Respiratory Medicine 252 (2026) 108639

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Respiratory syncytial virus in high-risk adults: A critical appraisal of therapeutic options and unmet needs

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ARTICLE INFO

Keywords:
Respiratory syncytial virus
Antivirals
Monoclonal antibodies
Adults
Respiratory infections
Therapeutics

ABSTRACT

Respiratory syncytial virus (RSV) has traditionally been viewed as a causative agent of pediatric illness, yet accumulating evidence shows substantial morbidity and mortality among adults, particularly older individuals, those with cardiopulmonary comorbidities, and the immunocompromised. Although recent vaccine approvals for older adults represent major progress in prevention, effective therapeutic options for established infection remain limited. Herein we provide a critical analysis of existing and emerging antiviral and monoclonal antibody (mAb) therapies for the management of RSV infection in adults, highlighting current options and compounds in clinical development. At present, ribavirin remains the only antiviral recommended for treatment in adults, and no mAb has received regulatory authorization for prophylaxis or therapy in this population. Several development programs for direct-acting antivirals have been discontinued for reasons unrelated to safety or efficacy in adults, contributing to an ongoing treatment gap. Nevertheless, newer drug candidates, including ziresovir, EDP-938, and S-337395, have shown encouraging antiviral activity and acceptable safety in adult studies. By examining both the scientific evidence and the structural factors shaping the current landscape, we emphasize the need for sustained adult-focused clinical development to complement preventive vaccination. Addressing this therapeutic gap will be essential to reduce the burden of RSV disease in high-risk adult populations, particularly as the global population ages.

1. Introduction

Respiratory syncytial virus (RSV) is a globally prevalent pathogen and a leading cause of lower respiratory tract infections (LRTIs). While it is traditionally associated with bronchiolitis and pneumonia in infants and young children, RSV also poses a significant clinical threat to vulnerable adults, particularly individuals over 60 years of age, those with comorbidities, and the immunocompromised [1,2]. In these populations, RSV infection is frequently underdiagnosed due to its nonspecific clinical presentation and limited routine testing, yet it is associated with substantial morbidity, hospitalizations, and mortality [3]. Despite the growing awareness of its impact, the burden of RSV in adults remains neglected in clinical practice and public health policy [3].

RSV is a member of the *Orthopneumovirus* genus within the *Pneumoviridae* family, which includes enveloped viruses with negative-sense, single-stranded RNA genomes [4]. The virus is surrounded by a lipid envelope that incorporates three key surface glycoproteins: the G protein, which facilitates viral attachment to host epithelial cells, the F protein that is responsible for mediating membrane fusion and viral entry and the SH protein that presumably modulates host immune responses and inhibits apoptosis [5,6]. In addition to the envelope glycoproteins, RSV encodes replication-associated proteins. These include the nucleoprotein (N), phosphoprotein (P), large polymerase subunit (L), and the transcription processivity factor (M2-1), all of which are under investigation as potential antiviral targets [5]. RSV is classified

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https://doi.org/10.1016/j.rmed.2026.108639
Received 9 November 2025; Received in revised form 5 January 2026; Accepted 6 January 2026
Available online 6 January 2026

into two major antigenic subtypes, RSV-A and RSV-B, based primarily on the genetic variability of the G glycoprotein [7].

Recent advances have led to the approval of three RSV vaccines for use in older adults, two protein subunit and one mRNA-based vaccine [8, 9]. These developments mark an important milestone in severe RSV disease prevention, particularly for high-risk individuals. Monoclonal antibodies (mAbs), which can also be used prophylactically, are currently licensed only for pediatric use, and no dedicated direct-acting antivirals (DAAs) are approved for the treatment or prevention of RSV in adults [7]. The absence of a dedicated therapeutic pipeline constitutes a persistent clinical gap.

In this narrative review, we examine the current therapeutic options available for the management of RSV infection in adults, with particular attention to high-risk populations such as the elderly and the immunocompromised. We provide a focused overview of DAAs and mAbs that have been evaluated in adult populations across various phases of clinical development. By identifying the current gaps and exploring emerging alternative treatments, our aim is to critically evaluate the therapeutic landscape to improve care for these increasingly recognized vulnerable populations.

2. Methods

References were identified through searches of PubMed, Scopus, Google Scholar, and ClinicalTrials.gov for articles published between Jan. 1, 2015, and Oct. 9, 2025, using combinations of MeSH terms and free-text keywords including: “respiratory syncytial virus”, “antivirals”, “fusion inhibitors”, “polymerase inhibitors”, “therapeutics”, “monoclonal antibodies”, “clinical trial”, “antiviral efficacy”, and “drug development”. The review primarily focused on compounds currently in development or clinical use for the treatment of RSV in adults, as well as in programs discontinued within the past decade. References published before 2015 were included only for established therapies such as ribavirin and intravenous immunoglobulins (IVIG). Reports from regulatory agencies [Food and Drug Administration (FDA), European Medicines Agency (EMA), and World Health Organization (WHO)] and selected industry or biotech websites were included if they provided original data or verified information regarding clinical trial outcomes or reasons for program discontinuation. Only English-language sources were considered, and non-peer-reviewed publications or conference abstracts were excluded.

