Revolutionising RSV infection prevention and control

Unveiling new options in the fight against RSV

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Respiratory syncytial virus (RSV) poses significant challenges, particularly in infants and older individuals. The advent of new vaccines and monoclonal antibodies in Australia marks a revolutionary shift in RSV infection prevention and control. Understanding these novel prophylactic options, including their efficacy, safety and access issues, is essential for optimising patient care.

KEY POINTS

- RSV burden: Respiratory syncytial virus (RSV) significantly impacts all age groups, causing severe respiratory illness, particularly in infants and elderly individuals.
- Past challenges: Early vaccine efforts, such as the formalin-inactivated RSV vaccine in the 1960s, failed and led to worse disease outcomes, demonstrating the complexity of RSV immunopathogenesis.
- Innovative monoclonal antibodies: Nirsevimab, a new long-acting monoclonal antibody, has shown high efficacy in preventing RSV-related hospitalisations in infants, marking a major advancement in RSV prophylaxis.
- Breakthrough vaccines: The introduction of the Arexvy and Abrysvo vaccines, targeting the RSV prefusion F glycoprotein, offers strong protection for older adults and pregnant women, ensuring newborn immunity.
- Accessibility and funding: Disparities in access and funding for nirsevimab and RSV vaccines across Australia highlight the need for equitable healthcare solutions to maximise the benefits of these innovations.
- Future prospects: Ongoing development of new antivirals and monoclonal antibodies, combined with addressing vaccine hesitancy and public awareness, is essential for the comprehensive control of RSV infection.

Respiratory syncytial virus (RSV) is a leading cause of respiratory illness across all age groups, causing significant morbidity and mortality in infants and older individuals and, thus, posing substantial challenges in primary care settings. GPs often encounter these cases, especially during the peak of the season. With the introduction of new vaccines and immunoprophylaxis in Australia, there is a pivotal shift in how GPs can help prevent RSV infection. This article details the newly available and soon-to-be available prophylactic options in Australia, and explores current access challenges including funding. This knowledge is crucial for optimising patient care while anticipating future developments in RSV infection management.

Past efforts in combatting RSV

Over the decades, various strategies have been trialled to combat RSV infection, ranging from vaccines to antivirals and immunoglobulin preparations. Early efforts in vaccine development, particularly in the 1960s, faced significant setbacks. The first RSV vaccines, based on formalin-inactivated virus, not only failed to provide adequate protection but also led to enhanced respiratory disease upon natural infection, particularly in infants.[1] This tragic outcome, resulting in severe respiratory distress, systemic inflammation and even fatalities, underscored the complexity of RSV immunopathogenesis and the need for safer and more effective vaccines.

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Antiviral treatments have also been explored. Ribavirin (a nucleoside analogue) was one antiviral drug used for severe RSV infections in children,[2,3] although it was also used off label in other populations.[4-6] When administered via inhalation, ribavirin showed variable efficacy in infants and young children with severe RSV bronchiolitis.[7] It was also extremely expensive, with a wholesale price of about US$30,000 per day,[8] and coupled with its toxicity issues, its widespread use was limited.[9] Moreover, its administration required a specific hospital setup; this posed logistical challenges, further restricting its practicality. Therefore, aerosolised ribavirin is no longer recommended for routine use in the UK, USA or Australia. Recently, small case series studies in adult haematopoietic stem cell transplant (HSCT) recipients with RSV infection showed that oral ribavirin was noninferior and substantially less expensive than aerosolised ribavirin, with an associated reduction in morbidity and mortality.[10,11] However, given none of these studies included a placebo, the clinical efficacy remains unknown. Despite these limitations, a combination of intravenous and/or oral ribavirin is employed in some Australian solid organ and HSCT units for high-risk, immunocompromised patients with laboratory-confirmed RSV infection.[6,12] Neither intravenous nor oral ribavirin are registered for this indication in Australia and are therefore accessed through the TGA Special Access Scheme. The RSV antivirals in development are discussed later in this article.

Immunoglobulin preparations, such as RSV immune globulin intravenous (RSV-IGIV), has been shown to provide passive immunity by delivering antibodies against RSV derived from pooled human sera. Although RSV-IGIV showed some prophylactic efficacy in reducing RSV infection-related hospitalisations,[13] it was expensive and required monthly intravenous infusions, making it impractical for large-scale use, particularly in primary care and outpatient settings. Safety concerns regarding hyperviscosity in preterm infants with congenital heart disease who had been administered RSV-IGIV also surfaced.[14] With further research showing it was significantly less potent than the new monoclonal antibody palivizumab,[15] RSV-IGIV was withdrawn from the market in the early 2000s. Regarding the utility of polyclonal immunoglobulin, a recent *Cochrane Review* indicated that treatment with these products had minimal impact on reducing the length of stay for infants and young children hospitalised with RSV lung infections, and the effectiveness in reducing mortality remains unclear.[16]

Palivizumab, a humanised immunoglobulin G1 monoclonal antibody, emerged in 1998 as a more convenient prophylactic option, offering monthly intramuscular injections during the RSV season. In Australia, palivizumab is TGA approved for the prevention of serious lower respiratory tract disease (LRTD) caused by RSV infection in high-risk children, specifically those born prematurely (<36 weeks' gestation), with haemodynamically significant congenital heart disease or with bronchopulmonary dysplasia.[17] Although palivizumab significantly reduces hospitalisations due to RSV infection,[18,19] its high cost and limited efficacy prevented its PBS listing; instead, the drug is provided at the discretion of state and territory health authorities and individual hospitals.[20]

Given there are no approved treatments for most individuals with RSV infection, management remains largely supportive through oral hydration, nutritional support, simple analgesia and antipyretics and, in severe cases, hospitalisation for supplemental oxygen or mechanical ventilation. Furthermore, bronchodilators, corticosteroids and decongestants have not shown a benefit for RSV infections, including in cases of bronchiolitis.[21]

Monoclonal antibody – nirsevimab for passive immunisation

The landscape of RSV prevention has been revolutionised with the introduction of nirsevimab, an injectable human immunoglobulin G1κ monoclonal antibody containing a mutation in the Fc domain to prolong the serum half-life,[22,23] enabling effective prophylaxis for at least five months after a single dose.[24] Nirsevimab targets the prefusion F glycoprotein of RSV, a critical component for viral entry into host cells.[25] Nirsevimab binds to this glycoprotein to neutralise the virus, preventing subsequent disease.[26] This advancement is built on the discovery and detailed description of the prefusion F glycoprotein's structure and function, which has provided a refined approach compared with the less specific and ineffective strategies of the 1960s. The ability to stabilise the prefusion F glycoprotein has been a game-changer in the fight against RSV, inducing a more potent immune response and providing better protection against RSV infection.

Nirsevimab gained TGA approval in November 2023 for the prevention of RSV LRTD in the following populations:[27]

- neonates and infants born during or entering their first RSV season
- children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season.

