



# Approaches to the Prevention and Treatment of Respiratory Syncytial Virus Infection in Children: Rationale and Progress to Date

Charl Verwey<sup>1,2</sup> · Ziyaad Dangor<sup>1,2</sup> · Shabir A. Madhi<sup>2,3</sup>

Accepted: 8 November 2023 / Published online: 30 November 2023  
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## Abstract

Respiratory syncytial virus (RSV) is the most common cause of lower respiratory tract infection (LRTI) in children, and is associated with long-term pulmonary sequelae for up to 30 years after infection. The mainstay of RSV management is supportive therapy such as supplemental oxygen. Palivizumab (Synagis™–AstraZeneca), a monoclonal antibody targeting the RSV F protein site II, has been licensed for the prevention of RSV in high-risk groups since 1998. There has been recent promising progress in preventative strategies that include vaccines and long-acting, high-potency monoclonal antibodies. Nirsevimab (Beyfortus™–AstraZeneca/Sanofi), a monoclonal antibody with an extended half-life, has recently been registered in the European Union and granted licensure by the US Food and Drug Administration. Furthermore, a pre-fusion sub-unit protein vaccine has been granted licensure for pregnant women, aimed at protecting their young infants, following established safety and efficacy in clinical trials (Abrysvo™–Pfizer). Also, multiple novel antiviral therapeutic options are in early phase clinical trials. The next few years have the potential to change the landscape of LRTI through improvements in the prevention and management of RSV LRTI. Here, we discuss these new approaches, current research, and clinical trials in novel therapeutics, monoclonal antibodies, and vaccines against RSV infection in infants and children.

## Key Points

Respiratory syncytial virus (RSV) is the most common cause of respiratory tract infections in children.

There are currently only two medications licensed for the prevention of RSV infection in infants: palivizumab (Synagis™–AstraZeneca) and nirsevimab (Beyfortus™–AstraZeneca/Sanofi).

Steady progress is being made with regard to new potential vaccine candidates targeting vaccination of pregnant woman and their infants, with the recent licensing of the first maternal vaccine against RSV (Abrysvo™–Pfizer).

## 1 Introduction

Lower respiratory tract infections (LRTIs) are the leading cause of death in children under 5 years outside the neonatal period, accounting for approximately 12% of global deaths in children [1, 2]. Most LRTIs in young children are caused

by viruses (60%), of which respiratory syncytial virus (RSV) accounts for the largest portion (31%) [3–5]. RSV is a single-stranded, negative-sense ribonucleic acid (RNA) virus, which is enveloped by a host plasma membrane-derived lipid bilayer. The ten-gene RSV genome encodes for 11 proteins, the two most important ones being transmembrane glycoproteins: attachment protein (G protein) and fusion protein (F protein) [6, 7]. The binding of RSV to the respiratory epithelial cell is enabled by the G protein [8–10], while the F protein mediates fusion between viral and cell membranes, thereby permitting viral penetration into the cell [11]. The F protein possesses two unique forms: before binding to the host cell, a stable pre-fusion conformation, and after binding, a highly stable post-fusion conformation [11, 12].

The range of infections caused by RSV extends across the whole spectrum of respiratory tract infections from asymptomatic upper respiratory tract infection to severe LRTI, and death [13, 14]. The most serious common presentation of RSV infection is bronchiolitis and pneumonia [13]. Most children are infected with RSV during the first year of life, and virtually all have been infected at least once by 2 years of age [15, 16]. RSV most commonly infects term infants, and the severity of the resulting disease is determined through the intensity of the initial infection, such as

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the initial viral load, and the response of the host to the infection [17, 18]. Specific underlying medical conditions predispose the infant to an increased risk of severe disease; these include prematurity, congenital cardiac disease, and bronchopulmonary dysplasia (BPD) [18–23].

In 2019, there were approximately 33.0 million RSV-associated acute LRTIs, 3.6 million RSV-associated acute LRTI hospital admissions, and 66,000–190,000 RSV-attributable deaths in children aged less than 60 months. More than 95% of RSV-associated deaths occur in low- and middle-income countries (LMICs), and 50% of deaths occur in infants less than 6 months of age [24, 25]. RSV LRTI during infancy has been reported to lead to long-term pulmonary sequelae, with multiple studies reporting an increase in recurrent wheezing episodes for at least the first decade after infection, and non-bronchodilator responsive obstructive lung disease [26–36].

