Lower respiratory tract infection caused by respiratory syncytial virus: current management and new therapeutics

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Respiratory syncytial virus (RSV) is a major worldwide cause of morbidity and mortality in children under five years of age. Evidence-based management guidelines suggest that there is no effective treatment for RSV lower respiratory tract infection (LRTI) and that supportive care, ie, hydration and oxygenation, remains the cornerstone of clinical management. However, RSV treatments in development in the past decade include 10 vaccines and 11 therapeutic agents in active clinical trials. Maternal vaccination is particularly relevant because the most severe disease occurs within the first 6 months of life, when children are unlikely to benefit from active immunisation. We must optimise the implementation of novel RSV therapeutics by understanding the target populations, showing safety, and striving for acceptable pricing in the context of this worldwide health problem. In this Review, we outline the limitations of RSV LRTI management, the drugs in development, and the remaining challenges related to study design, regulatory approval, and implementation.

Introduction

Respiratory syncytial virus (RSV) bronchiolitis contributes greatly to mortality in children under 5 years of age,[1] and has implications for long-term respiratory health.[2] Nearly all children in the world will be infected with RSV by 2 years of age.[3]

Several evidence-based guidelines for the management of bronchiolitis exist, with differing recommendations, but all agree on supportive management in the inpatient setting. A guideline published by the American Academy of Pediatrics[4] reported insufficient evidence for any intervention except respiratory support and hydration. In view of the paucity of therapeutic alternatives, it is essential to understand the existing challenges to the development of prevention and treatment options for RSV.

Key messages

- RSV LRTI is a worldwide health problem; it is a major cause of morbidity and mortality in children under 5 years old and has a high socioeconomic burden, yet the mortality burden is still poorly understood
- A rigorous analysis confirms that there are no effective evidence-based therapeutic or preventive interventions for RSV, and supportive care (hydration and oxygenation) remain the cornerstone of clinical management
- The past decade has been characterised by new therapeutics in clinical development including 10 vaccines and 11 antivirals
- We are now challenged to optimise these new therapeutics, with remaining challenges to development and implementation, including the need for regulatory guidance on drug testing, establishment of clinically relevant outcomes for vaccine and therapeutic efficacy, establishment of target populations and subpopulations, acceptable pricing, and logistic barriers to distribution in regions where mortality is highest

Burden of disease

In the USA, RSV is the leading cause of hospital admission in children under 1 year of age, causes about 150 000 hospital admissions per year in children under 2 years of age, and accounts for 18% of all emergency department visits in children under 5 years of age.[5–7] Beyond the substantial disease burden during acute infection, evidence suggests that RSV bronchiolitis plays a causal part in the development of recurrent wheeze, and is associated with the development of asthma and subsequent respiratory morbidity.[5,8–10] Evidence supports a transient association of RSV lower respiratory tract infection (LRTI) and recurrent wheeze, which subsides after the school years,[11,12] and a more permanent effect on long-term respiratory health and asthma in the adult years.[10] If the consequences of RSV LRTI are more permanent and extend to adult asthma, then RSV vaccination will have repercussions into adulthood, which underscores the importance of developing preventive and therapeutic strategies, such as vaccination, beyond prevention or treatment of acute infection.

The pathogenesis of long-term RSV morbidity is incompletely understood. Evidence supports the role of both a genetic and physiological predisposition for severe disease and recurrent wheeze, and a role for RSV in respiratory epithelium damage with subsequent development of recurrent wheeze.[2,13,14] Biological mechanisms that might explain the association between RSV infection and the development of asthma include persistent airway hyper-responsiveness after RSV infection, impaired T-regulatory function, persistent activation of the innate immune response, T-helper-2 activation leading to airway remodelling, and increased susceptibility to allergen sensitisation because of reduced airway epithelial barrier function.[15] Differential persistence of RSV recurrent wheeze might be explained by the severity of the initial episode, with these long-term sequelae occurring more frequently in

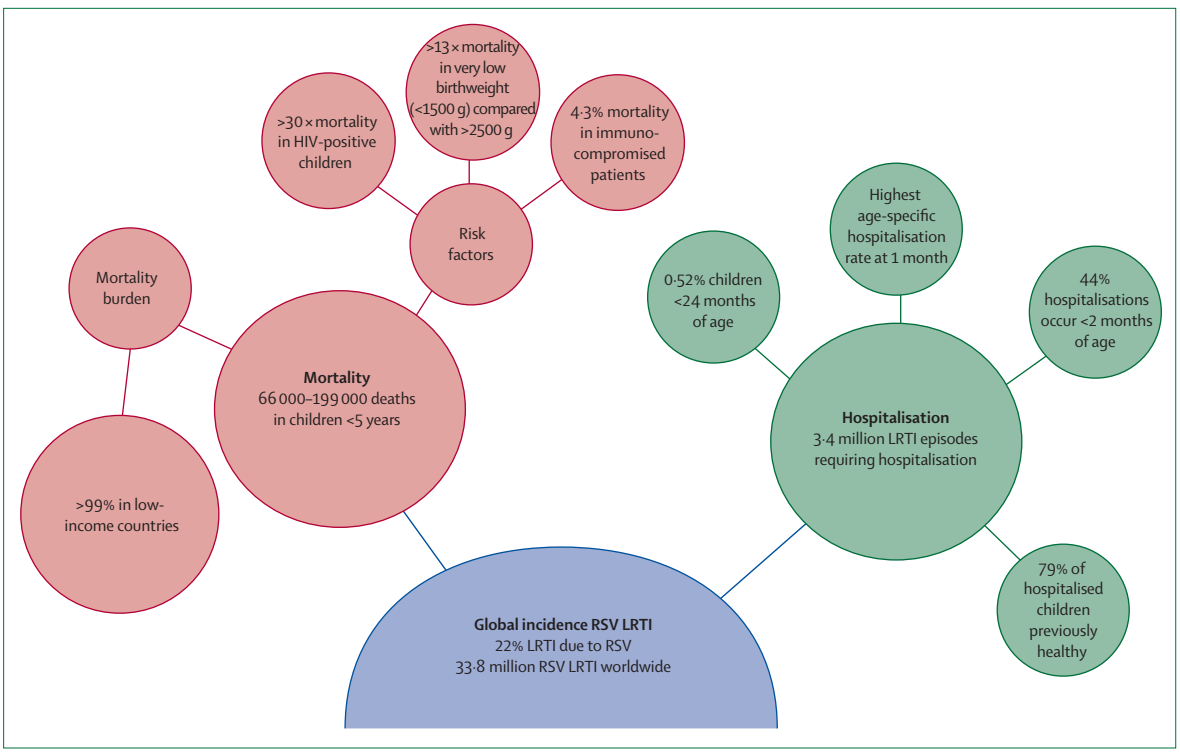

Figure 1: **RSV burden of disease: key facts and figures**
LRTI= lower respiratory tract infection. RSV=respiratory syncytial virus.[18-22]