Efficacy and safety of nirsevimab

The efficacy and safety of nirsevimab in preventing medically attended (MA) RSV lower respiratory tract (LRT) infection in full term and preterm infants during their first RSV season were assessed in two randomised, double-blind, placebo-controlled, multicentre trials (D5290C00003 [phase 2b][28] and MELODY [phase 3][29]), both involving Australian sites. In the phase 2b trial, the incidence of MA RSV LRT infection was 70.1% lower with nirsevimab prophylaxis than with placebo, and that of hospitalisation for RSV LRTD was 78.4% lower with nirsevimab than with placebo (0.8% *vs* 4.1% of infants, respectively).[28] In the MELODY trial, the efficacy of nirsevimab was 74.5%, and that against hospitalisation for RSV LRTD was 62.1%, compared with placebo (0.6% *vs* 1.6% of infants, respectively).[28]

The safety profile of nirsevimab was shown to be favourable, with similar incidences of adverse events across treatment groups in the phase 2/3 MEDLEY trial, which compared nirsevimab with palivizumab in high-risk infants.[30] Common adverse reactions included rash (0.7%), pyrexia (0.5%) and nonserious injection-site reactions (0.3%) occurring shortly after dosing. The HARMONIE study, a phase 3b real-world trial, further supported the efficacy of nirsevimab in a cohort of 8,058 infants, demonstrating an 83.2% efficacy against hospitalisation for RSV LRT infection and 75.7% against very severe RSV LRT infection.[31] Results from early implementation programs with inirsevimab, such as in France,[32] Luxembourg,[33] Spain,[34-37] and the USA,[38] confirm the efficacy seen in the clinical trials. Furthermore, in a continuation of the MELODY trial, concerns of enhanced disease in infants during the second RSV season following nirsevimab administration were unfounded, with an ongoing low incidence of RSV infection and no increase in disease severity compared with placebo.[39]

TABLE 1. INDICATIONS AND RECOMMENDED DOSAGES OF NIRSEVIMAB[24,27]

Indication	Dosage
Neonates and infants: first RSV season (based on body weight)*	
Weight less than 5 kg	50 mg by intramuscular (IM) injection
Weight 5 kg or greater	100 mg by IM injection
Children who remain at increased risk for severe RSV disease: second RSV season	
Up to 24 months of chronological age and for conditions including, but not limited to: • chronic lung disease of prematurity • haemodynamically significant congenital heart disease • immunocompromised states • Down syndrome • cystic fibrosis • neuromuscular disease • congenital airway anomalies	200 mg administered as two IM injections (2 × 100 mg) at the same time
Children undergoing cardiac surgery with cardiopulmonary bypass	
First RSV season	
If surgery is within 90 days after receiving nirsevimab	Additional dose based on body weight, as above
If more than 90 days have elapsed since receiving nirsevimab	Additional 50 mg dose, regardless of body weight
Second RSV season	
If surgery is within 90 days after receiving nirsevimab	Additional 200 mg dose, regardless of body weight
If more than 90 days have elapsed since receiving nirsevimab	Additional 100 mg dose, regardless of body weight

*The benefits and risks of nirsevimab use in infants <1 kg should be carefully considered. There are limited data available for extremely preterm infants (gestational age <29 weeks) less than 8 weeks of age. No clinical data are available for infants with a postmenstrual age (gestational age at birth plus chronological age) of less than 32 weeks.

Administration of nirsevimab

Nirsevimab is available as a 50 mg solution in a 0.5 mL prefilled syringe (purple plunger rod), and as a 100 mg solution in a 1 mL prefilled syringe (light blue plunger rod); needles are not included.[27] Table 1 lists the indications and recommended dosages of nirsevimab.[24,27] The drug must be stored at 2°C to 8°C and protected from light. Once removed from refrigeration, nirsevimab must be used within eight hours or discarded. Administration is via an intramuscular injection, preferably in the anterolateral aspect of the thigh. Injection into the gluteal muscle should be avoided because of the risk of sciatic nerve damage. Coadministration of nirsevimab with other childhood vaccines is permitted.[27] Nirsevimab-mediated drug–drug interactions have not been studied, nor is there information regarding coadministration with other immunoglobulin products.[20] Palivizumab administration is contraindicated in infants who have received nirsevimab during the same RSV season. Conversely, nirsevimab can be administered prior to or during a second RSV season in children up to 24 months of age who remain at risk of severe RSV disease and have previously received palivizumab during their first RSV season.[27] Furthermore, the US Advisory Committee on Immunization Practices[40] and the American Academy of Pediatrics[41] recommend that infants who initially received fewer than five doses of palivizumab for the season should be given a single dose of nirsevimab. Subsequent doses of palivizumab should not be given. Additionally, there is no required minimum interval between the final dose of palivizumab and the administration of nirsevimab. However, as the protective effect of palivizumab diminishes after 30 days, it is advisable to administer nirsevimab within 30 days following the last dose of palivizumab, whenever feasible.

Availability of nirsevimab in Australia

To date, only three Australian states have made nirsevimab available. WA and Queensland offer free, large-scale programs open to all newborns as well as infants at increased risk of severe RSV disease due to

1. ELIGIBILITY ACCORDING TO NIRSEVIMAB STATE PROGRAMS[42-46]

Western Australia[42,43]
Between 1 April 2024 and 30 September 2024, nirsevimab is offered:

- as a catch-up program for babies born between 1 October 2023 and 30 April 2024
- to all Aboriginal or Torres Strait Islander children born between 1 October 2022 and 30 September 2024
- to some medically at-risk (see Box 1) children in their second RSV season born between 1 October 2022 and 30 September 2023
- at birth to all babies born between 1 May 2024 and 30 September 2024

Queensland[45]
From 15 April 2024, nirsevimab is offered to:

- all infants born on or after 1 February 2024
- all Aboriginal and Torres Strait Islander infants less than 8 months of age
- infants with certain complex medical conditions (see Box 2) from birth to younger than 8 months of age
- children with certain complex medical conditions (see Box 2) from 8 months to younger than 20 months of age, until 31 October 2024

New South Wales[46]
Between 25 March 2024 and 30 September 2024, nirsevimab is offered to:

- all premature infants (less than 37 weeks' gestation at birth) born after 31 October 2023
- all Aboriginal and Torres Strait Islander infants born after 31 October 2023
- other vulnerable infants (see Box 3)

complex medical conditions, whereas NSW only offers nirsevimab to certain vulnerable infants. See Box 1, Box 2, Box 3 and Box 4 for the various program details.[42-46] In WA and Queensland, nirsevimab is also available through GPs and routine immunisation providers.[42-45] In NSW, nirsevimab for eligible infants can only be accessed through treating hospitals.[46] Nirsevimab will be considered for General Schedule Restricted Benefit listing on the PBS at the July 2024 meeting of the Pharmaceutical Benefits Advisory Committee.[47]

New vaccines for active immunisation

The TGA approval of the RSV vaccines Arexvy[48] (RSVPreF3 OA) in January 2024 and Abrysvo[49] (RSVpreF vaccine) in April 2024 represents a significant breakthrough for RSV infection prevention in Australia Table 2 summarises the key characteristics and definitions for these vaccines.[47,50-66] These vaccines are designed to induce robust immune responses that protect against RSV infection in older adults and, with Abrysvo, in pregnant women with the additional placental transfer of immunity to newborns.[67] Both Arexvy and Abrysvo target the prefusion F glycoprotein of RSV, with Arexvy utilising an adjuvant ($AS01_E$) to enhance the immune response in older patients who may have immunosenescence (similar to some influenza vaccines designed for recipients of older age).[50]

Indications for RSV vaccines

In Australia, Arexvy and Abrysvo are indicated for the active immunisation of individuals aged 60 years and older to prevent LRTD associated with RSV infection.[68,69] Abrysvo is also approved for the active immunisation of pregnant women between 24 and 36 weeks' gestation for the prevention of LRTD caused by RSV in infants from birth through 6 months of age.[69] The recently updated *Australian Immunisation Handbook* recommends RSV vaccination for the following groups:[24]

- all adults aged 75 years and older
- Aboriginal and Torres Strait Islander people aged 60 years and older
- adults aged 60 years and older with risk factors for severe disease due to RSV (see Box 5)
- pregnant women to protect their newborn infant.