The mechanism of transmission of RSV is droplet spread, either via airborne particles or contact with contaminated surfaces. Inoculation occurs through the nasopharyngeal mucosa or conjunctival membranes [37], with an incubation period of 3–5 days, followed by viral spread to the smaller airways [37–40], with subsequent destruction of the epithelium and loss of ciliary motion, as well as indirect host immune response effects [41].

## 2 Immunology of RSV

An understanding of the immunology involved during an RSV infection is imperative in understanding the host's response to an RSV infection, the mechanisms that RSV employ to evade the host's immune system, and the potential targets for prevention and treatment of RSV infection.

Cytotoxic T cell immune responses are essential for the resolution of RSV infection. CD4+ T cells stimulate B cell antibody production, and CD8+ T cells are cytopathic to RSV-infected cells [42]. Acquisition of specific immunological memory, including humoral immune responses, results in neutralizing antibodies and production of RSV-specific cytotoxic T cells, resulting in a lower likelihood of severe disease following subsequent RSV infections [43].

Serum neutralizing antibodies against RSV are associated with a reduced risk of RSV infection progressing to LRTI. However, neutralizing antibodies acquired through natural RSV infection are generally transient [44, 45]. Maternal acquired RSV antibodies, gained through transplacental and breastmilk transfer, confer some protection, with a lower risk of RSV during early infancy; however, this is also transient [46–48]. Transplacental antibody transfer is less efficient during the early stages of pregnancy, and this contributes greatly to the severity

of infection experienced in prematurely born children [49, 50].

RSV employs multiple mechanisms to decrease the effectiveness of the host's immune response: NS1+NS2 (non-structural proteins) inhibition of interferon responses [51], interference in the Toll-like receptor (TLR) signaling pathway through the binding of protein F to TLR 4 [52], and CX3CR1 (fractalkine) binding by secretory protein G binding, thereby altering chemotaxis, as well as acting as a decoy for antibody binding [8, 53].

Six main antigenic epitopes are found on the RSV F protein surface (Ø and I–V). Sites Ø, III, and V are only exposed during the pre-fusion F protein conformation, while I, II, and IV are exposed on both the pre- and post-fusion F protein conformations [11, 12, 54]. The F protein is the main target for interventions such as vaccines and monoclonal antibodies. This is due to the number of exposed surface epitopes, its requirement for cell penetration, and the fact that it is highly genetically conserved. Epitopes II and IV are the main neutralizing epitopes, and whilst they do not prevent viral attachment to the affected cells, they effectively block fusion of the viral and host cellular membranes [54]. The G protein is a less efficient neutralization antigen than the F protein.

Treatment of RSV infection is largely symptomatic, with few specific treatment options available. Therefore, the management of RSV has focused mainly on prevention of the disease, through two approaches: passive and active immunization. The purpose of this review is to give an update on progress made in the prevention and treatment of RSV infection in children.

## 3 Passive Immunization

Passive immunization involves administration of antibodies targeting a specific pathogen, and is used in instances where immediate protection is required or where timeous production of antibodies is not possible, such as in newborns and during early infancy. Prevention of RSV through passive immunization involves administration of polyclonal or monoclonal RSV-neutralizing antibodies (Table 1).

The first commercially available preparation was RSV immune globulin intravenous (RSV-IGIV) (RespiGam™) in 1992. This preparation contained purified polyclonal antibodies from donors with high-titer RSV neutralizing activity [55]. Administered monthly to at-risk children under 2 years, RSV-IGIV resulted in a decreased risk of RSV LRTI, severe RSV LRTI, and RSV hospitalization and decreased the duration of RSV-associated intensive care unit (ICU) admission [56, 57]. RSV-IGIV did result in an increase in hypersensitivity reactions, but not more than was reported for standard intravenous immunoglobulin preparations [58].