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children admitted to hospital than in children treated as outpatients with RSV infection.[16] These respiratory sequelae result in a disproportionate health-care and financial burden for children under 5 years of age.[17]

More than 99% of deaths associated with RSV occur in low-income countries.[18] In all low-income countries, LRTI is the leading cause of death, and RSV is one of the most common pathogens causing LRTI.[1] Two estimates of mortality from RSV have been reported using different modelling approaches.[1,18] A systematic review of epidemiology data reported the estimated incidence of RSV-associated LRTI of 33·8 million cases in children under 5 years old worldwide in 2005, of which 3·4 million (10%) were admitted to hospital and an estimated 66 000–199 000 died (figure 1). This estimate assumed that RSV causes negligible mortality in children older than 2 years of age. The lower bound estimate was generated using pooled case fatality ratios from hospital-based data, which probably underestimate true mortality rates. The upper bound was estimated under the assumption that all excess LRTI mortality during the RSV season was RSV-associated, after extrapolation from a single study.[18] The second mortality estimate was derived from the Institute for Health Metrics and Evaluation global all-cause of death analysis compiling mortality data from 1990 to 2013, in which RSV pneumonia was reported to cause an estimated 41 100 deaths in children under 5 years of age in 2013 (95% CI 23 000–65 500).[1] High-risk groups include premature infants, HIV-infected children, children with other immunocompromised status, and infants with very low birthweight.[19–21] Although risk factors for severe disease have been identified, most children admitted to hospital with RSV LRTI were previously healthy (figure 1).[22] Obstacles limiting the ability to compile an accurate worldwide estimate of disease burden of RSV LRTI include absence of a universal definition, quality of monitoring methods, paucity of monitoring outside the hospital setting, and scarcity of diagnostic confirmation of RSV infection.

Clinical management: less is more

Bronchiolitis is a variable but usually self-limiting disease, and it is estimated to resolve in 90% of children about 21 days after symptom onset.[23,24] However in the case of severe disease (defined by respiratory distress or dehydration) children need to be managed with intravenous fluids and supplemental oxygen as inpatients.

The American Academy of Pediatrics (AAP) bronchiolitis guideline[4] restricts the use of therapeutic interventions that are not evidence based. Moreover, the Cochrane reviews[25–27] support the absence of efficacy of systemic corticosteroids and bronchodilators as suggested by the guidelines.[4] Tables 1 and 2 outline differences between the AAP and three additional

	Recommended	Not recommended
American Academy of Pediatrics, 2014[4]	Supplemental oxygen optional if SpO_2 is greater than 90%, nebulised hypertonic saline optional for hospitalised children with expected length of stay longer than 72 h, nasogastric or intravenous fluids if oral hydration cannot be maintained	Albuterol, epinephrine, nebulised hypertonic saline in emergency department, systemic corticosteroids, antibacterial medicine (unless concomitant bacterial infection), chest physiotherapy, continuous pulse oximetry
Royal Australian College of General Practitioners, 2008[28]	Supplemental oxygen, saline nasal drops, nasal suctioning, comfortable positioning (prone or supine if unable to position self), continuous pulse oximetry monitoring if in prone position, oral feeding can continue unless respiratory distress increases, trial of β_2 agonist bronchodilators for children older than 9 months (discontinue if no response), antibiotics if clinical signs or symptoms of bacterial infection, paracetamol or ibuprofen can be used if pyrexia is present	Chest physiotherapy, routine mist, routine steam, routine nebulised saline, routine nebulised adrenaline, routine β_2 agonist bronchodilators, routine ipratropium bromide, routine antibiotics, routine corticosteroids, routine ribavirin, routine immunoglobulin, routine oral antitussives, oral expectorants or oral decongestants
Scottish Intercollegiate Guidelines Network, 2006[29]	Supplemental oxygen if SpO_2 is less than 92% or if severe respiratory distress or cyanosis, nasogastric feeding if child cannot maintain hydration or oral intake, nasal suction for hospitalised infants showing respiratory distress, pulse oximetry 8 to 12 h after supplementary oxygen is discontinued	Nebulised ribavirin, antibiotic therapy, inhaled β_2 agonist bronchodilators, nebulised ipratropium or epinephrine, inhaled or oral corticosteroids, chest physiotherapy
NICE, 2015[30]	Supplemental oxygen if SpO_2 is less than 92%, continuous positive airway pressure if impending respiratory failure, upper airway suctioning in children who have respiratory distress or feeding difficulties because of upper airway secretions or children who present with apnoea, fluids by nasogastric or orogastric tube if children cannot take fluid orally, intravenous isotonic fluids to children who do not tolerate nasogastric or orogastric fluids or have impending respiratory failure, consider capillary blood case testing in children with severe worsening respiratory distress or impending respiratory failure	Chest physiotherapy for children who do not have relevant comorbidities, antibiotics, hypertonic saline, nebulised adrenaline, salbutamol, montelukast, ipratropium bromide, systemic or inhaled corticosteroids and nebulised adrenaline, routine upper airway suctioning, routine blood gas testing

Peripheral capillary oxygen saturation=SpO_2. Guidelines included are either accepted on a national level (not hospital based) and apply a clearly defined evidence-based framework to recommendations

