Respiratory Syncytial Virus 2024 1

Severe respiratory syncytial virus infection in children: burden, management, and emerging therapies

Natalie I Mazur, Mauricio T Caballero, Marta C Nunes

The global burden of respiratory syncytial virus (RSV) lower respiratory tract infection (LRTI) in young children is high. The RSV prevention strategies approved in 2023 will be essential to lowering the global disease burden. In this Series paper, we describe clinical presentation, burden of disease, hospital management, emerging therapies, and targeted prevention focusing on developments and groundbreaking publications for RSV. We conducted a systematic search for literature published in the past 15 years and used a non-systematic approach to analyse the results, prioritising important papers and the most recent reviews per subtopic. Annually, 33 million episodes of RSV LRTI occur in children younger than 5 years, resulting in 3·6 million hospitalisations and 118 200 deaths. RSV LRTI is a clinical diagnosis but a clinical case definition and universal clinical tool to predict severe disease are non-existent. The advent of molecular point-of-care testing allows rapid and accurate confirmation of RSV infection and could reduce antibiotic use. There is no evidence-based treatment of RSV, only supportive care. Despite widespread use, evidence for high-flow nasal cannula (HFNC) therapy is insufficient and increased paediatric intensive care admissions and intubation indicate the need to remove HFNC therapy from standard care. RSV is now a vaccine-preventable disease in young children with a market-approved long-acting monoclonal antibody and a maternal vaccine targeting the RSV prefusion protein. To have a high impact on life-threatening RSV infection, infants at high risk, especially in low-income and middle-income countries, should be prioritised as an interim strategy towards universal immunisation. The implementation of RSV preventive strategies will clarify the full burden of RSV infection. Vaccine probe studies can address existing knowledge gaps including the effect of RSV prevention on transmission dynamics, antibiotic misuse, the respiratory microbiome composition, and long-term sequalae.

Lancet 2024; 404: 1143–56

Published Online September 9, 2024 https://doi.org/10.1016/S0140-6736(24)01716-1

This is the first in a Series of four papers about respiratory syncytial virus (papers 2 and 3 appear in *The Lancet Respiratory Medicine*). All papers in the Series are available at thelancet.com/series/https://www.thelancet.com/series/respiratory-syncytial-virus

Department of Pediatrics, Wilhelmina Children's Hospital, Utrecht, Netherlands (N I Mazur MD PhD); **Centro INFANT de Medicina Traslacional (CIMeT), Escuela de Bio y Nanotecnología, Universidad Nacional de San Martín (UNSAM), Buenos Aires, Argentina** (M T Caballero MD MSc); **Consejo Nacional de Investigaciones Científicas y Técnicas, Buenos Aires, Argentina** (M T Caballero); **Center of Excellence in Respiratory Pathogens, Hospices Civils de Lyon and Centre International de Recherche en Infectiologie, Équipe Santé Publique, Épidémiologie et Écologie Évolutive des Maladies Infectieuses, Inserm U1111, CNRS UMR5308, ENS de Lyon, Lyon, France** (M C Nunes PhD); **South African Medical Research Council, Vaccines & Infectious Diseases Analytics Research Unit, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa** (M C Nunes)

Correspondence to: Natalie I Mazur, Department of Pediatrics, Wilhelmina Children's Hospital, Utrecht 3584EA, Netherlands **n.i.mazur@umcutrecht.nl**

See Online for appendix

Introduction

Worldwide, respiratory syncytial virus (RSV) is associated with substantial morbidity and mortality in infants and young children.[1,2,3] RSV is one of the most common pathogens associated with pneumonia hospitalisations in children.[4,5] The clinical diagnosis of RSV disease in infants is challenging because of non-specific symptoms resembling other respiratory illnesses.[6] Recognising the clinical features of RSV infection in infants and young children is crucial for clinical management, epidemiological surveillance, and in the development of clinically relevant endpoints for randomised clinical trials (RCTs).[7] Although there is no specific treatment for RSV, we have reached a turning point for RSV prevention with two immunisations approved in 2023 to prevent RSV in infants[8,9] as well as three vaccines for adults.[10] As such, RSV can now be considered a vaccine-preventable disease.

Although most children with severe RSV disease are previously healthy, understanding groups at high risk for severe disease could allow early prioritisation for targeted prevention of RSV as an interim strategy towards universal immunisation. Disease burden estimates and recognition of the associated risk factors by policy makers worldwide are also crucial to evaluate the implementation strategies available.

In the past 15 years, major knowledge has been gained regarding protective immune responses against RSV and quantification of the real RSV burden, including data from low-income and middle-income countries (LMICs). Nonetheless there are still many knowledge gaps (panel). The implementation of RSV prevention by means of vaccine probe studies will contribute to addressing some of these knowledge gaps. In the first paper in this Series on RSV, we describe the clinical presentation, burden of disease, hospital management, emerging therapies, and targeted prevention of RSV, focusing on developments and groundbreaking publications in the last 15 years. The second paper presents the association between early RSV infection and long-term sequelae including recurrent LRTI and all-cause pneumonia, recurrent wheezing, and asthma.[11] The authors also discuss possible causal

Search strategy and selection criteria

References for this Series paper were identified through a search of PubMed and the Cochrane Library for original research and reviews with no language restrictions from Jan 1, 2009, to May 1, 2024. We did not intend to do a systematic review of the literature with evidence grading. No inclusion or exclusion criteria were used. Instead, we selected articles that were most relevant to the subheadings used in this Series paper. We searched using the terms "respiratory syncytial virus" or "bronchiolitis" and "infant" or "child" or "pediatric" and "management" or "treatment" or "interventions" or "severity" or types of therapies or supportive care (appendix p 4).

Key messages

- Severe respiratory syncytial virus (RSV) disease presents as three age-related clinical syndromes (sepsis in neonates, bronchiolitis in infants, and pneumonia in young children) but cannot be clinically distinguished from other respiratory illnesses without viral testing
- The worldwide burden of RSV is inequitably distributed, with the majority of life-threatening disease occurring in low-income and middle-income countries (LMICs; figure 1). All children are infected with RSV; approximately 5% develop RSV lower respiratory tract infection, 0·4% are hospitalised, and 0·02% die (figure 2)
- A substantial proportion (16%) of infants with life-threatening RSV infection have severe comorbidities, even if the majority of infants with severe RSV are term and previously healthy
- There is no treatment for RSV and hospital management consists of supportive care; high-flow nasal cannula therapy has been widely implemented for respiratory support despite insufficient evidence of efficacy against life-threatening disease
- Prevention is key for RSV as antivirals are not yet available; RSV should be considered a vaccine-preventable disease for all infants globally; high-risk groups, especially in LMICs, should be prioritised as an interim strategy on the road to universal immunisation
- The effect of RSV prevention on RSV transmission dynamics, antibiotic misuse, the respiratory microbiome composition, and long-term respiratory sequalae are crucial knowledge gaps (panel)

mechanisms to explain the association between RSV infection and asthma and full public health value of RSV prevention. The third paper focuses on RSV infections in adults and discusses diagnosis and disease burden, infection in vulnerable adult populations, prevention, and cost of care.[10] The fourth paper reviews the efficacy and safety of RSV vaccination and immunoprophylaxis in young children, explores potential regulatory, policy, and implementation pathways for the RSVpreF maternal vaccine and nirsevimab, and discusses and the health economic evidence to inform product introduction decisions.[12]

Clinical presentation

Severe paediatric RSV disease can be roughly classified by clinical syndrome in three age groups: neonates present with sepsis-like illness[13–15] or apnoea,[16] children younger than 2 years with bronchiolitis,[6] and older children with pneumonia.[17] Infants can develop respiratory failure, which can be life threatening. Bronchiolitis and pneumonia are primarily diagnosed based on clinical evaluation, and laboratory tests might not substantially change the management of these conditions. However, confirming a viral cause through molecular testing can be important to avoid the unnecessary use of antibiotics during severe lower respiratory tract infections (LRTIs). Advances in RSV testing in the past 10 years include RSV molecular point-of-care testing, allowing for rapid and affordable testing at the bedside, with a sensitivity and specificity that is non-inferior to PCR testing.[18] A clinical dilemma for RSV LRTI is that the site of infection cannot be sampled (the lungs), except when a child is intubated; however, there is high concordance (0·89) for RSV PCR positivity between the upper and lower respiratory tract.[19] One of the major challenges for clinicians is to predict who will progress towards severe disease. Research efforts have validated clinical tools to predict progression to severe disease to aid clinicians in early disease stages, yet these tools are not widely implemented.[20]

The majority of RSV infections in infants are asymptomatic or manifest with mild, self-limiting symptoms; however, RSV is also a leading cause of severe LRTI among young children.[21] Among those who have at least one clinical sign of acute respiratory infections, only six of 100 children per year will fulfil the classic influenza-like illness definition.[22] Therefore, the absence of consistent clinical presentations could lead to an underestimation of RSV incidence by 50–80% if influenza-like illness or severe acute respiratory infection (SARI) criteria alone are used.[23] Moreover, severe RSV disease usually presents with hypoxaemia, wheezing, and chest in-drawing, which are not included in SARI or influenza-like illness case definitions.[24] The WHO extended SARI case definition[25] is more sensitive in detecting severe RSV cases, with only 3% of cases missed in paediatric intensive care units (PICUs) in LMICs.[26]

Although there are no pathognomonic clinical signs for severe RSV disease, it manifests primarily with upper respiratory symptoms such as rhinorrhoea and cough, before progressing to pulmonary symptoms (figure 2).[6] Fever is not usually associated with RSV infection, occurring in about 15% of symptomatic cases,[22,29] although the presence of fever increases with age.[30] However, in the context of life-threatening RSV in LMICs, the presence of fever upon admission was high, with 58% of children presenting with a fever.[26] After 4–6 days of upper respiratory tract clinical signs, children can develop increased breathing effort accompanied by retractions, wheezing, tachypnoea, and feeding difficulties.[6] Eventually, children with severe clinical progression can have hypoxaemia, anorexia, apnoea, lethargy, or irritability, indicating the need for hospitalisation.[31]

One of the major challenges facing clinicians is to predict who will progess towards severe disease. Standardised methods to assess RSV severity in infants are not available, making it difficult to reach a consensus on the endpoints needed to measure vaccine efficacy. Additionally, there are no standardised criteria for hospital or PICU admissions or for initiating respiratory support.[32–34] Multiple scoring systems and cutoffs in key respiratory variables have been suggested to define outcomes for RSV intervention

