Pneumonia

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RSV: an overview of infection in adults

Charles Feldman[1*] and Ronald Anderson[2]

Abstract

Background Respiratory syncytial virus (RSV) infection was originally considered to be simply a disease of childhood. However, it has increasingly been recognized that the virus may also cause infection in adults. Furthermore, great strides have been made in understanding the clinical manifestations, as well as aspects of its management and prevention, requiring the need for greater awareness of the various aspects of this infection in adults.

Main body There are several potential reasons that RSV may have been overlooked in adults. Firstly, it was due to a lack of knowledge that this infection could occur in this age group. Secondly, there was infrequent testing for RSV infection in adults, both for this reason and because RSV antigen testing in adults is less sensitive than in children. Thirdly, RSV diagnosis, therefore, required the performance of polymerase chain reaction (PCR) testing, which is both expensive and underutilized. Finally, there was also the belief at that time that if the infection was due to RSV, there was little one could do to about it in terms of treatment and/or prevention. More recently, however, enormous advances have been made particularly in the management and prevention of this infection. This manuscript, which is an extensive literature review, describes the modern understanding of the burden of infection, the clinical presentation, risk factors, immunopathogenesis, management, and prevention of RSV infections in adults.

Conclusion RSV virus is a common cause of respiratory tract infections in adults and advances in recent research have not only enhanced our knowledge of this infection but have led to the development of effective treatment and prevention of the infection.

Background

While originally considered a childhood infection, more recently it has been increasingly recognized that respiratory syncytial virus (RSV) may also cause infection in adults [1]. A potential reason that RSV may have been overlooked in adults previously was a lack of knowledge that this infection could occur at this age, with infrequent testing for RSV infection in adults. There was also at that time the belief that if the infection was documented to be due to RSV, there was little one could do to about it in terms of treatment and/or prevention. Furthermore, there was also the recognition that RSV antigen testing in adults was less sensitive than in children, thus requiring the performance of polymerase chain reaction (PCR) testing for RSV diagnosis, which is expensive and underutilized [2]. More recently, however, enormous advances have been made in the prevention and management of this infection thus requiring further awareness of its occurrence in adults. This manuscript reviews the virus itself, its immunopathogenesis, the role of RSV-pneumococcal interaction in disease pathogenesis, clinical aspects of the infection, the burden of disease, complications, mortality, treatment, and prevention of RSV infections in adults. The main purpose of this review was to describe multiple aspects of RSV infection in one review, incorporating new aspects from the recent literature that

*Correspondence:
Charles Feldman
charles.feldman@wits.ac.za
[1]Department of Internal Medicine, Faculty of Health Sciences, University of the Witwatersrand Medical School, 7 York Road, Parktown, Johannesburg 2193, South Africa
[2]Department of Immunology, Faculty of Health Sciences, University of Pretoria, Pretoria, South Africa

have not been described in previous reviews, including that of immunopathogenesis, with the purpose of bringing to the attention of the readers the frequency and significance of RSV infection in adults.

Introduction

Human RSV was discovered more than 60 years ago and was reclassified in 2016 into the family *Pneumoviridae*, genus *Orthopneumoviridae* [1]. Prior to this the taxon *Pneumoviridae* was a subfamily within the *Paramyxoviridae.* The virus is a medium sized, pleomorphic enveloped virus, with a negative sense, single stranded RNA genome, which encodes 11 proteins, two non-structural and nine structural proteins [1]. G (attachment), F (fusion), and SH (proposed viroporin) are surface glycoproteins that are important for infectivity, as maximally efficient fusion requires the participation of all three glycoproteins; however, these glycoproteins are also the focus of protective antibodies, and therefore are potential therapeutic targets [1]. RSV isolates are divided into two major antigenic groups, A and B, which are further divided into 13 RSV A genotypes and 20 RSV B genotypes, and while strains of both groups can circulate together during outbreaks, the proportions of groups A and B and the subtypes varies yearly [1, 3]. The genetic diversity between A and B resides mainly in the G protein. However, the F protein is highly conserved between the strains and is recognized by broadly cross-neutralizing antibodies and therefore is an ideal RSV vaccine antigen candidate. In temperate climates, RSV circulates throughout the winter season while in tropical countries, outbreaks of RSV occur during hot, humid, and rainy days in the summer season [1].

While it has commonly been thought that RSV subtype A may have a more severe clinical course, particularly in infants with bronchiolitis, but also in adults with infection, several other studies have indicated that there is no difference between the two serotypes, with regards to disease severity, or that RSV subtype B may cause more severe disease than subtype A [4, 5]. One recent study indicated that while the clinical course may be partly related to RSV subtypes, it is more closely related to the specific genotype [4].

RSV is effectively transmitted via large nasopharyngeal secretion droplets from infected persons and aerosolization is less important [1]. Close person-to-person contact is required, or contact with contaminated surfaces and autoinoculation is important, but small particle aerosols are not a major route as the virus is not stable when aerosolized [3]. Regarding transmission of RSV, the concept of the reproductive ratio (R_0), describing the degree of transmissibility (contagiousness) of the virus, is important [6]. The R_0 indicates how many people can be infected by one person [7]. The R_0 of RSV varies from one to five, but most typically is estimated to be three, meaning that one adult infected with RSV can typically infect three others. Interestingly, subtype A has been noted to have higher transmissibility than subtype B, and therefore the R_0 of RSVA may be higher than RSVB [6].

The mean incubation period is 5 days after which the virus spreads by intracellular transmission, cilial motion, or aspiration of nasopharyngeal secretions to the rest of the airway [8]. In addition to age and pre-existing comorbidities often associated with immunosuppression, other determinants of the dynamics of transmission of RSV and associated disease severity and reinfection, include geographic region, particularly regions with a low sociodemographic index (SDI), seasonality and the virulence of the prevalent strain of the virus [9–11]. Moreover, the duration of immunity following natural infection in both adults and children is brief, resulting in frequent reinfection, even with the original causative strain of the pathogen [12]. In this context, the impact of novel vaccine strategies on RSV transmission dynamics and duration of protective immunity, albeit in children, as well as adults, represent "knowledge gaps", which remain to be resolved [13], while the issue of cross immunity induced by different strains of RSV remains a topic of active research.

