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Review

The recent landscape of RSV vaccine research

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***Abstract*:** Respiratory syncytial virus (RSV) causes a significant burden of acute respiratory illness across all ages, particularly for infants and older adults. Infants, especially those born prematurely or with underlying health conditions, face a high risk of severe RSV-related lower respiratory tract infections (LRTIs). Globally, RSV contributes to millions of LRTI cases annually, with a disproportionate burden in low- and middle-income countries (LMICs). The RSV virion outer capsule contains glycoproteins G and F which are essential for viral entry into respiratory epithelial cells and represent key targets for therapeutics development. The F-glycoprotein has several highly conserved antigenic sites that have proven useful targets for the development of monoclonal antibodies (mAbs) against RSV. Historically, prevention in infants was limited to the mAb palivizumab, which, despite its efficacy, was costly and inaccessible in many regions. Recent advancements include nirsevimab, a long-acting mAb that has shown substantial efficacy in reducing medically attended RSV-related disease in infants, in phase III clinical trials, early regional and national real-world data. In addition, three new vaccines have been approved: two protein subunit vaccines and a messenger RNA vaccine. The vaccines are all licenced for use in older adults, with one also approved as a maternal vaccine. Promising candidates in development include the mAb clesrovimab, which has an extended half-life and high levels in the nasal epithelial lining and high safety and efficacy profiles in late-stage trials. There are also a wide range of vaccine candidates currently in late-stage clinical trials. These developments signify a major advancement in RSV prevention strategies, offering improved protection for high-risk populations. With the ongoing rollout of the recently licenced vaccines and mAbs internationally, the landscape of RSV care is rapidly changing. We also must ensure these advances reach those in LMICs who need these therapies most.

Plain language summary

What's new in preventing RSV? A common cause of serious chest infections in infants and the elderly.

RSV (respiratory syncytial virus) is a virus that causes colds and chest infections. Babies and older adults, whose immune systems are more vulnerable, are much more likely to become severely unwell with RSV and need treatment in hospital. RSV causes millions of people to have serious chest infections worldwide each year. Death is common in lower income countries while in high income countries RSV contributes disproportionately to healthcare expenditure for children and older adults. Recent studies have shown that RSV is a bigger cause of severe illness and death in older adults than previously recognised. RSV has a surface protein, the F protein, that helps it infect cells. Viral proteins usually change frequently, but parts of the F protein are highly conserved (unchanging), making it a key target for new treatments. Monoclonal

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antibodies (mAbs) are customised medicines working similarly to natural antibodies in our bodies. RSV mAbs attach to the F protein, stopping RSV from entering human cells. Vaccines stimulate the body to produce similar antibodies. For many years, the only option to prevent RSV in infants was monthly injections of the mAb, palivizumab. Although effective, it was too expensive for widespread use. Recently, a new mAb, nirsevimab, showed great promise in protecting infants from RSV and is longer acting, highly effective, has no significant side effects and has high uptake, as shown in clinical trials and early real-world reports. There are also three newly approved vaccines: Abrysvo, Arexvy and mRESVIA. The vaccines were effective in clinical trials at preventing severe chest infections caused by RSV in older adults and were generally well tolerated. A small number of cases of Guillain Barre syndrome (GBS) (a nerve problem) have been reported following RSV vaccination in older adults, however a definitive link has not been established and safety surveillance is ongoing. Innovative upcoming treatments include a promising new monoclonal antibody, and multiple vaccines employing varied technologies. These developments mark a significant step forward in preventing severe RSV infections, offering better protection for those most at risk.

Keywords: infants, monoclonal antibodies, older adults, vaccines

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Introduction

Respiratory syncytial virus (RSV) causes a respiratory tract infection (RTI) that affects all age groups but has a significant disease burden in infants and older adults. For many years, the only available preventative measure was a monoclonal antibody (mAb) – palivizumab. Whilst effective, palivizumab is recommended for high-risk infants only and is prohibitively expensive. It is therefore not accessible to low and middle-income countries (LMICs) and the majority of infants in high-income countries. However, recent breakthroughs in understanding RSV virion structure have yielded new target antigens and allowed for the development of new RSV vaccines and mAbs. In this article, we discuss the changing landscape of the recently licenced and upcoming RSV vaccines and mAbs.

Virology

RSV is a negative-sense, single-stranded RNA virus. It belongs to the Orthopneumovirus genus of the *Pneumoviridae* family of viruses, which also contains the human metapneumoviruses.[1] RSV is a medium-size virus (120 nm–300 nm diameter) containing 10 genes that code for 11 proteins; 2 non-structural proteins (NS1, NS2) and 9 structural proteins (N, P, M, SH, G, F, M2.1, M2.2, L) (Figure 1).[2] The SH, G and F proteins are lipophilic transmembrane glycoproteins responsible for the virus gaining entry to respiratory cells (infectivity) and so represent targets for drug development. The G protein is used for viral attachment to ciliated cells and shows substantial genetic variation. RSV has two antigenic groups (RSV-A and RSV-B) which derive from the distinctiveness of their G proteins and tend to alternate from season to season in dominance. The F-protein is a type 1 fusion glycoprotein and leads to the fusion of infected respiratory cells with adjacent cells leading to multinucleated RSV syncytia (from which the virus derives its name).[2] F-proteins have been highly conserved over time and across both RSV-A and RSV-B virus subtypes.[3,4] Initial targets for vaccines and monoclonal antibodies (mAbs) focused on post-fusion antigenic sites (I, II and IV), though it was recognised from serological studies that most natural immunity must be targeted against pre-fusion F-protein antigens.[5] In 2011, the pre-fusion form of the RSV-F glycoprotein was stabilised and it was found targeting this form produced significantly higher levels of neutralising antibodies than the post-fusion form.[5] One locus was isolated

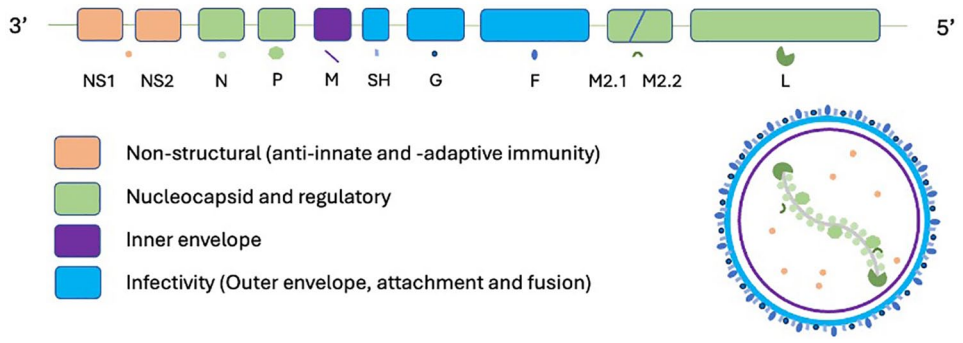

Figure 1. The RSV genome and virion.
RSV, Respiratory syncytial virus.