Palivizumab (Synagis™–AstraZeneca) is a humanized monoclonal antibody directed at RSV protein F site II epitope, and until recently, it was the only licensed treatment for the prevention of RSV LRTI [59]. In a randomized, double-blind, placebo-controlled trial in high-income countries (HICs) (IMPact-RSV), children at high risk for severe RSV LRTI (prematurity or BPD) received either monthly palivizumab or placebo for 5 months [60]. Children receiving palivizumab with prematurity and no BPD had a 78% risk reduction for hospitalization, whilst a 39% risk reduction was shown for children with prematurity and BPD.

The high cost of palivizumab restricts its use, even in HICs such as the USA, where the cost runs to approximately \$1700–12,500 per RSV season [61–63]. This has led to specific restrictive recommendations being applied even in those countries and regions where it is available, such as the USA, Europe, and Australasia [64–66].

The development of next-generation, single-dose, long-acting monoclonal antibodies was facilitated through the initial introduction of a triple YTE mutation (M252Y/S254T/T256E) into the CH<sub>2</sub> domain of the Fc portion of MEDI-524 (IgG1), resulting in motavizumab (Numax™–MedImmune, Inc.) [67, 68]. This addition enhances Fc receptor binding, with a subsequent increase of up to four times the half-life, with this increase not being due to interactions with serum components, as well as an increase in serum levels, not due to alteration in distribution. Importantly, the YTE mutation resulted in no discernable structural changes to the IgG molecule, nor any functional impairment. Motavizumab provides 20 times higher in vitro neutralization activity, due to it having 70 times the affinity for the RSV F protein compared with palivizumab [69]. Motavizumab was non-inferior to palivizumab in a large, phase 3, randomized, double-blind study comparing outcomes in children born before 36 weeks gestation, either younger than 6 months or younger than 2 years with chronic lungdisease. Motavizumab was associated with a relative risk reduction of 26% and 50% for RSV hospitalization and acute, medically attended (MA) LRTI (MALRTI), respectively [70]. However, due to an increase in cutaneous hypersensitivity reactions in recipients, motavizumab was not granted licensure by the US Food and Drug Administration (FDA), and further development has been discontinued [71].

Suptavumab (Regeneron Pharmaceuticals, Inc.), a long-acting monoclonal antibody with affinity for the F protein pre-fusion site IV epitope, was discontinued after failing to show protection against RSV-associated hospitalization or outpatient illness in a phase 3 efficacy trial in healthy preterm infants less than 6 months of age [72]. This failure was likely due to a novel genetic strain of RSV B harboring target epitope site mutations.

Nirsevimab (Beyfortus™–AstraZeneca/Sanofi), a recombinant human IgG1 monoclonal antibody that targets the

highly conserved site Ø of the pre-fusion RSV F protein, can be administered as a single dose prior to the RSV season, intramuscularly [73]. Nirsevimab inhibits the fusion of the RSV and the respiratory epithelium, thereby inhibiting viral entry into the cell, and is equally effective against both RSV A and RSV B strains. In a phase 2b, randomized, placebo-controlled trial in healthy premature infants (< 37 weeks gestation), a single dose of nirsevimab was reported to have a 70% and 78% vaccine efficacy (VE) against RSV MALRTI and RSV LRTI hospitalization [74]. Furthermore, in late preterm (> 34 weeks gestation) and term infants, the VE was 74% and 62% against RSV LRTI and hospitalization for RSV LRTI, respectively, through to 180 days post-enrolment [75]. Nirsevimab also continued to confer protection through into the second RSV season, as indicated by a 43% lower risk of RSV MALRTI in the treatment group between 361 and 511 days [76]. In a pooled analysis of the preterm and term infant data mentioned above, nirsevimab resulted in a 80% relative risk reduction for RSV MALRTI [77]. Nirsevimab was registered for use in the European Union and the United Kingdom in November 2022 and granted licensure by the US FDA in July 2023, and was recommended by the Centre for Disease Control and Prevention Advisory Committee on Immunization Practices and the American Academy of Pediatrics in August 2023, providing the first additional option for the prevention of RSV LRTI in over 20 years. Possible side effects are the development of a rash and local effects at the site of the injection, as well as hypersensitivity reaction, whereas contra-indications include administering the drug to children that have any history of serious hypersensitivity reactions to the active ingredients in the preparation.