Immunopathogenesis

Respiratory syncytial virus infection of adults and older children (≥ 5-years of age) manifests mostly as mild-to-moderate upper respiratory disease, often recurrent, occasionally progressing to pneumonia in more severe cases, which present with predisposing factors, particularly conditions associated with immune suppression of primary or secondary origin [14–18]. On the other hand, unlike adults, neonates and infants aged ≤ one-year are broadly predisposed for development of severe lower respiratory tract disease due to the immaturity of their developing respiratory and immune systems [14–18]. In these very young children, replication of RSV in the nasopharynx is followed by spread of the viral pathogen via cell-to-cell migration along the respiratory epithelium of the lower airways. This is achieved by mechanisms involving progressive induction of cell fusion and syncytium formation, possibly augmented by aspiration of nasopharyngeal secretions, as well as infection of alveolar macrophages [16, 19].

Acute RSV infection of the lower airways of very young children is characterized by the development of a high viral load in the setting of significant damage to the airway bronchial epithelium and attenuation of epithelial cell restitution, particularly in the terminal bronchioles, which is a prominent site of viral replication [20]. The consequence is perpetuation of ciliated airway epithelium dysfunction, resulting in mucus blockade of the bronchial lumen. These events are exacerbated by the

small diameter of the immature paediatric bronchioles, as well as by the small numbers and size of the alveoli, predisposing for development of bronchiolitis and pneumonia, respectively [16, 17, 21, 22]. In very young children, the absence of protective airway defense mechanisms, together with poor bronchial reserve, are therefore likely to represent the prominent reasons for development of severe respiratory disease and dysfunction, predisposing for significant morbidity and mortality.

Unlike very young children, however, vigorous recruitment of neutrophils to the lower airways is not a feature of RSV infection of adults. Notwithstanding structural maturity of the adult airways, attenuation of neutrophil recruitment together with pre-existing mucosal antibodies and efficient induction of anti-RSV airway cellular immune responses is likely to provide adults with an early degree of protection against this respiratory viral pathogen. These mechanisms are likely to be complemented by the efficacy of airway mechanisms which control the intensity of harmful inflammatory responses.

Until recently, lack of insight with respect to the key immunological correlates of protection of adults against development of severe RSV infection has presented an obstacle to the design of efficacious RSV vaccines. Aspects of the anti-RSV immune response which necessitate clarification include: (i) identification of the most prominent epitopes on the viral F protein in particular, as well as on the G protein, these being recognized as the key viral antigens for inclusion in RSV vaccines; (ii) genetic promiscuity of the major histocompatibility (MHC) class II molecules interactive with key epitopes on the viral F and G proteins; (iii) the probable instability of these interactions, underscoring the necessity to target multiple antigenic sites on the F and G target proteins; (iv) MHC haplotype restriction; and (v) the roles and exact mechanisms of the cell-mediated immune responses targeted against the F and G proteins.

Although it is well recognized that antibodies, via production of nasal virus-specific IgA antibodies [23], and $CD8^+$ cytotoxic T lymphocytes [24], cooperate in promoting host defense against RSV, the involvement of $CD4^+$ T cells has been largely unexplored. This issue has recently been investigated by Guvenel et al., who probed the dynamics of "epitope-specific airway-resident $CD4^+$ T cells during experimental human RSV infection" [25].

In this study, the authors recruited 48 healthy, non-smoking adults aged 18–55 years during the summer months outside of the RSV infection season [25]. Following induction of experimental infection via intranasal inoculation of 1×10^4 plaque-forming units of RSV strain AM37, participants were quarantined for a period of 10 days. A combination of analytical technologies (immunochemistry performed on endobronchial biopsies, cellular immunophenotyping and enumeration by flow cytometry analysis of bronchoalveolar lavage fluid (BAL), bronchial brushings and broncho-absorption) was applied to elucidate pulmonary T lymphocyte dynamics, undertaken prior to and 7, 10, and 28-days post-induction of experimental infection [25]. Additional complementary studies to enumerate epitope-specific lung $CD4^+$ T cells were undertaken using the combination of IFN-γ ELISpot screening and MHC tetramer binding based on two MHC-restricted, immunodominant epitopes, F-EFY and G-DDF, representative of the viral F and G proteins, respectively.

During the course of experimental RSV infection, the authors observed increasing numbers of resident $CD4^+$ memory T (Trm) cells in the airways. These cells were recruited by the chemokine, CXCL10, produced by airway epithelial cells, and characterized by expression of the Trm cell activation marker, CD69. Although outnumbered by $CD69^+/CD103^+$-expressing $CD8^+$ cytotoxic Trm cells, the $CD4^+$ Trm cells were found to be mainly responsive to the viral F and G proteins, while $CD8^+$ Trm cells responded to the M, NS1 and NS2 proteins [25]. Importantly, however, $CD4^+$ Trm cell responses to the immunodominant F-EFY epitope were highly constrained by MHC restriction, but considerably less so in the case of the G-DDF epitope. Based on these observations, the authors proposed that combining the F and G proteins in a single vaccine may enhance $CD4^+$ T cell help [25].

Interestingly, the authors observed that their model of experimental RSV infection was also associated with increased numbers of regulatory CD4+ T cells (Tregs in BAL), seemingly as a mechanism to limit RSV infection-associated immunopathology. In this context, an earlier experimental study described the involvement of granzyme-expressing T regs in limiting immunopathology in the lungs of RSV-infected mice [26].

Finally, in an even more recent study, De et al. also investigated the role of human T cells in controlling RSV infection by comparing the progression of disease in engineered mice with a functional respiratory system and a genetically-depleted immune system (LOM mice) with that of mice reconstituted with an autologous HLA-matched human immune system, encompassing both innate and adaptive immune systems (BLT-L mice) [27]. The authors observed prolonged RSV infection in LOM mice. In contrast, RSV infection of BLT-L1 mice resulted in induction of a virus-specific antibody response characterized by production of IgM and IgG antibodies, as well as a T cell response, which collectively protected against RSV reinfection [27]. Importantly, the authors also demonstrated that adoptive transfer to LOM mice of primed human $CD8^+$ T cells and, to a somewhat lesser extent, $CD4^+$ T cells, conferred protection against RSV infection, leading the authors to conclude that these T cells

"efficiently and independently control RSV infection in human lung tissue in the absence of an RSV-specific antibody response" [27].