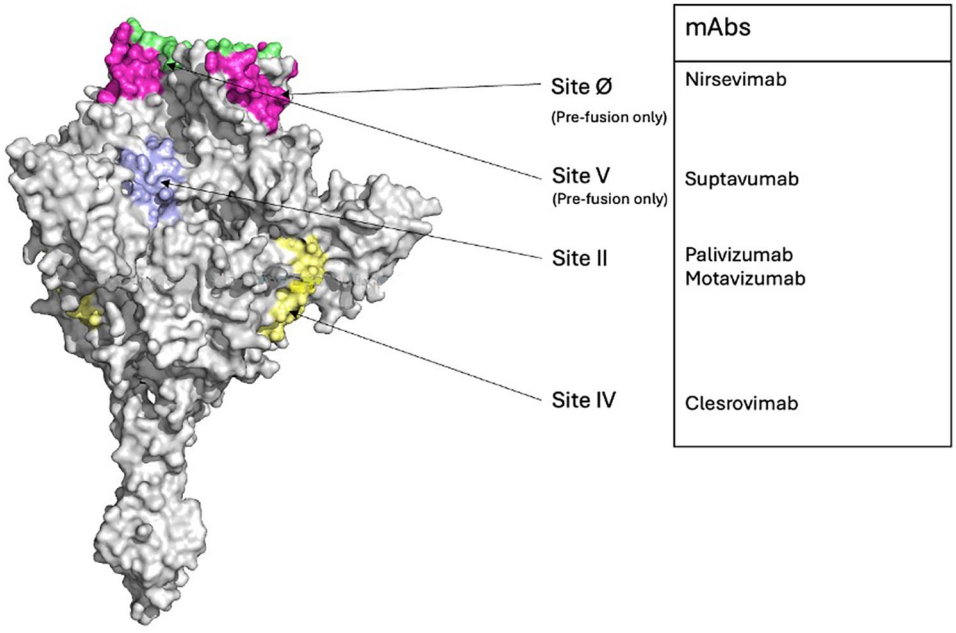

Figure 2. Antigenic sites of the pre-fusion F-protein targeted by various mAbs.

and named antigenic site Ø and has become one of the most promising immunological targets and the focus of the majority of emerging RSV immunological therapies. It is the antigen of choice in the three recently licenced RSV vaccines and the mAb Nirsevimab. Nirsevimab targets an antigenic region (site Ø) on the pre-F conformation of the F-protein (which is conserved among circulating RSV-A and RSV-B isolates) and thereby prevents RSV fusion with the host cell.[6] The binding site of nirsevimab is a highly conserved epitope, which has not changed significantly since 1956.[3] Other highly conserved sites include sites II and IV, targeted by palivizumab and clesrovimab (a promising mAb in phase III trials; Figure 2).[4,7] Site IV is currently thought to have the lowest mutation rate of the antigenic sites discovered to date.[8]

Immunology

The immune systems of very young infants have an increased susceptibility to RSV as they face challenges in generating effective immunity to RSV. There are several factors contributing to this – immature germinal centres and bone marrow niches, dampened interaction between T and

B cells compared with adults and interference from circulating maternal antibodies.[9] Transplacental antibody movement begins from the second trimester and continues until birth. Antibody levels are concentrated and become higher in full-term infants than their mothers.[10] Several current vaccines rely on this passive transfer to protect very young infants. Many countries implement the maternal Tetanus, diphtheria and acellular pertussis (Tdap) vaccine and influenza vaccine routinely in pregnancy to protect infants from pertussis, neonatal tetanus and influenza respectively.[11]

Older adults, in addition to multiple comorbidities, experience immunosenescence, leading to diminished T and B cell function. Aged memory T cells show reduced proliferation, and aged memory B cells have a decreased capacity to differentiate.[12] These changes lead to increased susceptibility to infections and a reduced ability to develop long-term immunity after vaccination or natural infection. Consequently, even with prior exposure to pathogens such as RSV, older adults can still experience severe or prolonged disease.

RSV neutralising antibody levels correlate inversely with this risk at all ages but do not appear to be lower on average in the elderly than those in young adults. The increased susceptibility in older adults appears to be due to reduced memory T-cell function and reduced RSV F-protein–induced cytokine release. Protection in this age group is therefore dependent on delivering or inducing additional high-quality antibody against RSV.[13]

Burden

RSV is a common cause of a wide range of acute respiratory illnesses across the human lifespan. It is a frequent cause of bronchiolitis and associated hospitalisation in children under the age of 1 year and an under-recognised cause of illness in older adults. In addition, there is increasing evidence of its association with pre-school wheezing, exacerbations of asthma and exacerbations of chronic obstructive pulmonary disease, as well as being a common cause of mild upper RTIs.[14,15]

Infants

The risk of medically attended RSV-associated LRTI varies due to many factors. Young age is the most significant risk factor due to smaller airway size and an immature immune system. Prematurity compounds this risk further due to reduced maternal antibodies and a higher incidence of chronic lung disease. Other underlying conditions such as congenital heart disease, Down syndrome, cystic fibrosis, and conditions of altered immunity are also associated with severe disease. In addition, environmental factors such as crowded living conditions, parental smoking, pollution, lower socioeconomic status and residency in low-income countries also significantly increase the risk of severe infection and mortality from RSV.[16] Despite this, the largest group of infants (79%) who experience severe disease in high-income countries continues to be infants with no clear risk factors.[17] This underscores the need for preventative agents to protect both healthy infants and those at increased risk from RSV.