3. The substantial clinical burden of RSV in high-risk adults

RSV displays a seasonal circulation pattern that varies by geographic region. In the Southern Hemisphere, RSV activity begins as early as March and typically wanes by October, while in the Northern Hemisphere, circulation generally starts between September and December, with epidemics subsiding by May [10]. Season length varies from ~3 months (e.g., Spain/UK) to ~10 months in tropical regions aligned with the rainy season [10]. During the first RSV season of the COVID-19 pandemic (2020–2021), incidence declined markedly, likely due to pandemic mitigation measures [11]. In contrast, a pronounced RSV resurgence was seen in the following season (2021–2022), coinciding with the relaxation of containment measures [11].

In high-income countries, RSV imposes a considerable health burden among adults aged ≥60 years. The estimated attack rate for RSV-associated acute respiratory infections (ARI) in this group is 1.62 %, with 0.15 % requiring hospitalization and an in-hospital case fatality rate of up to 7.13 % [12]. In 2019 alone, approximately 33,000 in-hospital deaths were attributed to RSV in this age group in high-income countries [12]. In the United States, the estimated annual incidence of hospitalization for community-acquired pneumonia associated with RSV is 0.7 cases per 10,000 adults overall, increasing to 0.8 among those aged 50–64 years, 2.5 among those aged 65–79 years, and 5.0 among individuals aged ≥80 years [13].

Additional population-based surveillance underscores this age dependency, with hospitalization rates approximately five times higher in adults aged 50–64 years and about fifteen times higher in those aged ≥65 years compared with adults aged 18–49 years [14]. The risk is further magnified by underlying health conditions. Compared with individuals without comorbidities, the incidence rate ratio for hospitalization was 4.0–33.2 for congestive heart failure, 3.2–13.4 for chronic obstructive pulmonary disease, 0.87–6.46 for coronary artery disease, 2.35–11.16 for diabetes, 2.04–3.60 for asthma, and 0.68–3.05 for obesity [14].

Among immunocompromised adults, particularly those with hematologic malignancy and hematopoietic stem cell transplant (HM/HSCT) recipients, RSV represents a substantial proportion of viral respiratory infections [15]. U.S.-based data indicate that RSV accounts for 30 %–37 % of viral respiratory infections in these populations, with 19 %–36 % progressing to LRTI requiring hospital admission [15]. This severe morbidity across the elderly and the immunocompromised underscores the critical disconnect between disease impact and the availability of effective, approved therapeutic agents.

4. Current treatment options

4.1. Ribavirin

Ribavirin is one of the limited approved therapies for RSV infections. It has been widely used as supportive RSV treatment in adults, and it is included among the possible therapeutic options in several clinical guidelines [16].

4.1.1. Proposed antiviral mechanisms and therapeutic complexity

Ribavirin is a guanoside analogue, exhibiting *in vitro* activity against a broad range of DNA and RNA viruses [17]. Both direct and indirect mechanisms have been proposed to explain its mechanism of action that nonetheless remains controversial. During RSV infection, the virus relies on the L protein, a component of the viral polymerase complex, to cap its mRNA transcripts [18]. As a guanosine analogue, ribavirin may interfere with the enzymes responsible for the capping process, thereby disrupting viral RNA synthesis [17]. Following cellular uptake, ribavirin is phosphorylated by adenosine kinase to its monophosphate form and subsequently to di- and triphosphate derivatives [19]. The triphosphorylated form directly inhibits the viral mRNA polymerase by occupying its nucleotide-binding site, which prevents incorporation of the correct nucleotides and leads to reduced viral replication or the production of defective virions [20].

Moreover, ribavirin increases the mutation rate of the viral RNA genome during replication, a process known as lethal mutagenesis, resulting in the accumulation of nonfunctional viral proteins and decreased infectivity [21]. Ribivirin has an additional inhibitory action against inosine monophosphate dehydrogenase, causing depletion of intracellular guanosine triphosphate pools essential for viral RNA synthesis [17]. Ribavirin also exhibits immunomodulatory properties, promoting a shift from a Th2- to a Th1-dominant immune response that supports antiviral activity [22]. Therefore, the antiviral properties of ribavirin likely stem from a combination of these multi-faced effects on both host and viral parameters.

