Respiratory Syncytial Virus infections in adults: a narrative review

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Summary

RSV is being increasingly recognized as an important pathogen in adults, especially among older people living with comorbidities. RSV is detected in 6-11% of outpatient respiratory tract infection (RTI) consultations in older adults and accounts for 4-11% of adult RTI hospitalizations, with 6-15% of these admitted to the ICU, and 1-12% of those hospitalized dying. Community-based studies estimate a yearly incidence of RSV infection at around 3-7% in adults aged 60 years and older. However, most infections are relatively mild. While RSV accounts for a similar disease burden to influenza in adults, hospitalized adults with severe RSV disease are typically older and have more comorbidities, with more respiratory symptoms and frequently absence of fever. Long term sequelae include deterioration of underlying disease, typically heart failure and COPD. Treatment options are currently limited, with supportive care the main modality. Two protein subunit vaccines for protection from severe RSV in adults aged over 60 years were licensed in 2023, with a third, a mRNA based vaccine, recently gained market approval in the USA. The Phase 3 studies showed good protection against severe disease, although there were very few participants aged 80 years and older. Given the considerable morbidity and mortality amongst those hospitalized with RSV, as opposed to the relatively low burden at community level, it is as yet unclear how best to make the most efficient and effective use of these new vaccines, and whether a universal approach of vaccinating all older adults would be most cost-effective, or whether targeting only well-defined high-risk groups would more efficiently achieve greater health gain. Data about real world vaccine effectiveness in older adults, including subgroups at high risks for RSV associated hospitalization are needed to determine the best use of these newly approved RSV vaccines. New diagnostics and therapeutics are being developed and will also need rigorous evaluation in their intended use populations to ensure they are used only for those for whom there is evidence of improved outcomes.

Introduction

Respiratory Syncytial Virus (RSV) is an enveloped RNA virus that causes respiratory infections in all age groups, in a predictable seasonal pattern in temperate climates, with incidence that is relative constant from year to year. Most infections are mild and self-limiting. However, RSV infection, particularly at the extremes of age and in those with comorbidities such as chronic obstructive airways disease and heart failure, may result in hospital admission and death. RSV has been considered a disease predominantly of

early childhood, but with increased testing, is now recognised as an important cause of mortality and morbidity in older adults. The prevention and therapeutics landscape for RSV is changing rapidly, with vaccines now approved for RSV, and new therapeutic and diagnostic approaches being developed. This review considers the diagnosis, disease burden and emerging preventative and therapeutic innovations for adults with RSV.

Clinical diagnosis

RSV in adults frequently causes only minor symptoms of upper respiratory tract infection.[1,2] Distinguishing RSV from other acute respiratory infections on clinical grounds is not possible with precision that is clinically useful.[3-5] Typical features of all acute viral-looking upper respiratory infections include runny nose, nasal congestion and sore throat, while symptoms of lower respiratory infections are predominantly cough and sputum production. Shortness of breath and difficulty breathing, chest pain, wheezing and coughing up blood are typical of more severe infection.[6] The clinical presentation may be an exacerbation of underlying chronic disease.

Severe RSV infection may present with typical features of lower respiratory tract infection, including cough, dyspnoea, chest pain and chest imaging changes, but can also be non-specific in older adults with features such as collapse, delirium and weakness.[2,7,8] Patients with chronic heart failure or airways diseases, especially COPD, frequently present with exacerbations of their underlying condition or develop exacerbations soon after presentation to healthcare.[9] Notably, upper respiratory tract symptoms in these patients are frequently minimal or absent.[10]

Aetiological diagnosis

The standard diagnostic procedure for RSV is a polymerase chain reaction (PCR) test form nasopharyngeal swabs wabs. However, in adults the viral load and duration of shedding is usually lower and shorter compared with children, making it more difficult to diagnose. Adding in tests on additional samples such as sputum, mouth and throat swabs, and saliva,[11] as well as serology testing may increase

diagnostic ascertainment by nearly a third to half in children and adults.[12,13] The analytic performance of rapid point of care test using PCR as a reference standard for RSV is now excellent.[14,15]

Although multiplexed assays have modestly lower sensitivity,[12] they are useful in distinguishing between respiratory viral pathogens. Several point of care multiplex PCR based testing platforms are now available and are useful for rapid diagnosis among adults presenting to primary care, pharmacy or emergency departments with relevant symptoms.[16] As the illness course progresses, sensitivity becomes poorer due to declining viral load, but using sputum samples in addition to nasal or nasopharyngeal swabs may improve case ascertainment.[17] Serological tests taken during convalescence can help diagnose infection retrospectively and are important in epidemiological studies, but are not useful for acute management.

Disease burden

The global number of hospital admissions for RSV-ARI in older adults was estimated at 336 000 hospitalizations with 14 000 in-hospital deaths.[18] In industrialised countries, 1.5 million episodes of acute respiratory infections, 336 000 hospitalizations, and 14 000 in-hospital deaths in adults aged 65 years or older are attributed to RSV infection annually.[18] There is a paucity of data for developing countries.[18]

Incidence, consultations and admissions among adults in the community

Community based studies have found RSV affects between 3-7% in community dwelling older adults each year.[4,5,19] The illness is generally mild in these cohorts; 17-28% of symptomatic RSV episodes resulted in a doctor's and no one was admitted to hospital. However, symptoms took about two to three weeks to resolve.[5,19] One community based study in adults at higher risk of a poor outcome due to cardiopulmonary comorbidity found an slightly higher annual RSV infection incidence of 4-10%, compatible with estimates for older adults in general. However, the illness was more severe in these higher risk people, with about 40% of RSV episodes requiring a doctor's visit, 16% requiring hospitalization, and 4% dying.[5] Studies that identify all episodes caused by RSV are important to

estimate incidence, severity and health care utilisation, but typically these community based studies are relatively small with cohorts consisting of 500-1000 participants. Outpatient and hospital based studies compliment community based prospective ascertainment studies to provide an estimate of the total healthcare burden from RSV (Figure 1, suppl tables 1 and 2). These hospital based studies found that 6-11% of all respiratory tract infection (RTI) outpatient visits in older adults are due to RSV,[3,20-22] and 12% of these were admitted to hospital.[20,23] In older adults admitted to hospital because of RTI, approximately one in 20 were diagnosed with RSV infection,[24-27] 11-18% of these required intensive care admission, and 6-9% died (Figure 1, suppl table 1).[28,29] People with comorbidities or advanced age are at higher risk of severe disease, including a need for hospitalisation. These figures are likely an underestimate as most studies have used only nasopharyngeal PCR for RSV diagnosis. Underestimation of incidence is an important limitation of all RSV studies due to diagnostic difficulties.[12] Li et al. adjusted incidence rates of RSV associated hospitalizations for case under-ascertainment caused by incomplete testing and concluded that in adults ≥ 65 years the hospitalization rate reported in existing studies should be up to 2.2-fold higher.[30]

Severe and complicated RSV infection in older adults and those with chronic disease

Hospitalisation rates for RSV infection are increased in patients with chronic obstructive pulmonary disease (COPD), ischaemic heart disease, chronic heart failure, previous stroke, diabetes, chronic kidney disease, obesity and immunosuppression.[31-36] The relative risk for admission conferred by these comorbidities are at least 2- to 4-fold[31] while for heart failure this may be 8-fold[36] or even higher.[35] These relative risks are higher in younger age groups, with older age conferring a significant risk in itself.[31,34,35] However, the vast majority (usually >90%) of patients admitted with RSV have at least one comorbidity, and multimorbidity is common.[9,32,34,37] Residents of long-term care facilities are over-represented among adults admitted with RSV infection.[34]

Respiratory failure, acute ischaemic cardiac events, cardiac arrhythmias and secondary bacterial infection are also common sequelae from RSV.[38,39] Bacterial infection can be especially difficult to diagnose accurately and many hospitalised patients with RSV infection are given antibiotics despite only a minority having positive bacterial cultures.[9,40] Woodruff et al. described acute cardiovascular complications in about 20% of 6248 hospitalised adults with RSV[38] while de Martino et al. noted some type of complication in about 50% of 175,392 patients with RSV infection in a community-based study.[39]

Risks for poor outcome vary by study and include markers of severity at admission such as abnormal white blood cell count, respiratory failure, tachypnoea or chest x-ray changes[9,41-44] as well as several comorbidities including chronic kidney disease and cerebrovascular disease.[31,45,46] However, most frequently implicated are COPD,[1,31,33-35,43,45,47] older age,[1,9,41-43,45,48,49] and heart failure.[1,33,34,41,45,50]

Similar findings have been described worldwide, with high rates of comorbidity and frequently poor outcome described in, for example, the Asia-Pacific region, Turkey, Central and South America and South-East Asia.[8,37,51,52]

In those who survive a severe initial illness, late complications can include sustained loss of function which affects about one third in the year following admission,[53] development or worsening of heart failure, cardiovascular events, decline in lung function, greater use of medications (including antibiotics, bronchodilators and inhaled or systemic steroids), impaired quality of life, fatigue and readmission to hospital.[37,53,54] Figure 2 summarises risk factors for admission and the spectrum of early and late complications in older adults.

RSV in immunocompromised adults

Immune deficiency is an independent risk factor for more severe disease, hospitalisation and death from RSV infection.[44,45,55] The most commonly described underlying conditions are haematopoietic stem cell transplant (HSCT) and lung transplant.[56,57] However, even higher hospitalisation rates have been reported among those with solid malignancy or on treatment for rheumatological diseases compared to HSCT,[58] and the impact of RSV in these other immunocompromising conditions requires further study.

Among recent recipients of HSCT, infection rates in adults are close to 10% and more common than influenza, adenovirus or human metapneumovirus.[56,59] Progression to lower respiratory tract infection (estimated at close to 40% in a recent meta-analysis),[56] bacterial co-infection and death (approximately 8%)[56] are common outcomes. In lung transplant recipients, complication are similarly high.[60]

Immunocompromised patients have additional risks from RSV infection. First, nosocomial outbreaks of infection have often been described.[61-67] Second, lung transplant recipients frequently suffer acute rejection or chronic lung allograft dysfunction (CLAD) with bronchiolitis obliterans and a significant decline in lung function parameters following RSV infection.[68-70] Bronchiolitis obliterans has also been

attributed to RSV infection in HSCT recipients with graft versus host disease.[71] Finally, infection duration and viral shedding can be very prolonged in those with immune deficiency.[57,72-74]

Duration of RSV PCR positivity is typically around 80 days in those with haematological disorders but can last considerably longer.[74] Importantly, intra-host viral evolution can occur during chronic RSV infection,[72] a phenomenon which has been noted with other RNA viruses[75,76] and was particularly implicated in the development of new variants of SARS-CoV-2.[77,78] In the absence of viral clearance, therapeutics given to immunocompromised patients could select for strains resistant to antivirals or for immune-evasive variants, for example in response to immunoglobulin-based treatments: again, this has been noted for SARS-CoV-2.[77,79,80] Antibody function seems particularly important in viral clearance[73] and antibody-deficient patients are at highest risk of prolonged SARS-CoV-2 infection.[81] This patient group therefore requires further research to investigate RSV infection duration and viral evolution. Prolonged detection of RSV has also been described in patients with COPD.[82-84] This may point towards impairment of mucosal immunity or systemic immunocompromise, for example from frequent corticosteroid usage.