In both temperate and tropical regions the RSV incidence peak starts predictably in late summer, peaking in mid-winter – slightly earlier than the influenza peak.[18] Children born during the summer (May–September in the northern hemisphere) have the highest risk of seeking healthcare due to an RSV-associated LRTI, whilst those born from September to December have the highest risk of hospitalisation and severe disease.[19,20]

Globally, in children under 5 years old, there are estimated to be between 25.4 and 44.6 million LRTIs, 2.9 to 4.6 million RSV-associated LRTI hospital admissions, and 84,500–125,200 RSV-attributable deaths each year.[17] This is estimated to represent 2% of worldwide deaths in children under 5 years old, with greater than 95% of RSV-associated LRTIs and 97% of mortality occurring in LMICs.[17] In LMICs, children under 6 months old are particularly at risk of poor outcomes with 44,700 RSV-attributable deaths in these infants in 2019 with up to a 6.6% case fatality ratio in the community in low-income countries.[21] Infants in low-income countries, therefore, clearly represent a key population on which to focus preventative measures going forward.

In high-income countries, RSV causes fewer fatalities but is vastly overrepresented as a cause of respiratory illness requiring hospitalisation, causing nearly 250,000 children under 5 years old to be hospitalised per year within the EU and the

United Kingdom.[22] In France admissions for RSV-associated LRTIs accounted for 28% of all hospitalisations of infants under 1 year of age, at a cost of €99.3 million in this age group in the 2017–2018 season.[20] Globally, in 2017, it was estimated that the total cost of RSV is in the region of €4.82 (95% CI, 3.47–7.93) billion per year in children less than 5 years old.[23]

Pregnant women

The burden of RSV infection in pregnant women is poorly understood due to limited available data. A systematic review focusing predominantly on Canada, the USA, and Europe reported that the incidence of RSV infection in pregnant women ranged from 10% to 13% during the RSV season. Another review which included LMIC reported that the proportion of acute respiratory infections in pregnant women attributable to RSV varied between 0.9% and 10.7%.[24,25] Hospitalisation and death from RSV infection are uncommon in this population. The impact of RSV infection on perinatal outcomes remains poorly understood. Whilst some data suggest a possible association between RSV infection and pre-term delivery, the evidence is currently insufficient to establish a definitive link.[24,25]

Elderly

Adults over the age of 60 years old are increasingly prone to RSV-associated medically attended illnesses, hospitalisations and death. RSV accounts for at least 470,000 hospitalisations and 33,000 in-hospital deaths per annum in high-income countries.[26] Understanding of the burden of RSV in adults is relatively limited with most studies to date having significant design limitations with factors related to sampling methods, diagnostic criteria favouring influenza-like symptoms, insufficient study durations and poor age stratifications which leads to underestimation of severe RSV in older adults.[27] It is therefore widely believed that the RSV burden in this age group is likely to be significantly higher than current data suggest.[27] We are also beginning to understand the relationship of bacterial co-infection with RSV in adults. RSV increases the acquisition rate and density of pneumococcal colonisation and may predispose to pneumococcal infection.[28] Thus preventing RSV infection may also reduce the burden of pneumococcal infection.

Past and current mAbs

Monoclonal antibodies against RSV have long been considered one of the key developments in the efforts to prevent severe RSV infection. Palivizumab (Synagis by AstraZeneca) was the first mAb against RSV in infants licenced by the US Food and Drug Administration (FDA) in June 1998 and the European Medicines Agency (EMA) in August 1999.

Palivizumab has a relatively short half-life of 20 days[29] and must be given as a dose of 15 mg/kg of body weight each month, for 5 months to cover the RSV season. It is highly effective, binding antigenic site II of the F-protein, and preventing RSV fusion with respiratory cells.[30] A systematic review of 3343 participants across 5 randomised controlled trials (RCTs) showed that in high-risk infants, at 2 years follow-up, the risk ratio (RR) of hospitalisation was 0.44 (95% CI 0.3–0.64). This equates to 98 RSV hospitalisations in the placebo versus 43 hospitalisations in the treatment group per 1000 participants at this time. Mortality was not significantly different between groups, with 23 deaths in the placebo group versus 16 (10–27) deaths in the treatment groups per 1000 participants. Adverse events were similar and low in both treatment and placebo groups at 150 days follow-up. In addition at 2 years follow-up, palivizumab lead to a modest but significant reduction in overall respiratory-related hospitalisations (RR 0.78, 95%CI 0.62–0.97), and more substantial reductions in RSV infection (RR 0.33, 95% CI 0.2–0.55), and the number of days wheezing (RR 0.39, 95% CI 0.35–0.44).[31] Further RCTs comparing the use of palivizumab with placebo during the first RSV season in healthy late pre-term infants showed a 61% reduction in wheeze-days in the first year of life and when followed to 6 years old, parent-reported current asthma was 14·1% (28 of 199) in the palivizumab group versus 24.0% (47 of 196) in the placebo group (absolute risk reduction (ARR) 9.9%, 95% CI 2.2–17.6).[32] FEV1 and physician-diagnosed asthma were, however, similar between the two groups.[32] Given the expense of palivizumab and the burden of monthly injections, it is broadly unsuitable to be rolled out to all infants even in high-income countries. Its use has been restricted to those at highest risk of severe RSV, including infants with congenital heart disease and chronic lung disease.

An intranasal formulation of palivizumab, Narsyn (UMC Utrecht) has also been investigated. In one trial it was given intranasally, daily throughout the RSV season, and compared with placebo. However, the trial was discontinued early due to lack of efficacy.[33]

Motavizumab (Numax, AstraZeneca) was another mAb derived from palivizumab, also targeting the site II antigen of the F-protein, with development aiming to improve efficacy compared with palivizumab but at a lower dose requirement (albeit not a reduced number of doses).[34] It was, however, declined FDA approval in 2010 for failing to achieve superior efficacy over palivizumab and concerns regarding hypersensitivity.[35]

Now, despite the patents expiring in Europe in August 2015 and in the United States in October 2015 there remain no cheaper biosimilar products to palivizumab on these markets. There has, therefore, been a drive to develop a mAb with a longer half-life that could be given as a single injection at the start of the RSV season and would provide protection against RSV disease for a whole season (approximately 5–6 months).