These recent insights into RSV-targeted cellular immune mechanisms are likely to have significant implications for future vaccine design. Currently, the three most effective licensed RSV vaccines recommended for protection of the elderly (≥60 years of age) are all based on targeting of the viral prefusion F glycoprotein, resulting in production of neutralizing antibodies, which prevent lower respiratory tract disease. Two of these are recombinant protein vaccines (GSK and Pfizer), while the third is an mRNA vaccine (Moderna). Vaccine preventive efficacy ranges from 66-83%, which although superior to predecessor RSV vaccines, the aforementioned experimental studies indicate that even higher levels of protection may be attainable through the design of combination vaccines (F and G proteins) and by effective harnessing of T cell-mediated immune responses.

Virulence mechanisms utilized by RSV to infect target cells and subdue innate and adaptive protective host airway responses

Several comprehensive and informative review articles have been written on this topic ([14–17, 28, 29], for example) and accordingly only the most prominent RSV virulence mechanisms operative in the elderly and, presumably to an extent in young children, are covered here. Foremost among these are the F, G, M, NS1 and NS2 proteins, with the other six proteins being intimately involved in viral replication and structural stability.

Invasion of target cells by RSV

As stated by Carvajal et al., following initial infection of the airway epithelial cells of the upper respiratory tract, RSV translocates to the lower respiratory tract, "reaching the bronchioles where viral replication is more effective" [16]. Notwithstanding invasion of ciliated bronchial epithelial cells and type I pneumocytes of the alveolus, RSV may also infect various types of innate immune cells of the lower airways such as alveolar macrophages and intra-epithelial dendritic cells [16, 19]. This versatility of RSV to target and engage various types of airway structural cells and effector cells of the innate immune system is most probably related to the receptor promiscuity of the viral G and F proteins.

The RSV G protein

In the case of the G protein, the primary function of this viral surface protein is to promote binding of virions to the cell membrane of lower airway epithelial cells, which is achieved via the attachment of RSV to several different cellular receptors, most importantly heparan sulfate proteoglycan, as well as annexin II and the CX3C chemokine receptor 1 (CX3CR1), which is the receptor for the chemokine, fractalkine (CX3CL1), a multifunctional chemokine which promotes leukocyte migration and macrophage chemotaxis [30–32]. In addition to the key role of the membrane bound form of the viral G protein in promoting attachment of the pathogen to its target cells, earlier studies also described an immunosuppressive activity of the soluble, detached form of the viral G protein. In this context, the G protein was found to antagonize antibody-mediated inhibition of viral replication by acting as a membrane-bound antigen decoy, which diverted the antiviral activity of Fc receptor-expressing leukocytes [33, 34].

The RSV F protein

The viral F protein, which is synthesized in a precursor form (FO), undergoes proteolytic cleavage to form a disulfide bond-linked heterodimer, which, in turn, is the forerunner of the mature F protein, which is a class II membrane fusion protein [16]. Like the membrane bound version of the viral protein, the F protein is also promiscuous with respect to receptor utilization on its target airway epithelial cells and other cell types. Cellular receptors utilized by the F protein include the broadly expressed adhesion molecule, intercellular adhesion molecule 1 (ICAM-1) [35], the multifunctional cytosolic and membrane protein, nucleolin [36], the epidermal growth factor receptor (EGFR) [37, 38], and as described more recently, the insulin-like growth factor-1 receptor (IGF1R) [39]. Importantly, interaction of the F protein with the EGFR also triggers an immune response. This is mediated via inhibition of activation of interferon (IFN) regulatory factor induction of synthesis of the type III antiviral IFN, IFN-lamda (IFN-λ). This cytokine is considered to be the most effective activator of innate mucosal antiviral immunity [38, 40]. In addition, the F protein of RSV has been reported to interact with and activate Toll-like receptor 4 (TLR-4), which is highly expressed in the apical zone of airway epithelial cells, resulting in the production of the cytokines, IL-6 and tumor necrosis factor-α (TNF-α), both of which induce mucin formation, leading to mucus hypersecretion and impairment of ciliated epithelial cell function [41, 42].

Most prominently the RSV F protein, and albeit to a somewhat lesser extent, the G protein, represent priority therapeutic and preventive vaccine and monoclonal antibody (mAb)/drug targets. However, as mentioned in the preceding sections, the broad promiscuity of the receptors utilized by these RSV cell attachment and fusion proteins may restrict the efficacy of individual agents, which selectively target complementary receptor binding regions of the RSV F and G proteins. Given the possible existence of this scenario, the design of therapeutic/preventive strategies based on the utility of mixed vaccines

or combinations of mAbs, which target both F and G RSV, proteins seem worthy of exploration.

The M, NS1 and NS2 proteins of RSV

These are non-structural proteins located in the cytosol of RSV-infected cells, which both individually and interactively, play a key role in antiviral immunity via targeting of antiviral type I IFNs [16, 43]. The viral M protein not only plays a critical role in viral assembly, but also translocates to the nucleus of the infected airway epithelial cell, where it modulates transcriptional activity, down-regulating synthesis of antiviral IFNs [17]. In the case of the viral N proteins, both NS1 and NS2 have been shown not only to attenuate the production of type I IFNs, but also the cellular signaling mechanisms utilized by these anti-viral cytokines, as well as that of type III IFN-λ [43–45]. In addition, NS1 has also been reported to inhibit the antiviral activities of cytotoxic $CD8^+$ T lymphocytes expressing the homing molecule, CD103, which directs these cells to the respiratory mucosal epithelium [46]. The aforementioned virulence mechanisms of RSV are summarized in Table 1.

