Clinical Endpoints for RSV Prophylaxis Trials in Infants and Children In Industrialized Countries

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ABSTRACT

RSV continues to cause significant clinical and economic burden around the world. Historically, RSV-associated hospitalization was used as a primary endpoint for RSV prophylaxis trials in infants. However, due to the changing epidemiology and healthcare system landscape, this endpoint has become a critical bottleneck on the pathway to licensure for new therapeutics. A panel of seven RSV experts were convened (Chicago, Illinois, 22 May, 2014) to evaluate the challenges of defining RSV prevention endpoints for clinical trials and to develop endpoints that are clinically meaningful while minimizing subjectivity and bias to achieve sufficient consistency of response for regulatory approval. Particular consideration was given to the ability to systematically and consistently collect data across countries with different healthcare practices and systems, while capturing the greatest proportion of disease impact. The group consensus is that a clinically meaningful primary endpoint should be expanded to include medically attended RSV illness in settings beyond RSV-associated hospitalizations alone. In particular the primary endpoint should be: reduction in hospitalization, emergency room, or urgent care center visit due to an RSV respiratory Infection. Relevant secondary endpoints should include a reduction in RSV lower respiratory tract infection (LRI), a reduction of recurrent wheezing or asthma, and prevention of costs.
INTRODUCTION

Progress in the prevention of RSV with new monoclonal antibodies or vaccines, necessitates clear definition of clinical endpoints that are medically relevant. Historical studies that assessed the efficacy of prophylaxis for RSV have used the endpoint of RSV hospitalization alone; although the greatest burden of RSV illness occurs in emergency rooms, urgent care centres and physician’s offices. Therefore, defining clinically relevant endpoints that include cases seen at these additional sites are needed to use in RSV prevention trials.

As an initial step in addressing these needs, Regeneron Pharmaceuticals Inc, and Sanofi Aventis convened a panel of seven RSV experts at a meeting (Chicago, Illinois, 22 May, 2014) to evaluate the challenges of defining RSV prevention endpoints for clinical trials in infants and to develop a consensus framework. The goal was also to develop endpoints that are clinically meaningful while minimizing subjectivity and bias to achieve sufficient consistency of response for regulatory approval. To define clinically relevant endpoints, important considerations to consider are the burden of disease caused by RSV, and the natural history of disease. This report summarizes the group’s recommendations for moving towards consensus, and the reasons for making these recommendations.
THE BURDEN OF RESPIRATORY SYNCYTIAL VIRUS IN YOUNG INFANTS AND CHILDREN

By the age of 1 year, 60–70% of children will have been infected by RSV (2–3% of whom are hospitalized),¹ and almost all are infected by 2 years.² Reinfection is also common. Global estimates of the annual RSV disease burden in children under 5 years old are 30 million lower respiratory tract infections (LRI), 3 million related hospitalizations and up to 200,000 associated deaths.³

Young infants and children are at highest risk for severe complications and hospitalization with RSV infection. Data from the U.S. National Hospital Discharge Survey (NHDS) from 1980–1996 estimated that 74,000–126,000 infant hospitalizations are from RSV annually. This number appears to be increasing in both the United States and Canada, especially among infants < 6 months of age.⁴⁵ This translates to an annual RSV hospitalization rates of between 25-40 per 1000 for infants and a rate 6-10 times lower in the second year of life.⁶⁻¹⁰ In keeping with this estimates RSV-coded hospitalization rates were 26 per 1000 infants in 1997–2006 and 1.8 per 1000 children 1–5 years old accounting for almost a quarter of all hospitalizations among children under five years of age.¹¹ While a 17% decrease in overall bronchiolitis hospitalization rates in children age < 2 years was demonstrated between 2000 and 2009, the hospitalization rate in children with high risk medical conditions increased by 34%.¹⁰

Prospective population-based surveillance studies have provided well defined rates of RSV hospitalizations among young children.¹⁻¹² A prime example is a 4 year study (2000 – 2004) that examined laboratory-confirmed RSV infections among 5,067 enrolled children < 5 years of age in 3 states.¹ During November–April each year, RSV was implicated in 20% of hospitalizations 18% of emergency department visits, and 15% of office practice visits for acute respiratory illnesses. The annual rates of hospitalization were 3 per 1000 for children under 5 years of age and 17 per 1000 infants.
age < 6 months. Similar rates of RSV-associated hospitalizations have been reported from other industrialized countries with rates reported of 9-28/1000 children for the first year of life and 3-6/1000 for children <5 years of age.\textsuperscript{13-17}