Suptavumab was developed by Regeneron with a half-life of 36 days and targeted to antigenic site V. It reached phase III trials comparing a two-dose schedule (30 mg/kg/dose), with a two-dose placebo schedule and a one-dose drug, one-dose placebo schedule in pre-term infants.[36] It showed promise in a phase II trial, but unfortunately the phase III trial showed no efficacy in preventing RSV hospitalisations. This was due to the circulation of a novel RSV-B strain with a two amino acid change in the binding site region which occurred in the 2016–2017 season. This led to the discontinuation of suptavumab as a candidate for licensure.[36]

Nirsevimab (Beyfortus by AstraZeneca and Sanofi) is currently the only licenced mAb on the market recommended for broad infant use. It is a recombinant human IgG1 kappa monoclonal antibody against RSV that targets the F1 and F2 subunits of the RSV fusion protein at antigenic site Ø. By binding in this location, the fusion protein becomes locked in the pre-fusion conformation, prohibiting entry into cells. A Spanish study that looked into the genetic variance of 77,441 RSV-positive respiratory samples from 2013 to 2023 noticed a higher evolution rate of the F-glycoprotein in the post-COVID-19 pandemic phase as compared with the pre-pandemic phase and discovered mutations in a number of therapeutically targeted antigens. There were two RSV-B mutations found at antigen site II (palivizumab targeted) and seven mutations noted at RSV-B site Ø, and two mutations at RSV-A site Ø (nirsevimab targeted). No mutations were discovered in epitope IV (clesrovimab targeted – see later).[8] Although a number of antigenic mutations were noted in this study, all three of these sites remain highly conserved with a low mutation rate and no monoclonal antibody-resistant mutants were detected. However, ongoing surveillance remains critical.[8]

The EMA has recommended nirsevimab's use for neonates and infants born during their first RSV season since November 2022 and adjusted this recommendation in June 2024 to include children up to 24 months of age at increased risk of severe disease in their second RSV season.[37] The FDA made recommendations in July 2023. The recommended dosing is 50 mg for infants under 5 kg and 100 mg for infants 5 kg and over, using a 100 mg/mL formulation intramuscularly into the thigh.[37,38] It has an extended half-life of approximately 69 days, allowing for a single dose to be protective against RSV for an entire season.[6]

Nirsevimab has been shown to be safe and effective at preventing RSV disease, admissions and adverse outcomes. Phase III trials showed a 71% decrease in RSV-associated LRTIs, a 78% reduction in RSV-associated hospital admissions in healthy pre-term (29–35 week gestation) infants[39] and a 75% decrease in RSV-associated LRTIs and a 62% decrease in RSV-associated hospitalisations in healthy late pre-term and full-term infants (over 35 weeks gestation).[40] A more recent large multinational phase III randomised control trial of 8058 healthy infants born at least 29 weeks of gestation were assigned in a 1:1 ratio to receive nirsevimab versus standard care. In the nirsevimab group (4037 infants), 0.3% (11/4037) were hospitalised with an RSV-associated LRTI and only 5 infants (0.1%) required oxygen during their admission. This is compared with 1.5% (60/4021) of infants hospitalised and 19 (0.5%) requiring oxygen in the standard care group.[41] This corresponded to a nirsevimab efficacy of

83.2% (95% confidence interval (CI), 67.8–92.0; $p < 0.001$) against hospitalisation and 75.7% (95% CI, 32.8–92.9; $p = 0.004$) against oxygen requirement during the 2022–2023 RSV season.[41] In addition, nirsevimab had an efficacy of 58.0% (nominal 95% CI, 39.7–71.2) against all-cause hospitalisation.

A number of countries and regions introduced a single nirsevimab dose for all neonates born during the 2023/2024 RSV season. Luxemburg noted that compared with the previous season, there was a decreased number of RSV-associated hospital admissions in infants under 6 month of age ($n = 72$ vs $n = 232$), mean age of RSV-associated hospitalisation increased (14.4 months vs 7.8 months in 2022; $p < 0.001$), and hospital length of stay (LOS) decreased (3.2 days vs 5.1 days; $p < 0.001$).[42]

The USA introduced nirsevimab nationally for infants in their first season and high-risk infants in their second RSV season; unfortunately, supply limitations, unexpectedly high demand and cost impeded rollout for the 2023–2024 season leading to rolling limitations on use.[43] There is, however, national surveillance data from the first season of use in the USA in children under 8 months old. A case-control study of efficacy in 699 patients admitted to hospital with LRTI, compared patients who received nirsevimab >7 days before admission with infants with no form of RSV immunological protection. Nirsevimab was found to be 90% (95% CI = 75–96) effective at preventing RSV hospitalisation.

In the same period, the Galicia region in Spain reported 82% effectiveness of nirsevimab against RSV LRTI and 87% effectiveness against severe RSV/need for oxygen support. The number needed to treat to prevent one hospitalisation was 25. They also showed a low rate of adverse events or RSV-related events in high-risk infants.[44] Galicia now recommends nirsevimab for all children less than 6 months of age at RSV season onset, infants born during the RSV season, or children who would otherwise qualify for palivizumab, and plans to continue monitoring this data for three RSV seasons.[45] A further, similarly-conducted population-based study of the Navarre region in Spain showed a decrease in RSV-associated hospitalisation from 8.5% (8/94) to 0.7% (8/1083) and estimated efficacy of 88.7% (95% confidence interval, 69.6–95.8).[46] In Madrid, in 2023, children born between the 1st of April and 31st of December were eligible for nirsevimab. A hospital in Madrid measured RSV-confirmed respiratory disease in children born between April and December inclusively and who presented between weeks 40–52 of 2022 compared with the same time in 2023. Of the total cases, 62.7% (472/765) cases presented in the 2022 season and 38.3% of cases (293/765) were presented in 2023, a decrease of 38%. The median age of RSV-positive respiratory infection increased from 9.6 months (IQR 3.2–25.1) in 2022 to 15.6 months (IQR 8.9–33) in 2023. They also compared the infants born between April to December 2022 with the same period in 2023 (when infants were eligible for nirsevimab) and found that 80.3% (212/264) were seen in 2022 and 19.7% (52/264) were seen in 2023. Of the 52 patients from 2023, 36.5% (19/52) received nirsevimab.[47]