4.1.2. Variable clinical efficacy and safety considerations

Ribavirin used for RSV treatment is available in both inhaled and oral formulations. The aerosolized formulation is primarily used in children. In adults, its use is limited due to side effects, cost and limited data from randomized control trials despite the potentially beneficial effects on the respiratory system. The drug is not specifically approved for adults by the FDA. Side effects include sudden deterioration of respiratory function due to bronchospasm and teratogenesis in animal models [23]. Studies of environmental exposure in treatment settings have shown that the drug can disperse into the immediate bedside area

during routine patient care activities [24]. Health care workers who are pregnant should consider avoiding direct care of patients receiving aerosolized ribavirin [24].

A systematic review of aerosolized ribavirin in immunocompromised patients conducted from 1966 to 2019 identified only observational trials of low-quality rating and concluded that there may be a mortality benefit when aerosolized ribavirin is initiated early after diagnosis [25]. In a systematic review and metanalysis conducted between 2001 and 2022 that included ten observational trials and one randomized controlled trial, there were no differences in mortality [risk ratio (RR): 0.63; 95 % confidence interval (CI): 0.28–1.42] in all subjects treated with aerosol/oral ribavirin compared to supportive care [26]. In subgroup analysis, mortality was significantly lower in hematological subjects (RR: 0.32; 95 % CI: 0.14–0.71), but it did not differ significantly in lung transplant recipients (RR: 0.89; 95 % CI 0.31–2.56) [26]. Oral ribavirin (vs. supportive care) was associated with increased viral clearance (RR: 2.60; 95 % CI: 1.35–4.99) [26].

In a systematic review and metanalysis conducted in patients with HM/HSCT that included fourteen observational trials and one randomized controlled trial, ribavirin use was not associated with lower all-cause or RSV-associated mortality [27]. In subgroup analysis, ribavirin use was associated with lower mortality in HM/HSCT patients with LRTI. In addition, aerosolized ribavirin was associated with lower progression to LRTI [27]. Among allogeneic hematopoietic cell transplant (allo-HCT) recipients, RSV infections have a wide spectrum of outcomes ranging from upper respiratory tract infections (URTIs) to LRTIs and death [27].

In 2014 an immunodeficiency scoring index (ISI) was developed, allowing progression predictions to LRTIs and death [28]. The ISI provides a score from 0 to 12 by considering 7 parameters (age, neutropenia, lymphocytopenia, myeloablative conditioning regimen use, graft-versus-host disease (GVHD) presence, corticosteroid use, recent HCT/lack of stem cell engraftment) [28]. A 0–2 score is considered low risk, 3–6 moderate and 7–12 high [28]. A significant trend of increasing LRTI incidence and RSV-associated mortality was observed as the risk increased from low to moderate to high ($P < .001$) [28]. Patients in the high-risk group had the greatest benefit of ribavirin-based therapy at the URTI stage and the highest risk for progression to LRTI and death when antiviral therapy was not given [28]. A retrospective trial included 124 allo-HCT recipients with RSV infections treated with oral or aerosolized ribavirin from September 2014 through April 2017 [29]. Mortality rates did not significantly differ between groups (30-day: aerosolized 10 %, oral 9 %, $P = 1.00$; 90-day: aerosolized 23 %, oral 11 %, $P = .10$) [29]. For patients with ISI $\geq$7, 30-day mortality was significantly increased overall, yet remained similar between the aerosolized and oral therapy groups (33 % for both) [29].

Among lung transplant patients, RSV may lead to severe infections due to immunosuppression as well as chronic lung allograph dysfunction (CLAD) [30]. One prospective study compared LRTIs with either parainfluenza virus, RSV, or human metapneumovirus treated with oral ribavirin ($n = 38$) with LRTIs not treated with ribavirin due to contraindications ($n = 29$) [31]. New onset CLAD at 6 months developed in 5 % of the ribavirin group versus 24 % of the non-ribavirin group ($P = .02$) [31]. Graft function recovered within 30 days in 84 % of ribavirin-treated patients and 59 % of the non-ribavirin group ($P = .02$) [31]. In contrast, in a 9-year multicenter retrospective study among RSV-infected lung transplant recipients, the forced expiratory volume in 1 s (FEV1) values at 3 months after infection of ribavirin-treated and-untreated recipients were not different [32]. Ribavirin did not influence hospital length of stay (LOS) or Intensive Care Unit (ICU) admission [32].

Among RSV-infected immunocompetent patients, the effect of ribavirin, based on clinical studies, is controversial. In a retrospective observational cohort study that included 175 immunocompetent ARI-RSV patients, ribavirin treatment significantly reduced mortality (both in univariate and multivariate analyses) and shortened hospital stay (only in the univariate model) [33].

4.2. Immunoglobulins: is it a real option?

(Polyclonal) immunoglobulins can modulate T-cells, B-cells and macrophages leading to antibody and cytokine production, as well as complement activation [34]. RSV-IVIG contains 5 times the RSV neutralizing titers found in standard IVIG (thus requiring significantly less fluid volume), but, crucially, it is not widely available anymore [35].