Table 1: **Treatment recommendations based on current evidence-based global management guidelines**

evidence-based guidelines[4,28–30] for the management of bronchiolitis; the main differences between the new and old AAP guidelines are summarised in the panel.[4,35] Oxygen supplementation is recommended when pulse oximetry shows peripheral capillary oxygen saturation (SpO_2) less than 90%.[35] When oxygen supplementation is not sufficient, invasive or non-invasive ventilatory support might be necessary. High-flow nasal cannula (HFNC) for oxygen delivery generates a positive airway pressure in bronchiolitis and is emerging as a potentially interesting delivery method. Respiratory support using HFNC is a promising strategy, because it seems safe for children that are managed in a general paediatric ward and might decrease the need for intubation or paediatric intensive care unit admission.[4,36,37] However, there are no randomised controlled trials for HFNC, so this method still lacks sufficient evidence for recommendation. There are various theoretical risks of using HFNC for babies with RSV LRTI, including the risk of delaying intubation and increased mortality because of HFNC failure.[38,39] The AAP guideline pre-dates evidence from a randomised controlled trial[39] that challenges the role of oximetry as an identifying criterion for bronchiolitis admissions. Pulse oximetry readings were artificially elevated, displaying 3% higher than true SpO_2—as recorded by pulse oximetry with non-artificially elevated levels. Artificial elevation resulted in a 16% decrease in the probability of hospital admission in two groups with similar outcomes, controlled for disease severity.[40] Although lower oxygen saturation thresholds seem safe, clinicians should not value oxygen saturation too highly as a single marker of disease severity and need for admission to hospital.

The European Respiratory Society 2004 Task Force assessed therapeutics often used to treat acute viral bronchiolitis using the Grades, Assessment and Evaluation method[41] and reported that nebulised hypertonic saline might be useful, but no other interventions are useful and should therefore not be used.[42] The AAP guidelines do not recommend giving nebulised hypertonic saline to infants in the emergency department and only weakly recommend its use in patients admitted to hospital with an average length of stay greater than 3 days. Evidence has been compiled from a meta-analysis of 11 trials[43] and data from four more recent trials[31–34] that compare various concentrations of nebulised hypertonic saline with normal saline. A reduction in length of hospital stay of 1·2 days was reported in the meta-analysis,[43] but has been contradicted by results of trials that reported no relevant reduction in length of hospital stay.[31–34] There is evidence that adverse effects after treatment with hypertonic saline are similar with or without concomitant bronchodilator use, but with the possibility of bronchospasm with hypertonic saline, the addition of a bronchodilator might ensure treatment

	2014 American Academy of Pediatrics[4]	2008 Royal Australian College of General Practitioners[28]	2006 Scottish Intercollegiate Guidelines Network[29]	NICE Guideline 2015[30]
Inhaled bronchodilators	Level B: albuterol (salbutamol) should not be given	Level A: β_2 agonists not recommended Level D: trial β_2 agonists if older than 9 months, discontinue if no response Level A: ipratropium bromide not recommended	Level B: β_2 agonists not recommended Level X: nebulised ipratropium not recommended	Not recommended
Systemic corticosteroids	Level A: not recommended	Level A: not recommended	Level A: not recommended	Not recommended
Ribavarin	No recommendation	Level A: not recommended	Level B: not recommended	No recommendation
Antibiotics (only if indications for bacterial co-infection present)	Level B: recommended	Level A: not recommended Level D: consider for secondary bacterial infection	Level X: not recommended	Not recommended
Chest physiotherapy	Level B: should not be used	Level A: not recommended	Level A: not recommended	Not recommended if children do not have relevant comorbities
Maintaining hydration and fluid balance	Level X: nasogastric or intravenous fluids if unable to maintain oral hydration	Level D: maintain oral feeding unless feeding increases respiratory distress	Level D: nasogastric feeding if child cannot maintain oral intake	Nasogastric or orogastric tube recommended when children cannot take enough fluid orally Intravenous isotonic fluids recommended for children who do not tolerate nasogastric or orogastric fluids, or have impending respiratory failure
Supplemental oxygen	Level D: choice not to administer if SpO_2 >90%	No recommendation	Level D: should be given for SpO_2 ≤92% or severe respiratory distress or cyanosis Level X: CPAP should be considered for severe respiratory distress or apnoea	Recommended for SpO_2 <92%
Pulse oximetry	Level C: continuous pulse oximetry not recommended	Level D: continuous pulse oximetry if in prone position	Level C: should be performed for every child attending hospital with acute bronchiolitis Level X: monitor 8-12 h after discontinuation of supplemental oxygen therapy	No recommendation
Epinephrine	Level B: should not be given	Level A: nebulised adrenaline not recommended	Level A: not recommended	Not recommended
Nebulised hypotonic saline, Normal Saline	Level B: can be given during hospitalisation*	Level D: mist, steam, nebulised saline not recommended	No recommendation	Not recommended
Paracetamol or ibuprofen	No recommendation	Level D: may be given	No recommendation	No recommendation
Antitussives, expectorants, decongestants	No recommendation	Not recommended	No recommendation	No recommendation
Capillary blood gas	No recommendation	No recommendation	No recommendation	Consider in children with severe worsening respiratory distress or impending respiratory failure Not recommended as routine
Nasal suctioning	No recommendation	Level D: may be trialled	Level D: should be used for children who exhibit respiratory distress due to nasal blockage	Recommended if respiratory distress or feeding difficulties or apnoea

Guidelines compared from table 1 based on level of evidence for each intervention. Level A: well designed randomised controlled trials; Level B: randomised controlled trials with minor limitations or overwhelming evidence from observational studies; Level C: observational studies (case-control and cohort); Level D: expert opinion, case reports; Level X: validating study not possible but clear benefit or harm or recommended practice by development group. CPAP=continuous positive airway pressure. *4 trials published after the publication of the 2014 American Academy of Pediatrics guidelines found no benefit of hypertonic saline therapy.[31-34]

Table 2: **Level of evidence per recommended intervention**

safety.[4,43] Furthermore, reduction in length of hospital stay was restricted to a few patients with moderate bronchiolitis and length of hospital stay greater than 72 h. Most trials included in the Cochrane review[43] had a relatively long length of stay (>3 days) in the trial group without hypertonic saline, which limits generalisation to settings in which length of stay is less than 3 days. The effect of continued nebulised hypertonic saline treatment in settings with shorter length of stay and treatment in the outpatient setting has yet to be examined.