A PICU in Barcelona measured all-cause bronchiolitis admissions over a 10-year period up to February 2024. They showed that the annual number of RSV admissions decreased from 5.4 (95% CI 4.9–5.8) per week to 4.3 (95% CI: 3.2–6.1) after the introduction of nirsevimab ($p < 0.001$). The main differences between the pre- and post-nirsevimab groups were age at admission (51 vs 80 days, $p < 0.001$), hospital LOS (11 vs 8 days, $p < 0.001$), RSV aetiology (67% vs 59%, $p = 0.039$), and Rhinovirus aetiology (26% vs 42%, $p = 0.002$).[48]

France had a similar experience following the introduction of nirsevimab. A case-control study, of 342 infants admitted to PICU in the 2023–2024 season found nirsevimab effectiveness to be 75.9% (95% CI 48.5–88.7).[49]

In a multicentre case-control study from France and Switzerland of 1035 infants, nirsevimab was 83.0% (95% CI 73.4–89.2) effective at preventing hospitalisation for RSV-associated bronchiolitis and 69.6% (95% CI, 42.9–83.8) effective against PICU admission and 67.2% (95% CI 38.6–82.5) effective at preventing the need for mechanical ventilation.[50]

Uptake has been high across regions where nirsevimab has been introduced – 84% (1277 doses per 1524 births) in Luxemburg,[42] 91.7% of

eligible infants (9408 of 10,259) in Galicia, Spain,[44] and 92% of studied children (1083 of 1177) in Navarre, Spain.[46]

In the clinical trials, reports of adverse events were similar between the placebo/standard of care groups and the nirsevimab groups.[41] The adverse events reported were mainly those commonly associated with all immunisations (e.g. tenderness, redness and swelling at the injection site, fever, irritability). In addition, no safety signal has arisen from the currently available real-world data).[39,40,42,44] Safety data also supports its use in extreme pre-term infants and those with cardiac and respiratory disease.[51]

Licenced vaccines

RSV vaccine development has faced multiple challenges, including hesitancy due to the legacy of the initial formalin-inactivated RSV vaccine that caused enhanced respiratory disease and difficulties identifying effective antigenic targets. In addition, the challenges inherent in understanding the immune systems of the target populations resulted in stagnation in RSV vaccine development for many years. However, in the last few years, there has been excellent progress with several recently licenced vaccines and more in development.

Between May 2023 and June 2024, the FDA approved the use of three RSV vaccines for older adults and one for use in pregnant women:

1. Abrysvo (RSVpreF) by Pfizer, is a bivalent subunit vaccine containing the pre-fusion forms of both RSV-A and RSV-B subtypes. It is licenced for use as a maternal vaccine as well as for older adults.[52]
2. Arexvy (RSV preF3) by GSK is a subunit vaccine containing a stabilised version of the trimeric pre-fusion form of the F-glycoprotein and uses the adjuvant system 01 (AS01E).[53]
3. mRESVIA (mRNA-1345) by Moderna is a messenger RNA (mRNA) vaccine encoding the pre-fusion form of the membrane-anchored RSV-F glycoprotein, derived from an RSV-A strain.[54]

In the same time period, the EMA approved Abrysvo and Arexvy and in June 2024 the Committee for Medicinal Products for Human Use (CHMP) gave a positive opinion for mRESVIA.[54–56]

Maternal vaccines

There is currently one licenced maternal RSV vaccine, but there have been other candidate vaccines that were investigated in later-stage clinical trials.

The Novavax RSV nanoparticle vaccine used the post-fusion form of the RSV-F protein as an antigenic target. The phase III trial, the PREPARE study, recruited from December 2015 to May 2018 and enrolled 4636 women between 28 and 36 weeks gestation. The study did not meet its primary endpoint of preventing RSV-associated LRTI in infants up to 90 days old. However, it succeeded in several secondary and exploratory goals, showing the vaccine's effectiveness in preventing hospitalisation and severe hypoxemia from all-cause and RSV-associated LRTI in infants up to 90 days old. Despite missing the primary objective, the data from secondary and exploratory goals suggested that a maternal RSV vaccine could protect infants from severe RSV infection.[57] The incidence of symptomatic RSV-associated respiratory infection in pregnant and postpartum women was also analysed in the PREPARE study and was found to be similar in women who had received the vaccine (4.9%) and the placebo (4.8%).[57]

Abrysvo, licenced by the US FDA for older adults, is also approved for use in pregnant women to protect infants through transplacental antibody transfer. The MATISSE trial, which ran from June 2020 to October 2022, evaluated the safety and efficacy of Abrysvo as a maternal vaccine. Over 7000 women were enrolled between 24 and 36 weeks gestation with uncomplicated singleton pregnancies (of whom just over 3600 received the vaccine).[58]

The study demonstrated an 81.1% (99.5% CI, 40.6–96.3) vaccine efficacy against severe RSV-associated LRTI (defined in Table 1) in infants within 90 days of birth and 69.4% (97.58% CI, 44.3–84.1) by 180 days. The MATISSE trial also evaluated vaccine efficacy for medically attended RSV-associated LRTI (defined in Table 1) in infants but did not meet statistical success for this

Table 1. Definition of the primary endpoints in MATISSE.

Medically attended RSV-associated lower respiratory tract illness in infants within 90, 120,150, and 180 days after birth:	Severe medically attended RSV-associated lower respiratory tract illness in infants within 90, 120,150, and 180 days after birth:
Medically attended respiratory tract infection visit AND RSV-positive test result	Medically attended respiratory tract infection visit AND RSV-positive test result
AND ⩾1 of the following : • Fast breathing (RR ⩾ 60 bpm for <2 months of age (<60 days of age), ⩾50 bpm for 2–<12 months of age, or ⩾40 bpm for 12–24 months of age) • SpO2 <95% • Chest wall indrawing	AND ⩾1 of the following : • Fast breathing (RR ⩾ 70 bpm for <2 months of age (<60 days of age), ⩾60 bpm for 2–<12 months of age, or ⩾50 bpm for 12–24 months of age) • SpO2 <93% • High-flow nasal cannula or mechanical ventilation (i.e. invasive or non-invasive) • ICU admission for >4 h • Failure to respond/unconscious

endpoint at 90 days of birth.[58] The incidence of RSV-associated infection in mothers was not evaluated in the trial.