In a retrospective chart review of immunocompromised patients who were admitted for a viral respiratory tract infection using medical record data from September 2011 to September 2016 at two large academic centers in the U.S., investigators evaluated the effect of IVIG treatment [36]. The study included 270 patients (73 % were transplant patients) and RSV was isolated in 26.3 % of the cohort. In the total population, the use of IVIG was significantly associated with a shorter ICU LOS and a longer hospital LOS. IVIG administered within 48 h of hospitalization was associated with a shorter ICU LOS and a shorter hospital LOS for patients hospitalized at least 2 days [36]. In the subgroup analysis, however, the above differences were not significant among RSV patients. Furthermore, there were no significant differences in readmission rates or death [36].

Recent efforts have focused on developing high-titer IVIG preparations with enhanced RSV-neutralizing capacity for immunocompromised patients. RI-001, a plasma-derived product enriched in anti-RSV antibodies, produced marked increases in serum neutralizing titers and was well tolerated in a Phase 2 compassionate-use study involving 15 immunocompromised individuals, with improved survival when administered early in infection [37,38]. RI-002, developed through a process that blends plasma with high RSV-neutralizing titers and standard donor plasma, showed comparable safety and efficacy in a pivotal open-label Phase 3 trial in patients with primary immunodeficiency [38,39]. In 2019, the FDA approved RI-002, marketed as Asceniv™, for antibody replacement therapy in adults and adolescents with primary humoral immunodeficiency [40].

Consequently, while specialized products exist, the overall evidence base and restrictive authorization limits immunoglobulins as a viable, broad therapeutic solution for RSV in the general high-risk adult population.

4.3. Palivizumab: the challenges of repurposing a pediatric prophylactic

Palivizumab is a recombinant humanized IgG mAb directed against the F protein on the RSV surface [41]. It has potent neutralizing fusion-inhibitory activity against both RSV subtype A and B strains [41]. Although licensed only for pediatric prophylaxis, its use has been explored in adult HM/HSCT, where the risk of severe RSV infection is high. However, efficacy data in this population remain highly limited.

Among the studies evaluating palivizumab in adults, the most recent investigation included 67 HM/HSCT patients and found no significant differences in mortality or readmission rates between those who received the antibody and those who received only supportive care [42]. A separate cohort of 40 allogeneic HSCT recipients reported similar findings, with comparable rates of progression from URTI to LRTI (56 % in both groups) and no difference in one-year survival, regardless of palivizumab use [43]. Outcomes in smaller series have been more variable. In one report of 26 RSV episodes, patients treated with palivizumab and aerosolized ribavirin experienced low short-term mortality (0 % at 30 days, 7.7 % at 90 days), whereas another study of eight patients treated with the same regimen observed substantially worse outcomes, including 25 % 30-day mortality, although most patients achieved RSV clearance [44,45].

Beyond retrospective data in HSCT recipients, palivizumab has also been assessed in a randomized, placebo-controlled challenge trial involving healthy adults aged 18–55 years (NCT04540627) [46].

Primary and secondary virologic endpoints, including peak viral load, duration of shedding, and time to peak viral load showed no meaningful differences between palivizumab and placebo [46].

These studies are limited by their small sample sizes, retrospective design, and frequent use of combination therapy, which complicates the attribution of benefit to palivizumab. Furthermore, the high cost of the drug and the lack of prospective randomized clinical trials in adults have limited its use in adult populations. The evidence suggests that palivizumab offers little support for established RSV infection in adult populations. To our knowledge, comparable studies evaluating nirsevimab and clesrovimab in adult populations have not been reported.

5. Emerging treatment options: progress or prerequisites?

The current therapeutic pipeline includes numerous DAAs and mAbs. In this environment, initial human studies in adults are consistently prioritized, in accordance to the International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines, for safety and pharmacokinetic assessment to enable subsequent efficacy trials in children. This structural prioritization subjects the adult therapeutic potential to the critical risk of program termination if pediatric development stalls or corporate strategy shifts.

5.1. Fusion inhibitors

5.1.1. Ziresovir

Ziresovir is an oral small-molecule RSV fusion inhibitor that binds the heptad-repeat C region of the F protein, inhibiting RSV F protein–mediated cell–cell fusion [47]. In cell-based assays it has shown potent activity against both RSV-A and RSV-B, including large panels of clinical isolates, with no measurable activity against other respiratory viruses [47]. In murine pharmacokinetic studies, drug exposure in lung tissue exceeded plasma levels and persisted longer, supporting its rationale for targeting LRTIs [47].