In view of widespread use of non-evidence-based therapies for bronchiolitis, reduction of unnecessary

***Panel*: Main changes in the American Academy of Pediatrics guidelines[4,35] between 2006 and 2014**

- Carefully monitored trial of bronchodilators no longer recommended
- Continuous pulse oximetry no longer recommended
- Nebulised hypertonic saline not recommended in the emergency department, weakly recommended for hospitalised children
- Discussion of high-flow nasal cannula without recommendation due to limited evidence
- Hydration support may be administered via nasogastric route as well as intravenously

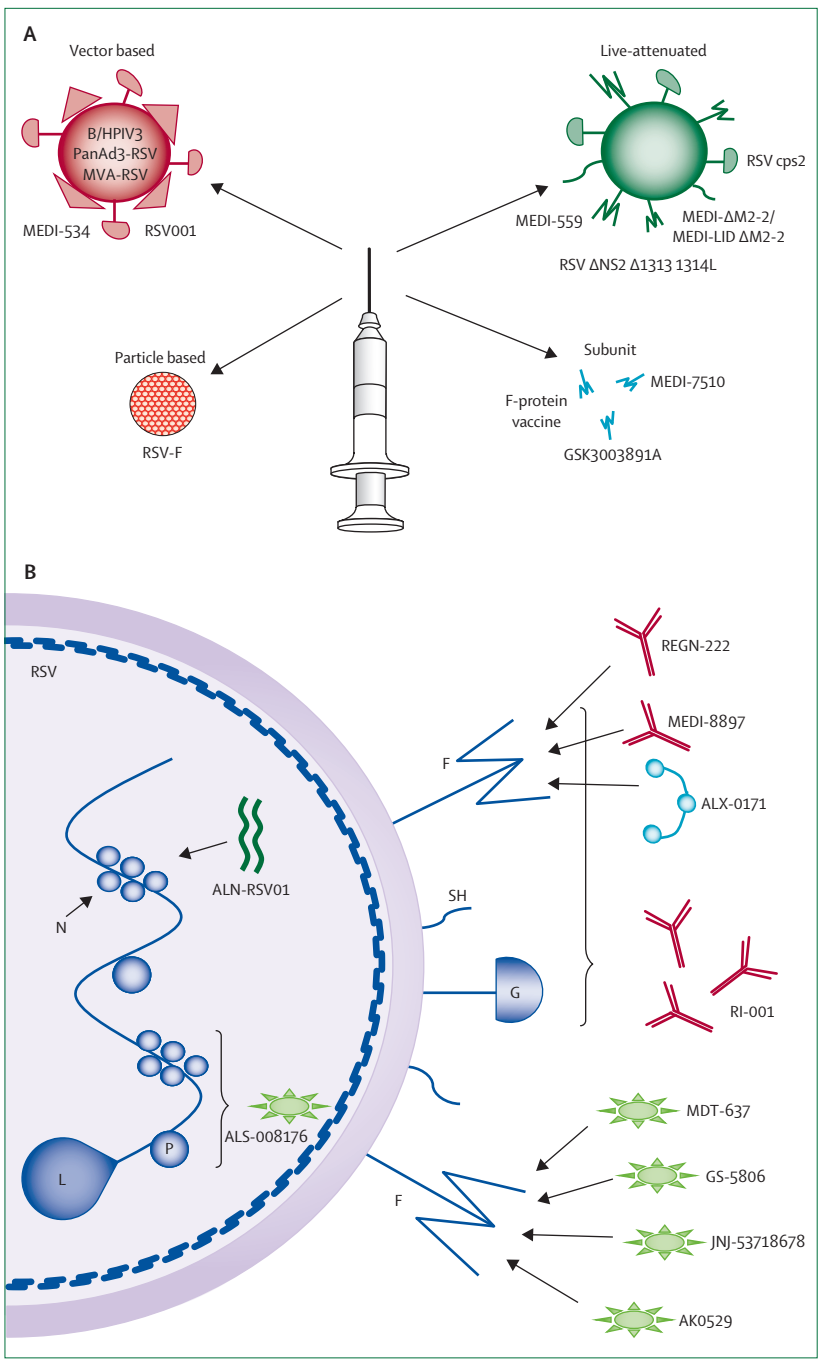

***Figure 2*: Vaccines, antivirals, and RSV targets**
(A) Vaccines. (B) Antivirals and RSV targets. A) RSV vaccines in clinical development. Vector-based vaccines MEDI-534 and RSV001 are delivered through humanised bovine parainfluenza type 3 chimeric vectors (B/HPIV3), simian adenovirus vectors (PanAd3-RSV) and modified vaccina virus ankara vectors (MVA-RSV).[48,49] RSV-F is a particle-based vaccine that expresses post-fusion F protein in baculovirus which forms nanoparticles.[50,51] Live-attenuated vaccine candidates include MEDI-559,[52] MEDI-ΔM2-2/MEDI-LID ΔM2-2, RSV ΔNS2 Δ1313, 1314L, RSV cps2.[53-55] MEDI-7510, F-protein vaccine (NCT02298179),[51] GSK3003891A[56] are subunit vaccines that display the RSV F protein.[52] (B) Antivirals are shown with arrows showing the RSV protein targets. RI-001 targets various surface epitopes, as it is a polyclonal antibody.[57] ALS-008176 targets the P, N, L polymerase complex in its entirety[58] whereas ALN-RSV01 is an siRNA targeting the N protein.[59] F protein is the target for most antivirals (MDT-637, GS-5806, JNJ-53718678, AK0529)[60] and antibodies (REGN-222, MEDI-8897, ALX-0171)[61-63] in clinical development. RSV=respiratory syncytial virus. SH=small hydrophobic protein. F=fusion protein. G=surface protein important for attachment. N=nucleoprotein. P=phosphoprotein. L=large polymerase. M=matrix protein.

therapies in the inpatient setting is essential. In the USA, a temporal association exists between the introduction of the 2006 AAP bronchiolitis guidelines and a reduction of therapeutic interventions, except for antibiotics.[44] The 2014 guidelines further restrict therapeutic intervention, which means the management of bronchiolitis can be summed up in three words: less is more. Nevertheless, further controlled studies stratifying children with bronchiolitis into subpopulations according to aetiology, age, and severity might uncover groups of children who could benefit from specific interventions that showed no benefit in the evidence-based guidelines for the treatment of bronchiolitis as a whole.