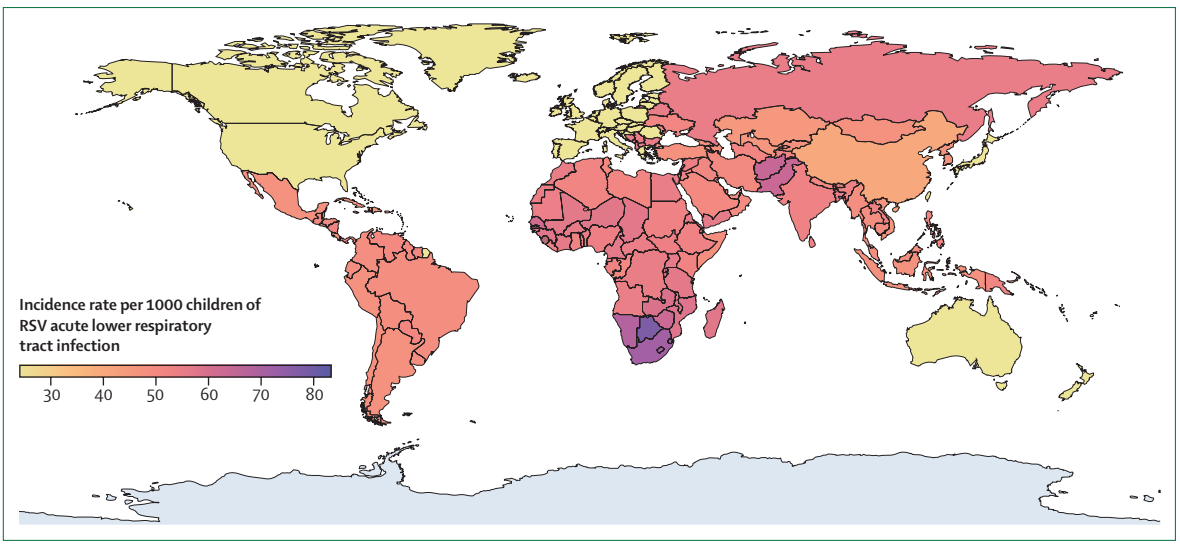

Figure 1: **Heat map of incidence rate estimates of RSV acute lower respiratory infection per 1000 children for children younger than 5 years in 2019**
Data from the latest global burden estimates for RSV was used to make a heat map of global incidence of RSV acute lower respiratory tract infection (data for 137 LMICs were available).[1] A scale of colours was used to show higher (purple) and lower (yellow) incidence. Country-specific incidence rates estimates were used if available. If country-specific data were not available, incidence for countries classified by World Bank income regions was used (ie, low income, lower-middle income, upper-middle income, and high income) and the aggregate value for the region was used. Ploty.js software was used to make the world map. RSV=respiratory syncytial virus.

trials.[7,20,35,36] Nevertheless, although some of these RSV clinical severity scores show promise, none of them are universally implemented due to either incomplete external validation in LMICs or the need for adaptation to challenging environments.[20,35] Moreover, various clinical variables (eg, retractions, wheezing, or crackles) pose challenges for parameterisation due to potential measurement biases, biological variations, inadequate sampling power, and population heterogeneity.[20,31,37,38] We have included an overview of the most frequently used clinical severity scores for bronchiolitis, the parameters used, and the level of validation (table).

Disease burden

The global incidence of RSV LRTI is inequitably distributed, with the highest incidence in LMICs (figure 1). An update on the global RSV LRTI burden among children younger than 5 years estimated that in 2019 33 million (95% uncertainty range [UR] 25·4–44·6) episodes of RSV LRTI resulted in 3·6 million (2·9–4·6) hospitalisations, 26 300 (48 000–74 500) in-hospital deaths and 118 200 overall deaths, translating to 0·02% of children younger than 5 years (figure 2).[1] RSV-attributable (ie, RSV identified in the causal chain) overall mortality could be as high as 101 400 (84 500–125 200) including out-of-hospital deaths.

Infants younger than 6 months have the highest disease burden (incidence of RSV LRTI: 96·3 [95% UR 67·9–142·6] per 1000 children per year), accounting for a fifth of all infections and nearly 40% of all RSV hospitalisations (appendix p 2). Of these hospitalisations, the majority (61%) were during the first 3 months of life. Infants younger than 6 months also accounted for more

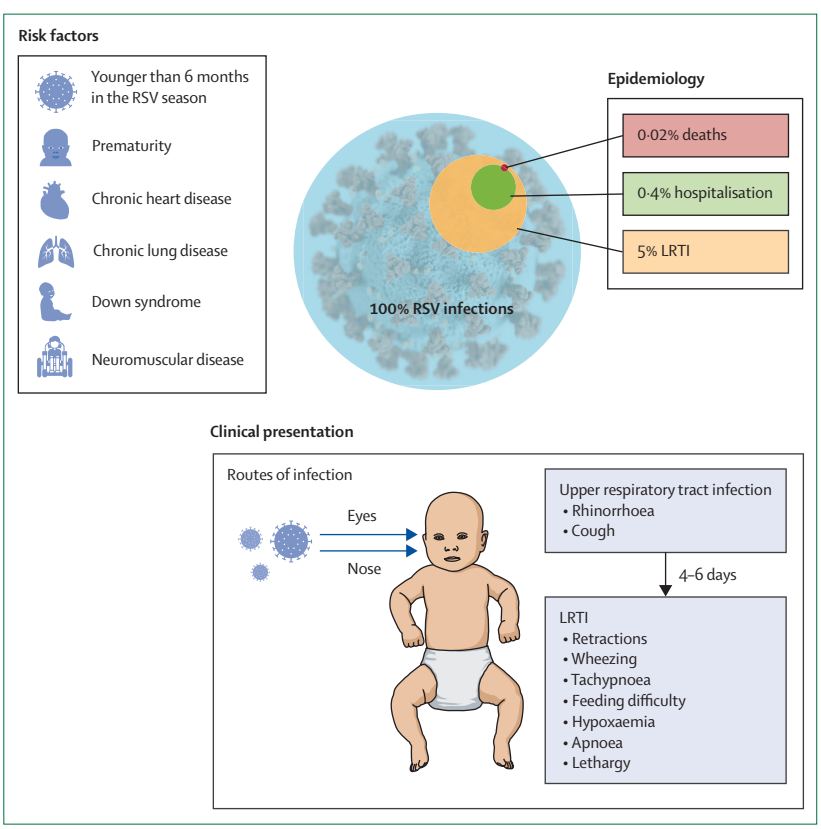

Figure 2: **Global epidemiology of severe RSV infection among children younger than 5 years**
Global epidemiology of severe RSV according to global burden estimates in 2019: all children are infected with RSV,[21] 33 million (5%) of 690 million children younger than 5 years have RSV LRTI,[27] 3 million (0·4%) are hospitalised, and 118 200 (0·02%) children die from RSV LRTI.[1] RSV infects primarily through the nose, but also through the eyes.[28] There are well defined risk factors for severe RSV disease. Figure was created using Piktochart. LTRI=lower respiratory tract infection. RSV=respiratory syncytial virus.

Panel: **Respiratory syncytial virus major new insights and remaining knowledge gaps**

Major new insights in the past 15 years

- The majority of life-threatening respiratory syncytial virus (RSV) infection occurs in low-income and middle-income countries (LMICs) and more than 70% of RSV deaths occur out of the hospital
- Infants younger than 6 months at the start of the RSV season are at the highest risk of death
- Insights into the structure of the surface RSV fusion protein have allowed an understanding of neutralising antibodies and have been the key to successful RSV vaccine development
- RSV is now a vaccine-preventable disease as new preventive interventions have been approved and implemented in several countries
- Initial real-world effectiveness data of RSV preventive monoclonal antibodies show high coverage and efficacy

Remaining knowledge gaps

- Burden: the global burden of RSV-associated paediatric intensive care unit admissions, community deaths, and severe disease in LMICs need to be further quantified to facilitate implementation of RSV vaccines; little is known about the burden of RSV during the neonatal period
- Management: further validation of a clinical severity score is needed to guide global uniformity in assessment of the severity of RSV infection; efficacy of widely implemented high-flow nasal cannula against clinical outcomes of RSV infection needs to be studied
- Vaccine impact: vaccine probe studies can allow assessment of the effect of new RSV prevention on secondary outcomes such as community mortality, all-cause lower respiratory tract infection, RSV transmission, antibiotic misuse, long-term respiratory sequelae, and the respiratory microbiome

than half of all in-hospital RSV-associated deaths and 45% of RSV-attributable deaths.[1] Although RSV is not a common cause of death in neonates, neonates account for approximately 1 of 5 RSV-attributable deaths in the first 6 months of life. However, data on neonatal RSV are scarce and potentially underestimated due to non-specific neonatal clinical presentation.

The RSV LRTI incidence in the community among infants younger than 6 months was three times higher in LMICs compared with high-income countries (HICs); whereas the incidence of RSV LRTI hospitalisation was lower in LMICs than HICs, suggesting inadequate access to health care in LMICs (appendix p 2). Moreover, LMICs have the highest burden of mortality with more than 97% of the overall RSV-attributable deaths occurring in LMICs and more than 70% of these occurring outside the hospital. Potentially the high rates of community deaths are due to insufficient awareness: in vulnerable contexts, inadequate parental awareness of severity could contribute to as many as 20% of out-of-hospital deaths attributed to RSV.[52–54] In addition, severe apnoea related to RSV can be a finding that is easily missed even for well trained physicians. Overall, RSV awareness is still insufficient, with only 3% of parents of children who were admitted to the PICU with life-threatening disease in LMICs having heard of RSV before hospital admission.[26]

Accurately quantifying RSV-associated deaths is challenging. Many RSV-associated deaths in LMICs occur in the community, making ascertainment difficult. Moreover, the role of RSV in mortality could be underestimated if the virus goes undetected at the time of death. By contrast, deaths among infants with RSV (classified as RSV-associated deaths) might be due to other pathogens, with RSV not being in the causal chain of death (ie, not RSV-attributable deaths).[55] An analysis from the Child Health and Mortality Prevention Surveillance (CHAMPS) Network on the causal pathways and pathogen-specific causes of fatal pneumonia in children aged 1–59 months (median age 9 months) revealed that RSV was causally associated with 29 (6%) of 455 fatal pneumonia episodes in six countries in sub-Saharan Africa and Bangladesh.[56] Therefore, estimates of RSV mortality should be considered as the minimum estimate of the true burden, particularly for out-of-hospital deaths, which account for 21·8% of the deaths included in the CHAMPS study. Further quantification of true burden of RSV community deaths is needed.