A further long-acting monoclonal antibody with affinity for epitope site IV of the RSV F protein, clesrovimab (Merck Sharp & Dohme), is being evaluated in a multicenter, randomized, partially blinded, phase 3 trial, with estimated completion in April 2026, after a phase 2a study reported a VE of 74% for prevention of MALRTI in infants during the first 6 months of life. Safety and efficacy will also be compared relative to palivizumab in infants and children at increased risk of severe RSV disease (NCT04938830 + NCT04767373).

## 4 Active Immunization

The initial 1966 failure of a formalin inactivated whole virus RSV vaccine (FIRSV) resulted in a decades-long delay in RSV vaccine development [78]. Children receiving the vaccine were provided no protection and developed more severe disease following RSV infection in the following season, including two deaths and 80% hospitalization in cases, especially if sero-negative prior to vaccination.

**Table 1** Current and future monoclonal antibodies targeting RSV

Monoclonal antibody	Description and targeted sites	Phase 3+	Efficacy results
Palivizumab (MEDJ-493) MedImmune LLC (Marketed)	Humanized monoclonal antibody (IgG1) binding RSV protein F epitope II Half-life: 20 days Monthly intramuscular injection	Phase 3: Efficacy vs placebo (IMPact-RSV) N = 1502: Premature infants (< 36 weeks GA) < 6 months or BPD ≤ 24 months of age	Decreased RSV-associated hospitalization (compared to placebo): Overall: 55% Prematurity: 78% Prematurity with BPD: 39%
Motavizumab (MEDJ-524) MedImmune LLC (Discontinued)	Humanized monoclonal antibody (IgG1 kappa) binding RSV F protein site II YTE mutation (M252Y/S254T/T256E) of Fc portion Half-life: 85–120 days Single injection	Phase 3: Efficacy and non-inferiority (palivizumab) N = 6635: Premature infants (< 36 weeks GA) < 6 months or CLD < 24 months Completed: August 2006 (NCT00129766) Phase 3: Efficacy vs placebo N = 2127: Healthy term Native American children < 6 months Completed: December 2010 (NCT00121108)	Decreased RSV-associated hospitalization (compared to palivizumab): 26% Decreased RSV-associated MALRTI (compared to palivizumab): 50% Decreased RSV-associated hospitalization (compared to placebo): 87% Increased hypersensitivity reactions in cases in both studies
Suptavumab (REGN2222) Regeneron Pharmaceuticals (Discontinued)	Humanized monoclonal antibody (IgG1) binding RSV F protein site IV Half-life: 36 days Two-dose regimen	Phase 3: Efficacy vs placebo and safety N = 1177: Healthy preterm infants (< 36 weeks GA) < 6 months Completed: November 2018 (NCT02325791)	Preventing RSV-associated MALRTI (compared to placebo): Overall: 1% risk reduction (single dose), – 16.7 risk reduction (2 doses) RSV A: Relative risk: 0.38 (95% CI 0.17–0.86) RSV B: Relative risk: 1.52 (95% CI 0.88–2.64)
Nirsevimab (Beyfortus) (MEDJ-8897) MedImmune LLC Sanofi Pasteur (Completed and ongoing phase 3) (Registered in European Union/United Kingdom; US FDA approved)	Humanized monoclonal antibody (IgG1) binding RSV F protein site Ø YTE mutation (M252Y/S254T/T256E) of Fc portion Half-life: 65–70 days Single injection	Phase 3: Safety and efficacy vs placebo N = 3013: Healthy late preterm (> 35 weeks GA) and term infants (MELODY) Completed: July 2022 (NCT03979313) Phase 3: Safety and efficacy N = 800: Preterm (> 29 weeks GA) and term infants < 1 year Started: November 2021, ongoing (NCT05110261) Phase 3: Efficacy N = 28,860: Premature (> 28 weeks GA) and term infants < 12 months Started: June 2022, ongoing (NCT05437510)	Vaccine efficacy (compared to placebo): Preventing RSV-associated MALRTI: 74.5% Preventing RSV-associated hospitalization: 62.1%

