Determining the outcomes of interventions to prevent respiratory syncytial virus disease in children: what to measure?

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Respiratory syncytial virus (RSV) is the most common cause of viral acute lower respiratory tract illness (LRTI) in young children, and a major cause of hospital admissions and health-care utilisation globally. Substantial efforts have been made to develop RSV vaccines and vaccine-like monoclonal antibodies to prevent acute RSV LRTI. Prevention of acute disease could improve long-term lung health, with potential effects on wheezing, asthma, and chronic lung disease. This Personal View describes assessments that should be initiated during clinical trials and continued after licensure to fully evaluate the effect of RSV preventive interventions. These assessments include recording the incidence of RSV-specific LRTI and all-cause LRTI through two RSV seasons, and assessment of the prevalence and severity of recurrent wheezing or asthma in children aged up to 6 years. Standardised assessments in diverse settings are needed to fully determine the effect of interventions for the prevention of RSV disease.

Introduction

Respiratory syncytial virus (RSV) is the most common global cause of viral acute lower respiratory tract illness (LRTI) in infants and children.1–3 In many high-income countries, RSV is a leading cause of hospital admission in infancy and accounts for a substantial proportion of outpatient visits in children aged under 5 years.4 Globally, RSV was most recently estimated to have caused 33.1 million (uncertainty interval [UI] 21.6–50.3) episodes of acute lower respiratory infection (ALRI), resulting in about 3.2 million hospital admissions (UI 2.7–3.8), and about 59,600 in-hospital deaths (UI 48,000–74,500) in children younger than 5 years.5 As assessed in one systematic review of 20 studies,6 several medical and environmental factors can increase the risk of RSV LRTI in children, including prematurity (odds ratio [OR] 2.0), low birthweight (OR 1.9), being male (OR 1.2), being a sibling (OR 1.6), maternal smoking (OR 1.4), a history of atopy (OR 1.5), not being breastfed (OR 2.2), and household crowding (OR 1.9); HIV infection in children was also reported to be associated with severe RSV LRTI in some of these studies. However, most RSV LRTIs occur in healthy, full-term infants without known risk factors for progression from upper respiratory tract illness (URTI) to LRTI,7 and the majority of RSV-associated deaths occur in low-income settings.8,9 Treatment of RSV LRTI is largely supportive, and antiviral drugs with proven efficacy are not yet available. For these reasons, universal prophylaxis with RSV vaccines or monoclonal antibodies, or both, to prevent RSV LRTI in infants and young children should be the most effective strategy to reduce the global burden of RSV disease.

Recognition of the importance of RSV as an acute cause of paediatric morbidity and mortality has led to a surge in RSV vaccine and monoclonal antibody development, with more than 15 vaccine or monoclonal antibody candidates currently being assessed in clinical trials. These products include RSV fusion glycoprotein subunit vaccines for maternal immunisation, live-attenuated RSV vaccines and adenovirus-vectored RSV vaccines for infant immunisation, and RSV extended half-life monoclonal antibodies for neonatal or seasonal infant immunisation.10–12 Rapid progress is being made, and one or more of these products could be available for use within the next 5–10 years. Since the intent is to make these products available for global use,13 governmental and supranational policy-making bodies are closely following these developments.10–12

When RSV vaccines or extended half-life monoclonal antibodies become available, policy-making and funding bodies will consider the investment case for various measures included in LRTI case definitions (eg, respiratory rate and SpO₂) should be archived individually and, when appropriate, as continuous variables so that outcomes can be compared between products, regardless of case definition.

For long-term respiratory outcomes, especially asthma, data on medically-attended wheezing illness should be prioritised, with optimum follow-up of patients until they are aged 6 years. Caregiver reports could provide supplementary information.

For long-term outcomes, longitudinal measurements of lung function in selected locations could provide useful data.

Development of objective, feasible, affordable, and reliable measurements of lung health in infants and young children that can be widely performed should be a research priority.