Studies from two African countries, one lower-middle-income (Kenya) and one upper-middle-income (South Africa), used different methodologies to estimate the annual incidence of severe RSV LRTI based on health-care use surveys and hospitalisation data among children younger than 5 years.[2,3] Non-hospitalisation rates (ie, children reporting symptoms of severe illness, yet who did not seek care at a hospital) were three times higher than hospitalisation rates in Kenya (1077 *vs* 349 per 100 000 children), whereas they were similar in South Africa (927 and 802 per 100 000 children), reflecting the inadequate hospital access in LMICs and therefore increased outpatient visits.[2,3] In Europe, a large prospective birth cohort study of healthy term-born infants, revealed that during the first year of life 1 in 56 of all symptomatic RSV episodes required hospitalisation.[57,58] Furthermore, among children hospitalised in HICs, approximately 4–6% necessitate intensive care support.[57,59,60] Data on the burden of RSV-associated intensive care unit admissions from LMICs are scarce; however, a 2024 large multicentre study identified RSV in 30% of children admitted to the PICU with SARI in ten LMICs eligible for Gavi, the Global Vaccine Alliance.[26]

Likewise, there is a high burden of disease in children born prematurely. The estimated global number of RSV LRTI in the first year of life among preterm

	Parameters	Designed for RSV	Target population	Outcome used to test the score	Study done to test or create the score	Model building method reported	Model performance and validation	User	Setting	Tested in LMICs	Comments
Wang Bronchiolitis Severity Score[39–41]	RR, retractions, wheezing, general condition	No	Younger than 24 months	Pulse oximetry	Cross-sectional study	No	Observer agreement	Physicians	Outpatient	Yes, Türkiye	Low performance and reliability
Modified Tal Score[42,43]	SpO2, RR, wheeze, accessory respiratory muscle use	No	Younger than 12 months	Supplementary oxygen	Randomised clinical trial	No	Reliability, ROC	Physicians	Outpatient	No	No prediction oxygen therapy
ReSVinet Score[38]	Feeding tolerance, medical intervention, respiratory difficulty, RR, apnoea, general condition, fever	No	Healthy, younger than 24 months	Wood-Downes Score, length of stay, PICU, treatments	Retrospective and prospective study	No	Cronbach's coefficient, reliability, ROC, external validation	Physicians and parents	Outpatient and inpatient	Yes, datasets from Colombia and Rwanda	Externally validated for RSV
Modified respiratory index score[44,45]	RR, retractions, wheezing, mental status	No	Younger than 24 months, less than four wheezing episodes	>2 days hospital stays, oxygen therapy, intravenous hydration	Prospective observational study	No	ROC, sensitivity analysis, positive and negative predictive values, external validation	Physicians	Inpatient	No	Low performance and reliability
Bronchiolitis Score of Sant Joan de Deu[42,46]	SpO2, heart rate, RR, wheeze, indrawing, air entry	No	Healthy, younger than 24 months	PICU, length of stay, mortality	Prospective observational study	No	Cronbach's coefficient, intraclass correlation coefficient reliability, ROC	Physicians	Inpatients	No	Evaluation of both validity and reliability
Global Respiratory Severity Score[41,42,47]	Appearance, wheezing, rales, retractions, cyanosis, lethargy, poor air movement, RR, SpO2 movement	Yes	Healthy, term, younger than 10 months	Length of stay	Prospective cohort study	Missing values imputation, factor analysis, likelihood ratio, logistic regression	ROC, correlation with length of stay, external validation	Physicians	Outpatient and inpatient	No	Internal consistency
Bronchiolitis Severity Score[48,49]	RR, retractions, dyspnoea, auscultation	No	Children with asthma, bronchiolitis or wheezing	Not specified	Retrospective and prospective study	No	Reliability, ROC	Physicians	Outpatient	Yes, India	Low performance and reliability
Escala de Severidad de la Bronquiolitis Aguda[42,50,51]	Wheezing, crackles, breathing effort, inspiratory to expiratory ratio, RR, heart rate	No	Healthy, term, younger than 12 months	Bronchiolitis severity (home, ward, PICU)	Cross-sectional study	No	Cronbach's coefficient, factor analysis, reliability	Physicians	Outpatient and inpatient	No	Internal consistency

Scores used or developed for asthma were excluded. The most frequently studied clinical severity scores according to a 2024 review[20] were all included in the table. LMICs=low-income and middle-income countries. PICU=paediatric intensive care unit. ROC=receiver operating characteristic curve. RR=respiratory rate. RSV=respiratory syncytial virus. SpO2=pulse oxygen saturation.

***Table*: Overview and evidence summary for severity scoring in lower respiratory tract illnesses**

infants in 2019 was 1·6 million (95% UR 1·4–2·0), with 533 000 (385 000–730 000) hospitalisations, and 26 760 (11 190–46 240) deaths attributable to RSV, with only 11% of these being in-hospital.[61] Of note, these estimates were inversely proportional to gestational age, with higher rates of RSV hospitalisation in infants born at lower gestational ages (appendix p 3). Preterm infants accounted for a fourth of all RSV LRTI hospitalisations. Early preterm infants (<32 weeks gestational age) were twice as likely to be hospitalised compared with late preterm infants (32–37 weeks gestational age), with this increased risk continuing in their second year of life. The majority of RSV LRTI cases (93%), hospitalisations (92%), and in-hospital deaths (89%) among preterm infants occurred in LMICs (appendix p 2).[61]

The burden of endemic respiratory viruses was substantially reduced globally during the first year of the COVID-19 pandemic.[62] A systematic literature review for studies published from Jan 1, 2020, to June 30, 2022, compared with data from 2019 found that the rates of RSV LRTI hospitalisation in 2020 decreased by nearly 80% in HICs, 13·8% in upper-middle-income countries, and 42·3% in Kenya (the only lower-middle-income country included) in children younger than 5 years.[63] In 2021, these rates started to increase, and in HICs, annualised rates had returned to similar levels as in 2019 by March, 2022. However, in middle-income countries, rates were still lower in 2022 than 2019.[63] Conversely, a South African study found that by 2021 the incidence of RSV LRTI hospitalisations in children younger than 5 years was similar to pre-pandemic years.[64] A systematic review also found a transient but significantly higher proportion of children aged 12–24 months were hospitalised with RSV LRTI in high-income and upper-middle-income countries during the pandemic years than in 2019.[63,65]

Hospital management

Supportive care by way of fluid hydration and respiratory support are the foundation of evidence-based in-hospital management of RSV-bronchiolitis and pneumonia.[66] There is, however, no evidence-based therapy for RSV infection (figure 3).[67–75] Low level of evidence for nebulised hypertonic saline suggested a reduced length of hospital stay of 0·40 days (95% CI –0·69 to –0·11), although this is not clinically relevant.[71]

The incidence of bacterial co-infections in patients with RSV infection is reported to be lower than 11%, but nearly a third of children with RSV LRTI are treated unnecessarily with antibiotics.[76,77] To prevent antibiotic misuse in the age of threatening global antimicrobial resistance, there should be a high threshold for

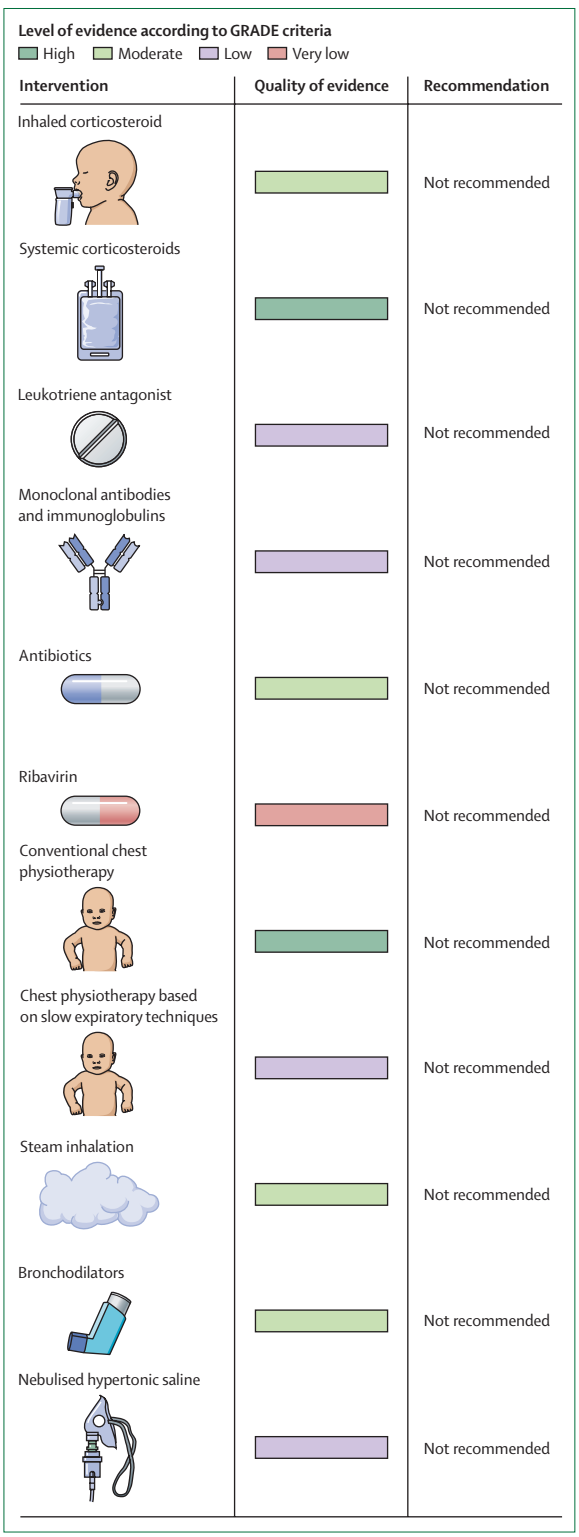

Figure 3: **Evidence-based treatment of severe RSV infection**
The intervention and recommendation for use in hospital management (recommended or not recommended) are listed, and the quality of evidence for this recommendation is presented (ie, high, moderate, low, or very low). Quality of evidence was assessed based on GRADE-criteria and if possible, taken from Cochrane review of the literature.[67–75] GRADE= Grading of Recommendations, Assessment, Development, and Evaluations. RSV=respiratory syncytial virus.

antibiotics administration in the case of RSV infection. The decision to administer antibiotics should not only be based on elevated c-reactive protein but also include overall indicators of serious bacterial infection, such as neonatal age and deterioration while ventilated.[76]

Practical tools are needed to help physicians identify serious bacterial infections in the case of RSV LRTI, allowing for more targeted antibiotic use. With worsening respiratory distress, children might be unable to maintain oral hydration, necessitating in-hospital hydration through nasogastric or isotonic intravenous fluids.[6] In two RCTs, there was no difference in length of hospital stay for both hydration modalities, and, as such, the nasogastric route might be preferred due to increased chance of success and less complications.[78] In the case of increasing respiratory distress, minimal handling has been the well accepted practice to allow a child to save all energy expenditure for breathing. A 2023 RCT challenged the value of minimal handling by showing no difference in time to improvement for the group with frequent changes in body position and physical activity compared with the minimal handling group.[79] Hospital admission is severely disruptive and can have an impact on patients and their families.[80] Psychological problems for parents can extend for more than 6 months after infant PICU admission.[81] Data on hospitalisation impact are often limited to data in premature infants although the majority of hospitalised infants were born at term.[82] Future management strategies should incorporate support for post-traumatic stress experienced by caregivers.

Oxygen therapy is a mainstay of RSV management, both in general hospital wards and PICUs. An evidence-based threshold of 90% oxygen saturation for oxygen supplementation has been established in a double-blind RCT in infants aged 6–52 weeks with bronchiolitis.[83] Notably, children aged 0–6 weeks were excluded, which is the typical age at presentation of severe bronchiolitis. Furthermore, a cohort study found no difference in outcomes in children aged 1–24 months who were hospitalised with bronchiolitis if adhering to a 90% threshold when awake and an 88% threshold when asleep compared with 90% for both thresholds.[84] Lack of long-term adverse outcomes for lower oxygen thresholds (as low as 88%) was supported by a 2023 systematic review.[85] Implementation of a 90% threshold for hospital referral and supplemental oxygen can improve patient management by reducing length of hospital stay, duration of oxygen supplementation, and costs. However, there is still a widespread implementation gap in clinical practice and national guidelines despite endorsement by WHO and the American Academy of Pediatrics. Respiratory support is the foundation of life-saving treatment for severe RSV, but supplementation and length of hospital stay can be reduced by adhering to evidence-based thresholds.