**Table 1** (continued)

Monoclonal antibody	Description and targeted sites	Phase 3+	Efficacy results
Clesrovimab (MK-1654) Merk Sharp & Dohme LLC (Ongoing phase 3)	Humanized monoclonal antibody (IgG1) binding RSV F protein site Ø YTE mutation (M252Y/S254T/T256E) of Fc portion Half-life: 65–70 days Single injection	Phase 3: Safety, efficacy, and pharmacokinetics N = 1000: Infants and children at increased risk for severe RSV disease Started: November 2021, ongoing (NCT04938830) Phase 3+4: Safety and efficacy N = 3300: Preterm (> 29 weeks GA) or term infants < 1 year Started: April 2021 (NCT04767373)	
RSM01 Bill & Melinda Gates Medical Research Institute	Humanized monoclonal antibody (IgG1) binding RSV F protein site Ø YTE mutation (M252Y/S254T/T256E) of Fc portion Half-life: 65–70 days Single injection		

*BPD* bronchopulmonary dysplasia, *CI* confidence interval, *CLD* chronic lung disease, *FDA* Food and Drug Administration, *GA* gestational age, *MALRTI* medically attended lower respiratory tract infection, *RSV* respiratory syncytial virus

The unfavorable outcome of the vaccine was attributed to vaccine-associated enhanced disease (VAED) due to a T-helper cell 2 type dominant immune response and induction of non-neutralizing antibodies. Neutralizing antibodies are the desired effect of vaccines against viral pathogens [79]. They bind to receptor binding domains of viruses and inhibit viral attachment, entry, and fusion with the host cell. They furthermore induce the formation of immune complexes, which triggers further enhancement of the immune response. An abnormal accumulation of these immune complexes may cause overstimulation of the immune response, and eventual VAED [79, 80].

There are numerous RSV vaccine candidates in various developmental stages, targeting different groups, including infants, pregnant women, and the elderly (see Table 2 and Supplementary Table 1 in the electronic supplementary material). The aim of maternal vaccination, with the subsequent maternal–fetal antibody transfer, is to prevent RSV LRTI in young infants, when 50% of RSV-associated hospitalizations and deaths occur [81–83]. The effectiveness of vaccinating pregnant woman as a strategy to prevent respiratory infections during infancy has been illustrated by the administration of inactivated influenza vaccine (IIV) and acellular pertussis vaccine to pregnant women [84, 85]. Infants born to women vaccinated with IIV were less likely to become infected with influenza during the first 6 months of life (VE 29%) and were 43% less likely to be hospitalized for all-cause pneumonia during the first 3 months of life [86, 87], while maternal acellular pertussis vaccination protected children for the age period of greatest mortality caused by pertussis, namely the first 2 months of life.

Numerous RSV vaccine candidates are currently being investigated [81]. For an updated snapshot, visit [PATH at https://www.path.org/resources/rsv-vaccine-and-mab-snaps-hot/](https://www.path.org/resources/rsv-vaccine-and-mab-snaps-hot/). Different mechanisms for stimulating the host immune response to provide a future protective response against RSV are being examined. These include live attenuated virus vaccines (LAV), chimeric vaccines, protein-based vaccines (sub-unit or particle, including nanoparticles), nucleic acid vaccines (NAV), and recombinant vector-based vaccines.

LAV contain live replicating pathogens with reduced virulence that elicit either a robust cellular or humoral immuneresponse, which in the past have been either too reactogenic or not reactogenic enough, highlighting the difficulties for this type of vaccine [88]. The intranasal route of LAV administration results in stronger mucosal immunity than systemic administered vaccines. Current RSV LAV include pathogens attenuated through reverse genetic engineering with deletion of proteins that regulate viral synthesis or responses [89]. Most LAV candidates are still undergoing phase 1 or phase 2 trials [90], including VAD00001 (SP0125), undergoing a safety, immunogenicity, and dosing, randomized, placebo-controlled trial in children 6–18 months.