Key messages

- For new preventive interventions for RSV, the primary outcome remains the effect on acute disease; however, measuring long-term respiratory outcomes will be important provided that the primary outcome is met.
- For acute disease, the incidence of RSV-associated LRTI and all-cause LRTI through two RSV seasons should be measured.
- Component measures included in LRTI case definitions (eg, respiratory rate and SpO₂) should be archived individually and, when appropriate, as continuous variables so that outcomes can be compared between products, regardless of case definition.
- For long-term respiratory outcomes, especially asthma, data on medically-attended wheezing illness should be prioritised, with optimum follow-up of patients until they are aged 6 years. Caregiver reports could provide supplementary information.
- For long-term outcomes, longitudinal measurements of lung function in selected locations could provide useful data.
- Development of objective, feasible, affordable, and reliable measurements of lung health in infants and young children that can be widely performed should be a research priority.
settings on the basis of efficacy data and incidence of vaccine-preventable or monoclonal antibody-preventable disease (defined as the incidence in the unimmunised population multiplied by the vaccine or monoclonal antibody efficacy). To date, the case for the development of RSV vaccines and monoclonal antibodies has focused largely on the prevention of acute RSV LRTI, with recognition of its substantial global disease burden. However, deployment of interventions that prevent RSV LRTI could have a broader impact on child health through potential effects on wheezing or asthma in early childhood, paediatric lung function, and the respiratory microbiome. Some studies also describe an association between early LRTI and chronic obstructive pulmonary disease (COPD) later in life, suggesting that prevention of RSV LRTI in infancy and early childhood might have sustained long-term effects.

In this Personal View, we describe our opinions on additional information that should be obtained to better inform decision making about products for the prevention of RSV disease in children. We will not focus on the assessment of the global burden of acute RSV, which has been done through several projects. We will also not address the many important practical country or region-specific questions that need to be answered before implementation—eg, knowledge, attitudes, feasibility of maternal immunisation, baseline rates of adverse birth outcomes, and baseline rates of adverse neurodevelopmental outcomes, and RSV seasonality for products that are intended to be administered seasonally. We will also not address questions related to RSV disease in older adults, who remain an important target for RSV disease prevention, nor will we address laboratory methods for the detection of RSV or for the measurement of immune responses to vaccination. Instead, our focus will be on the clinical outcomes that should be directly addressed in the cohorts of children enrolled in RSV disease prevention trials, either during the period in which primary efficacy is assessed, or during longer-term follow-up.

**Acute respiratory outcomes**

**Bronchiolitis is not a useful outcome measure**

Historically, many studies have used a diagnosis of bronchiolitis during the winter season as a surrogate for RSV LRTI. However, the diagnosis of bronchiolitis is inconsistently made across and within health-care settings. Definitions and guidance vary by region—eg, American and Canadian guidelines restrict the diagnosis of bronchiolitis to children younger than 2 years, and South African and British guidelines highlight that infants are prone to bronchiolitis without indicating an upper age limit. Other diagnostic terms could also be used, such as wheezy bronchitis, viral-associated pneumonia, or viral-associated wheeze. In addition to variations in age limits and terminology, bronchiolitis could encompass a spectrum of diseases, influenced by the infecting organism or organisms, the host, and environmental factors. Distinct clinical phenotypes of bronchiolitis have been identified using latent-class analysis in two multicentre studies of children admitted to hospital for bronchiolitis; in a USA study four distinct phenotypes were identified, with two of these phenotypes replicated in a Finnish cohort and a third mixed phenotype identified. Phenotypes were characterised by a number of parameters, including disease severity, history of eczema or wheezing, wheezing at presentation, age, sex, and detection of either rhinovirus or RSV in nasal secretions. These distinctions could be helpful for determining the cause of infection, for the prediction of patients’ response to bronchodilators, and potentially for predicting long-term outcomes and future risks of developing asthma. However, further studies are needed to define bronchiolitis subtypes, especially in low-income and middle-income countries. From a clinical trials perspective, the heterogeneity of disease and inconsistency of definitions suggest that incorporating bronchiolitis into a clinical case definition of RSV disease could be problematic. A better approach might be to record a patient’s individual signs and symptoms (as described in the next section), and to use a term such as RSV-associated LRTI as a broad classification to cover the full spectrum of LRTIs, including pneumonia and bronchiolitis.