Available emergency department data reflect a significant healthcare impact from confirmed RSV illness. In emergency departments in the United States, 64% of ED visits for bronchiolitis are caused by RSV in children < 2.\textsuperscript{18} The rate of emergency department visits for RSV during the winter has been estimated as 21.5/1000 among children under 8 years of age,\textsuperscript{19} 28/1000 children under 5 years of age, and 55/1000 under 6 months.\textsuperscript{1}

Visits for RSV illness to pediatric practices are notably greater than to emergency rooms. Though outpatient disease with RSV infection confers significant clinical burden, information on the RSV burden from outpatients is limited and underappreciated. While the annual rate of outpatient RSV infection was 77 per 1000 children under 3 years of age, in a German study,\textsuperscript{13} it was 80/1,000 children < 5 years old and 132/1,000 children < 6 months of age in a US study.\textsuperscript{1}

Few studies have defined and characterized the national healthcare impact from confirmed RSV illnesses among ambulatory patients, especially among those cared for in pediatric offices. Extrapolating the available data to the entire U.S. population suggests that among children <5 years of age, RSV results in 1 of 334 hospitalizations, 1 of 38 emergency department visits, and 1 of 13 primary care office visits each year.\textsuperscript{1,20}

Mortality associated with RSV infection is uncommon among young children in industrialized countries. Less than 500 fatal cases are estimated to occur in the U.S. per year.\textsuperscript{9,21-23} RSV is thought to cause a greater number of deaths in children compared to influenza, which is vaccine preventable. Since 2004, influenza-associated pediatric deaths have been a reportable condition in the National Notifiable Diseases Surveillance System by the Centers for Disease Control and Prevention. Similar to the reporting
of influenza-associated pediatric deaths, more accurate reporting of RSV-associated pediatric deaths should be developed.  

Economic burden of RSV disease in the U.S. and in other developed countries is appreciable. The greatest proportions of these costs are engendered by RSV illness among infants and the elderly. In the U.S. the annual costs for RSV-related hospitalization are estimated to have increased from $1.34 to $1.73 Billion between 2000 and 2009.  

A recent review provided greater insight, estimating the annual US medical cost for RSV at $1.15B; the main cost driver being inpatient costs ($530MM), followed by physician’s office visits ($220MM), ER visits ($215MM), asthma sequelae ($135MM), and hospital outpatient visits ($55MM). In addition lost income and other expenses for caregivers was estimated at $625MM annually. Thus direct costs from hospitalization account for approximately a third to a quarter of the overall RSV cost burden.

Following RSV bronchiolitis, some children develop a post-bronchiolitic wheezing syndrome, but whether RSV-associated wheezing confers long-term risk for subsequent development of asthma remains controversial.  

A recent meta-analysis of published data suggests a causal association between infant RSV hospitalization and respiratory morbidity (asthma/wheezing) that decreases as the child gets older, but RSV may even have longer term respiratory morbidity. Early studies of RSV prophylaxis with RSV IVIG and palivizumab conducted in the USA, Canada, Europe and Japan suggested that preventing RSV LRTI in high-risk infants prevented subsequent recurrent wheezing up to 3 years of age. Similarly, a recent placebo-controlled trial in healthy preterm infants showed that palivizumab reduced the number of days of wheezing in the first year of life. If this association is causal, the development of an even more effective preventative agent against RSV could have a major impact beyond the acute effects of RSV infection.
CLINICAL FEATURES OF RSV IN INFANTS AND YOUNG CHILDREN

Primary RSV Infection often occurs during the first encounter with RSV, which is usually in infancy, and essentially all children become infected by two years of age. The singular clinical features of RSV primary infection are that most children are symptomatic, lower respiratory tract involvement is frequent, wheezing is prominent, and the very young, those in the first 3 months of life, are most severely affected.

Typically RSV infection starts with several days of mild upper respiratory tract signs, cough, and low-grade fever. A worsening cough is usually heralded by lower respiratory tract involvement, and the infant becomes tachypneic and may have progressively more labored breathing, with dyspnea and retractions of the chest wall. The most common auscultatory signs are crackles and wheezes, but they are often variable over minutes to hours. A percentage of children will be hypoxemic, partly dependent on the altitude at which they live and the age of the child. Radiologic findings most frequently show hyperinflation and peribronchial thickening. Scattered interstitial infiltrates may be present, but more characteristic are areas of atelectasis, particularly in the right middle and upper lobes. The physical examination and radiographic findings commonly do not reflect the degree of illness, e.g. severely ill children may have little or no fever and minimal auscultatory findings.