Clinical evaluation in adults has focused primarily on safety and pharmacokinetics. Several Phase 1 trials in healthy volunteers investigated single and multiple ascending oral doses, metabolism, excretion, and the effect of food [48–51]. Ziresovir was well tolerated, with no major safety concerns, although detailed results remain unpublished. More recently, a multicenter, randomized, placebo-controlled Phase 2 trial enrolled adults hospitalized with RSV infection, including older adults and patients with cardiopulmonary comorbidities, chronic kidney disease, or immunosuppression, to evaluate safety, pharmacokinetics, and preliminary efficacy (NCT06942299) [52]. This study has been completed, but results have not been reported yet. A thorough QT/QTc study is planned to further evaluate potential cardiac effects in healthy adults (NCT06591845) [53].

Although efficacy data in adults remain unavailable, ziresovir has advanced further in pediatric development. A Phase 3 trial in infants hospitalized with RSV infection (NCT04231968) showed significantly greater reductions in viral load and faster clinical recovery compared with placebo [54,55]. These findings stand in contrast to the disappointing late-stage outcomes of other RSV entry inhibitors.

5.2. RSV-L (large) nucleos(t)ide analog inhibitors

5.2.1. Molnupiravir

Molnupiravir is an orally administered prodrug of the nucleoside analogue β-D-N4-hydroxycytidine, which induces error catastrophe through the accumulation of mutations during viral RNA replication [56]. Originally developed for SARS-CoV-2, it has also been evaluated as a potential therapeutic for RSV [57].

In a randomized, placebo-controlled Phase 2a human challenge trial (NCT05559905), 116 healthy adults were inoculated with RSV and randomized to receive molnupiravir for prophylaxis, as treatment after infection confirmation, or placebo [56]. The study did not meet its primary endpoints since neither prophylactic nor therapeutic dosing significantly reduced RSV viral load compared to placebo [56]. However, participants treated with molnupiravir experienced faster symptom resolution, and the drug was generally well tolerated with comparable rates of adverse events between groups.

Ongoing studies continue to investigate its role in the management of RSV infections. A Phase 2 adaptive platform trial is currently recruiting adults with early symptomatic RSV to assess viral clearance under different antiviral regimens, including molnupiravir (NCT06488300) [58]. In addition, an observational study in the U.S. Veterans Health Administration (NCT06160128) is establishing a framework to evaluate the real-world use of antiviral agents, including molnupiravir, across respiratory viruses [59]. While its primary focus is COVID-19, the study also aims to capture outcomes in patients with RSV infection, which may provide indirect insights into the drug's role in this setting [59].

5.2.2. S-337395

S-337395 is an oral RSV antiviral that inhibits the RNA-dependent RNA polymerase (RdRp) activity of the viral L protein, thereby blocking transcription and replication within infected cells [60]. A Phase 1 study in healthy adults (NCT06270511) evaluated multiple oral formulations, relative bioavailability, food effects, pharmacokinetics, safety, and tolerability using an open-label crossover part and a double-blind multiple-dose part [61].

A subsequent Phase 2 randomized, double-blind, placebo-controlled human challenge study in 114 healthy adults reported that once-daily S-337395 for five days achieved the primary endpoint with a statistically significant reduction in viral load versus placebo, including an 88.94 % reduction in the highest-dose cohort [60]. The same report described significant improvements in clinical symptom scores and a favorable safety profile with no serious or severe adverse events and no dose-related increase in adverse events [60]. S-337395 has been granted fast track designation by the FDA, reflecting its potential to address the current lack of effective antiviral treatments for RSV [60].

5.3. RSV-L (large) cap domain inhibitors

5.3.1. EDP-323

EDP-323 is an orally administered, first-in-class non-nucleoside inhibitor of the RSV L protein, which disrupts the viral RdRp complex and blocks replication [62]. In a randomized, double-blind, placebo-controlled Phase 1 study in healthy adults, single and multiple ascending doses of EDP-323 were evaluated under both fed and fasted conditions [62]. The agent was well tolerated at all tested doses, including the maximum regimen of 800 mg once daily, with only mild adverse events reported, headache most commonly [62]. Pharmacokinetic analyses demonstrated rapid oral absorption and a terminal half-life consistent with once-daily dosing, while food intake did not meaningfully alter drug absorption [62].

A Phase 2a randomized, double-blind, placebo-controlled human challenge study (NCT06170242) evaluating multiple oral doses of EDP-323 in healthy adults experimentally infected with RSV-A has been completed [63]. Results have been submitted to ClinicalTrials.gov but are currently under quality control review and have not yet been officially released [63].

5.4. RSV-N nucleoprotein inhibitors

5.4.1. EDP-938

EDP-938 is an orally administered, non-fusion replication inhibitor of RSV that targets the viral N protein [64]. Preclinical studies demonstrated potent antiviral activity against both RSV-A and RSV-B laboratory strains and clinical isolates, as well as efficacy in animal models of infection [64].