Other adults aged 60 to 74 years may consider vaccination, bearing in mind the benefits may be reduced.

Administration of RSV vaccines

A single-dose Arexvy vaccine consists of two components: a lyophilised,

2. WA ELIGIBILITY CRITERIA FOR NIRSEVIMAB: CONDITIONS AT INCREASED RISK FOR SEVERE RSV DISEASE[42,43]

- Cardiac disease with a haemodynamic impairment, including
  - cyanotic heart disease
  - acyanotic heart disease, such as a VSD requiring heart failure treatment
  - cardiomyopathy (congenital or acquired)
- Chronic respiratory conditions, including
  - chronic lung disease of prematurity or bronchopulmonary dysplasia requiring medical support (chronic corticosteroid treatment, diuretic therapy or supplemental oxygen) at any time in the six months before the start of the second RSV season
  - need for respiratory support, such as tracheostomy or noninvasive ventilation (BiPAP or CPAP)
- Premature infants:
  - born at ≤28 weeks' gestation
  - born at >28 to ≤32 weeks' gestation
  - aged <12 months at the beginning of the RSV season
- Neuromuscular disorders that impair respiratory function, including
  - SMA
  - cerebral palsy
  - metabolic disorders with neuro/muscular impairment
- Immunocompromising conditions, including
  - primary immunodeficiencies, such as severe combined immunodeficiency disease, congenital agammaglobulinemia, post-haematopoietic stem cell transplant
  - post-solid organ transplant
  - end-stage organ disease (awaiting transplant)
  - those on highly immunosuppressive therapy or completed in the last six months
- Congenitally diagnosed genetic conditions that impair respiratory function, including
  - trisomy 21

Abbreviations: BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; RSV = respiratory syncytial virus; SMA = spinal muscular atrophy; VSD = ventricular septic defect; WA = Western Australia.

3. QUEENSLAND ELIGIBILITY CRITERIA FOR NIRSEVIMAB: COMPLEX MEDICAL CONDITIONS[44,45]

- Prematurity (infants born at <32 weeks' gestation AND aged <12 months)
- Chronic neonatal lung disease (neonates requiring home oxygen or other respiratory support aged <20 months
- Infants aged <20 months with significant respiratory conditions requiring respiratory support such as tracheostomy, noninvasive ventilation (BiPAP or CPAP) or cystic fibrosis with severe lung disease or weight for length of less than 10th percentile
- Infants with haemodynamically significant congenital heart disease, aged <20 months
- Severe primary immunodeficiency (at the clinical discretion of a paediatric immunologist), aged <20 months AND not yet received curative treatment
- Trisomy 21, aged <20 months
- Infants aged <20 months post-solid organ transplant or end-stage organ disease, awaiting transplant
- Infants aged <20 months AND currently receiving active chemotherapy
- Infants aged <20 months within 28 days prior to HSCT or prior to engraftment post-HSCT
- Infants aged <20 months with neuromuscular disorders and associated with significantly impaired respiratory function, such as SMA
- Other infants aged <20 months by exception only with complex medical conditions after discussion with paediatric infectious diseases specialist

Abbreviations: BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; HSCT = haematopoietic stem cell transplantation; RSV = respiratory syncytial virus; SMA = spinal muscular atrophy.

freeze-dried powder in a 3 mL glass vial with a stopper, containing RSV glycoprotein prefusion F stabilised in the prefusion conformation, and a liquid suspension in a 3 mL glass vial with a stopper, containing the GSK proprietary $AS01_E$ liposome-based adjuvant system. After reconstitution, one 0.5 mL dose contains 120 micrograms of RSVPreF3 antigen adjuvanted with $AS01_E$. Prior to reconstitution, it must be stored at 2°C to 8°C and protected from light. Once removed from refrigeration, the vaccine should be reconstituted and used within four hours or discarded. Administration is via an intramuscular injection, preferably in the deltoid muscle. Arexvy may be given concomitantly with other vaccines in older adults, including SARS-CoV-2, seasonal influenza, pneumococcal and recombinant zoster (Shingrix) vaccines.[24]

Each single-dose Abrysvo vaccine consists of three components: sterile water diluent in a 1 mL prefilled type 1 glass syringe with a stopper and a tip cap, lyophilised RSVpreF vaccine in a 2 mL type 1 glass or equivalent vial with a stopper, and a vial adapter. Following reconstitution, one 0.5 mL dose contains 60 micrograms of RSV subgroup A stabilised prefusion F glycoprotein, and 60 micrograms of RSV subgroup B stabilised prefusion F glycoprotein. Prior to reconstitution, it must be stored in its original packaging in a refrigerator at 2°C to 8°C. After reconstitution, Abrysvo should be administered within four hours (maximum room temperature <30°C) and must not be re-stored in a refrigerator (2°C to 8°C) or allowed to freeze. Administration is via an intramuscular injection, preferably in the deltoid muscle.

4. NSW ELIGIBILITY CRITERIA FOR NIRSEVIMAB: OTHER VULNERABLE INFANTS[46]

Infants with chronic neonatal lung disease (neonates requiring home oxygen or other respiratory support at 36 weeks or older corrected age), aged <12 months

Infants with haemodynamically significant congenital heart disease, aged <24 months

Infants with other conditions, including:*

- combined immunodeficiency, aged <24 months AND not yet received curative treatment
- trisomy 21, aged <12 months
- other paediatric chronic and complex conditions that significantly impair respiratory function, aged <12 months
- children within 28 days before HSCT or prior to engraftment after HSCT, aged <24 months

Abbreviations: HSCT = haematopoietic stem cell transplantation; NSW = New South Wales.
*At clinician's judgement in consultation with specialist paediatric infectious diseases physician, specialist in paediatric immunisation or designated nirsevimab program lead at a NSW Health facility. This group includes children with conditions or disorders requiring continuous home oxygen or respiratory support including neurological conditions, congenital malformations of the upper and/or lower airways and chronic suppurative lung diseases including cystic fibrosis with severe respiratory function impairment.

Efficacy and safety of RSV vaccines

In an ongoing phase 3 clinical trial, a single dose of Arexvy in adults aged 60 years and older (n=24,966 at interim analysis) demonstrated 82.6% efficacy in preventing symptomatic, laboratory-confirmed RSV LRTD (primary endpoint a), 94.1% efficacy against severe RSV LRTD (primary endpoint b) and 71.7% efficacy against RSV-associated acute respiratory infection (secondary endpoint), compared with placebo.[51] The vaccine maintained its protective effects throughout the first RSV season (median follow-up: 6.7 months) and was well tolerated, with the most common side effects being mild to moderate injection-site reactions and systemic symptoms, such as fatigue and headache. Recent results analysing one Arexvy dose through a second RSV season (up to 22 months following vaccination) showed a modest, although reduced, efficacy of 67.2% against laboratory-confirmed RSV LRTD, and 78.8% against severe RSV LRTD.[52] Revaccination at the beginning of the second season showed no change in efficacy.