**Table 2** Maternal RSV immunization studies: protein-based vaccines

Research company with molecule descriptions	Current and past trials	Trial description	Basic findings of trial	Specific results of trials (when available)
Novavax RSV F vaccine with and without adjuvant Intramuscular (Discontinued)	Phase 3 (N = 4636)	Safety and efficacy of maternally transferred antibodies in preventing RSV disease in their infants Maternal: Pregnant adult females third trimester (18–40 years) Completed: July 2019 (NCT02624947)	Did not meet pre-specified success criterion	Vaccine efficacy against RSV-associated disease in infants: MALRTI: 39.4% LRTI with severe hypoxemia: 48.3% Hospitalization: 44.4%
GSK RSVpreF (GSK3888550A) RSV MAT 009 Intramuscular (Discontinued)	Phase 3 (N = 369) (N = 10,640)	Efficacy in preventing RSV-associated LRTI in infants Maternal: Pregnant women (15–49 years) (GRACE) Started: November 2020 (NCT04605159) Immunogenicity and reactivity in mother and infants Maternal: Pregnant women (15–49 years) Completed: June 2022 (NCT04980391)	Discontinued following recommendation by independent data monitoring committee	
RSVpreF (GSK3003891A) Intramuscular	Phase 2 (N = 406)	Safety, reactogenicity, and immunogenicity Maternal: Female adult (18–40 years) Completed: February 2018 (NCT02956837)	Safe and immunogenic	
Pfizer RSVpreF (Abrysvo) (Completed phase 3) (FDA approval August 2023)	Phase 2 (N = 102)  Phase 3 (N = 7358)	Safety, reactogenicity, and immunogenicity Female adult (18–45 years) Completed: June 2016 (NCT02753413)  Efficacy and safety of maternally transferred antibodies in preventing RSV disease in their infants (MATISSE) Maternal: Pregnant adult females third trimester (18–40 years) Completed: October 2023 (NCT04424316)	Safe and immunogenic  FDA approval	Vaccine efficacy against RSV severe MALRTI during first 90 days of life: 81.8% Vaccine efficacy against RSV severe MALRTI during first 180 days of life: 69.4%

FDA Food and Drug Administration, LRTI lower respiratory tract infection, MALRTI medically attended lower respiratory tract infection, RSV respiratory syncytial virus

Chimeric vaccines are hybrid organisms comprising selected attenuated viruses with genetic material from the organism of interest. There are three candidates currently in phase 1 trials: parainfluenza 5 virus/RSV chimera, Bacillus Calmette-Guerin expressing RSV N gene, and Sendai virus/RSV protein F [90].

Protein-based vaccines can be particle or sub-unit based and elicit a robust humoral and cellular immune response. They contain nanoscopic particles that mimic selected antigens on the viral surface. The F protein, both pre-fusion and post-fusion conformations, has been the main antigenic protein utilized, but G protein, small hydrophobic protein, matrix protein, and nucleocapsid (N) protein have also been investigated. There are two maternal F protein vaccines currently in phase 3 trials, with the Abrysvo™ (Pfizer) becoming the first maternal vaccine receiving FDA approval (Table 2). The F protein vaccine, albeit in early phase trials, is also being evaluated in the pediatric population, and two F protein vaccines in adults older than 65 years of age have recently become the first RSV vaccines to be licensed [91, 92].

In a phase 3, randomized, observer-blind, placebo-controlled trial, a pre-fusion RSV F nanoparticle vaccine (Novavax) administered to healthy pregnant women between 28 and 36 weeks gestational age did not meet predetermined efficacy targets [83]. A single dose of vaccine was associated with a 39% reduction of the primary endpoint of RSV-associated MALRTI in the first 3 months of life in the infants, with a VE of 40.5% in LMICs compared to 37% in HICs.

A further phase 3, randomized, double-blind, placebo-controlled study, evaluating the VE of a single dose of intramuscular pre-fusion RSV F protein vaccine (RSVPreF3–GlaxoSmithKline) administered to pregnant women 18–49 years of age for protecting against RSV-associated LRTIs in their infants (NCT04605159), was voluntarily halted pending safety data analysis, due to an excess of premature deliveries and associated higher infant mortality rate in the vaccine arm [93]. Safety data presented recently (unpublished data) reported that RSVPreF3-Mat had an acceptable reactogenicity profile in maternal participants and that no imbalances were observed in pregnancy outcomes between groups, including fetal deaths. Preterm births were considered an identified risk for pregnant women following RSVPreF3-Mat vaccination, which led to the discontinuation of RSVPreF3-Mat development.