In a Phase 2a randomized, double-blind, placebo-controlled human

challenge study (NCT03691623), healthy adults experimentally infected with RSV received EDP-938 for five days at different dose levels [65]. Treatment led to substantial reductions in viral load and symptom severity compared with placebo [65]. Participants receiving EDP-938 also exhibited markedly lower mucus production, approximately 70 % less than placebo, and faster improvement of URTI symptoms [65]. There were no apparent safety concerns in all tested doses of EDP-938 [65].

Subsequent genomic analysis of nasal-wash samples from respondents of the same study confirmed that EDP-938 has a high barrier to resistance [66]. Among 37 treated participants, only one developed a resistance-conferring substitution in the RSV N gene, L139I [66]. The L139I variant produced roughly a 10-fold reduction in drug susceptibility *in vitro*, but at an associated cost of diminished viral fitness [66]. No reduction in viral clearance was observed in the participant carrying the L139I change [66]. E112G was another, transient treatment-emergent change that did not, nonetheless, affect the sensitivity of RSV to EDP-938 [66].

EDP-938 has also advanced into Phase 2b evaluation across distinct adult populations with RSV infection (NCT05568706) [67]. A randomized, double-blind, placebo-controlled trial in non-hospitalized adults at high risk for RSV-related complications has been completed, though results have not yet been reported [67]. This study aimed to assess the efficacy and safety of oral EDP-938 in patients with ARI-RSV managed in the outpatient setting [67].

Another Phase 2b multicenter trial in adults with community-acquired RSV infection and acute URTI (NCT04196101) did not meet its primary endpoint of reducing total symptom scores compared with placebo, nor did it achieve key secondary antiviral endpoints [68,69]. However, a greater proportion of participants in the EDP-938 group achieved undetectable RSV RNA levels at the end of treatment (day 5), and no safety issues were identified [68,69]. A separate Phase 2b multicenter study evaluated EDP-938 in HCT recipients with URTI (NCT04633187) [70]. This trial was terminated early due to a strategic business decision, not safety concerns [70].

5.5. Monoclonal antibodies in early clinical development

Two mAbs are currently undergoing early clinical evaluation. SIBP-A16 is investigated in a Phase 1a randomized, double-blind trial in healthy adults using multiple ascending doses and nirsevimab as an active comparator (NCT07106918) [71]. GR2102 is in a Phase 1 randomized, placebo-controlled study in healthy adult Chinese participants assessing safety, tolerability, pharmacokinetics, and immunogenicity following single-dose administration (NCT06313697) [72].

A summary of investigational antiviral and monoclonal antibody therapies evaluated for RSV infection in adults is presented in Table 1.

6. The strategic abandonment of discontinued therapeutics

Several RSV antivirals and mAbs that initially showed promise in preclinical or early studies in adults have been discontinued during clinical development. In most cases, these programs were halted following insufficient efficacy in pediatric trials, pediatric-specific safety concerns, or strategic business decisions, rather than lack of safety or pharmacologic activity in adults. These discontinuations reflect the pediatric-driven focus of RSV therapeutic development and underscore the limited evaluation of these compounds in adult populations.

Table 2 provides an overview of RSV therapeutics discontinued over the past decade.

Among discontinued agents, clinical trials of presatovir, enzaplatovir and ALX-0171 demonstrated antiviral activity but failed to translate it into meaningful clinical benefit as defined by the endpoints of the respective studies. Presatovir showed antiviral activity in early human studies but failed to improve virologic or clinical outcomes in adults with naturally acquired RSV, leading to the discontinuation of the clinical program [73–75]. Enzaplatovir, a fusion inhibitor evaluated in a Phase 2a randomized, placebo-controlled challenge study in healthy adults, was well tolerated but did not meet its primary efficacy endpoints, leading to discontinuation of its development (NCT02718937) [75,76]. Likewise, the inhaled nanobody ALX-0171 achieved rapid viral clearance in hospitalized infants, yet it did not improve clinical recovery outcomes, resulting in the termination of its pediatric and overall development (NCT03418571) [77,78].

Several other RSV antivirals were discontinued for business or sponsor-driven reasons despite favorable safety findings in adult studies. Rilematovir, an oral RSV fusion inhibitor, showed modest antiviral activity in non-hospitalized adults and limited efficacy in pediatric patients, with multiple trials terminated before completion (e.g., NCT04583280; NCT04978337) [79–82]. Lumicitabine, a nucleoside analog targeting the RSV polymerase, produced marked viral load reductions in adults, but failed to demonstrate clinical benefit in hospitalized infants [83]. The evaluation of lumicitabine was subsequently discontinued by the sponsor likely due to safety concerns (dose-related neutropenia) that had been observed in pediatric trials, although no formal reason was given [84]. RV-299, a small-molecule N-protein inhibitor, advanced through early-phase adult studies with acceptable safety outcomes, but its development was also discontinued (NCT06067191; NCT06033612) [85,86].