**Case definitions and assessment of acute RSV disease severity**

Efforts have been made to reach a consensus on case definitions and key outcome measures to assess the severity of RSV LRTI in infants and young children. A consultation sponsored by Regeneron Pharmaceuticals Inc and Sanofi Pasteur held in May, 2014, sought to define endpoints for clinical trials investigating RSV illness prevention that could be used for objective assessment of paediatric study participants from high-income and middle-income countries. The consensus recommendation was that primary endpoints should focus on health-care use, including reductions in RSV-associated hospital admissions, and emergency-room and urgent-care centre visits. Recommendations for secondary endpoints included reductions in RSV-associated LRTI and length of intensive care unit stay, reductions in recurrent wheezing or asthma, and direct and indirect costs. These recommendations were reviewed during the initial WHO consultation on RSV vaccines in 2015, which focused primarily on assessment in low-income and middle-income countries. Health-care use outcomes were thought to be less useful for low-income and middle-income countries than for high-income countries, both because of great variations in clinical practice and health-care access between and within countries, and because these outcomes would not fully capture the burden of severe RSV-associated morbidity and mortality in these
### Symptoms or signs in children

<table>
<thead>
<tr>
<th>Respiratory tract illness</th>
<th>LRTI*</th>
<th>Medical significance and measures of clinical severity*</th>
<th>Case definition</th>
<th>Prespecified severity in case definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO**</td>
<td>Cough or difficulty breathing, Fast breathing:</td>
<td>Severe LRTI:</td>
<td>- RSV LRTI;</td>
<td>- RSV LRTI; severe RSV LRTI; very severe RSV LRTI</td>
</tr>
<tr>
<td></td>
<td>• ≥50 breaths per min (age 2–12 months);</td>
<td>• lower respiratory tract infection, and</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>• ≥40 breaths per min (age 1–5 years);</td>
<td>• lower chest wall indrawing, or</td>
<td></td>
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<tr>
<td></td>
<td>Oxygen saturation:</td>
<td>• SpO &lt;93%;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• SpO &lt;95%</td>
<td>Very severe LRTI:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• lower respiratory tract infection, and</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>• SpO &lt;90%, or</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>• inability to feed, or</td>
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<td></td>
<td></td>
<td>• failure to respond, or</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>• unconscious</td>
<td></td>
<td></td>
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<tr>
<td>Janssen; infant vaccine;</td>
<td>Respiratory tract illness, and either;</td>
<td>Severe LRTI:</td>
<td>- RSV LRTI;</td>
<td>- RSV LRTI; severe RSV LRTI</td>
</tr>
<tr>
<td>MedImmune; monoclonal</td>
<td>More than 48 h of:</td>
<td>• lower respiratory tract infection, and</td>
<td></td>
<td></td>
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<tr>
<td>antibody† (NCT02878330)</td>
<td>• runny nose; or</td>
<td>• lower chest wall indrawing, or</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>• sneezing; or</td>
<td>• SpO &lt;93%</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>• nasal congestion; and 24 h or more of:</td>
<td></td>
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<tr>
<td></td>
<td>• coughing; or</td>
<td></td>
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<tr>
<td></td>
<td>• abnormal breathing, or</td>
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<td></td>
<td>• fever; or</td>
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<tr>
<td></td>
<td>• lethargy, or</td>
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<tr>
<td></td>
<td>• decreased appetite</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Novavax; maternal vaccine</td>
<td>Not specified</td>
<td>Increased respiratory rate:</td>
<td>- 1 lower</td>
<td>Not specified</td>
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<tr>
<td>(NCT02624947)</td>
<td>Rhonchi</td>
<td>• ≥60 breaths per min (age &lt;2 months);</td>
<td>respiratory</td>
<td></td>
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<tr>
<td></td>
<td>Rules</td>
<td>• ≥50 breaths per min (age 2–12 months);</td>
<td>tract finding,</td>
<td></td>
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<tr>
<td></td>
<td>Crackles</td>
<td>• ≥40 breaths per min (age 1–5 years);</td>
<td>and</td>
<td></td>
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<tr>
<td></td>
<td>Wheeze</td>
<td>Oxygen saturation:</td>
<td>medically</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>• SpO &lt;95%</td>
<td>significant</td>
<td></td>
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<td>finding</td>
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<td>concurrently</td>
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All cases of RSV were detected using RT-PCR. LRTI = lower respiratory tract illness. RSV = respiratory syncytial virus. SpO₂ = oxygen saturation measured with pulse oximetry. *Age of infant indicated in parentheses where appropriate. †Developed before new WHO guidance in 2014. ‡According to these new guidelines, a child with lower chest wall indrawing is classified as having LRTI rather than severe LRTI. ‡‡Information from personal communications from Melanie Saville (Janssen), Pamela Griffin (MedImmune), and Gregory Glenn (Novavax).