Abrysvo demonstrated similar efficacy and safety results in adults aged 60 years and older in the continuing phase 3 RENOIR trial.[53] Interim analysis (n=34,284) after the first RSV season (mean follow-up, seven months) showed a 66.7% efficacy in preventing laboratory-confirmed RSV LRTI with two or more signs or symptoms (primary endpoint a), an 85.7% efficacy against RSV LRTI with

TABLE 2. KEY CHARACTERISTICS AND CLINICAL TRIAL-RELATED DEFINITIONS FOR THE RSV VACCINES AREXVY AND ABRYSVO[47,50-66]

Characteristic	Arexvy (RSVPreF3 OA; GlaxoSmithKline)	Abrysvo (RSVpreF vaccine; Pfizer)
Vaccine type	Recombinant, protein-based subunit	Recombinant, protein-based subunit
	Single-valent, derived from RSV-A strain, with proprietary adjuvant $AS01_E$	Bivalent, containing both circulating RSV-A and RSV-B glycoproteins
Vaccine target	RSV F glycoprotein	RSV F glycoprotein
Developmental phase	Phase 3, continuing	Phase 3, continuing
Target population	Adults aged ≥60 years	• Adults aged ≥60 years, and • Pregnant women between 24-36 weeks' gestation
Dosage	Single intramuscular injection	Single intramuscular injection
Primary endpoint	a. Prevention of LRTD b. Prevention of severe RSV LRTD	a. Prevention of LRTI with at least two signs or symptoms b. Prevention of LRTI with at least three signs or symptoms
Secondary endpoint	Prevention of RSV-associated acute respiratory infection	Prevention of RSV-associated acute respiratory disease
Indicated for pregnant women	No	Yes
Regulatory status in Australia	TGA approved; available via private prescription only	TGA approved; available via private prescription only
NIP funded	No; to be considered at the July 2024 meeting of the PBAC[47]	Recommended for NIP listing in May 2024 by the PBAC;[66] awaiting ministerial approval

Definitions

***Arexvy trials*[50-52,54,55]**

- **LRTD:** at least two lower respiratory signs or symptoms (including at least one lower respiratory sign) or at least three lower respiratory signs or symptoms lasting for at least 24 hours
- **Lower respiratory symptoms:** new or increased sputum, new or increased cough, new or increased dyspnoea
- **Lower respiratory signs:** new or increased wheezing, new or increased crackles/rhonchi based on chest auscultation, respiratory rate ≥20 respirations/min, low or decreased oxygen saturation (<95% or ≤90% if pre-season baseline is <95%), need for oxygen supplementation
- **Severe RSV LRTD:** either (i) at least two lower respiratory signs and an LRTD episode assessed as 'severe' by the investigator, or (ii) presence of an LRTD with at least one of the following criteria: need for oxygen supplementation, or need for positive airway pressure therapy (e.g. continuous positive airway pressure), or need for other types of mechanical ventilation
- **Acute respiratory infection:** at least two respiratory symptoms or signs or at least one respiratory and one systemic symptom or sign lasting for at least 24 hours
- **Respiratory symptoms and signs:** nasal congestion/rhinorrhoea, sore throat, new or increased sputum, new or increased cough, new or increased dyspnoea, new or increased wheezing, new or increased crackles/rhonchi based on chest auscultation, respiratory rate ≥20 respirations/min, low or decreased oxygen saturation (<95% or ≤90% if pre-season baseline is <95%), need for oxygen supplementation
- **Systemic symptoms and signs:** fever ≥38.0°C or feverishness, fatigue, body aches, headache, decreased appetite

***Abrysvo trials*[53,56-65]**

- **LRTI:** either (i) at least two signs or symptoms (i.e. cough, wheezing, sputum production, shortness of breath or tachypnoea [≥25 breaths/min or ≥15% increase from resting baseline]) lasting more than one day, or (ii) at least three signs or symptoms (indicating a worse clinical disease presentation) lasting more than one day
- **Severe RSV LRTI:** a subset of RSV LRTI with at least two signs or symptoms, including cases hospitalised for RSV LRTI, requiring new or increased oxygen supplementation or requiring new or increased mechanical ventilation (including continuous positive airway pressure, noninvasive positive pressure ventilation or bilevel positive airway pressure)
- **Acute respiratory disease:** at least one symptom (sore throat, cough, nasal congestion or discharge, wheezing, sputum production or shortness of breath, any of which were new or had increased in intensity)

Abbreviations: LRTD = lower respiratory tract disease; LRTI = lower respiratory tract illness; NIP = National Immunisation Program; PBAC = Pharmaceutical Benefits Advisory Committee; RSV = respiratory syncytial virus.

5. MEDICAL CONDITIONS ASSOCIATED WITH AN INCREASED RISK OF RSV DISEASE COMPLICATIONS FOR WHICH RSV VACCINATION IS RECOMMENDED IN ADULTS AGED ≥60 YEARS*[24]

Cardiac disease
- Congenital heart disease
- Congestive heart failure
- Coronary artery disease

Chronic respiratory disease
- Suppurative lung disease
- Bronchiectasis
- Cystic fibrosis
- Chronic obstructive pulmonary disease
- Chronic emphysema
- Severe asthma (requiring frequent medical consultations or the use of multiple medicines)

Immunocompromising conditions
- HIV infection
- Malignancy
- Immunocompromise due to disease or treatment
- Asplenia or splenic dysfunction
- Solid organ transplant
- Haematopoietic stem cell transplant
- Chimeric antigen receptor T-cell therapy

Chronic metabolic disorder
- Type 1 or 2 diabetes
- Amino acid disorders
- Carbohydrate disorders
- Cholesterol biosynthesis disorders
- Fatty acid oxidation defects
- Mitochondrial disorders
- Organic acid disorders
- Urea cycle disorders
- Vitamin/cofactor disorders
- Porphyria

Chronic kidney disease stage
- Stage 4 or 5

Chronic neurological condition
- Hereditary and degenerative central nervous system diseases
- Seizure disorders
- Spinal cord injuries
- Neuromuscular disorders
- Conditions that increase respiratory infection risk

Abbreviation: RSV = respiratory syncytial virus.
* These examples are not exhaustive, and providers may include individuals with conditions similar to those listed above based on clinical judgement.

three or more signs or symptoms (primary endpoint b) and a 62.1% efficacy against RSV-associated acute respiratory disease (secondary endpoint), compared with placebo. The Abrysvo vaccine was also well tolerated, with common side effects including mild to moderate injection-site reactions and fatigue. Results through a second RSV season included in a recent Pfizer press release,[70] although not yet peer-reviewed and published, revealed a vaccine efficacy of 65.1% against two or more signs or symptoms after the first season, and 55.7% following the completion of the second season. Even more notable is an efficacy of 88.9% after the first and 77.8% at the conclusion of the second season against three or more signs or symptoms.

The side effects with both vaccines are generally mild, and include soreness at the injection site, fatigue and low-grade fever, with serious adverse reactions being rare.[68,69]

Agents on the horizon

Several promising medicines for treating RSV infection are in development. These include next-generation antivirals, such as RSV fusion inhibitors and RNA polymerase inhibitors, designed to target critical steps in the viral replication cycle.