A phase 2, observer-blind, placebo-controlled trial of an RSV pre-fusion maternal vaccine administered to 213 pregnant women 18–40 years old during the second or third trimester found the vaccine to be well tolerated, with successful induction and transfer of maternal neutralizing antibodies against both RSV A + B to the newborn (NCT04126213) [94]. A further phase 2b trial, evaluating the efficacy of a bivalent maternal RSV A and RSV B stabilized pre-fusion

protein vaccine administered to women between 24 and 36 weeks gestational age, reported robust neutralizing antibody responses in the pregnant women, with highly efficient trans-placental antibody transfer to the newborn (NCT04032093). Neutralizing antibodies in the infant persisted above the protective threshold against RSV LRTI through to 180 days of age. The MATISSE trial (NCT04424316) further reported a VE against severe RSV MALRTI during the first 90 days of life at 81.8% (99.5% confidence interval [CI] 40.6–96.3) and 69.4% (97.58% CI 44.3–84.1) through to 180 days of life [95, 96]. These results led the US FDA to grant licensure in August 2023, the first vaccine licensed for maternal vaccination (Abrysvo™–Pfizer). Although, after sub-group analysis of live birth outcomes by country income status, there was no difference between HICs and LMICs with regard to increase in incidence of preterm birth, an increase in preterm births was noted in vaccine recipients (8.3%) compared with placebo recipients (4.0%) in South Africa (upper middle-income country) [97].

NAV such as messenger RNA (mRNA) vaccines were successfully utilized for coronavirus disease 2019 (COVID-19) vaccines [98]. Laboratory-based, pre-fabricated mRNA is utilized to stimulate the recipient's cellular nucleus to encode for the production of a protein or part thereof [99]. This stimulates the host immune system to produce specific antibodies. An mRNA-1345 vaccine (Moderna), which encodes stabilized RSV pre-fusion protein, is being evaluated in women of child-bearing age (18–40 years) and RSV sero-positive children aged 12–59 months, with results expected by September 2023 (NCT04528719).

Replicating or non-replicating viruses with extra genetic material from a pathogen of interest make up recombinant vector vaccines, with this engineered genetic material delivered to the recipient, eliciting an immune response. An adenovirus vector vaccine, Ad26.RSV.pre-F, is currently undergoing a phase 2 trial in RSV sero-positive toddlers, evaluating its safety, tolerability, and immunogenicity. Enrolment has been completed.

## 5 Treatment of RSV infection

The management of RSV LRTI is mainly supportive, with oxygen therapy and nutritional support. Nebulized hypertonic saline, beta<sub>2</sub>-agonists, nebulized adrenalin, nebulized ipratropium bromide, montelukast, and corticosteroids have been shown to be largely ineffective and are not recommended [100–111].

The development of a satisfactory antiviral medication against RSV infection remains elusive; however, steady progress is being made, with many potential candidate molecules undergoing clinical trials. One of the difficulties of RSV treatment is that medications need to be administered

very early in the disease process, due to the RSV inoculation time being 3–5 days and severe disease generally developing within 4 days of symptom onset, a very small window of opportunity. There are no biomarkers available to indicate which children might develop severe disease, and the majority will not develop severe disease, thereby not necessitating treatment.

The most researched antiviral drug targeting RSV is ribavirin, a broad-spectrum antiviral guanosine analog that inhibits the inosine monophosphate dehydrogenase enzyme, leading to decreased levels of guanosine triphosphate, which is needed by RSV for replication [112, 113]. Although ribavirin is available in both oral and intravenous preparations, its use has been hampered by its high cost, poor tolerability, and many reported side effects. In a recent systematic review, no difference in mortality rate was shown between individuals treated for RSV LRTI with ribavirin and those receiving supportive care, except for a lower mortality in individuals with hematological disease [114]. Furthermore, studies comparing oral and aerosolized preparations in adult recipients of hematopoietic cell and lung transplants have shown similar outcomes and safety profiles [112, 115–117].

Novel drug therapies being investigated include an F protein binding nanobody (ALX-0171 [Gontivimab–Ablynx], fusion inhibitors (GS-5806 [presatovir–Gilead Sciences], JNJ-53718678 [rilematovir–Janssen Pharmaceutical], BTA-C585 [enzaplatovir–Aviragen Therapeutics], and AK-0529 [ziresovir–Ark Biopharmaceutical]), a non-fusion N protein inhibitor (EDP-938 [Mavyret–Enanta Pharmaceuticals]), and an RSV polymerase inhibitor (ALS-008176 [lumicitabine–Alios BioPharma/Janssen Pharmaceuticals]) [118–122].