Table 1: Case definitions used by organisations and in clinical trials of vaccines and monoclonal antibodies to prevent RSV disease in infants

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countries. For this reason, a case definition was proposed that drew on the contemporary Integrated Management of Childhood Illness (IMCI) classifications of severe and very severe pneumonia, which included pulse-oximetry measurements, tachyphonya, lower chest wall indrawing, and additional non-specific indicators of very severe illness (eg, inability to feed or failure to respond; table 1). The US Food and Drug Administration and National
Institutes of Health workshop, which was held in 2015 to discuss challenges and opportunities in RSV vaccine development, reaffirmed concerns about using hospital admission as a primary outcome measure, and highlighted the rarity of severe and very severe pneumonia in high-income countries. Outpatient LRTI was considered an important outcome measure for high-income countries, with age-stratified tachypnoea, lower chest wall indrawing, apnoea, and pulse-oximetry measurements (using pulse oximetry to measure oxygen saturation, SpO₂) determined to be potentially important components of the LRTI case definition.

Ongoing phase 2 and phase 3 trials of RSV extended half-life monoclonal antibodies and RSV vaccines have used modified versions of the LRTI case definition proposed at the WHO consultation (table 1). Each of these trials includes RSV LRTI in the case definition, with respiratory rate, SpO₂, and, in some cases, other signs or symptoms, as measures of severity. However, different cutoffs in SpO₂ measurements are used, and the stratification of RSV disease into severe or very severe is included in some studies but not others. Health-care use outcomes, such as incidence of RSV-associated hospital admission, outpatient visits for RSV LRTI, and the need for ventilatory assistance, are explicitly included in some case definitions (Novavax; table 1), implied in another (such as through use of the terms ventilatory failure, or dehydration due to respiratory distress requiring intravenous hydration; MedImmune), and not included in the remaining (WHO and Janssen).

As is clear from table 1, RSV intervention studies are being conducted using various case definitions and outcome measures. For these reasons, collecting clinical data with methods that will allow cross-study comparisons will be crucial—eg, respiratory rate and SpO₂ should be collected using standardised methods and as continuous variables. Additionally, collecting information on altitude will be necessary and SpO₂ measurements should be interpreted in that context. Training to standardise the assessment of LRTI signs, symptoms, and measurements of SpO₂ will be crucial. The recently completed Pneumonia Etiology Research for Child Health Study (PERCH) study provides an example of such training.

In the 1960s, a formalin-inactivated RSV vaccine was associated with the tragic occurrence of enhanced RSV disease in RSV-naïve infants who were subsequently naturally infected with RSV, leading to admission to hospital for severe RSV disease and the death of two young children with respiratory failure. It is extremely unlikely that maternal RSV immunisation or infant immunisation with a live-attenuated RSV vaccine would predispose infants to enhanced RSV disease; nevertheless, assessment of this outcome should be a crucial component of the safety evaluation for any study investigating RSV preventive interventions involving young infants. Since the manifestations of enhanced RSV disease are identical to severe acute RSV disease, the case definitions that are used to assess efficacy can also be used to monitor for enhanced RSV disease.

Assessment of all-cause LRTI in early life: replacement infections and the effect of RSV LRTI on bacterial pathogens

Although globally RSV is the most common cause of acute LRTI in infancy, several other viral respiratory pathogens, including influenza, parainfluenza, human metapneumovirus, and rhinovirus, are also associated with a substantial burden of paediatric respiratory disease. If effective prophylactic strategies are developed to prevent RSV LRTI, replacement of RSV by another respiratory pathogen could be possible. For example, in a study of late preterm infants who received palivizumab prophylaxis or placebo, the incidence of all-cause wheezing illness was lower in infants given palivizumab, but proportionally more infections with non-RSV respiratory viruses occurred in infants given palivizumab than in those given placebo. Although primary efficacy outcomes will include RSV-associated illnesses, secondary or exploratory outcomes should include all-cause LRTI. When possible, further elucidation of the causes of non-RSV LRTI through testing for other viruses in respiratory specimens should be done.

The associations between RSV LRTI, bacterial infection, and the host respiratory microbiome are only beginning to be understood. A randomised trial of a nine-valent pneumococcal vaccine reported a 31% reduction in subsequent hospital admissions for viral-associated LRTI in children given the vaccine compared with children given placebo, including a 22% reduction in confirmed RSV-associated pneumonia, which represents a substantial reduction in HIV-uninfected children. This finding suggests that RSV-pneumococcal interactions could lead to severe LRTI resulting in a patient’s admission to hospital. Further support for this finding was provided by a study in the USA that showed a strong correlation between peak timing of RSV-related hospital admissions and pneumococcal-related hospital admissions, with substantial decreases in the hospital admission of infants who were 3–11 months old for RSV following the introduction of pneumococcal conjugate vaccine. Additionally, severe RSV disease appears to be associated with predominance of Haemophilus influenzae or Streptococcus spp in the nasopharynx, associated with overexpression of genes related to Toll-like receptor signalling and neutrophil activation. The directionality of these bacterial and viral interactions is not clear—ie, whether severe RSV infection predisposes a patient to bacterial colonisation, inflammatory responses, or invasive bacterial disease, or whether the opposite is true. Regardless of the causal pathway, these associations highlight the importance of determining whether RSV vaccines affect all-cause LRTI as well as RSV-specific disease.
Duration of protection
Paediatric RSV LRTI is typically most severe in infancy. This severity is probably due to small airway diameters, replication of the virus to high concentrations in the ciliated respiratory epithelium, sloughing of epithelial cells into the alveoli or bronchi, and innate immune and inflammatory responses, all of which could contribute to varying degrees of lower airway obstruction and mucus plugging. However, RSV LRTI also occurs beyond the first year of life. Therefore, passive RSV immunisation of infants, whether via maternal immunisation or administration of extended half-life monoclonal antibodies, could potentially prevent RSV LRTI during a child's first RSV season, but allow RSV LRTI to occur more frequently during the second RSV season once passive protection has waned. Although a higher incidence of RSV LRTI in the second year of life has not been observed in studies of preterm infants who have been given passive RSV prophylaxis (using palivizumab or motavizumab), this question has not been addressed in the study of passive prophylaxis in full-term infants, nor in low-income settings. For these reasons, follow-up of children for RSV LRTI during a second RSV season should be an important component of these passive RSV immunisation studies. Moreover, follow-up for two RSV seasons should enable an assessment of the duration of protection in infants and children who are actively immunised with RSV vaccines.

Long-term respiratory outcomes: assessing the effect of RSV prophylaxis on early-childhood wheezing and asthma
The association between early-life RSV LRTI and the development of long-term respiratory disease in childhood or later is controversial, but it is an important area to consider when assessing the impact of RSV disease prevention strategies. Several observational cohort or case-control studies have reported an association between early or severe RSV and the development of wheezing in infancy or early childhood. However, whether RSV disease is the first manifestation of wheezing illness in infants who are predisposed to wheezing or asthma, or whether RSV disease damages the airways and leads to wheezing or asthma, is unclear. Many studies have also investigated the association between early RSV disease and the development of subsequent asthma, with some reporting an association and others reporting none. Among children who developed RSV bronchiolitis, severe disease or hereditary factors, particularly a family history of asthma, were predictors for the subsequent development of asthma. Intervention studies have provided inconsistent information on the effect of passive prophylaxis with RSV monoclonal antibodies (palivizumab or motavizumab) on long-term wheezing. Three studies in preterm infants (ranging from 33 to 36 weeks gestational age) reported a subsequent reduction in recurrent wheezing ranging from 7% to 13% during follow-up periods of 1–5 years. In contrast, a study of Native American healthy term infants in the USA reported no reduction in medically attended wheezing during 3 years of follow-up. Importantly, these studies differed in ways that preclude direct comparisons. Key differences included study designs, inhomogeneous patient populations (preterm vs full-term infants), duration of follow-up, type of follow-up (parental report vs medically attended wheezing), and atopic predisposition (ie, the presence or absence of a family history of atopy or asthma). Additionally, these studies were done in high-income countries.

Increasing evidence links the emergence of chronic non-communicable lung diseases, such as asthma or COPD, with early childhood LRTI. Data from an African birth cohort suggest that LRTI during infancy could have long-term consequences for lung health by reducing lung function. Infants who had an episode of LRTI in infancy had lower lung function at the age of 1 year, independent of their baseline lung function. Furthermore, more severe LRTI was associated with greater reductions in lung function, whereas recurrent episodes of LRTI had a cumulative impact in further decreasing lung function at 1 year. As RSV was the most common identifiable cause of LRTI in this cohort by a case-control analysis, the effect on lung function could be associated with RSV disease. However, the specific effect of RSV-associated LRTI on lung function has not been well studied.

With the increasing development of preventive strategies for RSV disease in infants, creating standardised methodologies for assessing such long-term outcomes is crucially important. In addition to assessing the effect of such interventions on the prevention of RSV LRTI in infants, it is important to reliably and consistently measure the possible effect of prevention of RSV LRTI on subsequent transient early wheezing, persistent wheezing, or asthma. To enable comparisons between studies and across study sites, robust measures of long-term outcomes that encompass measures of chronic respiratory disease are needed. As a practical matter, the potential for long-term follow-up needs to be considered when intervention trials are first initiated to ensure the continuity of assessment for trial participants. However, long-term follow-up will not be needed if the primary efficacy endpoints (ie, prevention of acute RSV LRTI; table 1) are not met. We would suggest a stepwise process in which the parents or guardians of the trial participants are informed at the outset that separate informed consent might be sought yearly for long-term follow-up. This process could then be terminated if the primary endpoints are not achieved.

Measurement of recurrent wheezing or asthma
The prevalence of recurrent wheezing or asthma are important outcomes to assess. However, standardised
measurement of these conditions at consistent timepoints might be challenging to do in young children across many sites globally and in populations that are mobile. Long-term follow-up for such outcomes requires high cohort retention and close follow-up. Furthermore, measurement of these outcomes largely relies on caregiver reporting, because objective measurement of lung function is not feasible in many locations. Proposed measurements include caregiver-reported wheezing, in addition to medically attended wheezing (episodes that are either ambulatory or after hospital admission), and lung function measurements (table 2). Ideally measurement of symptoms, healthcare use for respiratory disease, and lung function assessment should be done because each of these factors provide independent, distinct, and important outcome measures.