In a collaborative study involving Australian researchers, sisunatovir (RV521), an oral inhibitor of RSV fusion to host cells, demonstrated oral bioavailability ranging from 42% to 100% and efficient penetration into lung tissue.[71] Furthermore, in healthy adult volunteers experimentally infected with RSV, the use of sisunatovir had a potent antiviral effect, significantly reducing both the viral load and symptoms.[71] Another potent, orally bioavailable protein inhibitor, ziresovir (AK0529), in a recently published phase 2 study involving hospitalised infants aged 1 to 24 month(s) with RSV infection (including 20 from subtropical regions of Australia), showed a reduction in viral load with 2 mg/kg twice-daily dosing compared with placebo.[72] Disease remission by day 5 was also achieved in 73% of patients compared with 31% receiving placebo (p=0.0412). Rilematovir (JNJ-53718678), another oral RSV fusion inhibitor, significantly reduced the viral load and clinical disease severity in a phase 2 trial.[73] A subsequent double-blind, phase 2a trial showed that individuals receiving rilematovir experienced greater reductions in RSV RNA viral loads and faster resolution of key RSV symptoms compared with placebo.[74] However, among the subset of high-risk adults (36% of participants), no significant efficacy was observed and, given the small sample size, data interpretation is problematic.

Although these new agents aim to provide more effective treatment options with improved safety profiles compared with existing therapies, such as ribavirin, none of these novel therapies appear close to regulatory approval at the time of writing this article. Additionally, many vaccines and monoclonal antibodies are in various stages of development (see Table 3),[75-77] with some targeting different viral epitopes and alternative pathways for controlling RSV infection.

In late May 2024, the US FDA approved mRESVIA (mRNA-1345, Moderna), an mRNA vaccine to protect adults aged 60 years and older from RSV LRTD.[75] This approval was based, in part, on an initial analysis (median follow up, 3.3 months) of the phase 2/3 ConquerRSV trial , which showed that the efficacy of mRESVIA was 83.7% against RSV-associated LRTD with at least two signs or symptoms and 82.4% with at least three signs or symptoms, compared with placebo.[78,79] No serious safety concerns emerged, with the most frequent adverse effects being injection site pain and fatigue. However, at a meeting of the US Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices on 26 June 2024, Moderna presented updated mRESVIA vaccine data (median follow-up, 18.8 months) demonstrating a reduction in efficacy to just 50.3% for

RSV-associated LRTD with at least two signs or symptoms, and 49.9% in those with at least three signs or symptoms.[79] Despite the lower than expected efficacy, Moderna claims the single-dose regimen in a convenient prefilled syringe containing 50 micrograms of modified mRNA sequence encoding the stabilised prefusion F glycoprotein will save vaccinators' time and reduce the risk of administration error.[79] Following the recent European Medicines Agency's Committee for Medicinal Products for Human Use positive opinion recommending the granting of marketing authorisation for mRESVIA in the EU (now pending European Commission approval), Moderna is currently preparing further approval applications for multiple countries, including Australia.[80]

Current challenges of available preventives

The implementation of nirsevimab and RSV vaccines in Australia faces several significant challenges that must be addressed to optimise the prevention and control of RSV infection.

Access and funding

One of the primary challenges in the prevention and control of RSV infection in Australia is the varied access to nirsevimab across different regions. Currently, only two states – WA and Queensland – have made nirsevimab freely accessible to all infants, as well as several paediatric groups at increased risk of severe RSV disease, whereas NSW provides limited access to infants with a narrow range of paediatric medical conditions. This lack of a national approach results in unequal protection against RSV infection, leaving children in other states without access to this vital prophylactic measure and exacerbating disparities in healthcare provision and outcomes.

Additionally, funding issues pose a significant barrier, particularly with the RSV vaccines not included in the National Immunisation Program (NIP) for older

TABLE 3. STATUS OF RSV VACCINES AND MONOCLONAL ANTIBODIES IN DEVELOPMENT (AS OF JULY 2024)[75-77]

Class	Manufacturer / target	Phase (target population)			Market approval
		1	2	3	
Live-attenuated/ chimeric vaccine	Blue Lake *PIV5 RSV*	O	P		
	Codagenix, LID/ NIAID/NIH *RSV*	P			
	Meissa Vaccines *RSV*		P		
	Sanofi, LID/NIAID/NIH *RSV*			P	
Protein-based vaccine	NIH/NIAID/VRC *RSV F Protein*	O, M			
	Clover Biopharma *RSV F Protein*	O, M			
	Virometix *VLP*	NS			
	Advaccine Biotechnology *RSV G Protein*		O, P		
	Daiichi Sankyo *Protein*		O		
	Icosavax *RSV/hMPV VLP*		O		
Nucleic acid vaccine	Innorna *RNA*	O			
	Moderna *RNA*		M, P		
	Sanofi *RNA*		O		
	mRESVIA (mRNA-1345), Moderna *RNA*				O May 2024 FDA approved[75]
Immunoprophylaxis (monoclonal antibody)	Gates MRI *Anti-F mAb*	P			
	Trinomab Biotechnology *Anti-F mAb*		P		
	Clesrovimab (MK-1654), Merck *Anti-F mAb*			P	

Abbreviations: hMPV = human metapneumovirus; LID = Laboratory of Infectious Diseases; M = maternal; mAb = monoclonal antibody; NIAID = National Institute of Allergy and Infectious Diseases; NIH = National Institute of Health; NS = not stated; O = older people; P = paediatric; PIV5 = parainfluenza virus 5-vectored; VLP = virus-like particles; VRC = Vaccine Research Center.
Adapted from: NCIRS. Summary of RSV Immunisation Product Efficacy and Safety as at 5 July 2024;[76] and PATH. RSV Vaccine and mAb Snapshot. PATH; 2024.[77]

individuals. The absence of NIP funding means they may only be available via private prescription, limiting their accessibility to those who can afford about $320 per dose. This financial barrier prevents widespread uptake and diminishes the potential public health impact of the vaccine. Advocacy for NIP inclusion of RSV preventives and interim funding solutions are necessary to broaden access and ensure equitable protection against RSV infection.

Timing challenges related to regional seasonality

Australia's diverse climate results in different RSV infection seasonality patterns across regions, complicating the timing of immunisation campaigns. For example, RSV activity peaks during the winter months in temperate regions, whereas tropical areas experience year-round circulation with seasonal spikes. This variability makes it challenging to implement a uniform timing strategy for nirsevimab administration and RSV vaccination, potentially impacting the effectiveness of these interventions. In contrast to nirsevimab administration targeted to cover the RSV season only, the UK is considering a year-round immunisation strategy for all infants at birth.[81] This approach aims to simplify implementation and address the unpredictability of RSV season onset and duration, although if adopted in Australia, it may offer limited benefit to infants born in temperate regions during spring or early summer. Data from countries using nirsevimab may provide valuable insights for optimising and implementing this strategy.

Vaccine hesitancy and public trust

The landscape of vaccine uptake has been significantly affected by the COVID-19 pandemic, leading to increased vaccine hesitancy, misinformation and a general lack of trust in public health initiatives. This hesitancy extends to new vaccines and, coupled with low public awareness of RSV infection, poses substantial additional barriers to achieving high coverage rates. Public health campaigns must address these concerns directly, providing clear, evidence-based information to rebuild trust and encourage vaccine acceptance.

Confusion over maternal vaccination and nirsevimab

There is considerable confusion among healthcare providers and the public regarding the roles of maternal vaccination and nirsevimab. Maternal vaccination aims to confer passive immunity to newborns through the transplacental transfer of antibodies, whereas nirsevimab provides direct passive immunisation to infants. The simultaneous availability of these two prophylactic options may lead to uncertainty about the best approach for protecting infants, particularly concerning the timing and co-ordination of these interventions. Clear guidelines and education are required to delineate the complementary roles of these preventive measures.