New therapeutics

RSV is a negative-sense single-stranded RNA virus encoding 11 proteins. RSV mainly infects the ciliated airway epithelial cells of the respiratory tract and causes both damage and inflammation of the bronchioles. Two surface proteins (G and F) play a part in RSV binding and fusion respectively. The RSV viral envelope protein, SH (small hydrophobic), is an ion channel whereas the inner envelope is formed by the M (matrix) protein. Inside the viral envelope, four proteins make up the nucleocapsid: N (nucleoprotein [protein that is conjugated with a nucleic acid]),[45] which binds the RNA; P (phosphoprotein [protein that can be modified post-translationally by attaching a phosphate group or a complex phosphate molecule]),[46] which is an important polymerase cofactor; L (polymerase); and M2–1, which is a transcription factor. M2–2 is postulated to have a regulatory role in RNA replication, and NS1 and NS2 are non-structural proteins that might downregulate RNA synthesis by inhibiting type I interferon responses.[47] Of all the RSV proteins, F and G are the most important surface epitopes for neutralisation and thus the most frequent targets for vaccine induced protective immunity and antivirals (figure 2).

There are only two licensed drugs for treatment of RSV infection. Inhaled ribavirin, a nucleoside analogue and virostatic, is approved by the Food and Drug Administration (FDA) for treatment of children with severe RSV-associated disease. However, this antiviral is no longer recommended in the AAP guideline because of insufficient evidence of effectiveness.[4] Palivizumab, a humanised monoclonal antibody that targets the RSV F protein, was approved by the FDA and European Medicines Agency for immunoprophylaxis in high-risk infants after the Impact trial[64] showed a 55% reduction in hospital admission attributable to RSV in high-risk children. With patent expiration for palivizumab expected as early as mid-2015, the opportunity arises for lower pricing, which will contribute to greater access for groups and populations with the greatest burden of disease, ie, low-income countries.

Vaccines

Vaccine development has been slower than expected, after use of a formalin-inactivated whole virus vaccine

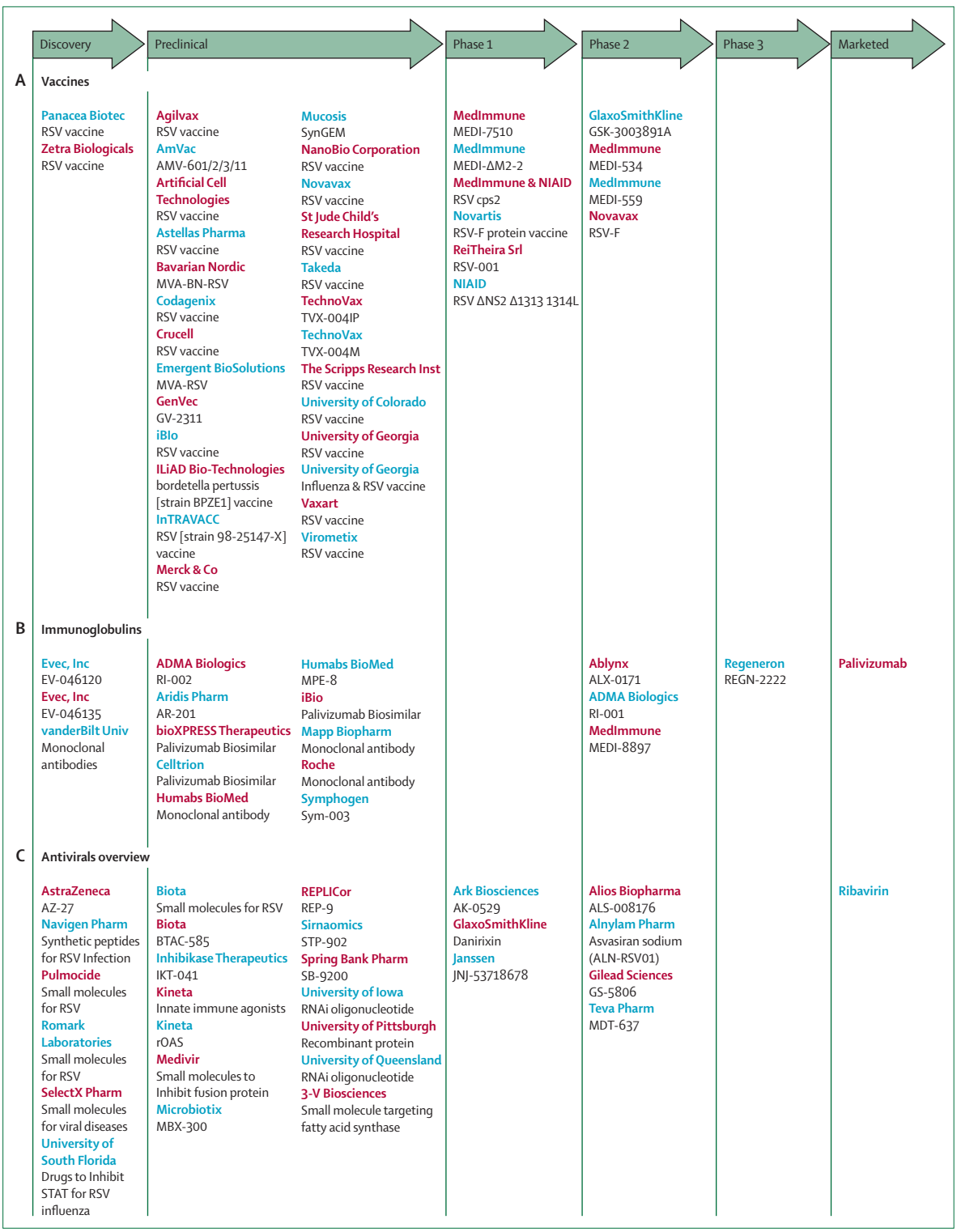

Figure 3: **Overview of RSV treatment in development**

(A) Vaccines. (B) immunoglobulins. (C) antivirals. Company and product name, if available, are classified by development stage (discovery, preclinical, phase 1–3, marketed). The image is up to date through April, 2015. Courtesy of GlobalData. RSV=respiratory syncytial virus. STAT=signal transducer and activator of transcription. See appendix for a more detailed description of methods.

See Online for appendix

in the 1960s resulted in RSV-enhanced disease with 80% hospitalisation and two deaths.[65] Four target populations that might benefit from an RSV vaccine have been identified: infants under 6 months, children older than 6 months, pregnant women, and elderly people (65 years or older).[66] Older siblings have emerged as a potentially effective target for vaccination. Transmission dynamics studied at the community level in Kenya show that transmission mainly occurs through introduction of RSV into the family unit via school-aged siblings, supporting the viability of indirect immunity in the household.[67] Identifying the most appropriate target population to vaccinate will be an important step in future immunisation strategies against RSV. Four vaccine approaches (live-attenuated, subunit, particle based and vector based) are in development, all of which have advantages for particular target populations (figure 2A).

Live-attenuated vaccines aim to achieve a tenuous double goal: safe attenuation of the virus while inducing maximum immunogenicity. In other words, a safe attenuated vaccine should avoid the immunological pitfalls of enhanced T-helper-2 responses and the development of non-neutralising antibodies, as induced by formalin-inactivated RSV, and mimic exposure to wild-type virus. Live-vaccine candidates are attenuated through reverse genetics using mutations to limit the chances of reversion to wild-type while containing mutations that have been shown to increase immunogenicity by augmenting host responses.[68] Mutations in the RNA sequences encoding M2–2, SH, NS2, and L are used in vaccine candidates.

Subunit vaccines provide a safe alternative to live-attenuated vaccine candidates with no chance of reversion to wild-type, but offer little immunogenicity in young children.[66] The F surface protein on the viral envelope and the N protein represent important vaccine antigens for subunit vaccines intended for maternal immunisation. Insight into pre-fusion and post-fusion conformational changes of the F protein presents the question of which epitope to target to provide greater immunogenicity and long-term protection in the development of subunit vaccine candidates.[69] Antibodies against metastable pre-fusion F are highly neutralising, whereas the post-fusion F protein is more stable and contains important neutralising epitopes, including the binding site for palivizumab.[70] Subunit vaccines would probably be more useful in adults or pregnant women for the protection of infants, as they do not carry the potential risks associated with mother to fetus transmission of live-attenuated vaccines.

Finally, two vector vaccine candidates aim to deliver RSV viral proteins using a more stable vector, although anti-vector immunity could pose a problem. Viral vectors, specifically adenovirus and human parainfluenza virus 3, and one particle-based vaccine through baculovirus nanoparticles (small stabilised structures consisting of viral antigens that are produced through Sf9–baculovirus recombinant technology), have been used to deliver RSV F, N, and M2–1 and elicit protective immunity.[71] Figure 3A gives an overview of RSV vaccines in preclinical and clinical trials and table 3 summarises the ten vaccines in clinical trials only.

With the approval of vaccines on the horizon it is important to make the most of emerging clinical interventions. Both maternal and paediatric immunisation could be powerful interventions to prevent severe RSV infection in early childhood. Maternal RSV vaccination studies are in progress to establish placental transfer of neutralising antibodies and postnatal half-life of these antibodies. These studies will be instrumental to optimise timing of vaccination. Limitations of active immunisation include the risk of enhanced disease, restricted immunogenicity of subunit vaccines, and possible attenuation of effectiveness because of interference by natural maternal derived antibodies. Maternal vaccination, although promising, might be limited by placental transfer, antibody decay rates, and safety in pregnant women. In view of the role of RSV LRTI in the pathogenesis of recurrent wheeze, the importance of vaccine development could extend beyond the prevention of hospital admission of infants to long-term respiratory health.

Antivirals

Because of the low immune responsiveness of young children who are at the highest risk of severe disease following RSV infection, and the need to induce a level of protection higher than natural immunity, vaccine development has been complemented by the development of therapeutic antiviral drugs.

11 antivirals for RSV are being investigated in clinical trials. These new compounds belong to four main therapeutic classes: immunoglobulins, siRNA-interference (post-transcriptional gene silencing), fusion inhibitors, and small molecules. These modalities target five of the 11 proteins encoded by the RSV genome including F (fusion), G (viral attachment), and N, P, and L (RNA polymerase) (figure 2B).

Both monoclonal and polyclonal antibodies neutralise RSV. Monoclonal antibodies show higher neutralising activity and fewer adverse effects than plasma-derived polyclonal antibodies, although this can be minimised with substantial purification. However, polyclonal antibodies targeting many epitopes are less susceptible to viral escape mechanisms. MEDI-8897 is a monoclonal antibody targeting the antigenic "site zero", an epitope unique to the pre-fusion RSV F protein. It is a promising drug candidate that has moved onto phase 2 trials as a passive immunisation strategy.[80] Using YTE technology (antibody half-life extension technology using three mutations to the fragment crystallisable domain of an antibody [M252Y, S254T, T256E]), this potent antibody has an extended half-life of 70–100 days, making a single injection a possibility.[71,81] Development has been