High-flow nasal cannula (HFNC) oxygen therapy has been increasingly used in the past decade for management

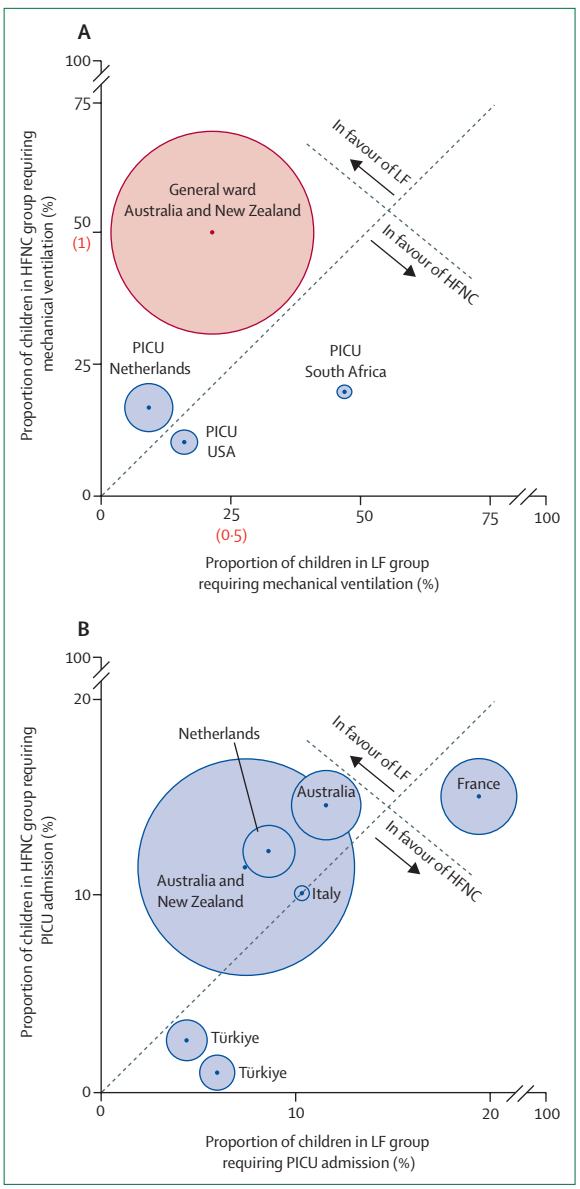

Figure 4: **Proportion of life-threatening RSV disease in children receiving HFNC compared with LF**

(A) Data on proportion of life-threatening RSV disease in children, defined as requiring mechanical ventilation, was extracted from all RCTs comparing HFNC and LF;[87-100] if the data on life-threatening disease were available, the RCT was included. A dual axis (red and black) is shown for interpretability, as trial size varied too much to fit in one figure. All studies in blue circles use the standard black axis. The Franklin trial, indicated in a red circle (comparatively large and percentages low [<1·5%]), uses the x axis indicated in red. The circle sizes are proportional to the sample size in the trial, with the center of the circle at the point estimate. Country and site of trial setting are written in the circles. The dotted line represents equal percentage of the outcome in both trial groups. (B) Data on proportion of life-threatening RSV disease in children, defined as PICU admission, was extracted from all RCTs comparing HFNC and LF; if the data were available, the RCT was included in the figure. The circle sizes are proportional to the sample sizes in the trial, where the centre of the circle at the point estimate. Country where the RCT was conducted is written in the circle. The dotted line represents equal percentage of the outcome in both trial groups. HFNC=high-flow nasal canula. LF=low-flow nasal canula. PICU=paediatric intensive care unit. RCT=randomised clinical trial.

of hospitalised infants besides standard low-flow nasal cannula (LF) oxygen therapy. HFNC uses humidified heated air blended with oxygen and, unlike LF, administers a degree of positive pressure to the airways. Practical advantages include ease of use for hospital staff and increased comfort. 11 RCTs comparing standard oxygen with HFNC showed an overall minor reduction in length of hospital stay and duration of oxygen therapy (<1 day).[86] Two RCTs showed lower rates of escalation of care for HFNC versus LF therapy, with no effect on duration of therapy, PICU admission rate, or length of hospital stay.[87,88] Higher rates of PICU admission were, however, observed in the HFNC group, underlying the importance of relevant trial endpoints (ie, PICU admission or mechanical ventilation) to properly assess efficacy of HFNC. Moreover, high rates of crossover to HFNC in the LF group showed that early initiation of HFNC can avoid late initiation of HFNC without any effect on clinical course of disease. In fact, use of HFNC can delay mechanical ventilation and put a child in an at-risk situation.[89]

In figure 4, we extracted relevant clinical endpoints if available from all conducted RCTs comparing HFNC and LF.[87,88,90–100] There was no trend towards efficacy against life-threatening RSV disease defined as mechanical ventilation (figure 4A) and PICU admission (figure 4B) for HFNC compared with LF. In fact, there was a trend towards increased PICU admissions and mechanical ventilation in the HFNC group. The global increase in PICU admission rates for viral bronchiolitis in the past decade can probably be explained by the concomitant adoption of HFNC,[101,102] or alternatively, by a low threshold of admission to critical care in viral bronchiolitis.[103]

Beyond HFNC, mechanical ventilation through endotracheal intubation was introduced in the management of viral bronchiolitis in the 1960s, and since the 1980s several options for non-invasive respiratory support are being increasingly used in the PICU due to the potential to avoid complications associated with invasive mechanical ventilation. Non-invasive ventilation includes options that provide volume or pressure support or provide pressure support upon spontaneous breathing, including nasal continuous positive airway pressure (CPAP) delivered via a face mask and HFNC. The effect of non-invasive respiratory support remains to be determined in PICU. A Cochrane review of CPAP for viral bronchiolitis found no reduction in the need for mechanical ventilation with a low level of evidence.[104] In summary, large adequately powered trials are needed to find out the efficacy of non-invasive ventilation compared with conventional oxygen supplementation against relevant clinical outcomes.[104] Until then, clinicians should be hesitant to use CPAP for bronchiolitis management due to potential adverse outcomes (eg, local nasal mucosal damage, aspiration secondary to gastric insufflation, and pneumothorax) and the delay of definitive care. Similarly, the insufficient evidence for efficacy, high costs, and increased PICU admissions support the removal of HFNC from standard care in general paediatric wards.

Emerging therapies

Treatment

Antiviral therapy has not shown much promise in the treatment of RSV infection, with the dilemma that the delay in treatment is too long for antivirals to effectively interrupt viral replication and therefore prevent an associated immune response. A phase 2b trial published in 2021 of ALX-0171, a trivalent RSV antiviral nebulised nanobody, showed no clinical response, measured as improved oxygen saturation levels or decrease in severity scores, despite a faster drop in viral load compared with placebo.[105] For most RSV therapeutic candidates development has halted. At least four antiviral compounds have been terminated or the development status is unclear in late-phase trials (NCT04225897, NCT04583280, NCT05559905, and NCT06170242):[106,107] EDP-938 failed phase 2b trials, although development is being continued for children and high-risk adults[106] and EDP-323 is being evaluated in a phase 2 controlled human infection model with expected completion in May, 2024 (NCT06170242). Overall, prevention of infection is a more promising approach than treatment as administering treatment within 24–48 h of symptom onset is rarely feasible. The therapeutic window has often passed once health care is sought (median symptom duration before hospitalisation is 4 days and before first health-care contact is 3 days).[108]

Prevention: non-pharmaceutical interventions and transmission

Although precise studies on the airborne transmissibility of RSV are scarce, RSV is known to be transmitted through direct and indirect contact with virus-contaminated droplets on hands or fomites.[109] Transmission in households generally occurs through school-aged children and adolescents, and viral shedding is more prolonged in young infants and symptomatic patients.[22] The COVID-19 pandemic led governments to implement a series of non-pharmacological measures to reduce the circulation of SARS-CoV-2.[63,110] These measures, which included physical distancing, quarantines, use of face masks, and handwashing, notably reduced the circulation of RSV and other respiratory viruses.[111] These measures resulted in a dramatic drop in outpatient consultations and hospitalisations due to RSV, especially in the southern hemisphere.[112] The implementation of simple non-pharmacological preventive measures, such as handwashing, could be useful in reducing infections by RSV and other viruses in young or at-risk infants. Disinfecting toys, surfaces, and fomites every 2 weeks significantly decreased the presence of viral genetic material for RSV and other respiratory viruses in the environment.[112,113]

Prevention: monoclonal antibodies

Advances in RSV vaccine research have been driven by insights into the immune responses to RSV and innovative applications of structural immunology in antigen design. The primary focus of these efforts has been the RSV surface prefusion (preF) glycoprotein.[114,115] Information regarding safety, regulatory, policy, and implementation pathways for RSV prevention is discussed separately in the fourth paper in this series.[12] In this Series paper, we discuss the two RSV preventive products approved in 2023, and refer to the fourth paper in this Series for a brief discussion of other vaccines in development for children.

Prophylaxis with monoclonal antibodies (mAbs) has been a time-tested approach to protect infants from RSV. Since 1998, palivizumab was the only market-approved prophylactic to protect infants against RSV-associated hospitalisation. Palivizumab use is largely limited to high-risk infants in HICs due to high costs and administration via monthly injections during the RSV season. In early 2023, nirsevimab, an extended half-life mAb against site Ø of preF, received market approval in Europe and the USA for all infants. The phase 3 MELODY trial showed 74·5% (95% CI 49·6–87·1) efficacy up to 150 days against medically attended RSV LRTI in healthy preterm and term infants.[116] The extended-half-life of this intervention was 68·7 (SD 10·9 days), which allows for improved protection over an entire RSV season with a single injection. First-year implementation experiences reported more than 92% coverage and real-life effectiveness against RSV hospitalisation as high as 96% in Spain.[117,118] High global demand could not keep up with supply due to production shortages.[119]

Other mAbs against RSV are on the horizon. Phase 3 trial results are expected at the end of 2024 for clesrovimab, an extended half-life mAb against site IV of preF. With a half-life of 43–48 days, the phase 2 results showed preliminary efficacy in infants of 80·6% (–141·2 to 99·6) against medically attended RSV LRTI up to 150 days.[120] Registration of this mAb is anticipated as early as 2026. Given the production costs and pricing, mAbs will probably not become widely available in LMICs.[121] The clinical development programme of RSM01, an extended-half-life mAb against site Ø, is aimed at LMIC access with the aim of affordable pricing at less than US$4 per dose. A phase 1 trial in adults was completed in 2022.[122] Implementation for mAbs includes administration at birth, which confers immediate protection and can be year-round or seasonal.