Conclusion

The recent introduction of new vaccines and monoclonal antibodies marks a pivotal shift in the prevention and management of RSV infection. Arexvy, Abrysvo and nirsevimab offer significant improvements over previous interventions, promising to reduce the burden of RSV-related illness, particularly in high-risk populations. However, challenges remain in ensuring broad access and addressing gaps in protection across all age groups. Ongoing research and development are essential to build on these advancements and achieve comprehensive control of RSV. MT

References

A list of references is included in the online version of this article (www.medicinetoday.com.au).

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Revolutionising RSV infection prevention and control

Unveiling new options in the fight against RSV

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References

1. Kim HW, Canchola JG, Brandt CD, et al. Respiratory syncytial virus disease in infants despite prior administration of antigenic inactivated vaccine. Am J Epidemiol 1969; 89: 422-434.
2. Woolnough E, Wade A, Sasadeusz J. Ribavirin. In: Grayson ML, Cosgrove SE, Crowe SM, et al., eds. Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs. 7th ed. Boca Raton, FL: Taylor & Francis Group; 2017. p. 4367-4408.
3. Ison MG. Antiviral treatments. Clin Chest Med 2017; 38: 139-153.
4. Marcelin JR, Wilson JW, Razonable RR; Mayo Clinic Hematology/Oncology and Transplant Infectious Diseases Services. Oral ribavirin therapy for respiratory syncytial virus infections in moderately to severely immunocompromised patients. Transpl Infect Dis 2014; 16: 242-250.
5. Wongsurakiat P, Sunhapanit S, Muangman N. Respiratory syncytial virus-associated acute respiratory illness in adult non-immunocompromised patients: outcomes, determinants of outcomes, and the effect of oral ribavirin treatment. Influenza Other Respir Viruses 2022; 16: 767-779.
6. de Zwart A, Riezebos-Brilman A, Lunter G, et al. Respiratory syncytial virus, human metapneumovirus, and parainfluenza virus infections in lung transplant recipients: a systematic review of outcomes and treatment strategies. Clin Infect Dis 2022; 74: 2252-2260.
7. Ventre K, Randolph AG. Ribavirin for respiratory syncytial virus infection of the lower respiratory tract in infants and young children. Cochrane Database Syst Rev 2007; (1): CD000181.
8. Chemaly RF, Aitken SL, Wolfe CR, Jain R, Boeckh MJ. Aerosolized ribavirin: the most expensive drug for pneumonia. Transpl Infect Dis 2016; 18: 634-636.
9. Gatt D, Martin I, AlFouzan R, Moraes TJ. Prevention and treatment strategies for respiratory syncytial virus (RSV). Pathogens 2023; 12: 154.
10. Trang TP, Whalen M, Hilts-Horeczko A, Doernberg SB, Liu C. Comparative effectiveness of aerosolized versus oral ribavirin for the treatment of respiratory syncytial virus infections: a single-center retrospective cohort study and review of the literature. Transpl Infect Dis 2018; 20: e12844.
11. Foolad F, Aitken SL, Shigle TL, et al. Oral versus aerosolized ribavirin for the treatment of respiratory syncytial virus infections in hematopoietic cell transplant recipients. Clin Infect Dis 2019; 68: 1641-1649.
12. Burrows FS, Carlos LM, Benzimra M, et al. Oral ribavirin for respiratory syncytial virus infection after lung transplantation: efficacy and cost-efficiency. J Heart Lung Transplant 2015; 34: 958-962.
13. The PREVENT Study Group. Reduction of respiratory syncytial virus hospitalization among premature infants and infants with bronchopulmonary dysplasia using respiratory syncytial virus immune globulin prophylaxis. Pediatrics 1997; 99: 93-99.
14. Simoes EA, Sondheimer HM, Top FH, Jr et al. Respiratory syncytial virus immune globulin for prophylaxis against respiratory syncytial virus disease in infants and children with congenital heart disease. The Cardiac Study Group. J Pediatr 1998; 133: 492-499.
15. Johnson S, Oliver C, Prince GA, et al. Development of a humanized monoclonal antibody (MEDI-493) with potent in vitro and in vivo activity against respiratory syncytial virus. J Infect Dis 1997; 176: 1215-1224.
16. Sanders SL, Agwan S, Hassan M, Bont LJ, Venekamp RP. Immunoglobulin treatment for hospitalised infants and young children with respiratory syncytial virus infection. Cochrane Database Syst Rev 2023; 10: CD009417.
17. Therapeutic Goods Administration. SYNAGIS palivizumab (rmc) 100 mg / 1 mL solution for injection vial (231139). Australian Register of Therapeutic Goods. Canberra: Australian Government Department of Health and Aged Care; 2023. Available online at: https://www.tga.gov.au/resources/artg/231139 (accessed July 2024).
18. The IMpact-RSV Study Group. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. Pediatrics 1998; 102: 531-537.
19. Anderson EJ, Carosone-Link P, Yogev R, Yi J, Simões EAF. Effectiveness of palivizumab in high-risk infants and children. Pediatr Infect Dis J 2017; 36: 699-704.
20. Therapeutic Goods Administration. Australian public assessment report for Beyfortus. Canberra: Australian Government Department of Health and Aged Care; 2024. 38p. Available online at: https://www.tga.gov.au/sites/default/files/2024-04/auspar-beyfortus-240412.pdf (accessed July 2024).
21. Walsh EE, Englund JA. Respiratory syncytial virus. In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 9th ed. Elsevier; 2020. p. 2093-2103.e6.
22. Robbie GJ, Criste R, Dall'acqua WF, et al. A novel investigational Fc-modified humanized monoclonal antibody, motavizumab-YTE, has an extended half-life in healthy adults. Antimicrob Agents Chemother 2013; 57: 6147-6153.
23. Griffin MP, Khan AA, Esser MT, et al. Safety, tolerability, and pharmacokinetics of MEDI8897, the respiratory syncytial virus prefusion F-targeting monoclonal antibody with an extended half-life, in healthy adults. Antimicrob Agents Chemother 2017; 61: e01714-16.
24. Australian Immunisation Handbook. Respiratory syncytial virus (RSV). Canberra: Australian Government Department of Health and Aged Care; 2024. Available online at: https://immunisationhandbook.health.gov.au/contents/vaccine-preventable-diseases/respiratory-syncytial-virus-rsv (accessed July 2024).
25. McLellan JS, Chen M, Leung S, et al. Structure of RSV fusion glycoprotein trimer bound to a prefusion-specific neutralizing antibody. Science 2013; 340: 1113-1117.
26. Zhu Q, McLellan JS, Kallewaard NL, et al. A highly potent extended half-life antibody as a potential RSV vaccine surrogate for all infants. Sci Transl Med 2017; 9: eaaj1928.
27. Therapeutic Goods Administration. Australian Product Information – Beyfortus (Nirsevimab) Solution for Injection (Sanofi-Aventis Australia Pty Ltd). Australian Register of Therapeutic Goods. Canberra: Australian Government Department of Health and Aged Care; 2023. Available online at: https://www.tga.gov.au/resources/artg/397898 (accessed July 2024).

28. Griffin MP, Yuan Y, Takas T, et al. Single-dose nirsevimab for prevention of RSV in preterm infants. N Engl J Med 2020; 383: 415-425.
29. Hammitt LL, Dagan R, Yuan Y, et al. Nirsevimab for prevention of RSV in healthy late-preterm and term infants. N Engl J Med 2022; 386: 837-846.
30. Domachowske J, Madhi SA, Simoes EAF, et al. Safety of nirsevimab for RSV in infants with heart or lung disease or prematurity. N Engl J Med 2022; 386: 892-894.
31. Drysdale SB, Cathie K, Flamein F, et al. Nirsevimab for prevention of hospitalizations due to RSV in infants. N Engl J Med 2023; 389: 2425-2435.
32. Paireau J, Durand C, Raimbault S, et al. Nirsevimab effectiveness against cases of respiratory syncytial virus bronchiolitis hospitalised in paediatric intensive care units in France, September 2023 – January 2024. Influenza Other Respir Viruses 2024; 18: e13311.
33. Ernst C, Bejko D, Gaasch L, et al. Impact of nirsevimab prophylaxis on paediatric respiratory syncytial virus (RSV)-related hospitalisations during the initial 2023/24 season in Luxembourg. Euro Surveill 2024; 29: 2400033.
34. Estrella-Porter P, Blanco-Calvo C, Lameiras-Azevedo AS, et al. Effectiveness of nirsevimab introduction against respiratory syncytial virus in the Valencian Community: a preliminary assessment. Vaccine 2024 Jun 3; e-pub (https://doi.org/10.1016/j.vaccine.2024.05.078).
35. Ezpeleta G, Navascues A, Viguria N, et al. Effectiveness of nirsevimab immunoprophylaxis administered at birth to prevent infant hospitalisation for respiratory syncytial virus infection: a population-based cohort study. Vaccines (Basel) 2024; 12: 383.
36. Lopez-Lacort M, Munoz-Quiles C, Mira-Iglesias A, et al. Early estimates of nirsevimab immunoprophylaxis effectiveness against hospital admission for respiratory syncytial virus lower respiratory tract infections in infants, Spain, October 2023 to January 2024. Euro Surveill 2024; 29: 2400046.
37. Mazagatos C, Mendioroz J, Rumayor MB, et al. Estimated impact of nirsevimab on the incidence of respiratory syncytial virus infections requiring hospital admission in children < 1 year, weeks 40, 2023, to 8, 2024, Spain. Influenza Other Respir Viruses 2024; 18: e13294.
38. Moline HL, Tannis A, Toepfer AP, et al. Early estimate of nirsevimab effectiveness for prevention of respiratory syncytial virus-associated hospitalization among infants entering their first respiratory syncytial virus season - new vaccine surveillance network, October 2023 – February 2024. MMWR Morb Mortal Wkly Rep 2024; 73: 209-214.
39. Dagan R, Hammitt LL, Seoane Nunez B, et al. Infants receiving a single dose of nirsevimab to prevent RSV do not have evidence of enhanced disease in their second RSV season. J Pediatric Infect Dis Soc 2024; 13: 144-147.
40. Jones JM, Fleming-Dutra KE, Prill MM, et al. Use of nirsevimab for the prevention of respiratory syncytial virus disease among infants and young children: recommendations of the advisory committee on immunization practices – United States, 2023. MMWR Morb Mortal Wkly Rep 2023; 72: 920-925.
41. American Academy of Pediatrics (AAP). AAP recommendations for the prevention of RSV disease in infants and children. Itasca, IL: AAP; 2024. Available online at: https://publications.aap.org/redbook/resources/25379/AAP-Recommendations-for-the-Prevention-of-RSV (accessed July 2024).
42. Respiratory syncytial virus (RSV) infant immunisation program: quick reference guide. Perth: Western Australia Government Department of Health; 2024. 2p. Available online at: https://www.health.wa.gov.au/~/media/Corp/Documents/Health-for/Immunisation/RSV/RSV-fact-sheet-quick-reference.pdf (accessed July 2024).
43. Respiratory Syncytial Virus (Rsv) infant immunisation program: fact sheet for providers. Perth: Western Australia Government Department of Health; 2024. 3p. Available online at: https://www.health.wa.gov.au/~/media/Corp/Documents/Health-for/Immunisation/RSV/RSV-Fact-Sheet-Providers.pdf (accessed July 2024).
44. Queensland Paediatric Respiratory Syncytial Virus Prevention Program. Brisbane: Queensland Health; 2024. Available online at: https://www.health.qld.gov.au/clinical-practice/guidelines-procedures/diseases-infection/immunisation/paediatric-rsv-prevention-program (accessed July 2024).
45. Queensland Paediatric Respiratory Syncytial Virus Prevention Program: clinical guidance for immunisation service providers 2024, Version 1.4. Brisbane: Queensland Health; 2024. 17p. Available online at: https://www.health.qld.gov.au/__data/assets/pdf_file/0017/1322144/rsv-prevention-program-clinical-guide.pdf (accessed July 2024).
46. Frequently asked questions about Beyfortus™ (nirsevimab) for health professionals. Sydney: New South Wales Ministry of Health; 2024. Available online at: https://www.health.nsw.gov.au/immunisation/Pages/nirsevimab-professionals.aspx#who (accessed July 2024).
47. Pharmaceutical Benefits Advisory Committee (PBAC) Meeting Agenda – July 2024 PBAC Meeting (Version 4). Canberra: Australian Government Department of Health and Aged Care; 2024. 31p. Available online at: https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/agenda/pdf/2024/PBAC-meeting-agenda-July-2024-v4.pdf (accessed July 2024).
48. Therapeutic Goods Administration. Australian Public Assessment Report for Arexvy. Canberra: Australian Government Department of Health and Aged Care; 2024. 34p. Available online at: https://www.tga.gov.au/sites/default/files/2024-05/auspar-arexvy-240503.pdf (accessed July 2024).
49. Therapeutic Goods Administration. Australian Public Assessment Report for Abrysvo. Canberra: Australian Government Department of Health and Aged Care; 2024. 59p. Available online at: https://www.tga.gov.au/sites/default/files/2024-05/auspar-abrysvo-240502.pdf (accessed July 2024).
50. Leroux-Roels I, Davis MG, Steenackers K, et al. Safety and immunogenicity of a respiratory syncytial virus prefusion F (RSVPreF3) candidate vaccine in older adults: phase 1/2 randomized clinical trial. J Infect Dis 2023; 227: 761-772.
51. Papi A, Ison MG, Langley JM, et al. Respiratory syncytial virus prefusion F protein vaccine in older adults. N Engl J Med 2023; 388: 595-608.
52. Ison MG, Papi A, Athan E, et al. Efficacy and safety of respiratory syncytial virus (RSV) prefusion F protein vaccine (RSVPreF3 OA) in older adults over 2 RSV seasons. Clin Infect Dis 2024; 78: 1732-1744.
53. Walsh EE, Perez Marc G, Zareba AM, et al. Efficacy and safety of a bivalent RSV prefusion F vaccine in older adults. N Engl J Med 2023; 388: 1465-1477.
54. Sacconnay L, De Smedt J, Rocha-Perugini V, et al. The RSVPreF3-AS01 vaccine elicits broad neutralization of contemporary and antigenically distant respiratory syncytial virus strains. Sci Transl Med 2023; 15: eadg6050.
55. Dieussaert I, Hyung Kim J, Luik S, et al. RSV prefusion F protein-based maternal vaccine – preterm birth and other outcomes. N Engl J Med 2024; 390: 1009-1021.
56. Schmoele-Thoma B, Zareba AM, Jiang Q, et al. Vaccine efficacy in adults in a respiratory syncytial virus challenge study. N Engl J Med 2022; 386: 2377-2386.
57. Baber J, Arya M, Moodley Y, et al. A phase 1/2 study of a respiratory syncytial virus prefusion F vaccine with and without adjuvant in healthy older adults. J Infect Dis 2022; 226: 2054-2063.
58. Simoes EAF, Center KJ, Tita ATN, et al. Prefusion F protein-based respiratory syncytial virus immunization in pregnancy. N Engl J Med 2022; 386: 1615-1626.
59. Walsh EE, Falsey AR, Scott DA, et al. A randomized phase 1/2 study of a respiratory syncytial virus prefusion F vaccine. J Infect Dis 2022; 225: 1357-1366.
60. Kampmann B, Madhi SA, Munjal I, et al. Bivalent prefusion F vaccine in pregnancy to prevent RSV illness in infants. N Engl J Med 2023; 388: 1451-1464.
61. Alvarez Aldean J, Rivero Calle I, Rodriguez Fernandez R, et al. Cost-effectiveness analysis of maternal immunization with RSVpreF vaccine for the prevention of respiratory syncytial virus among infants in Spain. Infect Dis Ther 2024; 13: 1315-1331.
62. Athan E, Baber J, Quan K, et al. Safety and immunogenicity of bivalent RSVpreF vaccine coadministered with seasonal inactivated influenza vaccine in older