The interaction of RSV and *Streptococcus pneumoniae*

Although known for a considerable period of time, there is an increasing understanding of the importance of the interaction between different pathogens. The role this interaction may play in the pathogenesis and presentation of the different respiratory tract infections in adults and children, including RSV and invasive pneumococcal disease, may be of particular importance [47]. One of the earliest interactions to be recognized was that between the influenza virus and *Streptococcus pneumoniae* (pneumococcus), with later studies suggesting that the interaction of these two pathogens may be associated with more severe respiratory disease and worse outcomes in adults [48]. Early on during the COVID-19 pandemic, studies appeared describing the occurrence of co-infections and secondary infections in association with the severe acute respiratory syndrome (SARS)-CoV-2 virus and other viruses, bacteria and fungal pathogens in adults [49]. More recently, considerable additional evidence of important broad biological and clinical interactions between RSV and the pneumococcus have been documented, particularly in infants and children [50, 51]. Very interestingly, these studies during the COVID-19 pandemic suggested that the decrease in invasive pneumococcal infections after introduction of non-pharmaceutical interventions for COVID-19 occurred in association with a decrease in these viral infections rather than a decrease in pneumococcal carriage (rates and density), and therefore, simply the transmissibility of pneumococcal infections [52, 53].

Possible mechanisms described as to how RSV may increase pneumococcal infectivity and/or virulence include: (i) RSV binding to penicillin binding protein 1a [54]; (ii) RSV (and rhinovirus) increasing pneumococcal carriage acquisition and density [55], (iii) RSV enhancing pneumococcal adherence to human epithelial cells and in association with this the demonstration of increased pneumococcal invasiveness in a murine model [56]; and (iv) RSV-mediated Gas6/Axl activity that attenuates macrophage-mediated protection against pneumococcal infection [57].

Table 1 Virulence factors of RSV and their mechanisms of action

Virulence factor	Mechanism(s) of action
G protein	• Promotes attachment of RSV to airway epithelial cells via binding to: - heparin sulfate proteoglycan - annexin II - CX3CR1 • Attenuates antibody-mediated inhibition of restriction of viral replication
F protein	• Promotes fusion of the virus with the airway epithelial cells and syncytium formation via binding to: - ICAM-1 - nucleolin - EGFR - IGT1R • Inhibits synthesis of antiviral IFN-λ • Promotes mucus hypersecretion via production of IL-6 and TNF-α by airway epithelial cells
M protein	• Down-regulates the synthesis of antiviral IFNs
NS1	• Attenuates the synthesis and signaling mechanisms of types I and III IFNs • Inhibits the antiviral activity of $CD8^+$ cytotoxic T cells
NS2	• Also attenuates the synthesis and signaling mechanisms of antiviral IFNs

The RSV virulence factors and mechanisms of action are based on references [26–42]

Abbreviations: *CX3CR1* CX3C chemokine receptor 1, *EGFR* epidermal growth factor receptor, *ICAM-1* intercellular adhesion molecule 1, *IFN* interferon, *IGF1R* insulin-like growth factor-1 receptor, *IL* interleukin; cell, *TNF-α* tumor necrosis factor alpha

Clinical features of RSV infection

RSV infection in adults

RSV was not recognized as a potentially serious infection in older adults until the 1970s when outbreaks of infection with the virus occurred in a long-term care facility [58]. Currently, RSV is one the most common causes of acute respiratory tract infections in adults, with clinical findings ranging from mild respiratory symptoms to severe lower respiratory tract infections (LRTIs) [1, 3]. The virus may also cause upper respiratory tract infections and exacerbations of underlying disease. The symptoms of RSV infection are generally clinically indistinguishable from other respiratory viruses [1, 59]. Most patients develop signs of upper respiratory tract infection such as nasal congestion and rhinorrhoea (22–78%) or sore throat (16–64%), while once the lower respiratory tract is infected symptoms including cough (85–95%), wheezing (33–90%) and dyspnoea 51–93%) are common [1]. Modelling studies have estimated that the burden of RSV infection in adults older than 65 years is similar to the burden of influenza in that age group [60]. Patients infected with RSV more commonly present with nasal congestion, productive cough, and wheeze, and less commonly with fever, than patients with influenza [3]. Asymptomatic infections are much less common in adults and older people [61].

RSV in healthy adults usually causes a mild-to-moderate upper respiratory tract infection of approximate duration of seven days or less, the symptoms of which mimic those of the common cold [23, 62]. However, in those adults who have significant risk factors, particularly those associated with secondary immunodeficiency, RSV infection portends severe disease associated with significant morbidity and mortality [15, 23, 62]. Advanced age (≥ 65 years), which is commonly associated with debilitating comorbidities such as chronic obstructive pulmonary disease (COPD), cardiovascular disorders and hematological malignancies, represents a major risk for development of RSV-associated pneumonia and bronchitis, as well as worsening of the aforementioned comorbidities, often necessitating hospitalization [2, 23, 63, 64]. Not surprisingly, the frequency of hospitalization due to RSV infection increases with advancing age [62], with hospitalization per se representing an additional risk for worsening disease due to the threat of superinfection with bacterial and viral respiratory pathogens, which exist in the hospital setting [64–66].

Risk factors for symptomatic RSV infection and progression to severe respiratory illness are documented in Table 2 [1–3, 59, 67–71]. Not surprisingly, immunocompromised patients have a greater risk of severe RSV infection, and subsequent mortality. It has been reported that hospital admission rates for RSV acute respiratory infections are 5–24 times higher in HIV-infected older persons than for persons without HIV [59]. RSV infection is particularly deadly in hematopoietic stem cell transplant (HSCT) patients, with progression from upper to lower respiratory tract infection in 40–60% of cases and a mortality among such patients with RSV lower respiratory tract infection (LRTI) exceeding 80% [59]. Also at greater risk are patients following lung transplant [1]. The chest radiograph in those with LRTIs due to RSV may show changes consistent with pneumonia, such as consolidation and ground glass opacities [59], but do not differentiate RSV pneumonia from bacterial infection [3]. Features include bilateral alveolar opacities most commonly but may also include interstitial changes. Computed tomography commonly shows pulmonary nodules and ground glass opacities [1].