	Company	Trial number	Target	Mechanism of action	Route of administration	Development status	Results summary	Target population
Vaccines: live-attenuated								
MEDI-559	MedImmune	NCT00767416	N/A	Attenuated with point and deletion mutations A2 cp248/404/1030/ΔSH	Intranasal	Phase 2c	Biologically active and immunogenic in seronegative children, increase in MA-LRIs require further safety studies, no enhanced disease	Paediatric[52]
MEDI-ΔM2–2/ MEDI-LID ΔM2–2	NIAID	NCT01459198	N/A	Deletion of RNA regulatory factor, M2–2	Intranasal	Phase 1	Restricted in replication, immunogenic after single dose in RSV-seronegative children	Paediatric[53]
RSV ΔNS2 Δ1313 1314L	NIAID	NCT01893554	N/A	Attenuating NS2 gene deletion, 1313 deletion, 1314L substitution and phenotypic stabilisation	Intranasal	Phase 1	Phase 1 ongoing	Paediatric[54]
RSV cps2	NIAID	NCT01852266	N/A	Codon-stabilised version MEDI-559 (at positions 248 and 1030 of the L gene)	Intranasal	Phase 1	Phase 1 ongoing	Paediatric[55]
Vaccines: vector								
MEDI-534	MedImmune	EudraCT2008-002651-24	N/A	Humanised bovine parainfluenza type 3 chimeric (B/HPIV3) vector displaying the RSV F protein	Intranasal	Phase 2c	Highest dose associated with increased MA-LRI but no increase in disease severity; suppression of viral shedding; no enhanced disease in seronegative infants	Paediatric[48]
RSV001	ReTheira Srl (formerly Okairos, acquired by GSK)	NCT01805921	N/A	F, N, M2–1 expressed in simian adenovirus (PanAd3-RSV) and modified vaccinia virus ankara (MVA-RSV)	PanAd3-RSV: Intranasal MVA-RSV: intramuscular	Phase 1	Safety demonstrated in adults, PanAd3-RSV and MVA-RSV are safe and immunogenic candidates	Paediatric[49]
Vaccines: particle-based								
RSV-F	Novavax	NCT02247726	N/A	Post-fusion F expressed in baculovirus, forms nanoparticles	Intramuscular	Phase 2	Starting phase 2 in pregnant women Well tolerated, no serious adverse event, high RSV antibody levels within 14 days, persist for 91 days in women of childbearing age	Maternal[50,72,73]
Vaccines: subunit								
MEDI-7510	MedImmune (together with Immune Design GLAAS)	NCT02289820	N/A	RSV F protein with GLA as adjuvant, selective binding to TLR-4	Intramuscular	Phase 1	Phase 1 ongoing	Paediatric[51,74]
F-protein Vaccine	Novartis	NCT02298179	N/A	Post-fusion F protein with aluminium hydroxide adjuvant	Intramuscular	Phase 1	Phase 1 ongoing	Maternal
NCT02360475 (Formulations 1–6)	GSK	NCT3003891A, NCT01905215	N/A	Passive immunisation via maternal transfer using purified recombinant F protein engineered to maintain pre-fusion F conformation as vaccine antigen	Intramuscular	Phase 2	Starting Phase 2 in healthy women First in human trial in healthy men ongoing, interim results: a rapid anamnestic anti-RSV neutralising antibody, acceptable adverse event profile in healthy men	Maternal[56]
Antivirals: antibodies								
RI-001	ADMA Biologics	NCT00632463, NCT01814800	Various viral epitopes	Polyclonal RSV neutralising antibody	Intravenously	Phase 2c	Significant improvement in RSV titre from baseline to D18; 9·24x in high dose group (n=21)[57] compassionate use (n=13): 4-fold rise in antibody titres RI-002 Ph3c for indication PIDD	..
Motavizumab (MEDI-524)	MedImmune	NCT00421304, NCT00435227	F	RSV neutralising monoclonal antibody	Intravenously	Interrupted	No effect on viral load, difference in hospital stay duration or severity score, more intensive care admissions in motavizumab arm[75]	..

(Table 3 continues on next page)

	Company	Trial number	Target	Mechanism of action	Route of administration	Development status	Results summary	Target population
(Continued from previous page)								
MEDI-8897 (derived from AIMM D25)	MedImmune	NCT02114268, NCT02290340	Prefusion F	RSV neutralising monoclonal antibody with extended half-life	Intramuscular or intravenously	Phase 2	Target population healthy infants. Ongoing RCT in healthy preterm infants	..
ALX-0171	Ablynx	NCT02309320	F	Antibody nanobody	Inhalation	Phase 2	In healthy male volunteers: no dose-limiting toxicity, no significant change lung function, opportunity for once daily dose[61,63] Phase 1 and phase 2a ongoing in toddlers and infants with RSV LRTI	..
REGN-2222	Regeneron	NCT02325791	F	Monoclonal antibody anti-RSV F	Intramuscular	Phase 1	Recruitment to start June, 2015	..
Antivirals: antisense								
ALN-RSV01	Alynam Pharmaceuticals	NCT00496821, NCT00658086, NCT01065935	N	Small-interfacing RNA's (siRNA)	Intranasal	Phase 2c	Safe and well tolerated in healthy adults[59] Phase 2a experimental infection: 40% relative reduction in infection rate ($p<0·01$)[76] Phase 2a lung transplant: 85% reduction in bronchiolitis obliterans syndrome ($p<0·02$)[76] Phase 2b: Treatment effect D90 and D180 Bronchiolitis Obliterans Syndrome 52–65%[76]	..
Antivirals: fusion inhibitors								
MDT-637 (VP014637)	Teva Pharmaceuticals (MicroDose Therapeutx)	NCT01355016	F	Prohibits cell entry	Inhalation	Phase 2	No significant adverse events in all three phase 1 trials (single and multiple dose in healthy adults or single dose in asthmatics), desirable pharmacokinetic profile[77]	..
GS-5806	Gilead	NCT01756482	F	Prohibits cell entry	Oral	Phase 2	Achieved lower viral load, lower mucus weight, lower symptom scores; adverse events include low neutrophil counts and increased alanine aminotransferase[60]	..
JNJ-53718678	Janssen	NCT02398591, NCT02387606	F	Prohibits cell entry	Oral	Phase 1	No study results available	..
AK0529	Ark Biosciences Inc	NCT02297594	F	Prohibits cell entry	Oral	Phase 1	Phase 1 ongoing	..
Antivirals: nucleoside analogue								
ALS-008176	Alios Biopharma	NCT01906164	RSV polymerase	Nucleoside analogue	Oral	Phase 2	Good safety profile, rapid decline of viral load and clearance of RSV RNA, decreased mucus weight and symptom score in healthy adults[58] Phase 1 ongoing in RSV hospitalised children	..
Antivirals: other								
Danirixin (GSK1325756)	GSK	NCT02201303	CXCR2	Selective, reversible CXCR2 antagonist	In vitro	Phase 1	Trial evaluating concentration necessary to inhibit neutrophil activation after in-vitro whole blood incubation[78,79]	..