Immunogenicity studies from a phase II trial involving Abrysvo demonstrated that maternal vaccine recipients had 11 (RSV-A) and 14 (RSV-B) fold higher Geometric Mean 50% Neutralising Titres (GMT) at delivery compared with placebo. Infants of vaccine recipients also had significantly higher GMT at birth compared with infants of the placebo group; 11.7-fold higher for RSV-A and 16.8-fold higher for RSV-B.[59]

Abrysvo as a maternal vaccine was well tolerated with no severe side effects. There were no safety signals associated with the trial intervention although there was a small, but non-significant increase in pre-term births in the vaccine group. Although the MATISSE trial included women from 24 weeks gestation, Abrysvo as a maternal vaccine has been licenced by the FDA for use from 32 weeks, the UK Medicines and Healthcare Products Regulatory Agency (MHRA) from 28 weeks and the EMA from 24 weeks gestation.[54,60,61]

GSK also had a maternal RSV vaccine candidate, RSVPreF3-Mat (a subunit vaccine based on the RSV fusion (F) protein stabilised in its pre-fusion conformation). The phase III trial was discontinued due to a safety signal of an increased incidence of pre-term births in the vaccinated group. The imbalance in pre-term birth was most pronounced in LMICs, and only during a short timeframe, and no clear cause for this association has been found.[62] Although pre-term birth was not associated with the vaccine in MATISSE, it remains an outcome of interest that needs ongoing surveillance.

Older adult vaccines

RENOIR, AReSVi-006 and ConquerRSV were the phase III trials in older adults for Abrysvo, Arexvy and mRESVIA respectively. They were conducted in adults 60 years old and above and had similar study designs. The RENOIR trial was conducted from August 2021 with interim analysis occurring in July 2022. It had a sample size of 34,284 participants of which 17,215 received the vaccine. AReSVi-006 trial enrolled between May 2021 and January 2022 and included just over 25,000 participants of which 12,467 received the vaccine. ConquerRSV, which enrolled between November 2021 and October 2022, recruited 35,541 participants with 17,793 in the vaccine group.[52,53,54] The trials are ongoing but successfully met their primary endpoints at an interim analysis which, for all three, were vaccine efficacy against prevention of RSV-associated LRTI with at least two or three symptoms/signs.

The case definitions for LRTI, whilst not identical, were very similar across the three trials. Vaccine efficacy against severe RSV-associated LRTI was not investigated in ConquerRSV; however, it was included as a primary endpoint in RENOIR and AReSVi-006. Notably, oxygen supplementation (either new or increased) was not automatically considered a severe disease in AReSVi-006 (Arexvy) whilst it was categorised as a severe LRTI in the RENOIR (Abrysvo) trial.

Vaccine efficacy for primary endpoints in the trials was considered to have been met provided the lower boundary of the confidence interval was more than 20%. This provision ensures that even at the lowest boundary, the vaccine would still significantly reduce the risk of developing RSV-associated LRTI compared with placebo.

A comparison of vaccine efficacy across the three trials is shown in Table 2.

All three vaccine trials in older adults will continue to run over multiple RSV seasons to measure vaccine efficacy over time. In addition, in AReSVi-006, the effectiveness of a single dose versus annual re-vaccination will be evaluated.

At the end of the second season (2022/2023) in AReSVi-006, there was no significant difference in vaccine efficacy between participants who received one dose of the vaccine Arexvy versus two.[63] Although efficacy decreased from the end of season one to season two in participants who received a single dose (82.6% (96.95% CI, 57.9–94.1) to 56.1% (95% CI, 28.2–74.4)), it remained comparable to the efficacy of two doses in preventing RSV-associated LRTI with at least three symptoms or signs in the second season (55.9% (95% CI, 27.9–74.3)).[63]

Pfizer has also released their top-line data from a second RSV season. In February 2024, they reported a single dose of Abrysvo was 77.8% (95% CI, 51.4–91.1) effective at preventing RSV-associated LRTI (defined as three or more symptoms) in season two, with only a small decrease in efficacy from season one (which was 88.9% (95% CI: 53.6–98.7)).[64]

When considering vaccine efficacy of a single dose against RSV-associated LRTI (with at least three or more signs and symptoms) across two RSV seasons, the results for the currently licenced adult vaccines stand as follows – 81.5% (95.0% CI, 63.3–91.6) for Abrysvo, 67.2% (97.5% CI, 48.2–80.0) for Arexvy and 49.9% (95% CI, 27.8–65.6) for mRESVIA.[63,66] At present, the re-vaccination interval for older adults is undecided.

Immunogenicity data available for the adult vaccines suggest a good neutralising antibody response following immunisation. Participants who received Arexvy demonstrated a rise in RSV preF3-specific antibody concentration by a factor of 13 one-month post-vaccination.[52] At 12 months post-vaccination, antibody concentrations were still 3.5-fold higher than pre-vaccination levels, suggesting a lasting immune response.[66] Recipients of mRESVIA also showed a good response with an 8.4 fold and 5.1 fold increase in geometric mean titres from baseline for RSV-A and RSV-B respectively 1 month after vaccination.[67] Immunogenicity data for RSV Pre-F (licenced as Abrysvo), available from a phase I/II trial, showed that administration of the vaccine elicited robust RSV- neutralising antibodies in older adults – 50% neutralising GMTs increased 9.8 times for RSV-A and 8.5 times for RSV-B 1 month post-vaccination.[68]

All three vaccines were well tolerated with the majority of adverse reactions ranging from mild to moderate and lasting on average 1–2 days. Injection site pain was the commonest local side effect and systemic side effects of fatigue, headache and myalgia were the most commonly reported in all three trials. There were two cases of pericarditis in the ConquerRSV trial which were not felt to be related to the vaccine.[53] There were three serious adverse events that were attributed to the receipt of Abrysvo, an allergic reaction and two immune-mediated conditions – Miller Fisher syndrome and Guillain Barre syndrome (GBS) which developed 6 and 7 days respectively post-vaccine administration.[69,70] One case of GBS reported during the AReSVi-006 trial was also possibly related to the administration of Arexvy.[66] As a result, although there is insufficient evidence to attribute the cases of GBS definitively to the vaccine, there remains a need for ongoing post-licensure surveillance. The US CDC monitored cases of GBS via a voluntary surveillance system (V-safe) over the period May 2023 – April 2024

Table 2. Comparison of vaccine efficacy of currently licenced adult RSV vaccines in season 1 (2021/2022) and season 2 (2022/2023).