RSV outcomes in comparison to influenza

The burden of RSV is frequently compared with influenza, and in general, regardless of setting, patients with RSV are older with more comorbidity, use more health care resources per admission, and have poorer outcomes (Table 1). In a recent large cohort of patients admitted to hospital with acute respiratory illness, those with underlying COPD or heart failure were more likely to have RSV than influenza.[32]

In studies from the US, RSV accounted for similar levels of health care utilisation as Influenza A in high-risk adults.[5] Despite influenza being more common, overall annual mortality from RSV among adults aged 65 years or older is only slightly lower at around 15 per 100 000 population versus around 20 per 100 000 population for influenza. In a prospective community study among healthy elderly patients, RSV infection generated fewer office visits overall than influenza; however, the use of health care services by high-risk adults was similar in the two groups.[85]

Prevention of RSV infection and severe outcomes

Environmental manoeuvres and advice to reduce the risk of infection

Prevention of RSV infection could consist of non-pharmacological interventions, vaccination and passive immunoprophylaxis with monoclonal antibodies. Non-pharmacological measures introduced in response to the COVID-19 pandemic were associated with an important reduction in RSV incidence.[86] RSV is generally spread via droplets and therefore through close contact between people or contaminated surfaces. Potentially effective prevention measures particularly relevant to older and at risk adults are summarised in suppl table 3. Many countries have guidelines which recommend at least some of these interventions, but there is considerable variability and currently most apply only to paediatric or immunocompromised populations.[87] There is an important evidence gap on how best to protect vulnerable older adults including those in long-term residential or nursing care.

Vaccination

The two most important surface glycoproteins of RSV are the G protein, which enables attachment of the virus to the cell and the Fusion (F) protein, which enables the virus membrane to fuse with the target cell membrane. The F-protein is an important target for both antiviral therapy and vaccines. RSV infection elicits neutralizing antibodies against both G and F glycoproteins.[88] Since the discovery of the pre-and postfusion configuration of the Fusion (F) protein,[88] vaccine development focused on the prefusion configuration of the F-protein, which has led to the licensing of two protein-based vaccines in 2023; an unadjuvanted bivalent prefusion-F vaccine and an AS01E adjuvanted RSV prefusion F vaccine for older adults.[89-91] Phase 3 studies of the bivalent prefusion-F protein-based vaccine found a vaccine efficacy of 67-86% against RSV-associated lower respiratory tract illness (LRTI) in adults ≥60 years (Figure 3, suppl table 4).[92] The same vaccine has also been approved as a maternal vaccine to protect infants against severe RSV disease (discussed in the infant immunisation paper in this series).[93] The phase three study on AS01E adjuvanted RSV prefusion F vaccine found an efficacy of over 80% against RT-PCR–confirmed RSV-related lower respiratory tract disease in adults ≥60 years (figure 3, suppl table 4).[94] Both vaccines caused only mild to moderate, mainly local, side effects, and were considered safe.[92,94]

A Phase 3 study of an mRNA RSV Pre-F vaccine (mRNA-1345) found a vaccine efficacy of over 80% against RSV-associated LRTI (Figure 3, suppl table 4).[95] This vaccine recently obtained market approval in the USA.[96]

Two adenovirus vector vaccines were in late-stage clinical development, but both companies halted their RSV vaccine programme in 2023. An adenovirus serotype 26 RSV vector vaccine encoding a prefusion F (preF) protein (Ad26.RSV.preF) in combination with RSV preF protein showed promising results in Phase 2b study, with a vaccine efficacy of 80% against RSV LRTI with at least three signs or symptoms (Supplemental Table 4).[97] A Phase 3 study of the adenovirus vector vaccine MVA-BN RSV did not meet the co-primary endpoint, with well below 50% vaccine efficacy against RSV LRTI with at least three signs or symptoms.[98]

With three licenced vaccines for older adults (Figure 3), evidence on uptake and real world effectiveness in the target groups is needed to determine the added value in older adults and other high risk groups. Current recommendations differ per country and are summarized in figure 3. During last RSV season uptake of the vaccines was considerable among older adults living in the USA with a vaccine effectiveness of 73-83% against RSV-associated hospitalization or emergency department encounters in adults ≥60 years.[99] When studying real world effectiveness, adults aged 80 and older need special attention, given that older age is a risk factor for severe RSV disease,[30] while vaccine efficacy might be lower due to Immunosenescence, causing lower immunogenicity at more advanced age.[100] The published Phase 3 studies found an vaccine efficacy of more than 90% in adults between 70-79 years. The number of adults aged 80 years and over included in these studies was too low to draw any conclusions about vaccine efficacy amongst those of most advanced age.[92,94,95]

A further open question is the duration of protection against RSV infection from vaccination: does it last for more than one season, or is yearly revaccination required? Schwartz et al[101] found that antibody titers were still well above their pre-vaccination baseline 12 months after immunization with the AS01E-adjuvanted respiratory syncytial virus (RSV) prefusion F protein–based vaccine. In addition, vaccine efficacy was similar in older adults in the second year after one dose of the AS01E-adjuvanted RSV prefusion F protein–based vaccine compared with older adults who received a second dose in the second year, suggesting that protection lasts for at least 2 RSV seasons.[102] Additional studies are ongoing.

These vaccines for older adults are also now being evaluated for safety and immune response in younger adults.

Prolonged contact between older adults and young children, for example grandchildren, appears to play an important role in the transmission of respiratory viruses.[103] Programmatic childhood vaccination against seasonal influenza decreased transmission and morbidity and mortality from pneumonia and influenza in older adults.[104,105] A similar effect has been observed after the introduction of routine pneumococcal vaccination in infants.[106,107] Modelling studies in the United Kingdom found that childhood influenza vaccination is cost-effective in preventing disease in older adults, and that this might lead to a greater reduction in RSV incidence compared to vaccinating older adults themselves.[108,109] None of the market approved RSV vaccines is currently licenced for use in children. However, a live attenuated nasal RSV vaccine for young children is being investigated in a Phase 3 trial following promising results from Phase 1 and 2 evaluations.[110,111]

The role of mucosal immunity to protect against infection is incompletely understood. IgA mucosal antibodies protected against infection in a human challenge study in young adults.[112] However, a recent human challenge study in older adults showed that older adults did no show an increase in secretory IgA after infection with RSV, despite a similar increase in serum antibodies compared with younger adults.[113]

Prophylaxis with monoclonal antibodies

Monoclonal antibodies targeting RSV are licensed for pre-exposure prophylaxis in high-risk infants and children, with trial data demonstrating efficacy for monthly palivizumab[114,115] and motavizumab[116] or the long-acting nirsevimab (see also the infant immunisation paper in this series).[117,118] Clesrovimab is another long-acting antibody in development.[119] A meta-analysis confirmed efficacy of monoclonals in children across multiple studies.[120] However, although these agents have been used in adults with active RSV infection,[121,122] immunoprophylaxis has not been investigated other than in children. While most adults respond to vaccination, some immunocompromised patients do not, as demonstrated with SARS-CoV-2 vaccination,[123] and vaccination is contraindicated in some. A proportion of these patients will have hypogammaglobulinaemia and recurrent bacterial infections making immunoglobulin replacement a viable preventative strategy, including products enriched for RSV antibodies,[124,125] but prophylaxis with long-acting monoclonal antibodies may be an attractive alternative for a subset of at-risk adults. Although not currently proven as efficacious or cost-effective, we believe these should be investigated.

Therapeutics

In common with other acute respiratory viral infections, antiviral therapy for RSV is challenging due to the limited window of opportunity for treatment. Antivirals work by inhibiting viral replication or viral entry into host cells. Viral replication generally begins to slow before symptoms peak. In healthy volunteer human challenge studies, RSV viral load was at its maximum 5-6 days post infection, with symptoms peaking one day later.[126] The virus usually becomes undetectable by day eight post infection, so if treatment cannot be initiated before around day four post-infection, which is approximately when symptoms start, antivirals may have limited effect in typical illness. However, viral dynamics may be altered in patients with co-morbidities, immunocompromise and/or increasing age, so the opportunity for effective initiation of treatment may be somewhat longer in these high risk groups. The window for early antiviral treatment seems to be a day or two longer for RSV than influenza or SARS-CoV-2.[126,127] Nevertheless, antiviral treatment strategies based on immediate initiation of therapy upon symptom presentation/positive rapid test or (post-exposure) prophylaxis have the highest probability of success, but may not be cost effective for all.

Ribavirin is a broad-spectrum antiviral which has been used since the 1970s against severe RSV in either systemic or nebulised forms, the latter in an attempt to limit haematological toxicity whilst delivering the drug to its main site of action in the lungs. Nebulised ribavirin is the only antiviral licensed for RSV, although evidence for efficacy is controversial.[128] Ribavirin has sometimes been used in transplant recipients and other immunocompromised patient groups who become infected with RSV. A systematic review found that whilst oral ribavirin may decrease viral loads faster than supportive care alone in lower respiratory tract RSV infection, clinical benefits were only seen in haematological stem-cell transplant recipients and patients with haematological malignancy.[129] The dearth of therapeutic options has led to an increase in antiviral research in recent years.

Nucleoside or nucleotide analogues with modes of action like ribavirin target viral RNA-dependent RNA polymerase (RdRp), so these agents tend to have broad-spectrum activity against RNA viruses.[130] Favipiravir and molnupiravir are examples, and following intracellular phosphorylation become incorporated into viral RNA. This causes characteristic mutagenic signatures, with favipiravir being substituted mainly for guanine and molnupiravir mainly for cytidine. Rather than inducing high rates of

mutagenesis, remdesivir and bemnifosbuvir cause chain elongation and termination respectively upon binding to the RdRp active site.[130]

One of the most promising RdRp inhibitors, lumicitabine, which causes immediate chain termination when binding to RSV RdRp, highlights a key problem with developing antiviral agents for acute treatment. Lumicitabine showed clear *in vivo* viral inhibition when given on Day four following infection in a human challenge study,[131] but there was no effect in hospitalised neonates and infants with confirmed RSV bronchiolitis.[132] Together with the drug's propensity to cause reversible neutropenia, this finding led to stopping further clinical development. In a human challenge study where lumicitabine was administered on day four post inoculation, viral load had yet to peak, whereas in the neonate and infant study, participants were already hospitalised and had to have a positive PCR test before commencing treatment, meaning the range of median time since symptom onset was 3.9 to 7.5 days. This is likely to be at the tail end of the viral dynamic curve when even a potent antiviral has limited potential to further reduce viral load and affect clinical outcome.

In addition to RdRp inhibitors, including newer non-nucleotide compounds targeting RdRp, antivirals with more specific action against RSV have been developed. Fusion inhibitors are the main class of these drugs and they inhibit viral entry into the cell through binding fusion (F) glycoprotein or inhibiting pre-fusion protein conformational changes required for cell entry, and agents targeting the viral nucleoprotein (N protein). Whilst such agents including presatovir,[133] JNJ-53718678[134] and EDP-938[135] have shown efficacy in human challenge studies, once trialled in patients, for example when presatovir was used in lung transplant recipients,[136] these agents often fail at Phase IIa. A likely contributing factor was that presatovir was not started until 6 days post symptom onset in that case.[136]

Initial platform trials during the SARS-CoV-2 pandemic gave antivirals too late, once patients has been symptomatic for several days and often hospitalised.[137] More recently however, the feasibility of recruiting at-risk patients very early post infection has been demonstrated[138] and this does lead to observed antiviral effects outside human challenge studies.[80] Future studies on antivirals for RSV should therefore focus on very early treatment in primary care, possibly with a combination of agents with differing modes of action to exploit likely additive and possibly synergistic effects that have yet to be

studies in detail for RSV. Immunomodulatory therapies, which have shown promise in the later stages of SARS-CoV-2 in hospitalised patients, might also benefit those with late Phase RSV disease.

Cost of care

Individual costs for nonhospitalized RSV episodes in older adults are relative low with an average total cost of €30.80 per RSV episode in a community based cohort study in older adults. This was lower compared with influenza episodes, for which the average total costs were €72.60, mainly due to a higher percentage of medically attended episodes.[139] Hospital care for RSV costs about $743.9 million each year in the US.[85] Each hospital stay for RSV cost $16 034 compared to $15 163 for influenza, with the difference attributed to slightly longer hospital stays in those with RSV.[140] For immunocompromised patients with RSV, hospital stays cost $66 000 on average.[141]

The total economic burden of RSV in adults aged ≥60 years in the USA was estimated to be $6.6 billion per year, based on 4.0 million annual RSV cases, including both direct and indirect costs.[142]

A recent modelling study estimated that in the USA an RSV vaccination program with (one of) the two licenced subunit vaccines (Arexvy and Abrysvo) for adults ≥60 years could be cost effective with a price of up to $130 per dose. Their calculations included costs for outpatient care, hospitalization and death, and estimated efficacy was based on phase 3 trials, using a willingness to pay of $95 000 per QALY gained.[143] Another Canadian modelling study estimated that one dose of the licenced subunit vaccines to protect residents of long-term care homes would be cost-effective with a price up to $177, using a willingness to pay of $50 000 per QALY gained. If the program was extended to all adults ≥60 years, the program would be cost effective with a price up to $143.[144] Real world vaccine effectiveness studies can help to generate more data to refine these models.

Future research

Apart from the wide range of ongoing vaccine development and evaluation research, key areas of research relevant to RSV in adults include immune response to infection and vaccination, novel therapeutics, and novel diagnostics including point-of-care tests. Relevant trials registered at clinicaltrials.gov are summarised in Table 2. Additional research priorities are summarised in Panel 1.

Research networks and infrastructure developed in response to COVID-19 could be readily repurposed to address some of these critically important questions.

Efficacy trials of therapeutics are often done among those at lower risk of poor outcome and rely on outcome measures such as viral clearance and time to recovery. However, once efficacy is demonstrated, larger scale trials of effectiveness are needed to determine which subgroups of people have a high chance of receiving clinically meaningful benefit, and which subgroups can safely be managed without specific antiviral treatment. The problem of antimicrobial resistance, partially driven by assumptions as opposed to evidence from clinical trials, serves as a caution. Antibiotics were widely prescribed in the community for common infections based on assumptions that they would prevent deterioration and expedite recovery decades before pragmatic clinical trials were conducted in this population. It was only in the 1970s that general practitioners began conducting randomised controlled trials of antibiotics for common infections that found that most individuals could be safely managed without antibiotic treatment.[145-147] Making the same mistakes and deploying antiviral drugs at scale without proper evidence carries similar risks, including the potential to drive viral mutations with global pandemic potential.

Panel 1. Summary of research questions in RSV.

RSV disease	- Disease burden in (older) adults in developing countries
	- Guidelines on patient management of severe RSV disease
Preventing RSV in adults	- Real-world assessments of vaccine efficacy (especially in the oldest age groups)
	- Assessment of optimal strategies for non-pharmacological prevention of infection
	- Studies on the effectiveness and cost-effectiveness of monoclonal antibodies to prevent infection in the immunocompromised who do not respond to vaccination, or in those where vaccination is contraindicated

Understanding chronic RSV - Investigation into the extent, impact and management of intra-host evolution during chronic viral shedding

Conclusion

Although generally mild and self-limiting, RSV accounts for considerable morbidity and mortality in adults, especially older adults and those with underlying chronic disease such as COPD, heart failure and immunocompromise. Adults admitted to hospital with RSV tend to be older and more vulnerable than those with influenza and accordingly have longer inpatient stays with high levels of medical intervention. The long-term sequelae of RSV are important including loss of function and independence in older adults, and progressive lung disease and chronic infection with viral evolution in the immunocompromised. There is an urgent need to reconceptualize this illness from one that is serious in children, but far less important than influenza in older people, to thinking of RSV as a major risk to health also in older people that needs well-targeted prevention and treatment. Fortunately, recent developments in vaccination and antiviral medications, driven in part by the response to the COVID-19 pandemic, have strengthened our armamentarium.

Key Messages

- RSV is a common infection in adults, with incidence likely underestimated by current tests
- RSV infection can be serious and result in hospitalisation, intensive care admission or death, especially in older adults with underlying morbidity such as heart failure or COPD
- Compared to patients admitted to hospital with influenza, those with RSV tend to be older with more comorbidity and have poorer outcomes; total healthcare resource utilisation is similar for RSV and influenza
- RSV infection can have serious short-term (eg cardiovascular events) and long-term (eg loss of independence) sequelae
- RSV confers particular risks for the immunocompromised including very prolonged infection and bronchiolitis obliterans

- Recently 3 vaccines for older adults have been market approved. Real world effectivity and duration of protection, especially in the highest risk groups is being studied
- Therapeutics to treat RSV infection remain limited

Search strategy and selection criteria

We searched PubMed for articles published in English between Jan 1, 1994, and June 15, 2024. Combinations of the following terms were used in the searches: “RSV”, “respiratory syncytial virus”, “hospitalisations”, “vaccine”, “vaccination”, “incidence”, “comorbidity”, “older adult(s)”, “adult(s)”, “monoclonal antibodies”, “antiviral”, “antiviral treatment”, “community”, “COPD”, “immunocompromise(d)”, “immune deficiency”. We also identified relevant articles through searches in the authors’ personal files and from the reference lists of selected papers.

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Authors’ contributions

All authors contributed to searching and reviewing the evidence, drafting the article, and approved the final version.

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Competing interests

CCB contributed to an Advisory Board on RSV for Moderna; has received funding for prospective observational research on the epidemiology of RSV, and other viral infections in older people in primary care, through the European Clinical Research Alliance on Infectious Diseases from Sanofi; and was an

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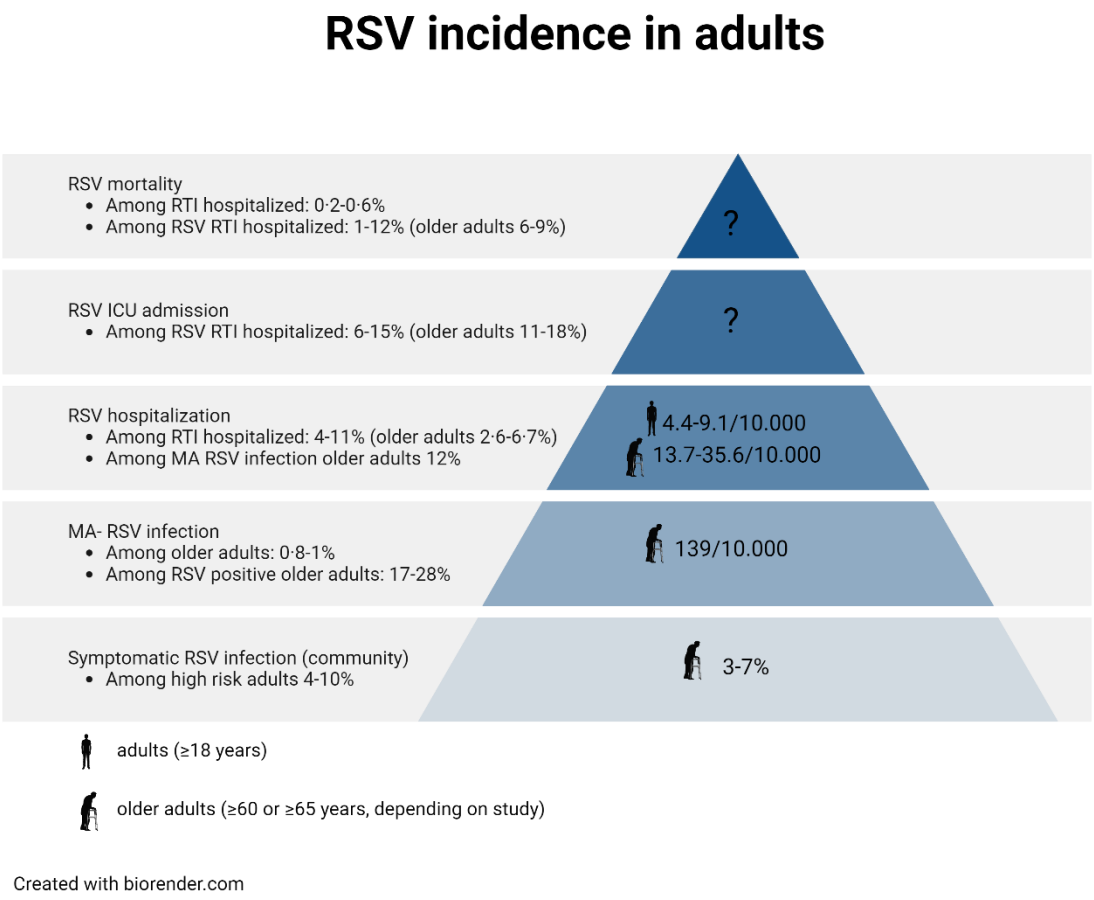
JGW has been an investigator for clinical trials funded by IMI/Horizon2020 and ZonMw and clinical trials sponsored by pharmaceutical companies including AstraZeneca, Merck, Pfizer, Sanofi, and Janssen. All funds have been paid to UMCU. JGW participated in advisory boards of Janssen and Sanofi and was a speaker at a Sanofi sponsored symposium with honoraria paid to UMCU.

D.M.L has received personal fees from Gilead for an educational video and from Merck for a roundtable discussion, speaker fees from Biotest, Takeda and Astra-Zeneca and support to attend a conference from Octapharma. D.M.L. also holds research grants from GSK and Bristol Myers Squibb and has received consultancy fees from GSK paid to his institution.

Figure 1. RSV incidence in adults.



Numbers in pyramid indicate population based incidence. Numbers based on published clinical studies. See supplementary table 1 for more details and references. RSV=respiratory syncytial virus. RTI=Respiratory Tract Infection. ICU=Intensive Care Unit. MA=Medically Attended.

Figure 2a. Risks and complications of RSV in older adults.

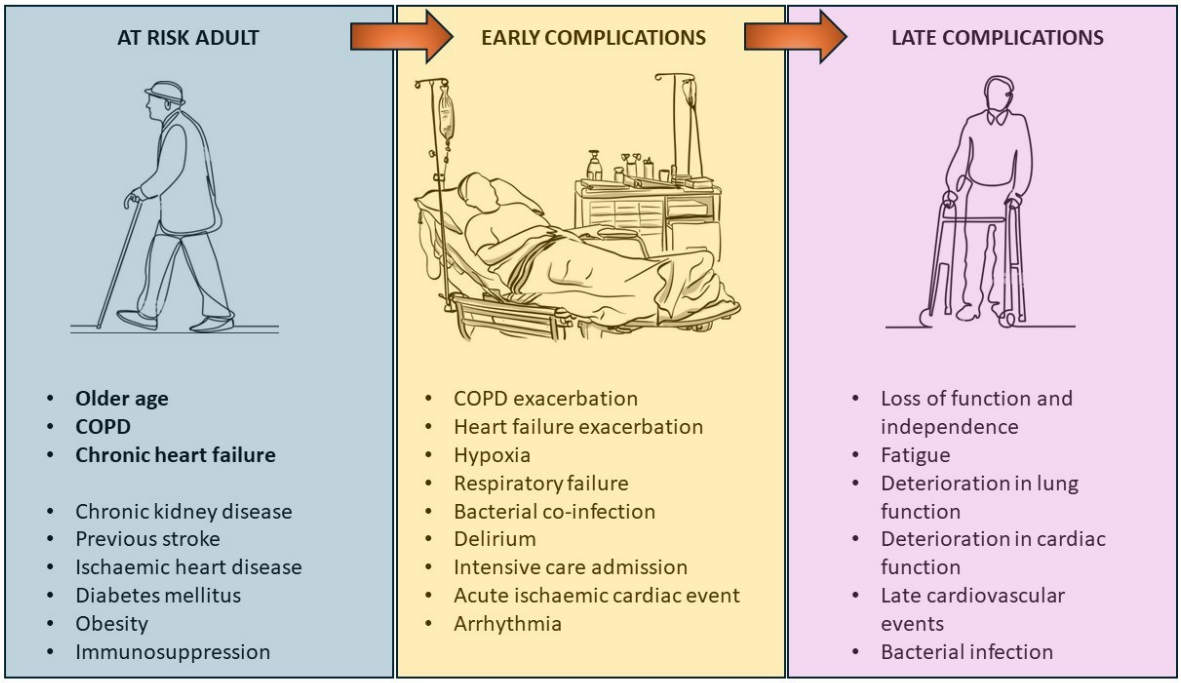


Figure 2b. Risks and complications of RSV in immunosuppressed adults.

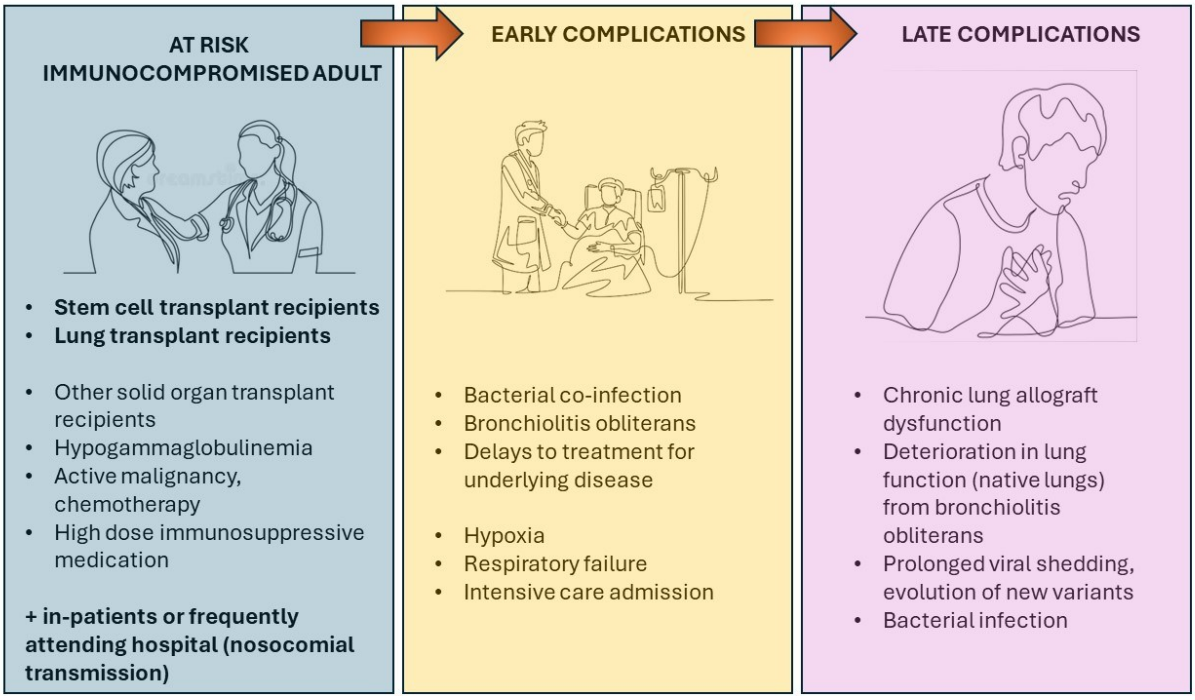


Figure 3 Overview of licensed RSV vaccines for older adults.

Overview licensed RSV vaccines older adults

Vaccine type	Vaccine efficacy	Duration of protection	Real world effectiveness	Recommendations
Bivalent prefusion-F protein-based (Abrysvo)	60-69 years: VE 58-78% 70-79 years: VE 78-100%	At least 2 years	USA: 73%-79% for RSV-associated hospitalization and ER visits in adults ≥60 years	CDC and ACIP (USA): Single dose for: • All adults aged 75 and older • Adults ages 60-74 who are at increased risk of severe RSV disease JCVI (UK): Single dose for: • older adults aged 75 and older NACI (Canada): Single dose for: • older adults aged 75 and older • Residents of nursing homes / chronic care facilities aged ≥60 • individual decision by adults 60 to 74 years ATAGI (Australia) Single dose for: • older adults aged 75 and older • Adults ages 60-74 who are at increased risk of severe RSV disease and indeginous people • individual decision by adults 60 to 74 years
AS01E adjuvanted RSV prefusion F protein based (Arexvy)	60-69 years: VE 81.0 (43.6 to 95.3) 70-79 years: VE 93.8 (60.2 to 99.9)	At least 2 years	USA: 77%-83% for RSV-associated hospitalization and ER visits ≥60 years	
mRNA RSV Pre-F vaccine (mRESVIA)	60-69 years: VE 76.0 (48.0 to 88.9) 70-79 years: VE 95.4 (65.9 to 99.4)	At least 1,5 years	Unknown	

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VE=vaccine efficacy. USA=United States of America. ER=Emergency Room. CDC=Centers for Disease Control. ACIP=Advisory Committee on Immunization Practices. JCVI=Joint Committee on Vaccination and Immunisation. UK=United Kingdom. NACI=National Advisory Committee on Immunization. ATAGI=Australian Technical Advisory Group on Immunisation.

Table 1. Summary of recent studies (published within last 5 years) comparing hospitalised patients with RSV and influenza

Study	Country	Inclusion and setting	N	Age	Comorbidity	Symptoms	Length of hospital stay	Oxygen therapy and ventilation	ICU admission	Early mortality	Bacterial coinfection	Other
Ambrosch, J Clin Virol 2023[7]	Germany	Adults hospitalised with respiratory viral infections, single hospital, 2017-2020	RSV 318 Influenza 880	No difference	COPD and renal disease more common in RSV	NR	Higher in RSV	Mechanical ventilation higher in RSV	Higher in RSV	Higher in RSV	Higher in RSV	
Mulpuru et al 2022[148]	Canada	COPD patients hospitalised with respiratory illness, nationwide, 2011-2015	RSV 145 Influenza 696	NR	NR	NR	NR	Non-invasive ventilation higher in RSV	Similar	Higher in influenza		
Hartnett et al 2022[37]; Falsey 2022[54]	Australia, Argentina, Brazil, Canada, France, Germany, Japan, Malaysia, Mexico, Rep of Korea, South Africa, USA	Adults hospitalised with respirator viral infection, multiple hospitals, 2017-2019	RSV 120 Influenza 280	Older in RSV	More pre-existing oxygen therapy in RSV	Symptom severity higher in RSV	Higher in RSV	Hypoxemia worse in RSV, oxygen therapy higher	Higher in RSV	NR	Higher in RSV	Exacerbation of COPD or heart failure more common in RSV. Cardiovascular complications higher in RSV. Use of medications up to 3 months higher in RSV.
Begley et al 2023[32]	USA	Adults hospitalised with acute respirator illness, multiple hospitals, 2016-2019	RSV 622 Influenza 1940	No difference	COPD and chronic heart failure more common, and total comorbidity	NR	Higher in RSV	Mechanical ventilation higher in RSV	No difference	No difference	NR	RSV more common in females

					indices higher, in RSV							
Quarg et al 2023[149]	Germany	Adults and children hospitalised with respirator viral infection	RSV 99 Influenza 148 [numbers of adult patients only]	No difference	COPD, heart failure, renal disease, rheumatic disease, immunosuppression more common, and total number of comorbidities higher, in RSV; more pre-existing oxygen therapy in RSV	More cough and dyspnoea in RSV; more fever in influenza	No difference	Non-invasive ventilation and low flow oxygen higher in RSV	No difference	No difference	NR	
Tian et al 2023[150]	China	Adults hospitalised with respiratory viral infection	RSV 74 Influenza 129	Older in RSV	COPD more common in RSV; any underlying disease more common in RSV	Shortness of breath and wheezing more common in RSV; fever more common in influenza	Higher in RSV	Non-invasive ventilation higher in RSV	No difference	No difference	Higher in RSV (especially Mycoplasma)	
Debes et al 2022[151]	Norway	Adults hospitalised with respiratory viral infection	RSV 179 Influenza 767	No difference	COPD and heart failure more common in RSV	National Early Warning Score (NEWS) ≥5 more common in RSV	No difference	No difference	No difference	No difference	Antibiotics given more commonly in RSV	C-Reactive protein and white blood cell count higher in RSV
Ackerson et al 2019[28]	USA	Adults ≥ 60 years hospitalized with RSV or influenza	RSV 645 Influenza 1878	Older in RSV	COPD and congestive heart failure more common in RSV, also diabetes, astma, malignancy more common in RSV	More LRTI symptoms in RSV	Higher in RSV	Oxygen need higher in RSV	Higher in RSV	Similar		Long term survival worse in RSV

Leaver et al 2022 [152]	Australia	Adults hospitalised with respiratory viral infection	RSV 193 Influenza 1128	Older in RSV	More comorbidity in RSV	Tachypnea more common in RSV, fever more common in influenza	Higher in RSV	NR		No difference	NR	Worse outcome at 6 months in RSV
Chuaychoo et al 2021[153]	Thailand	Adults hospitalised with respiratory viral infection	RSV 141 Influenza 421	Older in RSV	More comorbidity in RSV	Productive cough more common in RSV; fever, myalgia, nausea and sore throat more common in influenza	Higher in RSV	No difference	NR	No difference	No difference in antibiotics use	

Table 2. Current registered studies on RSV in adults (excluding novel vaccines).

Research area	Current studies	Clinicaltrials.gov ID
Immune response to RSV infection and vaccination in adults, including challenge studies	Immunogenicity of RSV Vaccines in Residents of Long-Term Care Facilities (LTCF)	NCT06077149
	Novel Mucosal Correlates Of RSV Protection In Older Adults (CHIRP01)	NCT06274619
	The Impact of Age on Adaptive Immunity in Adults Infected With Respiratory Syncytial Virus (INFLAMMAGE)	NCT03728413
	Identification and Clinical Validation of Biomarkers Associated With Clinical Severity in Adults Infected With RSV (ARF-RSV)	NCT06197152
	Mucosal Immunity: Influence on Infectious Viral Load: a Prospective Observational Study (MIViral)	NCT05794412
	Inpatient Challenge Study of rRSV A/Maryland/001/11, a Human Respiratory Syncytial Virus Challenge Strain, Administered to Healthy Adult Volunteers	NCT03624790

Antivirals and other therapeutics for RSV	A Controlled Phase 2a Study to Evaluate the Efficacy of EDP-323 Against Respiratory Syncytial Virus Infection in a Virus Challenge Model	NCT06170242
	A Study of EDP-938 in Non-hospitalized Adults With RSV Who Are at High Risk for Complications. (RSVHR)	NCT05568706
	Assessing Antiviral Treatments in Early Symptomatic RSV (ARSYNAL-FC) [Ribavirin, molnupiravir, favipiravir]	NCT06488300
	A Study to Learn About the Study Medicine Sisunatovir in Adults With Respiratory Syncytial Virus (RSV) Infection	NCT06079320
	Treatment of Respiratory Complications Associated With COVID19,Influenza ,Metapneumovirus,RSV Infection Using ProTrans® [Mesenchymal stem cells]	NCT04896853

	A Study to Evaluate the Safety, Immunogenicity, and Pharmacokinetics of GR2102 in Healthy Adult [Monoclonal antibody]	NCT06313697
Diagnostics for RSV	Combined Molecular Testing for Influenza, SARS-CoV-2, and RSV RNA From Different Upper Airway Specimens. Clinical Performance Study for EDAN's COVID-19/Flu A/Flu B/ RSV Test Kits on Subjects Suspected of Respiratory Infection Evaluation of Performance of the LumiraDx Influenza A/B + RSV Test at POC Testing Sites (INSPIRE) FINDER® Instrument and FINDER® FLU A/B, RSV, SARS-CoV-2 Test Clinical Evaluation Protocol Clinical Performance Evaluation of the NeuMoDx™ FluA/FluB/RSV/ Severe Acute Respiratory Syndrome-CoV-2 Assay Clinical Evaluation of SARS-COV-2 (COVID-19), Influenza and RSV 8-	NCT05765838 NCT06175611 NCT04288921 NCT05928507 NCT05162547

	Well MT-PCR Panel for In Vitro Diagnostics LIAISON NES Influenza (FLU) A/ B, Respiratory Syncytial Virus (RSV), & Coronavirus Disease 2019 (COVID-19) in Symptomatic Patients in Australia	NCT05946538 NCT06392451

References

1. Belongia EA, King JP, Kieke BA, et al. Clinical Features, Severity, and Incidence of RSV Illness During 12 Consecutive Seasons in a Community Cohort of Adults ≥60 Years Old. *Open Forum Infect Dis* 2018; **5**(12): ofy316.
2. Boattini M, Almeida A, Comini S, Bianco G, Cavallo R, Costa C. From Forgotten Pathogen to Target for New Vaccines: What Clinicians Need to Know about Respiratory Syncytial Virus Infection in Older Adults. *Viruses* 2024; **16**(4).
3. Bruyndonckx R, Coenen S, Butler C, et al. Respiratory syncytial virus and influenza virus infection in adult primary care patients: Association of age with prevalence, diagnostic features and illness course. *Int J Infect Dis* 2020; **95**: 384-90.
4. Nicholson KG, Kent J, Hammersley V, Cancio E. Acute viral infections of upper respiratory tract in elderly people living in the community: comparative, prospective, population based study of disease burden. *BMJ* 1997; **315**(7115): 1060-4.
5. Falsey AR, Hennessey PA, Formica MA, Cox C, Walsh EE. Respiratory syncytial virus infection in elderly and high-risk adults. *N Engl J Med* 2005; **352**(17): 1749-59.
6. Kenmoe S, Nair H. The disease burden of respiratory syncytial virus in older adults. *Curr Opin Infect Dis* 2024; **37**(2): 129-36.
7. Ambrosch A, Luber D, Klawonn F, Kabesch M. Focusing on severe infections with the respiratory syncytial virus (RSV) in adults: Risk factors, symptomatology and clinical course compared to influenza A / B and the original SARS-CoV-2 strain. *J Clin Virol* 2023; **161**: 105399.
8. Sivgin H, Cetin S, Ulgen A, Li W. Diabetes and bacterial co-infection are two independent risk factors for respiratory syncytial virus disease severity. *Front Med (Lausanne)* 2023; **10**: 1231641.
9. Mokrani D, Le Hingrat Q, Thy M, et al. Clinical characteristics and outcomes of respiratory syncytial virus-associated ARF in immunocompetent patients: A seven-year experience at a tertiary hospital in France. *J Infect* 2024; **89**(1): 106180.
10. Zwaans WA, Mallia P, van Winden ME, Rohde GG. The relevance of respiratory viral infections in the exacerbations of chronic obstructive pulmonary disease—a systematic review. *J Clin Virol* 2014; **61**(2): 181-8.
11. Ramirez J, Carrico R, Wilde A, et al. Diagnosis of Respiratory Syncytial Virus in Adults Substantially Increases When Adding Sputum, Saliva, and Serology Testing to Nasopharyngeal Swab RT-PCR. *Infect Dis Ther* 2023; **12**(6): 1593-603.
12. Onwuchekwa C, Moreo LM, Menon S, et al. Underascertainment of Respiratory Syncytial Virus Infection in Adults Due to Diagnostic Testing Limitations: A Systematic Literature Review and Meta-analysis. *J Infect Dis* 2023; **228**(2): 173-84.
13. Onwuchekwa C, Atwell J, Moreo LM, et al. Pediatric Respiratory Syncytial Virus Diagnostic Testing Performance: A Systematic Review and Meta-analysis. *J Infect Dis* 2023; **228**(11): 1516-27.
14. Verbakel JY, Matheeussen V, Loens K, et al. Performance and ease of use of a molecular point-of-care test for influenza A/B and RSV in patients presenting to primary care. *Eur J Clin Microbiol Infect Dis* 2020; **39**(8): 1453-60.
15. Zuurbier RP, Korsten K, Verheij TJM, et al. Performance Assessment of a Rapid Molecular Respiratory Syncytial Virus Point-of-Care Test: A Prospective Community Study in Older Adults. *J Infect Dis* 2022; **226**(Suppl 1): S63-S70.
16. Bernknopf AC, Koski RR, Konieczny AM, Covyeou JA, Klepser ME. Multiplex CLIA-waived point-of-care tests for SARS-CoV-2, influenza A and B, +/- other respiratory pathogens: A systematic review. *J Am Pharm Assoc (2003)* 2024: 102090.

17. Falsey AR, Formica MA, Walsh EE. Yield of sputum for viral detection by reverse transcriptase PCR in adults hospitalized with respiratory illness. *J Clin Microbiol* 2012; **50**(1): 21-4.
18. Shi T, Denouel A, Tietjen AK, et al. Global Disease Burden Estimates of Respiratory Syncytial Virus-Associated Acute Respiratory Infection in Older Adults in 2015: A Systematic Review and Meta-Analysis. *J Infect Dis* 2020; **222**(Suppl 7): S577-S83.
19. Korsten K, Adriaenssens N, Coenen S, et al. Burden of respiratory syncytial virus infection in community-dwelling older adults in Europe (RESCEU): an international prospective cohort study. *Eur Respir J* 2021; **57**(4).
20. Belongia EA, King JP, Kieke BA, et al. Clinical Features, Severity, and Incidence of RSV Illness During 12 Consecutive Seasons in a Community Cohort of Adults >/=60 Years Old. *Open Forum Infect Dis* 2018; **5**(12): ofy316.
21. Sundaram ME, Meece JK, Sifakis F, Gasser RA, Jr., Belongia EA. Medically attended respiratory syncytial virus infections in adults aged >/= 50 years: clinical characteristics and outcomes. *Clin Infect Dis* 2014; **58**(3): 342-9.
22. Antalis E, Oikonomopoulou Z, Kottaridi C, et al. Mixed viral infections of the respiratory tract; an epidemiological study during consecutive winter seasons. *J Med Virol* 2018; **90**(4): 663-70.
23. Falsey AR, McElhaney JE, Beran J, et al. Respiratory syncytial virus and other respiratory viral infections in older adults with moderate to severe influenza-like illness. *J Infect Dis* 2014; **209**(12): 1873-81.
24. Nolen LD, Seeman S, Desnoyers C, et al. Respiratory syncytial virus and influenza hospitalizations in Alaska native adults. *J Clin Virol* 2020; **127**: 104347.
25. Widmer K, Zhu Y, Williams JV, Griffin MR, Edwards KM, Talbot HK. Rates of hospitalizations for respiratory syncytial virus, human metapneumovirus, and influenza virus in older adults. *J Infect Dis* 2012; **206**(1): 56-62.
26. Loubet P, Lenzi N, Valette M, et al. Clinical characteristics and outcome of respiratory syncytial virus infection among adults hospitalized with influenza-like illness in France. *Clin Microbiol Infect* 2017; **23**(4): 253-9.
27. Malosh RE, Martin ET, Callear AP, et al. Respiratory syncytial virus hospitalization in middle-aged and older adults. *J Clin Virol* 2017; **96**: 37-43.
28. Ackerson B, Tseng HF, Sy LS, et al. Severe Morbidity and Mortality Associated With Respiratory Syncytial Virus Versus Influenza Infection in Hospitalized Older Adults. *Clin Infect Dis* 2019; **69**(2): 197-203.
29. Binder W, Thorsen J, Borczuk P. RSV in adult ED patients: Do emergency providers consider RSV as an admission diagnosis? *Am J Emerg Med* 2017; **35**(8): 1162-5.
30. Li Y, Kulkarni D, Begier E, et al. Adjusting for Case Under-Ascertainment in Estimating RSV Hospitalisation Burden of Older Adults in High-Income Countries: a Systematic Review and Modelling Study. *Infect Dis Ther* 2023; **12**(4): 1137-49.
31. Osei-Yeboah R, Johannesen CK, Egeskov-Cavling AM, et al. Respiratory Syncytial Virus-Associated Hospitalization in Adults With Comorbidities in 2 European Countries: A Modeling Study. *The Journal of infectious diseases* 2024; **229**(Supplement_1): S70-s7.
32. Begley KM, Monto AS, Lamerato LE, et al. Prevalence and Clinical Outcomes of Respiratory Syncytial Virus vs Influenza in Adults Hospitalized With Acute Respiratory Illness From a Prospective Multicenter Study. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2023; **76**(11): 1980-8.
33. Prasad N, Walker TA, Waite B, et al. Respiratory Syncytial Virus-Associated Hospitalizations Among Adults With Chronic Medical Conditions. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2021; **73**(1): e158-e63.

34. Havers FP, Whitaker M, Melgar M, et al. Characteristics and Outcomes Among Adults Aged ≥60 Years Hospitalized with Laboratory-Confirmed Respiratory Syncytial Virus - RSV-NET, 12 States, July 2022-June 2023. *Am J Transplant* 2023; **23**(12): 2000-7.
35. Branche AR, Saiman L, Walsh EE, et al. Incidence of Respiratory Syncytial Virus Infection Among Hospitalized Adults, 2017-2020. *Clin Infect Dis* 2022; **74**(6): 1004-11.
36. Kujawski SA, Whitaker M, Ritchey MD, et al. Rates of respiratory syncytial virus (RSV)-associated hospitalization among adults with congestive heart failure-United States, 2015-2017. *PLoS One* 2022; **17**(3): e0264890.
37. Hartnett J, Donga P, Ispas G, et al. Risk factors and medical resource utilization in US adults hospitalized with influenza or respiratory syncytial virus in the Hospitalized Acute Respiratory Tract Infection study. *Influenza Other Respir Viruses* 2022; **16**(5): 906-15.
38. Woodruff RC, Melgar M, Pham H, et al. Acute Cardiac Events in Hospitalized Older Adults With Respiratory Syncytial Virus Infection. *JAMA Intern Med* 2024; **184**(6): 602-11.
39. DeMartino JK, Lafeuille MH, Emond B, et al. Respiratory Syncytial Virus-Related Complications and Healthcare Costs Among a Medicare-Insured Population in the United States. *Open Forum Infect Dis* 2023; **10**(5): ofad203.
40. Sano E, Chang B, Sieling W, et al. Bacteremia in Adults Admitted from the Emergency Department with Laboratory-Confirmed Respiratory Syncytial Virus. *J Emerg Med* 2022; **62**(2): 216-23.
41. Celante H, Oubaya N, Fourati S, et al. Prognosis of hospitalised adult patients with respiratory syncytial virus infection: a multicentre retrospective cohort study. *Clin Microbiol Infect* 2023; **29**(7): 943.e1-.e8.
42. Malik A, Szpunar S, Sharma M, Johnson LB, Saravolatz L, Bhargava A. Predictors of prolonged length of stay in adult patients with respiratory syncytial virus infections - a multi-center historical cohort study. *Front Microbiol* 2024; **15**: 1385439.
43. Lee N, Lui GC, Wong KT, et al. High morbidity and mortality in adults hospitalized for respiratory syncytial virus infections. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2013; **57**(8): 1069-77.
44. Tseng HF, Sy LS, Ackerson B, et al. Severe Morbidity and Short- and Mid- to Long-term Mortality in Older Adults Hospitalized with Respiratory Syncytial Virus Infection. *The Journal of infectious diseases* 2020; **222**(8): 1298-310.
45. Wyffels V, Kariburyo F, Gavart S, Fleischhackl R, Yuce H. A Real-World Analysis of Patient Characteristics and Predictors of Hospitalization Among US Medicare Beneficiaries with Respiratory Syncytial Virus Infection. *Adv Ther* 2020; **37**(3): 1203-17.
46. Boattini M, Almeida A, Christaki E, et al. Severity of RSV infection in Southern European elderly patients during two consecutive winter seasons (2017-2018). *J Med Virol* 2021; **93**(8): 5152-7.
47. Walsh EE, Peterson DR, Falsey AR. Risk factors for severe respiratory syncytial virus infection in elderly persons. *The Journal of infectious diseases* 2004; **189**(2): 233-8.
48. Volling C, Hassan K, Mazzulli T, et al. Respiratory syncytial virus infection-associated hospitalization in adults: a retrospective cohort study. *BMC Infect Dis* 2014; **14**: 665.
49. Pilie P, Werbel WA, Riddell Jt, Shu X, Schaubel D, Gregg KS. Adult patients with respiratory syncytial virus infection: impact of solid organ and hematopoietic stem cell transplantation on outcomes. *Transpl Infect Dis* 2015; **17**(4): 551-7.
50. Mehta J, Walsh EE, Mahadevia PJ, Falsey AR. Risk factors for respiratory syncytial virus illness among patients with chronic obstructive pulmonary disease. *Copd* 2013; **10**(3): 293-9.
51. Kurai D, Song J, Huang YC, et al. Targeted Literature Review of the Burden of Respiratory Syncytial Infection among High-Risk and Elderly Patients in Asia Pacific Region. *Infect Dis Ther* 2023; **12**(3): 807-28.

52. Praphasiri P, Shrestha M, Patumanond J, et al. Underlying cardiopulmonary conditions as a risk factor for influenza and respiratory syncytial virus infection among community-dwelling adults aged ≥ 65 years in Thailand: Findings from a two-year prospective cohort study. *Influenza Other Respir Viruses* 2021; **15**(5): 634-40.
53. Ubamadu E, Betancur E, Gessner BD, et al. Respiratory Syncytial Virus Sequelae Among Adults in High-Income Countries: A Systematic Literature Review and Meta-analysis. *Infect Dis Ther* 2024.
54. Falsey AR, Walsh EE, Osborne RH, et al. Comparative assessment of reported symptoms of influenza, respiratory syncytial virus, and human metapneumovirus infection during hospitalization and post-discharge assessed by Respiratory Intensity and Impact Questionnaire. *Influenza Other Respir Viruses* 2022; **16**(1): 79-89.
55. Loubet P, Lenzi N, Valette M, et al. Clinical characteristics and outcome of respiratory syncytial virus infection among adults hospitalized with influenza-like illness in France. *Clin Microbiol Infect* 2017; **23**(4): 253-9.
56. Riccò M, Parisi S, Corrado S, Marchesi F, Bottazzoli M, Gori D. Respiratory Syncytial Virus Infections in Recipients of Bone Marrow Transplants: A Systematic Review and Meta-Analysis. *Infect Dis Rep* 2024; **16**(2): 317-55.
57. Villanueva DH, Arcega V, Rao M. Review of respiratory syncytial virus infection among older adults and transplant recipients. *Ther Adv Infect Dis* 2022; **9**: 20499361221091413.
58. Chatzis O, Darbre S, Pasquier J, et al. Burden of severe RSV disease among immunocompromised children and adults: a 10 year retrospective study. *BMC Infect Dis* 2018; **18**(1): 111.
59. Samad SA, Jethani J, Kumar L, Choudhary A, Brijwal M, Dar L. Respiratory Syncytial Virus Infection among Adults after Hematopoietic Stem Cell Transplantation. *J Glob Infect Dis* 2022; **14**(3): 112-6.
60. Weigt SS, Gregson AL, Deng JC, Lynch JP, 3rd, Belperio JA. Respiratory viral infections in hematopoietic stem cell and solid organ transplant recipients. *Semin Respir Crit Care Med* 2011; **32**(4): 471-93.
61. Lee I, Barton TD. Viral respiratory tract infections in transplant patients: epidemiology, recognition and management. *Drugs* 2007; **67**(10): 1411-27.
62. Abbas S, Raybould JE, Sastry S, de la Cruz O. Respiratory viruses in transplant recipients: more than just a cold. Clinical syndromes and infection prevention principles. *Int J Infect Dis* 2017; **62**: 86-93.
63. Whimbey E, Englund JA, Couch RB. Community respiratory virus infections in immunocompromised patients with cancer. *Am J Med* 1997; **102**(3a): 10-8; discussion 25-6.
64. Jalal H, Bibby DF, Bennett J, et al. Molecular investigations of an outbreak of parainfluenza virus type 3 and respiratory syncytial virus infections in a hematology unit. *J Clin Microbiol* 2007; **45**(6): 1690-6.
65. Taylor GS, Vipond IB, Caul EO. Molecular epidemiology of outbreak of respiratory syncytial virus within bone marrow transplantation unit. *J Clin Microbiol* 2001; **39**(2): 801-3.
66. Kassis C, Champlin RE, Hachem RY, et al. Detection and control of a nosocomial respiratory syncytial virus outbreak in a stem cell transplantation unit: the role of palivizumab. *Biol Blood Marrow Transplant* 2010; **16**(9): 1265-71.
67. Machado AF, Sallum MA, Vilas Boas LS, Tateno AF, Machado CM. Molecular characterization of strains of respiratory syncytial virus identified in a hematopoietic stem cell transplant outpatient unit over 2 years: community or nosocomial infection? *Biol Blood Marrow Transplant* 2008; **14**(12): 1348-55.
68. Testaert H, Bouet M, Valour F, et al. Incidence, management and outcome of respiratory syncytial virus infection in adult lung transplant recipients: a 9-year retrospective multicentre study. *Clin Microbiol Infect* 2021; **27**(6): 897-903.

69. Hopkins P, McNeil K, Kermeen F, et al. Human metapneumovirus in lung transplant recipients and comparison to respiratory syncytial virus. *American journal of respiratory and critical care medicine* 2008; **178**(8): 876-81.
70. Martín-Cerezuela M, Cuéllar-Monreal MJ, Monte-Boquet E, Solé-Jover A, Poveda-Andrés JL. Oral Ribavirin for Treatment of Respiratory Syncytial Virus in Lung Transplantation Recipients. *Transplant Proc* 2021; **53**(9): 2702-5.
71. Versluys AB, Rossen JW, van Ewijk B, Schuurman R, Bierings MB, Boelens JJ. Strong association between respiratory viral infection early after hematopoietic stem cell transplantation and the development of life-threatening acute and chronic alloimmune lung syndromes. *Biol Blood Marrow Transplant* 2010; **16**(6): 782-91.
72. Avadhanula V, Agustinho DP, Menon VK, et al. Inter and intra-host diversity of RSV in hematopoietic stem cell transplant adults with normal and delayed viral clearance. *Virus Evol* 2024; **10**(1): vead086.
73. Ye X, Iwuchukwu OP, Avadhanula V, et al. Humoral and Mucosal Antibody Response to RSV Structural Proteins in RSV-Infected Adult Hematopoietic Cell Transplant (HCT) Recipients. *Viruses* 2021; **13**(6).
74. Lehners N, Tabatabai J, Prifert C, et al. Long-Term Shedding of Influenza Virus, Parainfluenza Virus, Respiratory Syncytial Virus and Nosocomial Epidemiology in Patients with Hematological Disorders. *PLoS One* 2016; **11**(2): e0148258.
75. Brown LK, Ruis C, Clark I, et al. A comprehensive characterization of chronic norovirus infection in immunodeficient hosts. *The Journal of allergy and clinical immunology* 2019; **144**(5): 1450-3.
76. Klapsa D, Wilton T, Zealand A, et al. Sustained detection of type 2 poliovirus in London sewage between February and July, 2022, by enhanced environmental surveillance. *Lancet* 2022; **400**(10362): 1531-8.
77. Kemp SA, Collier DA, Datir RP, et al. SARS-CoV-2 evolution during treatment of chronic infection. *Nature* 2021; **592**(7853): 277-82.
78. Choi B, Choudhary MC, Regan J, et al. Persistence and Evolution of SARS-CoV-2 in an Immunocompromised Host. *The New England journal of medicine* 2020; **383**(23): 2291-3.
79. Rockett R, Basile K, Maddocks S, et al. Resistance Mutations in SARS-CoV-2 Delta Variant after Sotrovimab Use. *The New England journal of medicine* 2022; **386**(15): 1477-9.
80. Standing JF, Buggiotti L, Guerra-Assuncao JA, et al. Randomized controlled trial of molnupiravir SARS-CoV-2 viral and antibody response in at-risk adult outpatients. *Nature communications* 2024; **15**(1): 1652.
81. Brown LK, Moran E, Goodman A, et al. Treatment of chronic or relapsing COVID-19 in immunodeficiency. *The Journal of allergy and clinical immunology* 2022; **149**(2): 557-61 e1.
82. Santiago-Olivares C, Martínez-Alvarado E, Rivera-Toledo E. Persistence of RNA Viruses in the Respiratory Tract: An Overview. *Viral immunology* 2023; **36**(1): 3-12.
83. Sikkel MB, Quint JK, Mallia P, Wedzicha JA, Johnston SL. Respiratory syncytial virus persistence in chronic obstructive pulmonary disease. *Pediatr Infect Dis J* 2008; **27**(10 Suppl): S63-70.
84. Wilkinson TM, Donaldson GC, Johnston SL, Openshaw PJ, Wedzicha JA. Respiratory syncytial virus, airway inflammation, and FEV1 decline in patients with chronic obstructive pulmonary disease. *American journal of respiratory and critical care medicine* 2006; **173**(8): 871-6.
85. Hansen CL, Chaves SS, Demont C, Viboud C. Mortality Associated With Influenza and Respiratory Syncytial Virus in the US, 1999-2018. *JAMA Netw Open* 2022; **5**(2): e220527.
86. van Summeren J, Meijer A, Aspelund G, et al. Low levels of respiratory syncytial virus activity in Europe during the 2020/21 season: what can we expect in the coming summer and autumn/winter? *Euro Surveill* 2021; **26**(29).

87. Dallagiacoma G, Arthur Rhedin S, Odone A, Alfvén T. A comparative analysis of non-pharmaceutical interventions for preventing the respiratory syncytial virus in 30 European countries. *Acta Paediatr* 2024; **113**(6): 1388-95.
88. McLellan JS, Chen M, Joyce MG, et al. Structure-based design of a fusion glycoprotein vaccine for respiratory syncytial virus. *Science* 2013; **342**(6158): 592-8.
89. Kingwell K. RSV vaccines score landmark FDA approvals. *Nat Rev Drug Discov* 2023; **22**(7): 523-5.
90. European Medicines Agency. News. First RSV vaccine to protect infants up to 6 months of age and older adults. July 21, 2023. https://www.ema.europa.eu/en/news/first-rsv-vaccine-protect-infants-6-months-age-older-adults (accessed Sept 9, 2023).
91. European Medicines Agency**.** Arexvy. https://www.ema.europa.eu/en/medicines/human/EPAR/arexvy (accessed June 15, 2024).
92. Walsh EE, Perez Marc G, Zareba AM, et al. Efficacy and Safety of a Bivalent RSV Prefusion F Vaccine in Older Adults. *N Engl J Med* 2023; **388**(16): 1465-77.
93. Kampmann B, Madhi SA, Munjal I, et al. Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants. *N Engl J Med* 2023; **388**(16): 1451-64.
94. Papi A, Ison MG, Langley JM, et al. Respiratory Syncytial Virus Prefusion F Protein Vaccine in Older Adults. *N Engl J Med* 2023; **388**(7): 595-608.
95. Wilson E, Goswami J, Baqui AH, et al. Efficacy and Safety of an mRNA-Based RSV PreF Vaccine in Older Adults. *N Engl J Med* 2023; **389**(24): 2233-44.
96. Mullard A. FDA approves mRNA-based RSV vaccine. *Nat Rev Drug Discov* 2024.
97. Falsey AR, Williams K, Gymnopoulou E, et al. Efficacy and Safety of an Ad26.RSV.preF-RSV preF Protein Vaccine in Older Adults. *N Engl J Med* 2023; **388**(7): 609-20.
98. Bavarian Nordic. Bavarian Nordic Provides update on RSV vaccine program. July 22, 2023. https://www.bavarian-nordic.com/investor/news/news.aspx?news=6808# (accessed June 15, 2024).
99. Centers for Disease Control (CDC). Healthcare Providers: RSV Vaccination for Adults 60 Years of Age and Over. https://www.cdc.gov/vaccines/vpd/rsv/hcp/older-adults.html#:~:text=The%20RSV%20vaccine%20is%20not,risk%20of%20severe%20RSV%20disease. Accessed 21 July 2024.
100. Gustafson CE, Kim C, Weyand CM, Goronzy JJ. Influence of immune aging on vaccine responses. *J Allergy Clin Immunol* 2020; **145**(5): 1309-21.
101. T FS, Hwang SJ, Ylisastigui P, et al. Immunogenicity and safety following one dose of AS01E-adjuvanted respiratory syncytial virus prefusion F protein vaccine in older adults: a phase 3 trial. *J Infect Dis* 2023.
102. Ison MG, Papi A, Athan E, et al. Efficacy and safety of respiratory syncytial virus prefusion F protein vaccine (RSVPreF3 OA) in older adults over 2 RSV seasons. *Clin Infect Dis* 2024.
103. Korsten K, Adriaenssens N, Coenen S, et al. Contact With Young Children Increases the Risk of Respiratory Infection in Older Adults in Europe-the RESCEU Study. *J Infect Dis* 2022; **226**(Suppl 1): S79-S86.
104. Loeb M, Russell ML, Moss L, et al. Effect of influenza vaccination of children on infection rates in Hutterite communities: a randomized trial. *JAMA* 2010; **303**(10): 943-50.
105. Reichert TA, Sugaya N, Fedson DS, Glezen WP, Simonsen L, Tashiro M. The Japanese experience with vaccinating schoolchildren against influenza. *N Engl J Med* 2001; **344**(12): 889-96.
106. Simonsen L, Taylor RJ, Young-Xu Y, Haber M, May L, Klugman KP. Impact of pneumococcal conjugate vaccination of infants on pneumonia and influenza hospitalization and mortality in all age groups in the United States. *mBio* 2011; **2**(1): e00309-10.
107. Griffin MR, Zhu Y, Moore MR, Whitney CG, Grijalva CG. U.S. hospitalizations for pneumonia after a decade of pneumococcal vaccination. *N Engl J Med* 2013; **369**(2): 155-63.

108. Hodgson D, Baguelin M, van Leeuwen E, et al. Effect of mass paediatric influenza vaccination on existing influenza vaccination programmes in England and Wales: a modelling and cost-effectiveness analysis. *Lancet Public Health* 2017; **2**(2): e74-e81.
109. Baguelin M, Camacho A, Flasche S, Edmunds WJ. Extending the elderly- and risk-group programme of vaccination against seasonal influenza in England and Wales: a cost-effectiveness study. *BMC Med* 2015; **13**: 236.
110. Mazur NI, Terstappen J, Baral R, et al. Respiratory syncytial virus prevention within reach: the vaccine and monoclonal antibody landscape. *Lancet Infect Dis* 2023; **23**(1): e2-e21.
111. PATH. RSV vaccine and mAb snapshot. April 25, 2024. https://www.path.org/our-impact/resources/rsv-vaccine-and-mab-snapshot/ (accessed June 15, 2024).
112. Habibi MS, Jozwik A, Makris S, et al. Impaired Antibody-mediated Protection and Defective IgA B-Cell Memory in Experimental Infection of Adults with Respiratory Syncytial Virus. *Am J Respir Crit Care Med* 2015; **191**(9): 1040-9.
113. Ascough S, Dayananda P, Kalyan M, et al. Divergent age-related humoral correlates of protection against respiratory syncytial virus infection in older and young adults: a pilot, controlled, human infection challenge model. *Lancet Healthy Longev* 2022; **3**(6): e405-e16.
114. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. The IMpact-RSV Study Group. *Pediatrics* 1998; **102**(3 Pt 1): 531-7.
115. Feltes TF, Cabalka AK, Meissner HC, et al. Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with hemodynamically significant congenital heart disease. *J Pediatr* 2003; **143**(4): 532-40.
116. O'Brien KL, Chandran A, Weatherholtz R, et al. Efficacy of motavizumab for the prevention of respiratory syncytial virus disease in healthy Native American infants: a phase 3 randomised double-blind placebo-controlled trial. *Lancet Infect Dis* 2015; **15**(12): 1398-408.
117. Griffin MP, Yuan Y, Takas T, et al. Single-Dose Nirsevimab for Prevention of RSV in Preterm Infants. *The New England journal of medicine* 2020; **383**(5): 415-25.
118. Hammitt LL, Dagan R, Yuan Y, et al. Nirsevimab for Prevention of RSV in Healthy Late-Preterm and Term Infants. *The New England journal of medicine* 2022; **386**(9): 837-46.
119. Phuah JY, Maas BM, Tang A, et al. Quantification of clesrovimab, an investigational, half-life extended, anti-respiratory syncytial virus protein F human monoclonal antibody in the nasal epithelial lining fluid of healthy adults. *Biomed Pharmacother* 2023; **169**: 115851.
120. Sun M, Lai H, Na F, et al. Monoclonal Antibody for the Prevention of Respiratory Syncytial Virus in Infants and Children: A Systematic Review and Network Meta-analysis. *JAMA Netw Open* 2023; **6**(2): e230023.
121. Shah JN, Chemaly RF. Management of RSV infections in adult recipients of hematopoietic stem cell transplantation. *Blood* 2011; **117**(10): 2755-63.
122. Tsitsikas DA, Oakervee H, Cavenagh JD, Gribben J, Agrawal SG, Mattes FM. Treatment of respiratory syncytial virus infection in haemopoietic stem cell transplant recipients with aerosolized ribavirin and the humanized monoclonal antibody palivizumab: a single centre experience. *Br J Haematol* 2009; **146**(5): 574-6.
123. Barnes E, Goodyear CS, Willicombe M, et al. SARS-CoV-2-specific immune responses and clinical outcomes after COVID-19 vaccination in patients with immune-suppressive disease. *Nat Med* 2023; **29**(7): 1760-74.
124. Wasserman RL, Lumry W, Harris J, 3rd, et al. Efficacy, Safety, and Pharmacokinetics of a New 10 % Liquid Intravenous Immunoglobulin Containing High Titer Neutralizing Antibody to RSV and Other Respiratory Viruses in Subjects with Primary Immunodeficiency Disease. *Journal of clinical immunology* 2016; **36**(6): 590-9.

125. Orange JS, Du W, Falsey AR. Therapeutic Immunoglobulin Selected for High Antibody Titer to RSV also Contains High Antibody Titers to Other Respiratory Viruses. *Frontiers in immunology* 2015; **6**: 431.
126. Bagga B, Woods CW, Veldman TH, et al. Comparing influenza and RSV viral and disease dynamics in experimentally infected adults predicts clinical effectiveness of RSV antivirals. *Antivir Ther* 2013; **18**(6): 785-91.
127. Gastine S, Pang J, Boshier FAT, et al. Systematic Review and Patient-Level Meta-Analysis of SARS-CoV-2 Viral Dynamics to Model Response to Antiviral Therapies. *Clin Pharmacol Ther* 2021; **110**(2): 321-33.
128. Simoes EAF, Bont L, Manzoni P, et al. Past, Present and Future Approaches to the Prevention and Treatment of Respiratory Syncytial Virus Infection in Children. *Infect Dis Ther* 2018; **7**(1): 87-120.
129. Tejada S, Martinez-Reviejo R, Karakoc HN, Peña-López Y, Manuel O, Rello J. Ribavirin for Treatment of Subjects with Respiratory Syncytial Virus-Related Infection: A Systematic Review and Meta-Analysis. *Adv Ther* 2022; **39**(9): 4037-51.
130. Stevaert A, Groaz E, Naesens L. Nucleoside analogs for management of respiratory virus infections: mechanism of action and clinical efficacy. *Curr Opin Virol* 2022; **57**: 101279.
131. DeVincenzo JP, McClure MW, Symons JA, et al. Activity of Oral ALS-008176 in a Respiratory Syncytial Virus Challenge Study. *The New England journal of medicine* 2015; **373**(21): 2048-58.
132. Oey A, McClure M, Symons JA, et al. Lumicitabine, an orally administered nucleoside analog, in infants hospitalized with respiratory syncytial virus (RSV) infection: Safety, efficacy, and pharmacokinetic results. *PLoS One* 2023; **18**(7): e0288271.
133. Roymans D, Alnajjar SS, Battles MB, et al. Therapeutic efficacy of a respiratory syncytial virus fusion inhibitor. *Nature communications* 2017; **8**(1): 167.
134. Stevens M, Rusch S, DeVincenzo J, et al. Antiviral Activity of Oral JNJ-53718678 in Healthy Adult Volunteers Challenged With Respiratory Syncytial Virus: A Placebo-Controlled Study. *The Journal of infectious diseases* 2018; **218**(5): 748-56.
135. Ahmad A, Eze K, Noulin N, et al. EDP-938, a Respiratory Syncytial Virus Inhibitor, in a Human Virus Challenge. *The New England journal of medicine* 2022; **386**(7): 655-66.
136. Gottlieb J, Torres F, Haddad T, et al. A randomized controlled trial of presatovir for respiratory syncytial virus after lung transplant. *J Heart Lung Transplant* 2023; **42**(7): 908-16.
137. Standing JF, Agyeman AA. Learning and confirming in publicly funded antiviral trials. *Lancet Infect Dis* 2023; **23**(2): 132-3.
138. Butler CC, Hobbs FDR, Gbinigie OA, et al. Molnupiravir plus usual care versus usual care alone as early treatment for adults with COVID-19 at increased risk of adverse outcomes (PANORAMIC): an open-label, platform-adaptive randomised controlled trial. *Lancet* 2023; **401**(10373): 281-93.
139. Mao Z, Li X, Korsten K, et al. Economic Burden and Health-Related Quality of Life of Respiratory Syncytial Virus and Influenza Infection in European Community-Dwelling Older Adults. *J Infect Dis* 2022; **226**(Suppl 1): S87-S94.
140. Ackerson B, An J, Sy LS, Solano Z, Slezak J, Tseng HF. Cost of Hospitalization Associated With Respiratory Syncytial Virus Infection Versus Influenza Infection in Hospitalized Older Adults. *J Infect Dis* 2020; **222**(6): 962-6.
141. Pastula ST, Hackett J, Coalson J, et al. Hospitalizations for Respiratory Syncytial Virus Among Adults in the United States, 1997-2012. *Open Forum Infect Dis* 2017; **4**(1): ofw270.
142. Carrico J, Hicks KA, Wilson E, Panozzo CA, Ghaswalla P. The Annual Economic Burden of Respiratory Syncytial Virus in Adults in the United States. *J Infect Dis* 2023.
143. Moghadas SM, Shoukat A, Bawden CE, et al. Cost-effectiveness of Prefusion F Protein-based Vaccines Against Respiratory Syncytial Virus Disease for Older Adults in the United States. *Clin Infect Dis* 2024; **78**(5): 1328-35.

144. Shoukat A, Bawden CE, Rost G, et al. Impact and cost-effectiveness analyses of vaccination for prevention of respiratory syncytial virus disease among older adults in Ontario: A Canadian Immunization Research Network (CIRN) study. *Vaccine* 2024; **42**(7): 1768-76.
145. Stott NC, West RR. Randomised controlled trial of antibiotics in patients with cough and purulent sputum. *Br Med J* 1976; **2**(6035): 556-9.
146. Anthierens S, Tonkin-Crine S, Cals JW, et al. Clinicians' Views and Experiences of Interventions to Enhance the Quality of Antibiotic Prescribing for Acute Respiratory Tract Infections. *Journal of General Internal Medicine* 2015; **30**(4): 408-16.
147. Little P, Stuart B, Moore M, et al. Amoxicillin for acute lower-respiratory-tract infection in primary care when pneumonia is not suspected: a 12-country, randomised, placebo-controlled trial. *Lancet Infect Dis* 2013; **13**(2): 123-9.
148. Mulpuru S, Andrew MK, Ye L, et al. Impact of respiratory viral infections on mortality and critical illness among hospitalized patients with chronic obstructive pulmonary disease. *Influenza Other Respir Viruses* 2022; **16**(6): 1172-82.
149. Quarg C, Jörres RA, Engelhardt S, Alter P, Budweiser S. Characteristics and outcomes of patients hospitalized for infection with influenza, SARS-CoV-2 or respiratory syncytial virus in the season 2022/2023 in a large German primary care centre. *Eur J Med Res* 2023; **28**(1): 568.
150. Tian J, Liu C, Wang X, et al. Comparative analysis of clinical features of lower respiratory tract infection with respiratory syncytial virus and influenza virus in adults: a retrospective study. *BMC pulmonary medicine* 2023; **23**(1): 350.
151. Debes S, Haug JB, de Blasio BF, Lindstrøm JC, Jonassen CM, Dudman SG. Clinical Outcome of Viral Respiratory Tract Infections in Hospitalized Adults in Norway: High Degree of Inflammation and Need of Emergency Care for Cases With Respiratory Syncytial Virus. *Front Med (Lausanne)* 2022; **9**: 866494.
152. Leaver BA, Smith BJ, Irving L, Johnson DF, Tong SYC. Hospitalisation, morbidity and outcomes associated with respiratory syncytial virus compared with influenza in adults of all ages. *Influenza Other Respir Viruses* 2022; **16**(3): 474-80.
153. Chuaychoo B, Rattanasaengloet K, Banlengchit R, et al. Characteristics, complications, and mortality of respiratory syncytial virus compared with influenza infections in hospitalized adult patients in Thailand. *Int J Infect Dis* 2021; **110**: 237-46.