Table 2 Risk factors for symptomatic RSV infection and for its progression to severe RSV-related disease in adults

Older age
Frailty and/or functional impairment
Living in a long-term care facility
Living at high altitude
Obesity
Malnutrition
Diabetes mellitus
Chronic or progressive neurological or neuromuscular conditions
Chronic kidney disease
Chronic liver disease
Immunocompromise, including patients on chemotherapy or chronic immunosuppression for connective tissue disease/vasculitis
Underlying comorbidities, including asthma, COPD, cardiovascular disease
Tobacco use
Bacterial co-infection or superinfection
Down's Syndrome

Refer to references: [1–3, 58, 59, 62–71]

Overall burden of disease

In 2015, an estimated 1.5 (95% CI 0.3 to 6.9) million episodes of RSV acute respiratory tract infections occurred in older adults in industrialised countries, and of these episodes, 14.5% involved hospitalization; furthermore in 2015, an estimated 14,000 in-hospital deaths were associated with RSV-related acute respiratory illness. RSV is said to be the causative agent in up to 12% of medical attended acute respiratory illnesses, although less than 1% of affected adults require hospitalization; however, among adults admitted to hospital with a positive RSV test, ~ 10–31% require intensive care unit (ICU) admission and 3–17% mechanical ventilation [1]. In one more recent systematic review and meta-analysis of data in high-income countries, translated into 5.2 million cases, 470,000 hospitalizations, and 33,000 in-hospital deaths in adults ≥ 60 years in 2019. Overall, the data lead to an estimation of the occurrence of 1620 RSV-related acute

respiratory infection and 150 RSV-related hospitalizations per 100,000 persons, with an in-hospital mortality of 7% [72]. Much less is known about the burden of RSV infection in lower-middle income countries (LMIC) than in high income countries, although it is considered to be higher in LMIC. Prior experience with influenza and COVID-19 has shown that social determinants of health including socioeconomic status and race are associated with a higher burden of infection, and in RSV socioeconomic status and crowding are important; furthermore, a very recent study indicated that people living with the most socially vulnerable census tracts had the highest need for hospitalization and ICU admission with RSV infection [73].

Burden of disease in women of reproductive age

One recent commentary on the burden of RSV infection in adults, which also highlighted the information known for women of reproductive age [68], indicated the limited and poor quality of evidence of currently available surveillance and natural history data, especially in low-to middle-income countries overall, where the disease burden is likely to be higher. However, even fewer data are available regarding RSV infection in women of childbearing age or related to pregnancy [68]. There are a number of reasons that understanding the burden of RSV disease in women of child-bearing age is important. Aside from the fact that a pregnant woman may receive an RSV vaccine to protect her child, there are also potential direct benefits to the mother. First, pregnancy is considered an immunologically attenuated state, and may be associated with more severe disease and adverse outcomes (for example fever, respiratory distress, hospitalization, preterm labour); second, family members, including the mother, may be the source of neonatal exposure RSV, which can be prevented; third, there may be vertical transmission of RSV, which, based on animal experiments could result in long-lasting immunological and pulmonary dysfunction, and lastly, the degree of disease burden may advise when in pregnancy vaccination should occur [68].

Burden of disease post-COVID-19

As a consequence of the non-pharmaceutical interventions (NPIs) and societal behavioural changes during the SARS-CoV-2 infection, there was not only a change in SARS-CoV-2 transmission, but also in the characteristic cyclical transmission of many endemic viral illnesses [74, 75]. This decrease in exposure to endemic viruses, was predicted to lead to an immunity gap (also called immunity debt, immunity pause, immunity deficit), within a group of susceptible individuals who avoided exposure, and therefore pathogen-specific immunity, to protect themselves against future infections [74, 75]. In the United States RSV prevalence decreased substantially initially during the COVID-19 pandemic, but rebounded thereafter, with unusual seasonality [76]. These same investigators undertaking a retrospective cohort from 2009 to 2023 noted that changes in the RSV diagnostic platform drove an increase in RSV detections in outpatient settings post 2020, and that hospitalized adults with RSV subtype A infections were at higher risk of ICU admission than those infected with sub-type B. Also, while the same reduction in burden of hospitalization associated with RSV occurred in children less than 5 years of age, the rebound to pre-pandemic rates seen in high income regions, was not seen in middle income regions, suggesting an ongoing negative impact of the pandemic on healthcare systems and access. The post-pandemic RSV surge in children was associated with markedly increased hospital volumes and need for respiratory support, even in older children with fewer comorbidities. Similar changes were seen in other countries, such as New Zealand, where increasing rates of RSV were seen not only in older children but also young adults [77]. Possible theories discussed to possibly explain the reason for the changes in RSV epidemiology in children include the occurrence of decreased viral immunity in vulnerable age groups due to prolonged decrease in RSV circulation, due to COVID-19 preventative strategies, potential SARS-CoV-2-induced immune dysregulation, viral interactions between SARS-CoV-2 and RSV and modifications in health-seeking behaviours as well as health system factors [78].

Other investigators documented variable changes in RSV antibody concentrations in children of different ages and that in older children with reduced antibody concentrations there was a significant increase in the number of RSV cases during the following RSV season [79]. It was predicted from modelling studies that larger outbreaks of both RSV and influenza would likely occur in the future [80]. The prediction of this "perfect storm" was followed by an unusually early RSV epidemic, a severe influenza virus epidemic, and a smouldering coronavirus pandemic, sometimes called the "tridemic" or "triple-demic" [81].

Complications

Common complications in adult patients with RSV infections include pneumonia, exacerbations of chronic respiratory conditions (patients with underlying asthma or COPD may experience worsening of symptoms, resulting in an acute exacerbation and an increased frequency of exacerbations), bronchiolitis, need for hospitalization, acute respiratory distress syndrome, with need for ICU admission and/or mechanical ventilation, secondary bacterial infections, cardiovascular complications including myocardial infarction and stroke, and death [71]. It is

now well characterized that underlying cardiac disease is a significant contributor to progression of RSV infection to severe illness [59]. Several studies have indicated that up to 50% of patients with RSV infection had underlying chronic cardiovascular disease and an association between RSV positivity and exacerbations of heart failure has been described [59]. These, and other, observations have led to the hypothesis that RSV infection may directly cause myocardial injury, similar to that of other pathogens. The potential mechanisms of this relationship need to be clarified, but may be due to RSV causing plaque destabilization, or a virally-induced hypercoagulable state, activation of the sympathetic nervous system leading to demand ischemia, direct RSV penetration into myocardial tissue, and transient pulmonary hypertension due to the effects of the infection on the respiratory system [59].

Mortality

LRTIs due to RSV are said to result in death in approximately ~ 2–5% of cases. In one surveillance study of healthy elderly and high-risk adults in the United States (US), RSV infection developed in 3–7% of the former group and 4–10% of the latter high-risk cases, and in the hospitalized cases, length of hospital stay, rates of ICU admission (15% and 12%) and mortality (8% and 7%), were the same in RSV cases compared to those with influenza [82]. However, a more recent study, also from the US, indicated that RSV infection in hospitalized older adults had greater morbidity and mortality than influenza [83]. Furthermore, a more recent study from China, which compared the clinical characteristics of three respiratory viruses, namely RSV, human metapneumovirus and human parainfluenza virus, noted that RSV caused more severe disease than the other two viruses, with a higher 30-day mortality [84]. This was supported by a further study by Falsey at al. [85], which found that patients hospitalized with RSV were more likely to require supplemental oxygen, suffer in-hospital complications, stay longer in hospital and need ICU admission. A study from Italy retrospectively evaluated consecutive cases referred to an emergency department with flu-like symptoms of acute respiratory failure (ARF) who had been tested for SARS-CoV-2, RSV and influenza A. RSV patients had the highest occurrence of ARF (62.7%), and severe disease (70.5%) [86]. Compared with influenza A, patients with RSV were older ($p = 0.009$), had a higher Charlston Index ($p = 0.001$), higher prevalence of chronic heart failure ($p = 0.001$), and were more frequently on inhaled corticosteroids and immunosuppressants. Heart failure, chronic exposure to inhaled corticosteroids and immunosuppressants predicted RSV infection. Glycemia ≥ 120 mg/dl, leukocytes ≥ 8000cells/µl and active or passive smoking predicted severe RSV disease. Mortality of RSV infection was similar to that of influenza A (6.6% versus 5.9%; ($p = 0.874$).

Treatment and prevention

Until very recently, the standard of care of RSV infections in adults was mainly limited to supportive care with bronchodilators, supplementary oxygen, intravenous fluids and antipyretics; in addition, no vaccines had yet been licensed [1]. While bronchodilators and corticosteroids had not been shown to be of benefit for infants, it seemed prudent to use them in adults known to have asthma and COPD, especially with evidence of bronchospasm [3]. While more than 50 years has passed since the first trial of an RSV vaccine, only recently have some vaccines been approved to prevent infection [87]. Improved understanding of the pathogenesis and immunopathology of RSV have led to significant advances in vaccine development and passive immunization, which together should provide coverage from infancy to old age [87].

Treatment with non-specific therapies

Several non-specific approaches to acute RSV bronchiolitis have been studied, and generally are not recommended or need further studies, and these include a variety of agents aimed at reversing airway obstruction, such agents are so-called "mucus therapies/mucolytics", bronchodilators, therapies targeting inflammation (e.g. glucocorticoids, ipratropium bromide, and leukotriene antagonists) and "manual therapies" in the form of physiotherapy [87].

Specific RSV therapy

Ribavirin is a broad-spectrum nucleoside analog that inhibits the replication of DNA and RNA viruses, and is available in aerosolized, oral and intravenous formulations [87]. Studies comparing ribavirin to placebo in infants and children with RSV-positive LRTIs showed no significant differences in various outcome parameters; however, a randomized control trial in bone marrow transplant recipients indicated that ribavirin treatment was associated with a reduction in viral load and pneumonia [87]. Treatment with ribavirin is complicated by cost, delivery and side-effect profile, so that it is not commonly used, except in immunocompromised cases with severe RSV LRTI [27]. A recent systematic review of ribavirin for treatment of subjects with RSV-related infections retrieved seven studies of subjects with hematological malignancy/stem cell transplant, two lung transplants and two otherwise healthy individuals [88]. A total of 788 subjects diagnosed with RSV were included, of whom 14,3% presented with only LRTI. In all cases there was no difference in mortality in all subjects treated with aerosol or oral ribavirin, compared to supportive care. In subgroup analysis, mortality was significantly lower

in hematological malignancy subjects, but not in lung transplant recipients. Oral ribavirin, compared with supportive care, was associated with increased viral clearance. Additionally in the analysis, the oral formulation appeared to be an easier, safe, and cost-effective, alternative to aerosolized ribavirin. In addition, a study comparing oral versus aerosolized ribavirin for the treatment of RSV in patients following hematopoietic stem cell transplants (HSCT), indicated similar outcomes and that oral ribavirin was and effective alternative with potential significant cost saving [89]. Another recent systematic review and meta-analysis in patients with hematological malignancies and HSCT confirmed that ribavirin was a reasonable option to treat RSV in patients with these conditions, in the absence of alternative effective antivirals [90].

Passive immunization

Passive immunization for prevention of RSV in children is undertaken through administration of mAbs or polyclonal RSV-neutralizing antibodies. The initial strategy was to use a mixture of human intravenous globulin IVIG), containing high concentrations of RSV protective antibodies, which reduced RSV hospitalizations, days in hospital, and days on oxygen in high-risk infants [1, 87].

The next strategy was the development of palivizumab which is a humanized mAb against the RSV fusion (F) protein, which inhibits the entry and infection by RSV, and which is administered intramuscularly once a month [1, 87]. This form of immune prophylaxis is targeted at prevention of infection in high-risk infants to reduce severe disease in a cost-effective manner (it reduces the rate of hospitalization due to RSV infection by 56%) but is limited by its cost and short effect duration. Most recently the efficacy and safety of palivizumab as a prophylaxis for RSV in young children was studied in a systematic review and meta-analysis and was found to be safe, well-tolerated, and effective in reducing RSV hospitalizations [91]. However, the authors indicated that further high quality randomized controlled trials were needed to determine its efficacy as a treatment for established infection.

There are several reports in the literature on the use of palivizumab in adults under different circumstances. One older systematic review evaluated the efficacy of palivizumab therapy of RSV, with the primary outcome being progression from upper respiratory tract infection (URTI) to lower respiratory tract infection (LRTI) and survival, in adults and children (136 cases in the combined studies) [92]. Overall, 3(12%) of 25 patients with URTI died of RSV and 5 of 88 patients with LRTI at the time of treatment died (6%). The authors concluded that larger randomized controlled trials would be needed before pavilizumab could be recommended for therapy of RSV in any clinical setting. An additional study conducted among 40 allogeneic stem cell transplant recipients found that palivizumab did not prevent progression to LRTI and had no impact on overall survival [93]. A nosocomial RSV outbreak in adults in a stem cell transplantation unit, was controlled with strict infection control interventions and immunoprophylaxis with palivizumab [94]. The authors concluded that the role of palivizumab in RSV hospital outbreaks warrants further evaluation. Shah and Chemaly presented a detailed review of the various options for the management of adult recipients of hematopoietic stem cell transplantation, used either alone or in combination including palivizumab [95]. Additional, more recent reviews, including a systematic review, describe strategies for prevention and/or treatment of RSV in older adults, patients with hematological malignancies, and cases with lung and other solid organ transplants [96–98]. A recent case report described the treatment of RSV in with palivizumab in an adult liver transplant recipient and reviewed the literature on use of palivizumab in immunocompromised adults [99]. The Practice Guideline Committee of the American Society of Transplantation and Cellular Therapy partnered with the Transplant Infectious Diseases Special Interest Group to update the guideline for management of RSV in patients with hematopoietic stem cell transplantation, describing in detail, the use of the various therapies including palivizumab [63].

Nirsevimab is a recombinant human IgG1 kappa mAb that binds the F1 and F2 subunits of the RSV fusion (F) protein at a highly conserved epitope [87]. This locks the RSV F protein in the prefusion conformation to block viral entry into host cells. It has been successfully investigated in a number of studies and has recently been approved by the European Union for the prevention of RSV in newborns and infants during their first RSV season [87]. It has also been approved by the Food and Drug Administration and recommended by the Advisory Committee of Immunization Practices in the United States since 2023 [100]. Several recent publications attest to the safety and efficacy of nirsevimab in children. Wilkins and colleagues confirmed that nirsevimab provided high and sustained levels of neutralizing antibodies throughout the infants' first RSV season and prevented RSV infection, while allowing the development of an immune response to the viral pathogen [101]. In children with heart or lung disease, entering their second RSV season, redosing with nirsevimab was safe and resulted in serum exposures associated with efficacy in healthy infants supporting efficacy in this high- risk population [102]. Effectiveness of nirsevimab against RSV has been demonstrated in outpatients [103], primary care and hospital settings [104] and even ICU settings [105]. Very interestingly, it has been suggested that use of nirsevimab for prophylaxis in children may also protect other populations at risk from RSV such as the elderly by reducing the spread of RSV, lowering the

viral load in infants [106]. However, the counter argument is that this may not be significant because RSV transmission in the elderly is usually via other elderly people or school-aged children, and also the fact that RSV may be transmitted at any time of the year not just during the period of the nirsevimab protection.

Other long-acting mAbs are under investigation [8], and inhaled nanobodies are said to be the next generation of mAbs to be used for local pulmonary delivery of antibodies for a variety of respiratory diseases [1].

Active immunization

Several active vaccine types are under investigation for preventing of RSV infection in infants, pregnant mothers, adults and the elderly. Towards the end of 2023 it was said that there were 34 different RSV vaccines in development, with 21 advancing through phase 1 to phase 3 clinical trials [87]. The most common vaccine target for RSV is the F protein, with the pre-fusion F protein recognized as having the most epitopes for neutralizing antibodies [1]. The G protein is also increasingly recognized as a critical target for vaccine development; however, while the F protein remains highly conserved between RSV A and B subgroups, the G Protein is more variable except for one highly conserved area [1]. Elevated concentrations of both anti-G and anti-pre-fusion F antibodies have been shown to be associated with lower scores of disease severity [1]. Potential vaccine types [60, 87] include the following:

- Live-attenuated
- Chimeric
- Protein-based
- Nucleic acid-based vaccines
- Recombinant-vector-based

Live-attenuated vaccines

These vaccines mimic natural infection to generate a potent immune response, including local mucosal antibody and cellular responses, while being attenuated to reduce virulence; the challenge is to achieve a favourable balance between safety (attenuation) and degree of immunogenic response [60, 87].

Chimeric live vaccines

These vaccines express RSV proteins in related, attenuated viruses and have a good safety profile, although there are only a few such vaccine candidates in development [87]. In contrast to vectored vaccine candidates, chimeric vaccines show favorable antigen presentation, which activates an adaptive immune response [60].

Protein-based vaccines

This vaccine approach is based on a display of various antigens (including whole inactivated virus, particle and subunit vaccines) to create an enhanced immunological reaction [87]. The current vaccines are designated for older adults and for protection of young children via maternal vaccination [87]. One recent maternal RSV F protein nanoparticle vaccination, which was assessed in pregnant women at 28 to 36 weeks, did not meet the primary endpoint of reduction of the rate of medically significant LRTIs in the first 90 days of life, but did have other potential benefits, such as such as a decrease in severe infections with hypoxemia and decreased hospitalization [107]. However, a second bivalent prefusion F vaccine administered to pregnant women was safe and effective against severe RSV-related LRTIs in infants [108].

Nucleic acid-based vaccines

The mechanism this vaccine uses is the introduction of messenger RNA (mRNA) encoding RSV antigens into the cells [87]. This type of vaccine has, in recent years, shown safety and high efficacy against SARS-CoV-2 infection.