Prevention: maternal vaccination

Vaccinating pregnant people is an alternative strategy for protecting infants against RSV. RSVpreF (Pfizer, Puurs, Belgium), a bivalent prefusion protein vaccine to be used during pregnancy, was approved in several countries from mid-2023.[8] A large global phase 3 trial that enrolled 31% of people who were pregnant in LMICs reported an efficacy in infants of 82·4% (95% CI 57·5–93·9) in preventing severe medically attended RSV LRTI within the first 90 days of life, and 70·0% (50·6–82·5) within 180 days.[8,123] To date, two other RSV maternal vaccine candidates with RSV F protein as the antigenic target were evaluated in phase 3 clinical trials, after which development was discontinued due to not achieving the study primary objective or safety concerns.[124,125] Additionally, one mRNA-based vaccine (mRNA-1345) is in phase 2 development. Although results among people who are pregnant are pending for mRNA-1345 (NCT06143046), it has an acceptable safety profile and good immunogenic responses in adults and people older than 60 years.[126–128] In older adults, mRNA-1345 showed more than 80% efficacy in preventing RSV LRTI for a median 112 days post-vaccination and more than 60% during an extended median follow-up of 8·6 months.[126,129] Advantages of maternal vaccination include a lower price than mAb therapy; however, factors such as timing in relation to birth, placental integrity, and maternal health might influence the effect of maternal vaccination.

Targeted prevention

Ideally, RSV prevention will target all infants but at a minimum, will target children at high risk of life-threatening disease as an interim strategy until RSV prevention is widely available. The research field of RSV prevention is rapidly changing with the implementation of preventive immunisations with nirsevimab or RSVpreF in multiple countries across the world.[117,130] Nonetheless, accessibility to these preventive measures poses challenges for many LMICs.[55] Risk factors associated with severe RSV disease are important to identify priority target populations for RSV prevention and designing cost-effective RSV prophylaxis strategies.

Patient-related risk factors

There are key clinical and epidemiological aspects of severe RSV disease in young children worldwide (eg, the higher burden of hospitalisations, intensive care unit admissions, and mortality among infants younger than 6 months)[1,25,131,132] to support the immunisation strategy to protect this vulnerable population.[1,133] Underlying medical conditions for severe RSV disease include prematurity, neurological disease, Down syndrome, chronic lung disease, immunodeficiency, and congenital heart disease (figure 1).[134–137] However, the majority of children hospitalised with RSV are born at term and have no underlying medical conditions, and among these children, younger age is the most important risk factor.[57] There is no clear underlying genetic risk profile; in large genome-wide association studies no single nucleotide polymorphisms were significantly associated with severity.[138,139] Single-cell sequencing, transcriptomics, lipidomics, and immune responses have helped to identify potential biomarkers for infants requiring RSV hospitalisation,[140–143] although there is no consensus on biomarkers, which makes the clinical application not yet clear.[144]

Exposure-related risk-factors

Associated viral factors, such as RSV strain and co-detection with other pathogens (except *Haemophilus* spp), were not associated with increased disease severity.[145] Another important aspect is the relationship between RSV seasonality and young age during the RSV season in countries with a clear seasonal pattern of viral circulation, with infants younger than 6 months during the period of viral circulation being at higher risk and with worse clinical outcomes than children aged between 6 months and 5 years.[57,146,147] Exposures to other children potentially carrying RSV, such as having siblings or attending daycare or nursery, are known risk factors for RSV infection.[148]

Socioeconomic risk factors

Although sociodemographic aspects are often overshadowed by biological factors, more than 70% of RSV-attributable deaths occur out of the hospital, where medical care is inadequate, particularly in conditions of structural poverty.[52,148–150] Therefore, gaining a detailed understanding of the pathways of community deaths from RSV could facilitate the implementation of RSV prevention in LMICs. 2021 reports showed that infants who die from RSV in the community are younger than 6 months, typically without severe underlying conditions, and often present mild clinical signs and symptoms compared with hospitalised children.[52,149,151] Moreover, these children usually live in socioeconomically vulnerable backgrounds, such as overcrowded houses in slums or impoverished, densely populated neighbourhoods with little access to public transportation and primary health-care facilities.[52,53,150,152] Other characteristics of infant RSV-associated community deaths compared with hospital deaths are shorter durations of disease and lower histopathological severity.[53] In order for RSV prevention to have the highest impact against life-threatening RSV, urgent access to preventive interventions is needed in vulnerable populations where access to new therapeutics will probably be delayed or not become available at all.

Long-term respiratory sequelae

Although several observational studies show an association between early-life RSV infection and recurrent wheezing and asthma in childhood,[153] there are few clinical trials that can establish a causal relationship. A population-based birth cohort study in the USA published in 2023 estimated that 15% of asthma diagnoses by age 5 years could be prevented by avoiding RSV infection during infancy.[154] Similarly, a birth-cohort study from South Africa found that a first episode of severe RSV LRTI in infancy was associated with an increased risk of recurrent wheezing in early childhood.[155] Infants with more severe RSV LRTI showed an increased risk of developing recurrent wheezing in the first year of life.[156] However, few randomised clinical trials have explored the efficacy of preventive immunisation with palivizumab in preterm infants to prevent recurrent wheezing and asthma in childhood.[157,158] These clinical trials did not show effective prevention of asthma onset at the age of 5 years compared with placebo. Large sample sizes and long-term follow-up are required to show efficacy of RSV prevention on the development of asthma. Therefore, understanding the long-term real-life impact of new preventive measures can not only address the longstanding question of the causal relationship between RSV infection and the development of wheezing phenotypes, but also allow the establishment of expanded objectives for implementation strategies and cost-effectiveness estimations. The link between RSV infection in early life and long-term respiratory health are further explored in the second paper in this Series.[11]

Conclusions and future directions

We have entered a new era of paediatrics in which RSV has become a vaccine-preventable disease in all children. Although universal immunisation should be the target, high-risk groups could be prioritised in the process of vaccine implementation, including LMIC populations carrying the highest burden of life-threatening RSV. Treatment of RSV shows little promise and supportive care is the foundation of management. The advent and widespread implementation of HFNC does not have an evidence base and this therapy should be removed from standard practice. Implementation of RSV preventive strategies as a vaccine probe study will help to address existing knowledge gaps (panel). Vaccine implementation will have real-world impact including effectiveness against all-cause LRTI and impact on the respiratory microbiome. Gaps in knowledge remain, including the effect of RSV prevention on long-term RSV sequalae (eg, wheezing and asthma), and vaccine implementation could elucidate the (causal) relationship between RSV infection and asthma. This knowledge can be discovered by investigating vaccine probe type approaches using real-world data in which the difference in the outcome of interest between immunised and non-immunised individuals or populations can be ascribed to the vaccine-specific pathogen, and as such outcomes that were not assessed in the licensure trials can be evaluated.[159] A vaccine probe study approach allows examination of associations between RSV infection (prevented by immunisation) and outcomes that might require large numbers of participants. Other gaps in knowledge include the potential of future paediatric vaccination to interrupt transmission of RSV to vulnerable populations and patterns of transmission between different populations (young children, older children, adults, and older adults). Furthermore, the effect of RSV vaccination against antibiotic misuse remains to be found out.

Contributors

All authors contributed to the conceptualisation, draft writing, data curation, and visualisation of the Series paper.

Declaration of interests

NIM report grants from the Gates Medical Research Institute, the Dutch Lung Foundation, and the Bill & Melinda Gates Foundation; consulting

and speaker fees have been paid to the University Medical Center Utrecht for Abbvie, Medimmune, Sanofi, and Merck; and ReSVinet and the Bill & Melinda Gates Foundation have provided support for NIM for attending meetings. MCN reports grants from the Bill & Melinda Gates Foundation, European & Developing Countries Clinical Trials Partnership, Pfizer, AstraZeneca, and Sanofi and personal fees from Pfizer and Sanofi. MTC reports grants from the Bill & Melinda Gates Foundation, and personal fees from Sanofi, outside the submitted work.

Acknowledgments
We would like to thank Milan Verrijn Stuart (Department of Paediatric Infectious Diseases and Immunology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, Netherlands) and Eddy Rigaud (Center of Excellence in Respiratory, Université Claude Bernard Lyon 1, Lyon, France) for their excellent assistance in designing the figures for this Series paper. We would like to acknowledge Manon van de Werff for assistance in manuscript formatting. Partial funding from the Dutch Lung Foundation Grant 5.2.20.020. Figures 2, 3, and 4 were created with BioRender.com.

Editorial note: The Lancet Group takes a neutral position with respect to territorial claims in published maps and institutional affiliations.