Table 2: Possible ways to measure recurrent wheezing or asthma

<table>
<thead>
<tr>
<th>Limitations</th>
<th>Suggested timepoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caregiver-reported wheezing</td>
<td></td>
</tr>
<tr>
<td>Validated questionnaire adapted from ISAAC66–68</td>
<td>Not validated for children younger than 6 years, recall bias, dependent on literacy, non-specific</td>
</tr>
<tr>
<td>Diary of days of wheezing and the number of wheezing episodes</td>
<td>Adherence could be poor, bias towards more severe cases completing diary, dependent on consistency of caregiver and understanding of the word wheeze</td>
</tr>
<tr>
<td>Medically attended wheezing</td>
<td></td>
</tr>
<tr>
<td>Health-care worker diagnosis by auscultation for episodes requiring emergency room visit, oral prednisone, or hospital admission</td>
<td>Requires presentation at a health-care facility, bias for most severe episodes, requires trained health-care workers and standardisation across sites</td>
</tr>
<tr>
<td>Lung function</td>
<td></td>
</tr>
<tr>
<td>Forced-oscillation technique, for spectral measurements and tracking; lung-clearance index; airway resistance interrupter technique; tidal breathing measurements with expiratory flow rates</td>
<td>Requires specialised equipment, trained staff, time, and resources; commercially produced devices for tracking when using forced-oscillation technique are still being developed</td>
</tr>
<tr>
<td>Spirometry and bronchodilator response</td>
<td>Requires child’s cooperation Reproducible from 5 years, but can be done in children aged &gt;3 years</td>
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One method of measuring wheezing and asthma is through questionnaire-based diagnosis. However, accurate diagnosis of childhood wheezing or asthma could be especially challenging in settings where respiratory infectious diseases predominate, in non-English-speaking populations where wheezing or asthma terminology is not easily translated, and in resource-poor countries with poor access to health care.59,60 Therefore, questionnaire-based studies should be interpreted with caution because they often rely on a literate population who understand the meaning of words like wheezing or asthma, and they could be prone to recall bias. The International Study of Asthma and Allergies in Childhood (ISAAC) has provided the most reliable global comparative data on the prevalence of asthma in children, which has been compiled from standardised and validated written and video-presented questionnaires from large, global epidemiology studies.66–68 These studies66–68 were done in two paediatric age groups: 6–7 years and 13–14 years. The large number of children (over 1 million), centres (n=233), and countries (n=98) that participated in the ISAAC phase 3 trial66 make it the most comprehensive epidemiological survey of childhood asthma globally. To overcome the language issues that could affect asthma diagnosis in such settings, a video component was included for the age group from 13 to 14 years. Results of the video responses have generally been consistent with the responses of the written questionnaire, but have found a lower asthma prevalence.71 The results of ISAAC questionnaires provide data on the prevalence of asthma and asthma severity as assessed by symptoms and the frequency of symptoms in the preceding 12 months, such as sleep disturbed by wheezing, exercise-induced wheezing, or wheezing that limits speech.

For the assessment of recurrent wheezing or asthma, use of validated ISAAC questionnaires to assess the prevalence of wheezing could be useful. However, limitations of the questionnaire’s reliability include reliance on caregiver recall and caregiver understanding of the word wheeze, and an absence of specificity and validation in children younger than 6 years. However, a similar tool to the ISAAC questionnaire has been developed that is designed to be completed by the child’s parent and has been validated for infants and children aged up to 3 years.72 Diary cards have been used in asthma studies to record the number of days when a child has episodes of wheezing, but their use is limited by poor adherence, reliability of caregiver reporting, and dependence on caregiver understanding of the word wheeze.

Another proposed measurement to assess recurrent wheezing or asthma is by recording the instances of medically attended wheezing. Diagnosis of wheezing by a health-care provider using auscultation has been widely used in birth-cohort studies that investigate the development of asthma and in clinical trials of asthma therapies in children aged up to 5 years.73 Severity of disease is an important outcome that can be measured using symptoms, clinical signs, hypoxia, or the need for
Provide objective data on lung health. However, lung-resistance and reactance measured with the multiple-breath washout technique and the lung-clearance index, which is measured with the multiple-breath washout technique, can be performed in early life, with successful and reproducible measurements reported in neonates and 6-week-old infants. Devices for forced-oscillation testing that only require tidal breathing, and therefore minimal cooperation, have been widely used in paediatric studies and normative data have been produced, but methodology and interpretation of results differ between commercially available equipment. Within breath changes in respiratory mechanics (tracking forced-oscillation method) have been shown to be highly sensitive for detecting airway obstruction in young children. These measurements provide a more sensitive and specific method for detecting impairment in lung function in individual children, and could be a promising measurement to assess recurrent wheezing and asthma once the equipment is commercially available. Measurement of lung clearance using the multiple-breath washout technique has shown potential in wheezy or asthmatic children, but the equipment is expensive and the measurement is time consuming. Spirometry with bronchodilator-reversibility measurements can be attempted in children aged 3 years and older, although this technique is generally reproducible only in children 5 years or older. Measurement of the forced expiratory flow-volume curve in infants (the raised volume rapid
for acute respiratory outcomes, we used the terms “RSV” OR “respiratory syncytial virus” AND “vaccine” OR “prophylaxis” AND “outcome measure” OR “scale” OR “score” OR “endpoint”. To identify references for long-term respiratory outcomes, we used the terms “RSV” OR “respiratory syncytial virus” AND “asthma” OR “wheeze” OR “lung function”. In both instances, we manually screened titles and abstracts to exclude unrelated studies and restricted our search to only articles published in English. For the respiratory outcomes, we restricted our literature review to articles that included children in the context of the discussed endpoints.