Operational or practical challenges have led to the termination of potentially promising programs as well. For instance, obeldesivir, a nucleoside analog prodrug with potent preclinical activity against RSV, entered Phase 2 adult and pediatric trials that were terminated early due to low RSV incidence during enrollment seasons (NCT06585150; NCT06784973) [87–89]. PC786, an inhaled RSV polymerase inhibitor,

Table 1
Investigational antiviral and monoclonal antibody (mAb) therapies evaluated for respiratory syncytial virus (RSV) infection in adults.

Compound	Target/Action	Formulation	Development phase	Key findings	Clinical trial identifier
EDP-323[a]	Non-nucleoside inhibitor of the RSV L polymerase that disrupts viral RNA replication	Oral	Phase 2a	Well tolerated in healthy adults	NCT06170242
EDP-938[a]	Nucleoprotein (N) inhibitor that blocks viral transcription and replication	Oral	Phase 2b	Reduced viral load and symptom severity in challenge studies	NCT05568706 NCT04196101
Molnupiravir	Nucleoside analogue that induces error catastrophe during viral RNA replication	Oral	Phase 2	Did not reduce viral load but accelerated symptom resolution and was well tolerated	NCT06488300 NCT06160128
Palivizumab	Humanized mAb targeting the RSV F protein and inhibiting viral fusion	Intramuscular	–	No significant clinical or virologic benefit compared with placebo in adult studies	NCT04540627
S-337395[a]	L polymerase inhibitor that blocks viral RNA transcription and replication	Oral	Phase 2	Significantly reduced viral load and symptom scores	NCT07214571
Ziresovir (AK0529, RO-0529)	Fusion inhibitor that targets the heptad-repeat C region of the RSV F protein and blocks membrane fusion	Oral	Phase 2	Well tolerated in adult studies; efficacy results pending	NCT06942299 NCT06591845

[a] These compounds have received fast tract designation by the FDA.

Table 2
Discontinued RSV therapeutics in clinical trials in the last 10 years.

Compound	Target	Development phase	Key findings in adult studies	Key findings in pediatric studies	Reason for termination
Gontivimab (ALX-0171)	Fusion protein	Phase 2 (NCT03418571)	N/A	Reduced viral load but lack of clinical efficacy; acceptable safety profile	Insufficient efficacy in pediatric trials
Enzaplatovir (BTA-C585)	Fusion protein	Phase 2a (NCT02718937)	No significant antiviral or clinical benefit in human challenge study	N/A	Lack of efficacy
Lumicitabine (ALS-8176)	RNA polymerase	Phase 2b (NCT03333317) (NCT03502694)	Potent antiviral activity; well tolerated	No clinical benefit; dose-related reversible neutropenia	Sponsor decision
Obeldesivir	RNA polymerase	Phase 2 (NCT06585150)	N/A	N/A	As a business decision due to low RSV incidence
PC786	RNA polymerase	Phase 2 (NCT03715023)	Reduced viral load and symptoms	N/A	Recruitment and logistical challenges
Presatovir (GS-5806)	Fusion protein	Phase 2b (NCT02534350)	Reduced viral load and symptoms; no clinical benefit in adult HCT or lung transplant recipients	N/A	Failed trials in adults with natural RSV infection
Rilematovir (JNJ-53718678)	Fusion protein	Phase 3 (NCT04583280)	Well tolerated with modest antiviral effect	Well tolerated but limited antiviral efficacy	Business reasons
RV-299	N-protein	Phase 1b (NCT06067191)	Safe and well tolerated	N/A	Business reasons
Sisunatovir (RV521)	Fusion protein	Phase 2/3 (NCT06079320)	Reduction in viral load, replication and symptom burden	N/A	Drug-drug interactions

showed significant antiviral efficacy in adults, but its subsequent study in HSCT recipients was discontinued for unresolved recruitment and logistics (NCT03715023) [90,91].

Sisunatovir (RV521), an oral fusion inhibitor, demonstrated significant antiviral activity and symptom reduction in adults in a challenge study and maintained a favorable safety profile across subsequent Phase 1 evaluations [92]. However, its Phase 2/3 program was discontinued after the sponsor cited unresolved developmental challenges, including pharmacologic interactions with acid-reducing agents, rather than safety concerns (NCT06079320) [55,93,94].

This consistent pattern highlights the need for the adoption of a mindset that recognizes favorable safety and initial efficacy data in adults warranting sustained investigation, irrespective of pediatric program outcomes.