References

1 Li Y, Wang X, Blau DM, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in children younger than 5 years in 2019: a systematic analysis. *Lancet* 2022; **399:** 2047–64.
2 Nyawanda BO, Murunga N, Otieno NA, et al. Estimates of the national burden of respiratory syncytial virus in Kenyan children aged under 5 years, 2010–18. *BMC Med* 2023; **21:** 122.
3 Moyes J, Tempia S, Walaza S, et al. The burden of RSV-associated illness in children aged < 5 years, South Africa, 2011 to 2016. *BMC Med* 2023; **21:** 139.
4 O'Brien KL, Baggett HC, Brooks WA, et al. Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study. *Lancet* 2019; **394:** 757–79.
5 Jain S, Williams DJ, Arnold SR, et al. Community-acquired pneumonia requiring hospitalization among U.S. children. *N Engl J Med* 2015; **372:** 835–45.
6 Florin TA, Plint AC, Zorc JJ. Viral bronchiolitis. *Lancet* 2017; **389:** 211–24.
7 Modjarrad K, Giersing B, Kaslow DC, Smith PG, Moorthy VS. WHO consultation on Respiratory Syncytial Virus Vaccine Development Report from a World Health Organization Meeting held on 23–24 March 2015. *Vaccine* 2016; **34:** 190–97.
8 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:** 1451–64.
9 Hammitt LL, Dagan R, Yuan Y, et al. Nirsevimab for prevention of RSV in healthy late-preterm and term infants. *N Engl J Med* 2022; **386:** 837–46.
10 Wildenbeest JG, Lowe DM, Standing JF, Butler CC. Respiratory syncytial virus infections in adults: a narrative review. *Lancet Respir Med* 2024; published online Sept 9. https://doi.org/10.1016/S2213-2600(24)00255-8.
11 Zar HJ, Cacho F, Kootbodien T, et al. Early-life respiratory syncytial virus disease and long-term respiratory health. *Lancet Respir Med* 2024; published online Sept 9. https://doi.org/10.1016/S2213-2600(24)00246-7.
12 Pecenka C, Sparrow E, Feikin DR, et al. Respiratory syncytial virus vaccination and immunoprophylaxis: realising the potential for protection of young children. *Lancet* 2024; published online Sept 9. https://doi.org/10.1016/S0140-6736(24)01699-4.
13 Cerone JB, Santos RP, Tristram D, et al. Incidence of respiratory viral infection in infants with respiratory symptoms evaluated for late-onset sepsis. *J Perinatol* 2017; **37:** 922–26.
14 Bonadio W, Huang F, Nateson S, et al. Meta-analysis to determine risk for serious bacterial infection in febrile outpatient neonates with RSV infection. *Pediatr Emerg Care* 2016; **32:** 286–89.
15 Kidszun A, Hansmann A, Winter J, et al. Detection of respiratory viral infections in neonates treated for suspicion of nosocomial bacterial sepsis: a feasibility study. *Pediatr Infect Dis J* 2014; **33:** 102–04.
16 Ralston S, Hill V. Incidence of apnea in infants hospitalized with respiratory syncytial virus bronchiolitis: a systematic review. *J Pediatr* 2009; **155:** 728–33.
17 Lee E, Kim CH, Lee YJ, et al. Annual and seasonal patterns in etiologies of pediatric community-acquired pneumonia due to respiratory viruses and *Mycoplasma pneumoniae* requiring hospitalization in South Korea. *BMC Infect Dis* 2020; **20:** 132.
18 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)**:** S63–70.
19 Osborne CM, Langelier C, Kamm J, et al. Viral detection by reverse transcriptase polymerase chain reaction in upper respiratory tract and metagenomic RNA sequencing in lower respiratory tract in critically ill children with suspected lower respiratory tract infection. *Pediatr Crit Care Med* 2024; **25:** e1–11.
20 Sheikh Z, Potter E, Li Y, et al. Validity of clinical severity scores for respiratory syncytial virus: a systematic review. *J Infect Dis* 2024; **229** (suppl 1)**:** S8–17.
21 Mazur NI, Martinón-Torres F, Baraldi E, et al. Lower respiratory tract infection caused by respiratory syncytial virus: current management and new therapeutics. *Lancet Respir Med* 2015; **3:** 888–900.
22 Cohen C, Kleynhans J, Moyes J, et al. Incidence and transmission of respiratory syncytial virus in urban and rural South Africa, 2017–18. *Nat Commun* 2024; **15:** 116.
23 Saha S, Pandey BG, Choudekar A, et al. Evaluation of case definitions for estimation of respiratory syncytial virus associated hospitalizations among children in a rural community of northern India. *J Glob Health* 2015; **5:** 010419.
24 Dvorkin J, De Luca J, Alvarez-Paggi D, Caballero MT. Responding to higher-than-expected infant mortality rates from respiratory syncytial virus (RSV): improving treatment and reporting strategies. *Infect Drug Resist* 2023; **16:** 595–605.
25 Hirve S, Crawford N, Palekar R, Zhang W. Clinical characteristics, predictors, and performance of case definition-interim results from the WHO global respiratory syncytial virus surveillance pilot. *Influenza Other Respir Viruses* 2020; **14:** 647–57.
26 RSV GOLD—ICU Network collaborators. Respiratory syncytial virus infection among children younger than 2 years admitted to a paediatric intensive care unit with extended severe acute respiratory infection in ten Gavi-eligible countries: the RSV GOLD—ICU Network study. *Lancet Glob Health* 2024; published online Aug 28. https://doi.org/10.1016/ S2214-109X(24)00269-9.
27 Our World in Data. Number of children under 5 years old. https://ourworldindata.org/grapher/under-5-population (accessed Sept 2, 2024).
28 Hall CB, Douglas RG Jr, Schnabel KC, Geiman JM. Infectivity of respiratory syncytial virus by various routes of inoculation. *Infect Immun* 1981; **33:** 779–83.
29 Munywoki PK, Koech DC, Agoti CN, et al. Frequent asymptomatic respiratory syncytial virus infections during an epidemic in a rural Kenyan household cohort. *J Infect Dis* 2015; **212:** 1711–18.
30 Colosia A, Costello J, McQuarrie K, Kato K, Bertzos K. Systematic literature review of the signs and symptoms of respiratory syncytial virus. *Influenza Other Respir Viruses* 2023; **17:** e13100.
31 Atwell JE, Geoghegan S, Karron RA, Polack FP. Clinical predictors of critical lower respiratory tract illness due to respiratory syncytial virus in infants and children: data to inform case definitions for efficacy trials. *J Infect Dis* 2016; **214:** 1712–16.
32 Friedman JN, Rieder MJ, Walton JM. Bronchiolitis: recommendations for diagnosis, monitoring and management of children 1 to 24 months of age. *Paediatr Child Health* 2014; **19:** 485–98.
33 Caffrey Osvald E, Clarke JR. NICE clinical guideline: bronchiolitis in children. *Arch Dis Child Educ Pract Ed* 2016; **101:** 46–48.
34 Ralston SL, Lieberthal AS, Meissner HC, et al. Clinical practice guideline: the diagnosis, management, and prevention of bronchiolitis. *Pediatrics* 2014; **134:** e1474–502.
35 Lalani K, Yildirim I, Phadke VK, Bednarczyk RA, Omer SB. Assessment and validation of syndromic case definitions for respiratory syncytial virus infections in young infants: a latent class analysis. *Pediatr Infect Dis J* 2019; **38:** 1177–82.
36 Pebody R, Moyes J, Hirve S, et al. Approaches to use the WHO respiratory syncytial virus surveillance platform to estimate disease burden. *Influenza Other Respir Viruses* 2020; **14:** 615–21.

37 Karron RA, Zar HJ. Determining the outcomes of interventions to prevent respiratory syncytial virus disease in children: what to measure? *Lancet Respir Med* 2018; **6:** 65–74.

38 Justicia-Grande AJ, Martinón-Torres F. The ReSVinet score for bronchiolitis: a scale for all seasons. *Am J Perinatol* 2019; **36:** S48–53.

39 Wang EEL, Milner RA, Navas L, Maj H. Observer agreement for respiratory signs and oximetry in infants hospitalized with lower respiratory infections. *Am Rev Respir Dis* 1992; **145:** 106–09.

40 Kubota J, Hirano D, Okabe S, et al. Utility of the Global Respiratory Severity Score for predicting the need for respiratory support in infants with respiratory syncytial virus infection. *PLoS One* 2021; **16:** e0253532.

41 De Rose DU, Maddaloni C, Martini L, Braguglia A, Dotta A, Auriti C. Comparison of three clinical scoring tools for bronchiolitis to predict the need for respiratory support and length of stay in neonates and infants up to three months of age. *Front Pediatr* 2023; **11:** 1040354.

42 Hakizimana B, Saint G, van Miert C, Cartledge P. Can a respiratory severity score accurately assess respiratory distress in children with bronchiolitis in a resource-limited setting? *J Trop Pediatr* 2020; **66:** 234–43.

43 McCallum GB, Morris PS, Wilson CC, et al. Severity scoring systems: are they internally valid, reliable and predictive of oxygen use in children with acute bronchiolitis? *Pediatr Pulmonol* 2013; **48:** 797–803.

44 Chong SL, Teoh OH, Nadkarni N, et al. The modified respiratory index score (RIS) guides resource allocation in acute bronchiolitis. *Pediatr Pulmonol* 2017; **52:** 954–61.

45 Chong SL, Lai OF, Castillo L, et al. Nasal high-mobility group box 1 and caspase in bronchiolitis. *Pediatr Pulmonol* 2018; **53:** 1627–32.

46 Balaguer M, Alejandre C, Vila D, et al. Bronchiolitis Score of Sant Joan de Déu: BROSJOD Score, validation and usefulness. *Pediatr Pulmonol* 2017; **52:** 533–39.

47 Walsh EE, Wang L, Falsey AR, et al. Virus-specific antibody, viral load, and disease severity in respiratory syncytial virus infection. *J Infect Dis* 2018; **218:** 208–17.

48 Siraj S, Stark W, McKinley SD, Morrison JM, Sochet AA. The bronchiolitis severity score: an assessment of face validity, construct validity, and interobserver reliability. *Pediatr Pulmonol* 2021; **56:** 1739–44.

49 Liu LL, Gallaher MM, Davis RL, Rutter CM, Lewis TC, Marcuse EK. Use of a respiratory clinical score among different providers. *Pediatr Pulmonol* 2004; **37:** 243–48.

50 Rivas-Juesas C, Rius Peris JM, García AL, et al. A comparison of two clinical scores for bronchiolitis—a multicentre and prospective study conducted in hospitalised infants. *Allergol Immunopathol (Madr)* 2018; **46:** 15–23.

51 Ramos Fernández JM, Cordón Martínez A, Galindo Zavala R, Urda Cardona A. Validación de una escala clínica de severidad de la bronquiolitis aguda. *An Pediatr (Barc)* 2014; **81:** 3–8.

52 Caballero MT, Bianchi AM, Nuño A, et al. Mortality associated with acute respiratory infections among children at home. *J Infect Dis* 2019; **219:** 358–64.

53 Caballero MT, Bianchi AM, Grigaites SD, et al. Community mortality due to respiratory syncytial virus in Argentina: population-based surveillance study. *Clin Infect Dis* 2021; **73** (suppl 3)**:** S210–17.

54 Koffi AK, Maina A, Yaroh AG, Habi O, Bensaïd K, Kalter HD. Social determinants of child mortality in Niger: results from the 2012 National Verbal and Social Autopsy Study. *J Glob Health* 2016; **6:** 010603.

55 Fitzpatrick MC, Laufer RS, Baral R, et al. Report of the WHO technical consultation on the evaluation of respiratory syncytial virus prevention cost effectiveness in low- and middle-income countries, April 7–8, 2022. *Vaccine* 2023; **41:** 7047–59.

56 Mahtab S, Blau DM, Madewell ZJ, et al. Post-mortem investigation of deaths due to pneumonia in children aged 1–59 months in sub-Saharan Africa and South Asia from 2016 to 2022: an observational study. *Lancet Child Adolesc Health* 2024; **8:** 201–13.

57 Wildenbeest JG, Billard MN, Zuurbier RP, et al. The burden of respiratory syncytial virus in healthy term-born infants in Europe: a prospective birth cohort study. *Lancet Respir Med* 2023; **11:** 341–53.

58 Hak SF, Venekamp RP, Billard MN, et al. Substantial burden of nonmedically attended RSV infection in healthy-term infants: an international prospective birth cohort study. *J Infect Dis* 2024; **229** (suppl 1)**:** S40–50.

59 Hartmann K, Liese JG, Kemmling D, et al. Clinical burden of respiratory syncytial virus in hospitalized children aged ≤5 years (INSPIRE Study). *J Infect Dis* 2022; **226:** 386–95.

60 Thwaites R, Buchan S, Fullarton J, et al. Clinical burden of severe respiratory syncytial virus infection during the first 2 years of life in children born between 2000 and 2011 in Scotland. *Eur J Pediatr* 2020; **179:** 791–99.

61 Wang X, Li Y, Shi T, et al. Global disease burden of and risk factors for acute lower respiratory infections caused by respiratory syncytial virus in preterm infants and young children in 2019: a systematic review and meta-analysis of aggregated and individual participant data. *Lancet* 2024; **403:** 1241–53.

62 Chow EJ, Uyeki TM, Chu HY. The effects of the COVID-19 pandemic on community respiratory virus activity. *Nat Rev Microbiol* 2022; **21:** 195–210.

63 Cong B, Koç U, Bandeira T, et al. Changes in the global hospitalisation burden of respiratory syncytial virus in young children during the COVID-19 pandemic: a systematic analysis. *Lancet Infect Dis* 2024; **24:** 361–74.

64 Izu A, Nunes MC, Solomon F, et al. All-cause and pathogen-specific lower respiratory tract infection hospital admissions in children younger than 5 years during the COVID-19 pandemic (2020–22) compared with the pre-pandemic period (2015–19) in South Africa: an observational study. *Lancet Infect Dis* 2023; **23:** 1031–41.

65 Bardsley M, Morbey RA, Hughes HE, et al. Epidemiology of respiratory syncytial virus in children younger than 5 years in England during the COVID-19 pandemic, measured by laboratory, clinical, and syndromic surveillance: a retrospective observational study. *Lancet Infect Dis* 2023; **23:** 56–66.

66 Verwey C, Dangor Z, Madhi SA. Approaches to the prevention and treatment of respiratory syncytial virus infection in children: rationale and progress to date. *Paediatr Drugs* 2024; **26:** 101–12.

67 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:** 4037–51.

68 Gadomski AM, Scribani MB. Bronchodilators for bronchiolitis. *Cochrane Database Syst Rev* 2014; **2014:** CD001266.

69 Farley R, Spurling GK, Eriksson L, Del Mar CB. Antibiotics for bronchiolitis in children under two years of age. *Cochrane Database Syst Rev* 2014; **2014:** CD005189.

70 Fernandes RM, Bialy LM, Vandermeer B, et al. Glucocorticoids for acute viral bronchiolitis in infants and young children. *Cochrane Database Syst Rev* 2013; **2013:** CD004878.

71 Zhang L, Mendoza-Sassi RA, Wainwright CE, Aregbesola A, Klassen TP. Nebulised hypertonic saline solution for acute bronchiolitis in infants. *Cochrane Database Syst Rev* 2023; **4:** CD006458.

72 Hartling L, Bialy LM, Vandermeer B, et al. Epinephrine for bronchiolitis. *Cochrane Database Syst Rev* 2011; **6:** CD003123.

73 Liu F, Ouyang J, Sharma AN, et al. Leukotriene inhibitors for bronchiolitis in infants and young children. *Cochrane Database Syst Rev* 2015; **2015:** CD010636.

74 Roqué-Figuls M, Giné-Garriga M, Granados Rugeles C, Perrotta C, Vilaró J. Chest physiotherapy for acute bronchiolitis in paediatric patients between 0 and 24 months old. *Cochrane Database Syst Rev* 2023; **4:** CD004873.

75 Sanders SL, Agwan S, Hassan M, Bont LJ, Venekamp RP. Immunoglobulin treatment for hospitalised infants and young children with respiratory syncytial virus infection. *Cochrane Database Syst Rev* 2023; **10:** CD009417.

76 van Houten CB, Naaktgeboren C, Buiteman BJM, et al. Antibiotic overuse in children with respiratory syncytial virus lower respiratory tract infection. *Pediatr Infect Dis J* 2018; **37:** 1077–81.

77 Obolski U, Kassem E, Na'amnih W, Tannous S, Kagan V, Muhsen K. Unnecessary antibiotic treatment of children hospitalised with respiratory syncytial virus (RSV) bronchiolitis: risk factors and prescription patterns. *J Glob Antimicrob Resist* 2021; **27:** 303–08.

78 Gill PJ, Anwar MR, Kornelsen E, Parkin P, Mahood Q, Mahant S. Parenteral versus enteral fluid therapy for children hospitalised with bronchiolitis. *Cochrane Database Syst Rev* 2021; **12:** CD013552.

79 Andersson Marforio S, Hansen C, Ekvall Hansson E, Lundkvist Josenby A. Frequent body position changes and physical activity as effective as standard care for infants hospitalised with acute respiratory infections—a randomised controlled trial. *Multidiscip Respir Med* 2023; **18:** 885.

80 Wrotek A, Wrotek O, Jackowska T. The estimate of parental quality of life loss due to respiratory syncytial virus (RSV) hospitalization. *Diseases* 2023; **11:** 126.

81 van Benthum MV, van Dijk T, Maas-van Schaaijk NM, van Zwol A. Psychological problems in parents of children with bronchiolitis following paediatric intensive care unit (PICU) admission. *Acta Paediatr* 2022; **111:** 1054–55.

82 Glaser EL, Hariharan D, Bowser DM, et al. Impact of respiratory syncytial virus on child, caregiver, and family quality of life in the United States: systematic literature review and analysis. *J Infect Dis* 2022; **226** (suppl 2)**:** S236–45.

83 Cunningham S, Rodriguez A, Adams T, et al. Oxygen saturation targets in infants with bronchiolitis (BIDS): a double-blind, randomised, equivalence trial. *Lancet* 2015; **386:** 1041–48.

84 Im JHB, Wahi G, Giglia L, et al. Oxygen saturation targets in infants hospitalized with bronchiolitis: a multicenter cohort study. *Hosp Pediatr* 2024; **14:** 67–74.

85 Louman S, van Stralen KJ, Pijnenburg MWH, Koppelman GH, Boehmer ALM. Oxygen saturation targets for children with respiratory distress: a systematic review. *ERJ Open Res* 2023; **9:** 00256–02023.

86 Armarego M, Forde H, Wills K, Beggs SA. High-flow nasal cannula therapy for infants with bronchiolitis. *Cochrane Database Syst Rev* 2024; **3:** CD009609.

87 Kepreotes E, Whitehead B, Attia J, et al. High-flow warm humidified oxygen versus standard low-flow nasal cannula oxygen for moderate bronchiolitis (HFWHO RCT): an open, phase 4, randomised controlled trial. *Lancet* 2017; **389:** 930–39.

88 Franklin D, Babl FE, Schlapbach LJ, et al. A randomized trial of high-flow oxygen therapy in infants with bronchiolitis. *N Engl J Med* 2018; **378:** 1121–31.

89 Meskill SD, Moore RH. High-flow oxygen therapy in infants with bronchiolitis. *N Engl J Med* 2018; **378:** 2444–47.

90 Abboud P, Roth P, Yacoub N, Stolfi A. 702: efficacy of high flow/ high humidity nasal cannula therapy in viral bronchiolitis. *Crit Care Med* 2015; **43:** 177.

91 Durand P, Guiddir T, Kyheng C, et al. A randomised trial of high-flow nasal cannula in infants with moderate bronchiolitis. *Eur Respir J* 2020; **56:** 1901926.

92 Milési C, Essouri S, Pouyau R, et al. High flow nasal cannula (HFNC) versus nasal continuous positive airway pressure (nCPAP) for the initial respiratory management of acute viral bronchiolitis in young infants: a multicenter randomized controlled trial (TRAMONTANE study). *Intensive Care Med* 2017; **43:** 209–16.

93 Eşki A, Öztürk GK, Turan C, Özgül S, Gülen F, Demir E. High-flow nasal cannula oxygen in children with bronchiolitis: a randomized controlled trial. *Pediatr Pulmonol* 2022; **57:** 1527–34.

94 Milani GP, Plebani AM, Arturi E, et al. Using a high-flow nasal cannula provided superior results to low-flow oxygen delivery in moderate to severe bronchiolitis. *Acta Paediatr* 2016; **105:** e368–72.

95 Murphy S, Bruckmann E, Doedens LG, Khan AB, Salloo A, Omar S. High-flow oxygen therapy vs standard care in infants with viral bronchiolitis. *South Afr J Crit Care* 2020; **36:** 110.

96 Türe E, Yazar A, Akin F, Pekcan S. High-flow nasal cannula is superior to standard face-mask oxygen therapy in viral bronchiolitis. *Signa Vitae* 2020; **16:** 47–53.

97 Borgi A, Louati A, Ghali N, et al. High flow nasal cannula therapy versus continuous positive airway pressure and nasal positive pressure ventilation in infants with severe bronchiolitis: a randomized controlled trial. *Pan Afr Med J* 2021; **40:** 133.

98 Cesar RG, Bispo BRP, Felix PHCA, et al. High-flow nasal cannula versus continuous positive airway pressure in critical bronchiolitis: a randomized controlled pilot. *J Pediatr Intensive Care* 2020; **9:** 248–55.

99 Sarkar M, Sinha R, Roychowdhoury S, et al. Comparative study between noninvasive continuous positive airway pressure and hot humidified high-flow nasal cannulae as a mode of respiratory support in infants with acute bronchiolitis in pediatric intensive care unit of a tertiary care hospital. *Indian J Crit Care Med* 2018; **22:** 85–90.

100 Kooiman L, Blankespoor F, Hofman R, et al. High-flow oxygen therapy in moderate to severe bronchiolitis: a randomised controlled trial. *Arch Dis Child* 2023; **108:** 455–60.

101 Schlapbach LJ, Straney L, Gelbart B, et al. Burden of disease and change in practice in critically ill infants with bronchiolitis. *Eur Respir J* 2017; **49:** 1601648.

102 Franklin D, Babl FE, Schlapbach LJ, et al. A randomized trial of high-flow oxygen therapy in nfants with bronchiolitis. *N Engl J Med* 2018; 378: 1121–31.

103 Bem RA, Bont LJ, van Woensel JBM. Life-threatening bronchiolitis in children: eight decades of critical care. *Lancet Respir Med* 2020; **8:** 142–44.

104 Jat KR, Dsouza JM, Mathew JL. Continuous positive airway pressure (CPAP) for acute bronchiolitis in children. *Cochrane Database Syst Rev* 2022; **4:** CD010473.

105 Cunningham S, Piedra PA, Martinon-Torres F, et al. Nebulised ALX-0171 for respiratory syncytial virus lower respiratory tract infection in hospitalised children: a double-blind, randomised, placebo-controlled, phase 2b trial. *Lancet Respir Med* 2021; **9:** 21–32.

106 Enanta Pharmaceuticals. Enanta Pharmaceuticals reports topline data from the RSVP study of EDP-938 in otherwise healthy adults with community-acquired respiratory syncytial virus (RSV). May 18, 2022. https://ir.enanta.com/news-releases/news-release-details/enanta-pharmaceuticals-reports-topline-data-rsvp-study-edp-938 (accessed May 13, 2024).

107 ArkBio. Ark Biopharmaceutical presents positive results in phase 3 AIRFLO study of ziresovir in RSV-infected hospitalized infants at 12th International RSV Symposium. Oct 7, 2022. https:// arkbiosciences.com/en_2022n/112 (accessed May 14, 2024).

108 DeVincenzo JP, Aitken JB, Harrison LG. Opportunities for early therapy of respiratory syncytial virus (RSV) infection: what happens before hospitalization. *Antiviral Res* 2004; **62:** 47–51.

109 Leung NHL. Transmissibility and transmission of respiratory viruses. *Nat Rev Microbiol* 2021; **19:** 528–45.

110 Remien KA, Amarin JZ, Horvat CM, et al. Admissions for bronchiolitis at children's hospitals before and during the COVID-19 pandemic. *JAMA Netw Open* 2023; **6:** e2339884.

111 Müller O, Razum O, Jahn A. Effects of non-pharmaceutical interventions against COVID-19 on the incidence of other diseases. *Lancet Reg Health Eur* 2021; **6:** 100139.

112 Eden J-S, Sikazwe C, Xie R, et al. Off-season RSV epidemics in Australia after easing of COVID-19 restrictions. *Nat Commun* 2022; **13:** 2884.