Trial	Name	Enrolment period	Number of participants (vaccine recipients)	Primary endpoint	Season 1 efficacy results	Season 2 efficacy results
RENOIR	Abrysvo	August 31, 2021–July 14, 2022	34,284 (17,215)	Vaccine efficacy against seasonal RSV-associated lower respiratory tract illness with at least two signs or symptoms	66.7% (96.66% CI, 28.8–85.8)	55.7% (95.0% CI: 34.7%, 70.4%)
RENOIR	Abrysvo	August 31, 2021–July 14, 2022	34,284 (17,215)	Vaccine efficacy against seasonal RSV-associated lower respiratory tract illness with at least three signs or symptoms	85.7%; (96.66% CI, 32.0–98.7)	77.8% (95.0% CI: 51.4, 91.1)
AReSVi-006	Arexvy	May 25, 2021–January 31, 2022	24,966 (12,467)	Vaccine efficacy of a single dose in the prevention of RSV-related lower respiratory tract disease during one RSV season *	82.6% (96.95% CI, 57.9–94.1)	56.1% (95% CI: 28.2–74.4%)
AReSVi-006	Arexvy	May 25, 2021–January 31, 2022	24,966 (12,467)	Vaccine efficacy against severe RSV-related lower respiratory tract disease	94.1% (95% CI, 62.4–99.9)	64.2% (95% CI: 6.2–89.2%)
ConquerRSV	mRESVIA	17 November 2021–31 October 2022	35,541 (17,793)	Vaccine efficacy in prevention of RSV-associated lower respiratory tract disease with at least two signs or symptoms	83.7% (95.88% CI, 66.0–92.2)	Pending
ConquerRSV	mRESVIA	17 November 2021–31 October 2022	35,541 (17,793)	Vaccine efficacy in prevention of RSV-associated lower respiratory tract disease with at least three signs or symptoms	82.4% (96.36% CI, 34.8–95.3)	Pending

*Defined as RSV-associated lower respiratory tract illness with at least three signs or symptoms.
RSV, Respiratory syncytial virus.

and found very small, but higher than expected, rates of GBS reported compared with the non-vaccinated population – 1.8 and 4.4 reports per million doses of Arexvy and Abrysvo administered, respectively.[71] Importantly, as V-safe is a voluntary reporting service it has a risk of reporting bias and incomplete reporting, thereby making determination of causality difficult. The present advice from the US Advisory Committee on Immunisation Practices (ACIP) is that the benefit from the vaccine significantly outweighs risk and RSV vaccination continues to be recommended.[71,72]

mAbs in development

One monoclonal antibody against RSV is in phase III development as of November 2024. Clesrovimab (MK-1654) by Merck is an extended half-life human IgG1 mAb against the highly conserved antigenic site IV of the RSV-F glycoprotein. It has activity against both the pre-F and post-F conformations.[73]

Two phase I trials have been conducted in adults. Both found clesrovimab to have safety profiles and tolerability similar to placebo and showed a half-life of 73–91 days, which would allow a single

dose to be effective for an entire RSV season. Both studies followed up with participants for 1 year.[74,75]

A further study has shown good levels of clesrovimab in nasal epithelial lining fluid and a high RSV local neutralising effect in human challenge models of RSV infection.[76] There are two phase III trials in progress comparing the use of clesrovimab with placebo (ClinicalTrials.gov identifier: NCT04767373) and with palivizumab (ClinicalTrials.gov identifier: NCT04938830). The published results of these trials are awaited,[77] however, in October 2024, MSD (Merck and Co.) announced that the interim analysis of their Phase IIb/III trial showed that at 5 months post-dose, clesrovimab resulted in the reduction in the incidence of RSV-associated MA-LRTI) requiring $\geqslant$1 indicator of LRTI or severity compared with placebo by 60.4% (95% CI: 44.1, 71.9, $p < 0.001$), RSV-associated hospitalisations by 84.2% (95% CI: 66.6, 92.6, $p < 0.001$) and RSV-associated LRTI hospitalisations by 90.9% (95% CI: 76.2, 96.5) after a single 100 mg dose, regardless of infant weight.[77] There were no safety concerns.

A phase II trial (ClinicalTrials.gov identifier: NCT05630573) is currently underway by Trinomab Biotechnology comparing the investigational mAb TNM001 with placebo in healthy term and pre-term infants.

A final candidate that has completed a phase I trial (ClinicalTrials.gov identifier: NCT05118386) is RSM01, an investigational mAb under development by the Bill and Melinda Gates Medical Research Institute aiming to provide an affordable mAb to LMICs. In November 2023, they reported it to have an extended half-life (79.1 days) formulation that targets the antigenic site Ø of the F-protein.[78,79] Thus far there are no concerns regarding the safety profile and bioavailability.[79]

Vaccines in development

The current landscape of potential RSV vaccines comprises a variety of vaccine platforms and antigenic candidates in differing phases of development. Vaccine platforms include live-attenuated, protein and nucleic acid vaccines. They are summarised in Table 3.

Live-attenuated/chimeric vaccines

Live-attenuated vaccines are an attractive option, particularly in children, as intranasal administration is preferable to an intramuscular injection and can induce IgA-mediated mucosal immunity in the upper respiratory tract.[80] IgA is present both in the serum in monomeric form and as secretory IgA, a polymeric structure, on mucosal surfaces. Through immune exclusion, secretory IgA forms a barrier at the mucosal surface, preventing pathogens from attaching to entry receptors and thereby blocking their entry into host cells.[81] Evidence suggests that this mechanism could be effective against RSV, as higher levels of RSV-specific nasal IgA have been associated with greater protection against RSV infection.[82]

Several pharmaceutical companies have opted for this vaccine platform. The vaccine furthest in development currently, by Sanofi, RSVt vaccine, is attenuated by deletion of the NS2 protein and a single codon encoding the polymerase protein L.[83] A phase III study evaluating the efficacy, immunogenicity and safety of RSVt vaccine in infants and toddlers is currently recruiting (ClinicalTrials.gov identifier: NCT06252285) with estimated completion by 2027. Previous phase 1 and 2 trials have confirmed the vaccine is well tolerated and immunogenic in children.[80,83]

Meissa Vaccines Inc's vaccine, MV-012-968 is attenuated by removal of the SH protein, decreased expression of the G protein and upregulated expression of the F-protein; it is in phase II development with a human challenge efficacy study in adults underway (ClinicalTrials.gov identifier: NCT04690335).[84]

CodaVax-RSV (by Codagenix), which is attenuated by codon deoptimisation, is currently in a phase I trial (ClinicalTrials.gov identifier: NCT04919109) evaluating safety and immunogenicity in RSV seropositive and seronegative children 2–5 years old.[85]

BLB201, by Blue Lake Biotechnology, is a chimeric viral-vector vaccine using parainfluenza virus 5 to encode the RSV-F protein.[71] Parainfluenza virus 5 is not known to cause disease in humans and preliminary results from a phase I/IIa trial (NCT05655182) in infants showed a 3.6- to 57-fold rise in neutralising

Table 3. RSV vaccine candidates in development (data from clinicaltrials.gov (accessed 30 July 2024)).