7. Therapeutic bottlenecks: analyzing the gaps and defining priorities for clinical development

While the implementation of vaccination programs has significantly advanced RSV prevention in older adults, the absence of effective treatment options constitutes a major persistent gap in clinical care [95,96]. Multiple DAAs have undergone early-phase clinical evaluation in adults, primarily to establish pharmacokinetic and safety profiles before pediatric testing [75]. Although agents such as rilematovir, lumicitabine, and ALX-0171 were well tolerated in adults, many programs were discontinued after pediatric studies showed limited efficacy or raised safety concerns [55]. Others, like obeldesivir and PC786, were halted for operational or recruitment-related reasons rather than safety or efficacy findings [89,91]. Only presatovir was discontinued following a clear lack of efficacy in adults with natural RSV infection [75]. By contrast, most other terminations reflected pediatric trial outcomes or operational/business factors rather than adult-specific safety or efficacy findings. This pattern suggests that some compounds with acceptable adult safety profiles may still hold potential value for older or immunocompromised patients [55]. The common practice of transitioning RSV therapeutics from adult safety studies directly to pediatric efficacy trials without continued in parallel investigation in adult cohorts reflects a pattern of strategic prioritization that has inadvertently limited therapeutic advances for adults.

The therapeutic strategy of utilizing combination regimens for RSV is primarily intended to bolster host defense mechanisms in patients with severe immune deficiencies [97]. By administering ribavirin alongside IVIG, clinicians aim to provide high titers of neutralizing antibodies that directly inhibit viral activity and support antibody-dependent cellular cytotoxicity [97,98]. This multi-targeted approach is frequently utilized in specialized settings to manage severe infections when the patient's endogenous immune response is insufficient [99]. Clinical data from adult bone marrow transplant recipients demonstrated that early initiation of this therapeutic combination before the onset of respiratory failure was associated with significantly improved survival outcomes compared to historical rates for ribavirin monotherapy [98]. Based on these findings, current European guidelines suggest that combining ribavirin and IVIG should be considered for high-risk HSCT recipients with severe immunodeficiency scores or established lower respiratory tract disease [97,99]. However, combining palivizumab with ribavirin remains discouraged in adults due to a lack of evidence from randomized trials and insufficient data regarding its clinical efficacy in this population [97,99].

Another issue to consider while evaluating antiviral compounds, and especially direct-acting agents, against RSV (or any virus for that matter), is the development of resistance that could limit the therapeutic benefit. Pursuing studies that map the genetic pathways to escape from the selection pressures of antivirals *in vitro* is certainly worthwhile during clinical development. Accordingly, mutations in the viral fusion protein can reduce drug susceptibility; furthermore, these changes have been shown to mediate cross-resistance among several fusion inhibitors that share overlapping binding regions [100]. Structural analyses indicate that these resistance-associated mutations cluster in adjacent sites of the prefusion F conformation, altering its stability and enhancing fusion activity [101]. Evidence indicates that while N-protein inhibitors may have a higher genetic barrier to resistance, the interplay between mutations across multiple viral proteins suggests that resistance evolution in RSV may be more complex than previously understood [102].

Although real-world data of recently approved vaccines show high effectiveness in preventing RSV-associated LRTI and hospitalizations, they do not offer complete protection against symptomatic disease particularly among immunocompromised adults and HSCT patients [103,104]. Data from large observational studies suggest that breakthrough infections in vaccinated older adults are generally less severe, characterized by a marked reduction in medically attended respiratory illness compared to unvaccinated individuals [103]. Current evidence indicates that evolutionary changes in the RSV F protein that is targeted by most vaccines have not compromised vaccine effectiveness thus far [105]. Furthermore, no clinical evidence currently exists to suggest that treatment protocols should differ for vaccinated patients who do progress to severe disease, and standard management with ribavirin remains the only available option regardless of vaccination status [106]. This highlights a persistent gap for immunocompromised patients and those with comorbidities, for whom vaccine effectiveness may be suboptimal and effective post-infection antiviral therapy thus remains a crucial

unmet need [106,107].

8. Conclusions

RSV remains a major cause of illness and death in adults, particularly among older individuals, the immunocompromised, and those with chronic medical conditions. Despite this significant burden, ribavirin is still the only recommended antiviral for clinical use, and no mAbs have been licensed for therapeutic use in adults. Although recent vaccine approvals have improved prevention in older populations, they do not address the lack of effective therapeutic options for established infections. The discontinuation of several investigational agents after suboptimal results, often in pediatric trials, has further delayed progress toward adult-specific treatments. Future RSV research should include the elderly and immunocompromised populations in antiviral and mAb trials. In a fast-aging world, broadening clinical development to these high-risk groups is essential to close the persistent therapeutic gap and reduce the overall burden of RSV disease across the adult population.

CRediT authorship contribution statement

Ilias Mariolis: Writing – original draft, Investigation, Conceptualization. **Kyriaki Ranellou:** Writing – review & editing, Writing – original draft, Investigation. **Antonios-Periklis Panagiotopoulos:** Writing – original draft, Investigation. **Cleo Anastassopoulou:** Writing – review & editing, Supervision, Conceptualization. **Athanasios Tsakris:** Writing – review & editing, Supervision, Conceptualization.

Funding

No specific funding was obtained for this study.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The publication of the article in OA mode was financially supported by HEAL-Link.

Data availability

Not applicable.

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