adults. Clin Infect Dis 2024; 78: 1360-1368.
63. Baker J, Aliabadi N, Munjal I, et al. Equivalent immunogenicity across three RSVpreF vaccine lots in healthy adults 18-49 years of age: results of a randomized phase 3 study. Vaccine 2024; 42: 3172-3179.
64. Otsuki T, Akada S, Anami A, et al. Efficacy and safety of bivalent RSVpreF maternal vaccination to prevent RSV illness in Japanese infants: subset analysis from the pivotal randomized phase 3 MATISSE trial. Vaccine 2024 Jun 8; e-pub (https://doi.org/10.1016/j.vaccine.2024.06.009).
65. Walsh EE, Falsey AR, Zareba AM, et al. Respiratory syncytial virus prefusion F vaccination: antibody persistence and revaccination. J Infect Dis 2024 Apr 12; e-pub (https://doi.org/10.1093/infdis/jiae185).
66. Pharmaceutical Benefits Advisory Committee (PBAC) meeting outcomes – May 2024 PBAC Meeting. Canberra: Australian Government Department of Health and Aged Care; 2024. 8p. Available online at: https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/pbac-outcomes/2024-05/pbac-web-outcomes-05-2024.pdf (accessed July 2024).
67. Ruckwardt TJ. The road to approved vaccines for respiratory syncytial virus. NPJ Vaccines 2023; 8: 138.
68. Therapeutic Goods Administration. Australian Product Information – Arexvy (Recombinant Respiratory Syncytial Virus Pre-Fusion F Protein) Powder and Suspension for Injection (GlaxoSmithKline Australia Pty Ltd). Australian Register of Therapeutic Goods. Canberra: Australian Government Department of Health and Aged Care; 2024. Available online at: https://www.tga.gov.au/sites/default/files/2024-05/auspar-arexvy-240503-pi.pdf (accessed July 2024).
69. Therapeutic Goods Administration. Australian Product Information – Abrysvo (Recombinant Respiratory Syncytial Virus Pre-Fusion F Protein) Vaccine (Pfizer Australia Pty Ltd). Australian Register of Therapeutic Goods. Canberra: Australian Government Department of Health and Aged Care; 2024. Available online at: https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent=&id=CP-2024-PI-01489-1&d=20240528172310101 (accessed July 2024).
70. Pfizer announces positive top-line data for full season two efficacy of ABRYSVO for RSV in older adults. [Press release]. New York, NY: Pfizer; 29 February 2024. Available online at: https://www.pfizer.com/news/press-release/press-release-detail/pfizer-announces-positive-top-line-data-full-season-two (accessed July 2024).
71. Cockerill GS, Angell RM, Bedernjak A, et al. Discovery of sisunatovir (RV521), an inhibitor of respiratory syncytial virus fusion. J Med Chem 2021; 64: 3658-3676.
72. Huang LM, Schibler A, Huang YC, et al. Safety and efficacy of AK0529 in respiratory syncytial virus-infected infant patients: a phase 2 proof-of-concept trial. Influenza Other Respir Viruses 2023; 17: e13176.
73. Stevens M, Rusch S, DeVincenzo J, et al. Antiviral activity of oral JNJ-53718678 in healthy adult volunteers challenged with respiratory syncytial virus: a placebo-controlled study. J Infect Dis 2018; 218: 748-756.
74. Nilsson AC, Pullman J, Napora P, et al. A pilot phase 2a, randomized, double-blind, placebo-controlled study to explore the antiviral activity, clinical outcomes, safety, and tolerability of rilematovir at two dose levels in non-hospitalized adults with respiratory syncytial virus infection. Clin Microbiol Infect 2023; 29: 1320-1327.
75. Moderna receives US FDA approval for RSV vaccine mRESVIAR. [Press release]. Cambridge, MA: Moderna; 2024. Available online at: https://investors.modernatx.com/news/news-details/2024/Moderna-Receives-U.S.-FDA-Approval-for-RSV-Vaccine-mRESVIAR/default.aspx (accessed July 2024).
76. National Centre for Immunisation Research and Surveillance (NCIRS). Summary of RSV Immunisation Product Efficacy and Safety as at 5 July 2024. Sydney: NCIRS; 2024. 17p. Available online at: https://ncirs.org.au/sites/default/files/2024-07/Summary%20of%20RSV%20immunisation%20product%20efficacy%20and%20safety%20as%20at%204%20July%202024.pdf (accessed July 2024).
77. PATH. RSV Vaccine and mAb Snapshot. PATH; 2024. Available online at: https://www.path.org/our-impact/resources/rsv-vaccine-and-mab-snapshot/ (accessed July 2024).
78. Wilson E, Goswami J, Baqui AH, et al. Efficacy and safety of an mRNA-based RSV preF vaccine in older adults. N Engl J Med 2023; 389: 2233-2244.
79. Das R. Overview of Moderna's investigational RSV vaccine (mRNA-1345) in adults ≥ 60 years of age. Paper presented at: Meeting of the Advisory Committee on Immunization Practices (ACIP), Centers for Disease Control and Prevention (CDC); June 26-28, 2024; Atlanta, GA, USA; 2024. Available online at: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2024-02-28-29/02-RSV-Adults-Das-508.pdf (accessed July 2024).
80. European Medicines Agency (EMA). Meeting highlights from the Committee for Medicinal Products for Human Use (CHMP) 24-27 June 2024. Amsterdam: EMA; 2024. Available online at: https://www.ema.europa.eu/en/news/meeting-highlights-committee-medicinal-products-human-use-chmp-24-27-june-2024 (accessed July 2024).
81. Joint Committee on Vaccination and Immunisation (JCVI). Respiratory Syncytial Virus (RSV) Immunisation Programme for Infants and Older Adults: JCVI Full Statement, 11 September 2023. London, UK: United Kingdom Department of Health and Social Care; 2023. Available online at: https://www.gov.uk/government/publications/rsv-immunisation-programme-jcvi-advice-7-june-2023/respiratory-syncytial-virus-rsv-immunisation-programme-for-infants-and-older-adults-jcvi-full-statement-11-september-2023 (accessed July 2024).