Search strategy and selection criteria

We searched PubMed up to March 1, 2017, and identified references without any date restrictions. To identify references for acute respiratory outcomes, we used the terms “RSV” OR “respiratory syncytial virus” AND “vaccine” OR “prophylaxis” AND “outcome measure” OR “scale” OR “score” OR “endpoint”. To identify references for long-term respiratory outcomes, we used the terms “RSV” OR “respiratory syncytial virus” AND “asthma” OR “wheeze” OR “lung function”. In both instances, we manually screened titles and abstracts to exclude unrelated studies and restricted our search to only articles published in English. For the respiratory outcomes, we restricted our literature review to articles that included children in the context of the discussed endpoints.

For the Pond5 library see https://www.pond5.com/sound-effects/1/wheezing.html
For the Soundsnap Library see http://www.soundsnap.com/tags/wheeze
For the Easy Auscultation library see http://www.easyauscultation.com/causes-listing-details?caseid=143
For more on devices for analysing wheezing sounds see http://www.imedicalapps.com/2015/09/wearable-device-analyzes-wheezing-sounds

thoracoabdominal compression technique) provides variables similar to those of spirometry.73 However, it requires sedation, which limits its use. Other techniques, including measurements of interrupter resistance, plethysmographic-specific airway resistance, and the rapid thoracoabdominal-compression technique during tidal breathing in infants, have been used, although predominantly in high-income research settings.74

Another method to measure and assess recurrent wheezing and asthma could be to record the wheezing sounds using a handheld device. Wheezing sounds can be recorded and interpreted and there are several sound libraries available on the internet (eg, the Pond5 wheezing library, the Soundsnap wheeze sounds library, and the Easy Auscultation heart and lung sounds reference guide). Handheld devices are being developed that can be applied to a child’s chest to record sounds; interpretation of these sounds can then be done to distinguish wheezing from other sounds. Such devices could offer a feasible point-of-care option for objective diagnosis of wheezing; however, further development, testing, and validation in infants and young children are needed.

Recommendations

To comprehensively assess the impact of RSV-preventive measures on acute disease and long-term respiratory outcomes (figure), we have some recommendations (panel).

Conclusions

New interventions against RSV disease have the potential to reduce acute RSV-associated LRTI and improve long-term lung health with reductions in wheezing illness or asthma. However, to assess the effect of such interventions, comprehensive measurements are needed for extended periods. RSV LRTI and all-cause LRTI should be measured for two RSV seasons after intervention, not only to assess the RSV burden but also to assess possible replacement disease, indirect effects related to viral-bacterial or viral-viral interactions, and the need for booster doses in the case of active immunisation. The prevalence and severity of recurrent wheezing or asthma should ideally be evaluated for up to 6 years. Product registration or licensure will be based on acute outcomes, but the planning and initiation of long-term assessments should begin during the clinical trial period. Standardised measurements of these long-term outcomes across locations and in diverse settings are needed to fully establish the effect of future interventions for the prevention of RSV disease.

Contributors

RAK and HJZ contributed equally to the conceptualisation, writing, and editing of the report.

Declaration of interests

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