MA-LRI=medically attended lower respiratory illness. RSV=respiratory syncytial virus. N/A=not available. RCT=randomised controlled trial. LRTI=lower respiratory tract infection. PIDD=primary immunodeficiency diseases.

Table 3: **Overview of RSV antivirals, therapeutics, and vaccines in clinical trials**

discontinued for motavizumab, a higher affinity variant of palivizumab with greater neutralising activity. A phase 3 clinical trial[82] showed similar efficacy between both monoclonal antibodies but a 2% greater incidence of cutaneous adverse events in motavizumab recipients compared with palivizumab recipients. Moreover, a

phase 2 randomised clinical trial[75] in which motavizumab was used as treatment in children with RSV LRTI showed no effect on viral load or clinical severity.

One therapeutic agent, ALN-RSV01, uses antisense technology (siRNA) to interfere with protein synthesis by targeting mRNA encoding the N protein. Of the four fusion inhibitors, GS-5806 was studied in a phase 2 randomised clinical trial[60] and showed an ability to reduce viral loads and disease severity in healthy adults. Finally, there are two small molecules inhibitors; ALS-008176 targets the RNA polymerase to interfere with protein synthesis, and danirixin is a CXCR2 antagonist. Figures 3B and 3C give an overview of all antivirals and other drugs in development and table 3 outlines the 11 antivirals and other therapeutics in clinical trials, including motavizumab, for which development has ended.

Nucleolin has emerged as a novel potential therapeutic target after being identified as a functional human receptor for the RSV F protein in vivo.[83] AS1411, a guanosine-rich oligonucleotide, is in phase 2 clinical trials for cancer patients and might be a potential therapeutic agent because it binds to the cell-surface nucleolin. It is patented for antiviral use for RSV but clinical trials for this indication have not started.[84]

Remaining challenges

Although the investment in RSV therapeutics has injected new hope in emerging RSV pharmaceuticals, challenges remain for their clinical development and implementation—namely absence of consensus on the most clinically relevant outcomes, the definitions of clear target populations, and barriers to drug access.

Consensus among academics, developers, and regulators is needed on clinical trial design, including identifying relevant endpoints and criteria of vaccine and therapy efficacy. In the absence of a universal severity score for RSV bronchiolitis and clinical, virological, and immunological endpoints to objectively assess RSV immune responses and disease severity, assessment of RSV interventions remains a challenge. Surrogate markers of disease severity and protection need to be better defined and clear endpoints established for successful clinical trials. Legal and regulatory guidance on clinical testing in RSV-naive infants, young children, and pregnant women are needed because of the risk of vaccine-enhanced disease or adverse effects in these vulnerable populations. Greater transparency and agreement is needed in the development chain to assess therapeutic efficacy, preferably in the form of an international protocol or guideline.

Different subpopulations with RSV LRTI should be defined and considered when testing therapeutic efficacy. For children with asthma, a hyper-reactive inflammatory immune response to viral infection might result in enhanced disease. Higher rates of bacterial co-infection, HIV exposure, and HIV infection should be taken into consideration in populations in low-income countries.[66] Patient subpopulations for therapeutic testing should be established for clinical trials to accurately measure therapeutic efficacy. Further advances in personalised medicine will help to identify the subset of children that could benefit from these interventions.

A more accurate characterisation of disease burden that includes active surveillance data and an understanding of the long-term consequences of RSV will be essential in establishing target populations for RSV prevention and therapeutics, and a comprehensive cost-effectiveness estimate. As the burden of disease disproportionately affects low-income countries, trials that establish a safe and effective profile within this population are essential to combat RSV.

Once approved, practical barriers remain to ensuring that new therapeutics address the worldwide burden of disease. Economic and logistic barriers are greatest in regions where the RSV disease burden is highest, and mechanisms such as differential pricing agreements and collaboration with local stakeholders can help with distribution in low-income countries.

Search strategy and selection criteria

References for this Review were identified through a search of PubMed and the Cochrane Library for original research and reviews, with no date or language restrictions, on Aug 1, 2015. 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 Review. We searched for original research and reviews using the terms "respiratory syncytial virus" or "viral" and "management", "therapeutics", "vaccines", "antivirals", and "treatment." Earlier landmark publications that are cited in these articles were added if judged to be relevant. ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform, and the European Union clinical trials register were searched for any drug with the indication "Respiratory Syncytial Virus" or "RSV".

Conclusion

RSV bronchiolitis represents a worldwide health problem, with a substantial disease burden in children less than 5 years of age and 66 000–199 000 estimated deaths worldwide per year. Beyond the acute disease, RSV is implicated in the pathogenesis of recurrent wheeze and possibly in the development of asthma. Evidence-based guidelines offer no obviously effective therapeutic interventions, leaving the standard management of RSV bronchiolitis dependent on adequate hydration and respiratory support. Active paediatric and passive immunisation via maternal vaccination are emerging preventive strategies. Antivirals and other novel molecules in clinical trials will hopefully offer clinicians new therapeutic options in a doctrine of non-intervention. The

definition of optimum clinical and laboratory endpoints to assess the efficacy of these preventive and treatment interventions against RSV is needed. Furthermore, there is a pressing need to characterise the morbidity and mortality of RSV worldwide, to define target populations for prevention and treatment, to have the mechanisms in place to ensure acceptable pricing, and to undertake trials that show safety and effectiveness in this young and vulnerable population.

Contributors

NIM, LB, and FM-T contributed to the concept and plan for this Review. Literature review was done by NIM in collaboration with LB. All authors contributed to the final manuscript. The Respiratory Syncytial Virus Network (ReSViNET) contributed figures 3A–C.

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