Investigational product	Manufacturer	Vaccine	Antigen	Target population	Trial number	Phase
mRNA-1345	Moderna	mRNA	Pre-fusion F-protein	Maternal	NCT06143046	II
mRNA-1345	Moderna	mRNA	Pre-fusion F-protein	Paediatric	NCT05743881	I
RSV ΔNS2/Δ1313/ I1314L (RSVt Vaccine)	Sanofi	Live-attenuated vaccine (intranasal)	Whole virus	Paediatric	NCT06252285	III
LNP CL-0059 and LNP CL-0137	Sanofi	mRNA	Not specified	Elderly	NCT05639894	II
BLB-201	Blue Lake Biotechnology Inc	Viral-vector – live attenuated (intranasal)	Whole F-protein	Paediatric	NCT05655182	I/IIa
BLB-201	Blue Lake Biotechnology Inc	Viral-vector – live attenuated (intranasal)	Whole F-protein	Elderly	NCT05281263	I
BARS13	Advaccine	Protein	RSV G protein	Elderly and paediatric	NCT04681833	II
IVX-A12	Icosovax/astra zenenca	Bivalent virus-like particle candidate vaccine	Pre-fusion F-protein of hMPV and RSV	Elderly	NCT05903183	II
IN006	Shenzhen Shenxin Biotechnology Co., Ltd (INNORNA)	Bivalent mRNA Vaccine	Pre-fusion F-protein of RSV-A and RSV-B	Not specified	NCT06287450	I
MV-012-968	Meissa vaccines Inc	Live-Attenuated Vaccine (intranasal)	Whole virus with SH deletion	Paediatric, elderly	NCT04690335	II
CodaVax-RSV	Codegenix	Live-attenuated vaccine (intranasal)	Whole virus	Paediatric	NCT04919109	I
CodaVax-RSV	Codegenix	Live-attenuated vaccine (intranasal)	Whole virus	Elderly	NCT04295070	I
V-306	Virometrix	Virus-like particle	Antigenic site II region of the F-protein	Not specified	NCT 04519073	I

RSV, Respiratory syncytial virus.

antibodies from baseline at one-month post-vaccination.[72]

Nucleic acid vaccines

Despite being conceptualised around three decades ago, mRNA vaccines were only recently utilised during the COVID-19 pandemic. They proved to be highly effective, leading to the adaptation of this platform for other infections, including RSV.

mRNA-1345, manufactured by Moderna, has already been approved for use in older adults (as

mRESVIA). The same vaccine is currently in phase I and II trials as a paediatric and maternal vaccine (ClinicalTrials.gov identifiers: NCT05743881, NCT06143046).

A phase II trial (ClinicalTrials.gov identifier: NCT05639894) sponsored by Sanofi to investigate safety and immunogenicity of an RSV mRNA vaccine candidate is active. However, details of the vaccine's target antigen are not available.

Others

Whilst the majority of vaccines (both approved and unapproved) use RSV-F protein as the primary vaccine antigen, BARS13 is a protein-based vaccine that uses the RSV-G protein. It is currently in phase II trials (ClinicalTrials.gov identifier: NCT04681833) in older adults and infants.

V-306 is a vaccine that uses VLPs to present its target epitope, antigenic site II of the F-protein, which is present on both the pre and post-fusion of the RSV-F protein. In a phase I trial (ClinicalTrials.gov identifier: NCT04519073), it was found to be safe and immunogenic in healthy non-pregnant women.[86]

Conclusions and looking ahead

RSV infection is a significant disease of childhood, and its role as a cause of severe LRTI in older adults is increasingly recognised. It forms a significant health and economic burden to individuals and healthcare systems globally.

RSV vaccines and monoclonal antibodies have the potential to transform overwhelmed paediatric wards during the RSV season and reduce health deterioration and hospitalisations for LRTI in older adults from both RSV directly and co-infection with pneumococcus.[28] In addition to the direct benefit of reducing RSV-associated LRTI, there are other positive indirect effects that may emerge, particularly in children. Emerging evidence hints at a possible link between severe RSV infection and recurrent wheezing and childhood asthma; as such RSV prevention may reduce the occurrence of both. Recurrent wheezing and asthma significantly contribute to medical visits and medication use in children, in addition, it can result in substantial time off school for children and work for their caregivers. Ameliorating the burden of both would improve the quality of life for individuals and reduce pressure on healthcare systems. Another exciting prospect is the ability of the newly licenced products to be available globally; as 95% of severe infant disease and 97% of mortality is concentrated in LMICs, having preventative therapies that are affordable and can be delivered to infants and older adults in LMICs is key to reducing much of the global RSV burden. Future vaccines that could co-administer RSV antigens with influenza and COVID-19 antigens could ease the vaccine burden on children, older adults and other vulnerable populations.

As varied treatments emerge we should monitor for the unintended consequence of altering population pathogen exposure (such as the oro-nasal microbiome changes) that were seen in the reanalysis of the MAKI (infant palivizumab) trial.[87]

We must also take great care to follow the evolution of RSV and continue to develop new therapies based on the most current knowledge of circulating strains due to the risk of escape mutations developing that could render current treatments ineffective.

Declarations

Ethics approval and consent to participate

Ethical approval was not required as no novel research was undertaken.

Consent for publication

Not applicable.

Author contributions

Karen Kelleher: Methodology; Writing – original draft; Writing – review & editing.

Nadisha Subramaniam: Methodology; Writing – original draft; Writing – review & editing.

Simon B. Drysdale: Conceptualisation; Methodology; Supervision; Writing – review & editing.

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Availability of data and materials

Not applicable.

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