113 Ibfelt T, Engelund EH, Schultz AC, Andersen LP. Effect of cleaning and disinfection of toys on infectious diseases and micro-organisms in daycare nurseries. *J Hosp Infect* 2015; **89:** 109–15.

114 Che Y, Gribenko AV, Song X, et al. Rational design of a highly immunogenic prefusion-stabilized F glycoprotein antigen for a respiratory syncytial virus vaccine. *Sci Transl Med* 2023; **15:** eade6422.

115 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:** e2–21.

116 Hammitt LL, Dagan R, Yuan Y, et al. Nirsevimab for prevention of RSV in healthy late-preterm and term infants. *N Engl J Med* 2022; **386:** 837–46.

117 López-Lacort M, Muñoz-Quiles C, Mira-Iglesias A, et al. Early estimates of nirsevimab immunoprophylaxis effectiveness against hospital admission for respiratory syncytial virus lower respiratory tract infections in infants, Spain, October 2023 to January 2024. *Euro Surveill* 2024; **29:** 2400046.

118 Ares-Gómez S, Mallah N, Santiago-Pérez M-I, et al. Effectiveness and impact of universal prophylaxis with nirsevimab in infants against hospitalisation for respiratory syncytial virus in Galicia, Spain: initial results of a population-based longitudinal study. *Lancet Infect Dis* 2024; **24:** 817–28.

119 Sanofi. Sanofi Beyfortus (nirsevimab-alip) Statement. Oct 26, 2023. https://www.news.sanofi.us/Sanofi-Beyfortus-Statement (accessed May 13, 2024).

120 Madhi SA, Simões EAF, Acevedo A, et al. A phase 1b/2a single ascending dose study to evaluate the safety, tolerability, and pharmacokinetics of an RSV-neutralizing sntibody, clesrovimab, in preterm and full-term infants. 8th ReSViNET Conference (RSVVW 2024); Feb 13–16, 2024.

121 Zar HJ, Piccolis M, Terstappen J, et al. Access to highly effective long-acting RSV-monoclonal antibodies for children in LMICs—reducing global inequity. *Lancet Glob Health* 2024; published online July 24. https://doi.org/10.1016/s2214-109x(24)00258-4.

122 Levi M, Watson S, Anderson AB, et al. 383 pharmacokinetics and safety in healthy adults of RSM01, a novel RSV monoclonal antibody, and population PK modeling to support pediatric development. *Open Forum Infect Dis* 2023; **10** (suppl 2)**:** ofad500.453.

123 Munjal, I, Pahus BA, Simões, EAF, et al. Prevention of infant RSV illness with a bivalent RSV prefusion F vaccine administered during pregnancy: efficacy results from a phase 3 global clinical trial. 8th ReSViNET Conference (RSVVW 2024); Feb 13–16, 2024.

124 Madhi SA, Polack FP, Piedra PA, et al. Respiratory syncytial virus vaccination during pregnancy and effects in infants. *N Engl J Med* 2020; **383:** 426–39.

125 Dieussaert I, Hyung Kim J, Luik S, et al. RSV prefusion F protein-based maternal vaccine—preterm birth and other outcomes. *N Engl J Med* 2024; **390:** 1009–21.

126 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:** 2233–44.

127 Shaw CA, Essink B, Harper C, et al. Safety and immunogenicity of an mRNA-based RSV vaccine including a 12-month booster in a phase 1 clinical trial in healthy older adults. *J Infect Dis* 2024; published online Feb 22. https://doi.org/10.1093/infdis/jiae081.

128 Shaw CA, Mithani R, Kapoor A, et al. Safety, tolerability, and immunogenicity of an mRNA-based respiratory syncytial virus vaccine in healthy young adults in a phase 1 clinical trial. *J Infect Dis* 2024; published online Jan 31. https://doi.org/10.1093/infdis/jiae035.

129 Wilson E, Goswami D, Doreski PA, et al. Efficacy and safety of mRNA-1345, an RSV vaccine, in older adults: results through > 6 months of follow-up. 8th ReSViNET Conference (RSVVW 2024); Feb 13–16, 2024.

130 Vizzotti C. Resolution 4218/2023. Dec 18, 2023. https://www.boletinoficial.gob.ar/detalleAviso/primera/300984/20231218 (accessed March 30, 2024).

131 Shi T, Vennard S, Mahdy S, et al. Risk factors for poor outcome or death in young children with respiratory syncytial virus-associated acute lower respiratory tract infection: a systematic review and meta-analysis. *J Infect Dis* 2022; **226** (suppl 1)**:** S10–16.

132 Cong B, Dighero I, Zhang T, Chung A, Nair H, Li Y. Understanding the age spectrum of respiratory syncytial virus associated hospitalisation and mortality burden based on statistical modelling methods: a systematic analysis. *BMC Med* 2023; **21:** 224.

133 Martinón-Torres F, Mirás-Carballal S, Durán-Parrondo C. Early lessons from the implementation of universal respiratory syncytial virus prophylaxis in infants with long-acting monoclonal antibodies, Galicia, Spain, September and October 2023. *Euro Surveill* 2023; **28:** 2300606.

134 Shi T, Balsells E, Wastnedge E, et al. Risk factors for respiratory syncytial virus associated with acute lower respiratory infection in children under five years: systematic review and meta-analysis. *J Glob Health* 2015; **5:** 020416.

135 Horvat C, Chauvel C, Casalegno JS, Benchaib M, Ploin D, Nunes MC. RSV severe infection risk stratification in a French 5-year birth cohort using machine-learning. *Pediatr Infect Dis J* 2024; published online May 7. https://doi.org/10.1097/INF.0000000000004375.

136 Trusinska D, Zin ST, Sandoval E, Homaira N, Shi T. Risk factors for poor outcomes in children hospitalized with virus-associated acute lower respiratory infections: a systematic review and meta-analysis. *Pediatr Infect Dis J* 2024; **43:** 467–76.

137 Thorburn K. Pre-existing disease is associated with a significantly higher risk of death in severe respiratory syncytial virus infection. *Arch Dis Child* 2009; **94:** 99–103.

138 Johnson M, Chelysheva I, Öner D, et al. A genome-wide association study of respiratory syncytial virus infection severity in infants. *J Infect Dis* 2024; **229** (suppl 1)**:** S112–19.

139 Egeskov-Cavling AM, van Wijhe M, Yakimov V, et al. Genome-wide association study of susceptibility to respiratory syncytial virus hospitalization in young children <5 years of age. *J Infect Dis* 2023; published online Sept 4. https://doi.org/10.1093/infdis/jiad370.

140 Zivanovic N, Öner D, Abraham Y, et al. Single-cell immune profiling reveals markers of emergency myelopoiesis that distinguish severe from mild respiratory syncytial virus disease in infants. *Clin Transl Med* 2023; **13:** e1507.

141 Flerlage T, Crawford JC, Allen EK, et al. Single cell transcriptomics identifies distinct profiles in pediatric acute respiratory distress syndrome. *Nat Commun* 2023; **14:** 3870.

142 Koch CM, Prigge AD, Setar L, et al. Cilia-related gene signature in the nasal mucosa correlates with disease severity and outcomes in critical respiratory syncytial virus bronchiolitis. *Front Immunol* 2022; **13:** 924792.

143 Taveras J, Garcia-Maurino C, Moore-Clingenpeel M, et al. Type 3 interferons, viral loads, age, and disease severity in young children with respiratory syncytial virus infection. *J Infect Dis* 2022; **227:** 61–70.

144 Kyo M, Zhu Z, Shibata R, et al. Respiratory virus-specific nasopharyngeal lipidome signatures and severity in infants with bronchiolitis: a prospective multicenter study. *J Infect Dis* 2023; **228:** 1410–20.

145 Lin G-L, Drysdale SB, Snape MD, et al. Targeted metagenomics reveals association between severity and pathogen co-detection in infants with respiratory syncytial virus. *Nat Commun* 2024; **15:** 2379.

146 Carroll KN, Wu P, Gebretsadik T, et al. Season of infant bronchiolitis and estimates of subsequent risk and burden of early childhood asthma. *J Allergy Clin Immunol* 2009; **123:** 964–66.

147 Li Y, Hodgson D, Wang X, Atkins KE, Feikin DR, Nair H. Respiratory syncytial virus seasonality and prevention strategy planning for passive immunisation of infants in low-income and middle-income countries: a modelling study. *Lancet Infect Dis* 2021; **21:** 1303–12.

148 Deng S, Cong B, Edgoose M, De Wit F, Nair H, Li Y. Risk factors for respiratory syncytial virus-associated acute lower respiratory infection in children under 5 years: an updated systematic review and meta-analysis. *Int J Infect Dis* 2024; **146:** 107125.

149 Mazur NI, Löwensteyn YN, Willemsen JE, et al. Global respiratory syncytial virus-related infant community deaths. *Clin Infect Dis* 2021; **73** (suppl 3)**:** S229–37.

150 Gill CJ, Mwananyanda L, MacLeod WB, et al. Infant deaths from respiratory syncytial virus in Lusaka, Zambia from the ZPRIME study: a 3-year, systematic, post-mortem surveillance project. *Lancet Glob Health* 2022; **10:** e269–77.

151 Geoghegan S, Erviti A, Caballero MT, et al. Mortality due to respiratory syncytial virus—burden and risk factors. *Am J Respir Crit Care Med* 2017; **195:** 96–103.

152 Murphy C, MacLeod WB, Forman LS, et al. Risk factors for respiratory syncytial virus-associated community deaths in Zambian infants. *Clin Infect Dis* 2021; **73** (suppl 3)**:** S187–92.

153 Caballero MT, Jones MH, Karron RA, et al. The impact of respiratory syncytial virus disease prevention on pediatric asthma. *Pediatr Infect Dis J* 2016; **35:** 820–22.

154 Rosas-Salazar C, Chirkova T, Gebretsadik T, et al. Respiratory syncytial virus infection during infancy and asthma during childhood in the USA (INSPIRE): a population-based, prospective birth cohort study. *Lancet* 2023; **401:** 1669–80.

155 Zar HJ, Nduru P, Stadler JAM, et al. Early-life respiratory syncytial virus lower respiratory tract infection in a South African birth cohort: epidemiology and effect on lung health. *Lancet Glob Health* 2020; **8:** e1316–25.

156 McGinley JP, Lin GL, Öner D, et al. Clinical and viral factors associated with disease severity and subsequent wheezing in infants with respiratory syncytial virus infection. *J Infect Dis* 2022; **226** (suppl 1)**:** S45–54.

157 Blanken MO, Rovers MM, Molenaar JM, et al. Respiratory syncytial virus and recurrent wheeze in healthy preterm infants. *N Engl J Med* 2013; **368:** 1791–99.

158 Scheltema NM, Nibbelke EE, Pouw J, et al. Respiratory syncytial virus prevention and asthma in healthy preterm infants: a randomised controlled trial. *Lancet Respir Med* 2018; **6:** 257–64.

159 Feikin DR, Scott JAG, Gessner BD. Use of vaccines as probes to define disease burden. *Lancet* 2014; **383:** 1762–70.