Recombinant-vector-based vaccines

These vaccines use a modified replication-defective virus to induce humoral and cellular immune responses by delivering the genes of the relevant RSV proteins.

Currently approved vaccines for RSV

Currently three vaccines are approved for use in adults 60 years of age and older in the United States (US), with the third one licenced in June 2024. Those currently licenced are the Pfizer vaccine, the GSK vaccine [109], and the Moderna vaccine [110]. These vaccines were approved largely on the basis of positive ongoing studies [110–112]. In addition, the Pfizer vaccine was approved for use in pregnant women, also based on a positive study mentioned above [108, 113]. Following licensing in the US, these vaccines were subsequently licenced in Europe and Canada [114]. The US began vaccinating adults over the age of 65 years in the 23/24 winter season, but the CDC reported that as of May 2024, only 24·4% of adults over 60 years were vaccinated and only a further 10·7% planned to get vaccinated. For pregnant women, overall coverage with the RSV vaccine was 17·8% [115]. Given the costs of vaccines, and shortages in supplies, it is important to identify those individuals and those areas which would most benefit from vaccination. The landscape for RSV prevention has changed dramatically over the last few years, based on new RSV vaccines and treatment. However, it remains essential that resources are delivered to those most in need, to achieve worldwide reductions in morbidity and mortality. Clearly, many of the newly approved vaccines will be unaffordable for LMICs and creating an affordable RSV intervention is vital in a situation where global results are prioritised over profit (https://www.cdc.gov/vaccines/imz-managers/coverage/rsvvaxview/index.html).

Table 3 New antiviral therapies for RSV infection under development

Types of Agents and designation	Description
1. Antibodies	
RI-001 and RI-002	Aqueous intravenous polyclonal human immunoglobulin G from pools of plasma of healthy adult donors with high levels of RSV- neutralizing antibodies
REGN2222	Fully human IgG1 mAb, produced in VelocImmune mice, that binds specifically, to the F protein of RSV
MEDI8897	Recombinant human IgG1k mAb with an engineered FC region to have a longer serum half-life and designed for prevention of RSV LRTI
ALX-0171	First nanobody for treatment of RSV infection, which is a trivalent nanobody (42hDa) that binds the antigenic site II of the RSV F protein and neutralizes both subtypes of RSV
mAB 131-2G	Murine mAb that binds to the central conserved region of the RSV G protein and interferes with the attachment process by blocking the G protein from binding to CX3CRI
Motavizumab	Recombinant humanized mAb that binds to a 24-residue, linear conformational epitope FFL on the RSV F glycoprotein
2. Small molecule fusion inhibitor	
GS-5806	Orally bioavailable RSV fusion inhibitor shown to prevent RSV entry by blocking the virus-cell fusion process
MDT-637	Fusion inhibitor that has been shown to inhibit RSV entry into cells
JNJ-53718678	JNJ-678 is an RSV-specific fusion inhibitor that has been shown to act as an effective anti-RSV in vitro, and in animal models. JNJ-53718678 reduces RSV viral load, RSV infection severity, and duration of the disease
AK-0529	A novel compound being developed to inhibit RSV replication by blocking viral entry into the target cells
TMC353121	A small substituted benzimidazole RSV fusion inhibitor, which is an improved derivative of JNJ2408068 (a compound with antiviral activity against RSV A and RSV B, but with long tissue-retention times in animal models which created concerns and stopped its further development)
3. Nucleoprotein inhibitors	
RSV-604	A small molecule with sub-micromolar RSV activity that was discovered through chemical optimization of an RSV high-throughput screen hit
ALN-RSV01	Small interfering RNA with 19 nucleotides targeting a highly conserved region of the RSV nucleoprotein gene
4. Nucleoside analog and non-nucleoside inhibitors	
ALS-008176	A nucleoside RSV polymerase inhibitor with a high level of oral bioavailability

This table was compiled from data extracted from reference [116]. For further information and interim results, please see the full article

Abbreviations: *LRTI* lower respiratory tract infections, *mAB* monoclonal antibody, *RSV* respiratory syncytial virus

Promising new antiviral agents

Several additional promising antiviral agents are currently undergoing investigation [27, 87, 116]. Various targets on RSV exist for the potential development of these novel agents [1]. However, there are a number of challenges to development of new agents against RSV, including underestimation of the burden of infection, and therefore, misinterpretation of the potential market size, difficulties with point-of-care diagnostic testing for RSV in adults, and even the fact that the virus may undergo genetic changes and mutations that may allow it to evade antiviral therapies and even vaccination [1]. The list of new agents under investigation is extensive and a full description of all of these is beyond the scope of this manuscript but has been extensively reviewed elsewhere [116]. Briefly, the list of agents include: (i) antibodies, (ii) small molecule fusion inhibitors, (iii) nucleoprotein inhibitors, and (iv) nucleoside analog and non-nucleoside inhibitors (Table 3). As an example, very recently, treatment with Ziresovir, a selective, orally administered, RSV F protein inhibitor, was found to reduce signs and symptoms of bronchiolitis in infants, and young children, hospitalized with RSV infection with no safety concerns [117].

Conclusions

While this is a comprehensive literature review describing multiple aspects of RSV infection, it does have some potential limitations. Most importantly, because of the enormous body of literature available it was impossible to review and report each individual scientific study of the current topic. Thus, the authors took the decision to include good quality review articles as references for some aspects of the manuscript, and even for these the number were numerous. Nevertheless, the review does indicate that RSV is increasingly being recognized as an important respiratory pathogen in both adults, as well as children. The burden in adults has been significantly underestimated until more recently. Part of the reason for this being that diagnostic antigen testing is much less sensitive in adults than in children, although advances in molecular diagnostics (PCR-based) have allowed more rapid identification of RSV infection. Several new antiviral therapies, as well as vaccines against RSV have been studied and are progressively been introduced both to prevent the infection, as well as to ameliorate the effects of the virus on patients.

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Charles Feldman acts on the Speaker's bureau of GSK and Pfizer; Ronald Anderson has nothing to declare.

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