ALX-0171 is a trimeric nanobody that binds the F protein epitope site II [123]. Nanobodies are the smallest available heavy-chain portion of an immunoglobulin that retains its function and lends itself to aerosol delivery [124]. However, in a double-blind, placebo-controlled, phase 2b trial evaluating the safety and antiviral properties of nebulized ALX-0171 in 175 children hospitalized with RSV LRTI, no difference in clinical outcomes, time to clinical response, or global severity score was shown [125].

Fusion inhibitors inhibit the fusion of RSV F protein with the cells of the respiratory tract and act on a late-stage fusion intermediate during the process of the RSV F protein conformational change [126]. In a phase 2b, double-blind, placebo-controlled, adult RSV, challenge study, presatovir reduced viral load and severity of the clinical illness in 54 cases [119]. However, in another phase 2b, double-blind, placebo-controlled trial, in 60 hematopoietic cell transplant recipients with RSV LRTI, presatovir did not improve virological or clinical outcomes [119, 127]. JNJ-53718678 was well tolerated and exhibited antiviral activity in a phase 1b trial in children 1–24 months of age, and caused a reduction in viral load and clinical disease severity in healthy adults in a challenge study [121,

128]. Further studies examining the efficacy of this compound will be forthcoming. Enzaplatovir is undergoing a phase 2a, double-blind, placebo-controlled, challenge study in healthy adult volunteers, evaluating its safety and antiviral activity (NCT02718937). In a phase 2 trial, AK-0529 was reported to be safe and to reduce the viral load in children (1–24 months) infected with RSV, and a phase 3, randomized, double-blind, placebo-controlled trial in infants hospitalized with RSV infection is underway (NCT04231968).

In a phase 2, randomized, double-blind, placebo-controlled, challenge study in 62 healthy adult volunteers, the polymerase inhibitor ALS-008176, which selectively inhibits RSV RNA polymerase activity, resulted in a decreased viral load and an improvement of clinical disease severity in the treatment group [120]. However, a further phase 2 trial evaluating the antiviral activity and clinical outcomes in hospitalized infants and children showed an increase in reversible neutropenia and no antiviral activity [129].

## 6 Conclusion

RSV is the most common cause of LRTI in children, and has been associated with long-term pulmonary sequelae after infection, but despite this, treatment and preventative options have remained very limited. Recent successes, such as the licensure of nirsevimab as a preventative monoclonal antibody treatment for infants and the approval of two vaccines targeting RSV in the elderly and one in pregnant women, has led to renewed hope, with multiple other vaccine candidates also under examination. It remains only a question of time until the RSV landscape changes forever.

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1007/s40272-023-00606-6>.

## Declarations

**Funding** Open access funding provided by University of the Witwatersrand. CV: Previously received personal funding from AstraZeneca, Merck, Cipla, and GSK. SAM and ZD: Grant support to institution from BMGF; involved in clinical trials with Pfizer, GSK, Merck, and AstraZeneca, with funding to institution. CV, ZD, and SAM are involved with a clinical trial for Enanta Pharmaceuticals. No funding was received for the preparation of this article.

**Conflict of interest** CV, SAM, and ZD declare no conflicts of interest related to this article.

**Data availability** All data represented are available in the public domain.

**Ethics approval** No ethics approval was required.

**Consent to participate** Patient consent not applicable.



**Author contributions** This article is the sole work of the authors. CV, SAM, and ZD contributed equally to the planning, development, writing, and final approval of the manuscript.

**Consent for publication** Not applicable

**Code availability** Not applicable

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## Authors and Affiliations

Charl Verwey<sup>1,2</sup> · Ziyaad Dangor<sup>1,2</sup> · Shabir A. Madhi<sup>2,3</sup>

✉ Charl Verwey  
Charl.verwey@wits.ac.za

<sup>1</sup> Department of Paediatrics and Child Health, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

<sup>2</sup> South African Medical Research Council Vaccines and Infectious Diseases Analytics Research Unit, Faculty

of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

<sup>3</sup> Wits Infectious Diseases and Oncology Research Institute, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa