are not at an increased risk for severe RSV disease are not recommended to receive an RSV vaccination at the time of this review, and no recommendations have been made by ACIP regarding RSV vaccination in patients aged 50 to 59 years.[22,23,46]

Current Uptake of Respiratory Syncytial Virus Preventive Agents

Medical record data were collected from the US Collaborative Network in TriNetX, which queried a total of 112 999 602 patient records at the time of review. Assessments of the rate of uptake of prophylactic agents during the 2023 to 2024 RSV season and overall demographics of patients receiving prophylaxis were completed. It should be noted that these results included all patients with a procedure code indicating administration of any RSV prophylactic agent, and patients included in each group may not be mutually exclusive. In addition, there were a substantial number of records indicating administration of an unknown RSV vaccine; therefore, results included a separate group for patients who received any RSV vaccine. Demographic information reported is from all patient records captured in the initial search for each term and is not limited to patients who received a prophylactic agent during the 2023 to 2024 RSV season.

It was observed that more patients received an RSV vaccine during the 2023 to 2024 RSV season compared with the number of patients receiving either of the monoclonal antibody products (Figure 1). High uptake of RSV vaccines in the first year following FDA approval may have been expected, particularly since patient populations eligible to receive these agents were not previously indicated to receive prophylaxis with palivizumab. Current guideline recommendations and available data do not suggest the need for revaccination; therefore, overall utilization of RSV vaccines may be expected to decline in subsequent years. However, there may be a slight increase in utilization following the expanded indication in patients aged 50 to 59 years with Arexvy, and additional indication expansions in the future would be anticipated to have a similar impact. Interestingly, the RSV vaccine with higher observed uptake during the time period assessed was Arexvy, which currently does not share the additional indication for maternal administration with its counterpart, Abrysvo (Figure 1). In accordance with clinical guideline recommendations, a larger number of patients received nirsevimab than palivizumab each month, despite the limited available supply.[52] Palivizumab use may be expected to continue to decline as nirsevimab production improves and as uptake of maternally administered RSV vaccines increases.

The assessment of population demographic information supported some anticipated trends and identified some potential areas for improvement (Table 2). The mean age reported is the patient's current age, not the age at administration. Therefore, the mean age of patients receiving palivizumab represents an average over the course of approximately 20 years since its approval and would roughly align with the mean age observed in patients receiving nirsevimab after accounting for that difference. The mean age of patients receiving an RSV vaccine was well above the 60-year age threshold in FDA labeling at the time (Table 2), which indicates advanced age was a common risk factor used to guide shared clinical decision-making before updated guidance from ACIP was published. The administration of Abrysvo in younger and more predominately female patients aligns with its additional indication for maternal administration compared with Arexvy (Table 2).

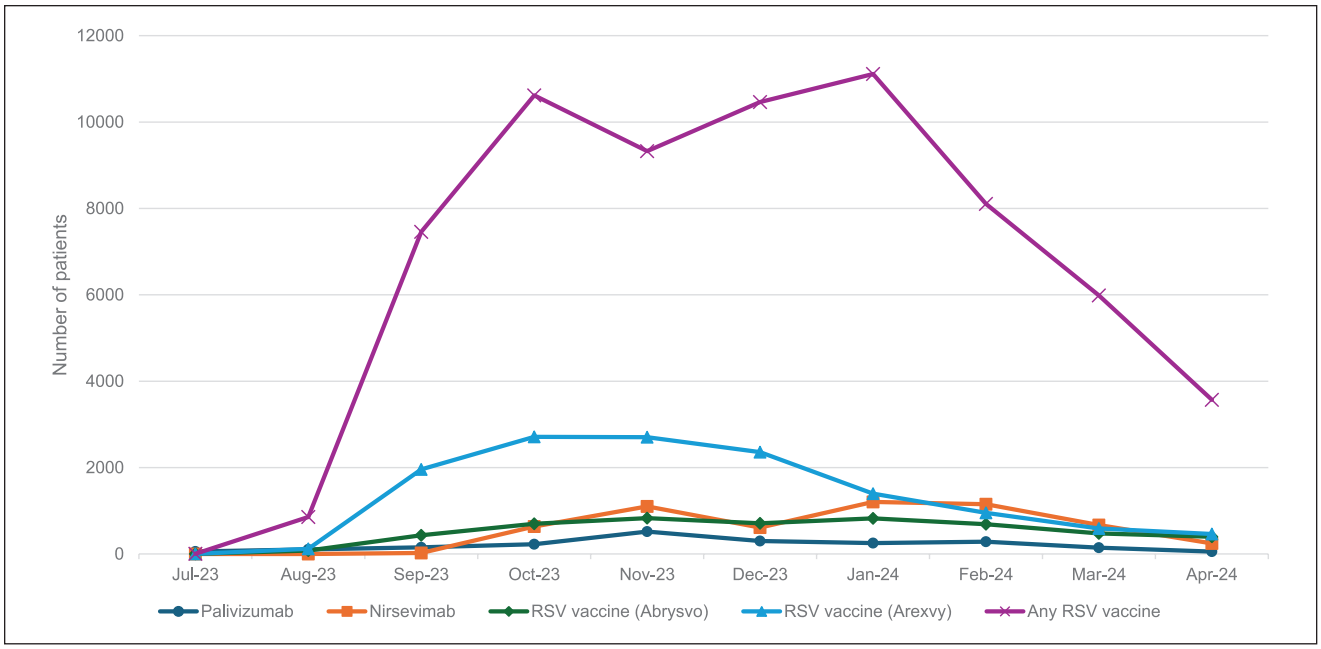

Figure 1. RSV prophylaxis agent uptake in the United States based on TriNetX data from July 2023 to April 2024.

Table 2. Population Demographic Among Patients Receiving RSV Prophylaxis.

Variable	Palivizumab	Nirsevimab	RSV vaccine (Abrysvo)	RSV vaccine (Arexvy)	Any RSV vaccine
Cohort size (N)	46894	5902	5804	18954	76210
Mean age (years)	9	1	65	73	71
Sex (%)					
Female	53.57	48.90	58.25	55.01	59.29
Male	45.83	50.74	36.03	40.53	39.16
Unknown	0.60	0.36	5.72	4.46	1.55
Race (%)					
American Indian or Alaskan Native	0.48	0.37	0.26	0.29	0.22
Asian	3.05	5.10	3.81	4.75	3.41
Black or African American	20.94	19.86	4.60	7.82	5.53
Caucasian	52.32	50.09	81.86	73.88	83.11
Native Hawaiian or Other Pacific Islander	0.43	0.71	0.34	0.69	0.39
Other	8.27	11.40	1.43	0.66	2.31
Unknown	14.51	12.47	7.70	11.91	5.03
Ethnicity (%)					
Hispanic or Latino	19.92	15.18	2.91	1.21	3.48
Not Hispanic or Latino	65.68	70.59	85.58	63.73	85.18
Unknown	14.40	14.23	11.51	35.06	11.34
Geographic distribution (%)					
Northeast	21	13	55	35	27
Midwest	24	25	28	32	34
South	40	53	9	27	28
West	15	8	8	6	10

Abbreviations: BPD, bronchopulmonary dysplasia; CHD, congenital heart disease; CLD, chronic lung disease; ECMO, extracorporeal membrane oxygenation; HIV, human immunodeficiency virus; RSV, respiratory syncytial virus.

Although the overall demographic information of queried patient records is not available for context, it may be concerning that substantially fewer patients of American Indian or Alaskan Native and Black or African American descent have received either of the RSV vaccines compared with the populations receiving prophylaxis with a monoclonal antibody. The same trend was observed in patients of Hispanic or Latinx ethnicity (Table 2). These findings may suggest the presence of health care disparities related to who is being offered RSV prophylaxis or patient education and health literacy surrounding the importance of RSV preventive care. Population demographics of patients receiving nirsevimab largely matched that of those receiving palivizumab (Table 2), which would have been expected based on FDA labeling and current guideline recommendations suggesting its role as a replacement for palivizumab. There were also interesting trends among the geographic distribution of patients defined by the location of their health care organization's headquarters. Utilization of RSV agents was the lowest among Western states across the board, which could suggest either smaller eligible populations in those states or fewer organizations sharing data with TriNetX in that region. Southern states typically have longer RSV seasons, and predictably, states in this region had the largest share of monoclonal antibody utilization. Uptake of the RSV vaccines appears to be distributed equally overall between the Northeast, Midwest, and South. However, the distribution of Abrysvo was markedly higher in the Northeast compared with other regions, which, based on its unique indication for maternal prophylaxis, could be reflective of contrasts in pregnancy care delivered in this region compared with other regions in the United States.

Conclusions

Information gathered in this review suggests a promising outlook for the future of RSV prophylaxis. Novel agents, including nirsevimab and 2 RSV vaccines, offer less burdensome dosing and administration, show promising efficacy and safety data, and have expanded the populations eligible to receive prophylaxis to include elderly patients and protection for infants at birth through maternal transfer of an RSV antibody. Clinical guidance has already been updated from multiple professional organizations and government agencies to support adoption of these newly available agents, and population-level data suggest these recommendations are being implemented by health care systems. Health care systems should continue to adopt new RSV preventive agents to cover eligible at-risk populations, with a particular focus on providing equitable care and prioritizing the highest-risk patients when supplies are limited. Although this review focused on RSV prophylaxis in the United States, the considerable impact of RSV in lower-income countries highlights a need for global distribution of novel treatments as they become readily available.

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Data Availability

Data included in this review were deidentified and uncoded from TriNetX and are available to its registered users.

Declaration of Conflicting Interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr NH reports employment with Cencora. All other authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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