The acute illness usually lasts about 5 to 10 days, but the cough may be prolonged for several weeks. The duration of hospitalization was a median of 2 days for 918 infants and children under 5 years of age with laboratory-confirmed RSV infection, and no children died. The most frequent discharge diagnosis among RSV positive hospitalized infants <1 year of age was bronchiolitis (85%) but among older children 2-5 years of age was asthma (60%) and pneumonia (51%). In this same study, RSV positive children seen in a clinician’s office or the emergency department were most commonly diagnosed with upper respiratory tract infections (32%), bronchiolitis (20%), asthma (13%), and
pneumonia (8%). A recent study further expanded on the hospital burden of illness. Amongst 2840 children hospitalized with RSV in Dallas between 2002-2007, the median length of stay was 3 days. Of hospitalized children in this study, 56% required oxygen for a median of 2 days, 11.6% were in the ICU for a median of 4 days, and 3 children died (0.1%).

Apnea may develop in 1.2% to 23.8% of infants and may be the initial manifestation before other respiratory signs are present. The apnea is generally self-limited, and not associated with severe LRI, is most common in premature infants, and does not recur with subsequent respiratory infections.

**CLINICAL ENDPOINTS**

The issue of clinically relevant endpoints in infants and children is of paramount importance from the industry and regulatory viewpoints. Only two products have been licensed for the prevention of severe RSV in children, respiratory syncytial virus immunoglobulin [RSV-IGIV, Respigam™] and palivizumab [Synagis™]. RSV-IGIV was indicated for the prevention of serious lower respiratory tract infection caused by RSV in children younger than 24 months of age with bronchopulmonary dysplasia (BPD) or a history of premature birth (gestation < 35 weeks gestational age). Palivizumab is indicated for the prevention of serious lower respiratory tract disease caused by RSV in pediatric patients at high risk of RSV disease. Safety and efficacy were established in infants with bronchopulmonary dysplasia (BPD) and infants with a history of prematurity (≤ 35 weeks gestational age). The pivotal trials for RSV-IGIV and for palivizumab utilized RSV-associated hospitalization as the primary endpoint. Medimmune Inc. carried out a large noninferiority trial with a second generation monoclonal antibody against RSV, comparing motavizumab to palivizumab. In this trial, a secondary clinical endpoint of outpatient medically attended LRI was proposed (outpatient MALRI). Outpatient MALRI included RSV-associated physician office, clinic or emergency room visits.
The following recent factors have become a critical bottleneck on the pathway to licensure, and prompted the panel to consider several clinically relevant endpoints for RSV preventive trials in its deliberations: 1) The changing epidemiology of RSV; 2) An increased and recent recognition of the true economic burden of RSV to the health system; 3) Changes in the insurance and reimbursement environment in the US, that discourage hospitalization, and thus transfer the burden of care to emergency rooms, urgent care units and physician’s offices; 4) The trend in the last 2-3 years that hospitalizations up to 2 days are reimbursed by the insurance companies as “Observations” so data derived from insurance claims may not capture the real impact; and 5) Finally, guidelines that discourage testing for RSV and other viral etiologies could have impacted the more recent numbers on hospitalizations. Hence the panel considered the following endpoints, and the pros and cons for each, in its deliberations.

**Primary endpoints considered:**

**Reduction in RSV Hospitalization**

**PRO:** Hospitalization for RSV is clinically meaningful to patients, physicians and regulators and has been used exclusively in previous Phase 3 trials evaluating polyclonal and monoclonal antibodies against RSV. RSV associated hospitalizations are relevant to payers and health economists because they account for the majority of the direct health related economic burden of RSV.

**CON:** Despite the clinical relevance of hospitalizations for RSV, its use as a sole endpoint in RSV prevention trials must take into account some limitations. The decision to hospitalize an infant with RSV is often based on subjective criteria, which vary greatly among different physicians responsible for admitting children. The threshold for hospitalization is highly variable across and within regions of the world, which may affect the interpretability and applicability of study results in specific regions, particularly in global studies. Although hospitalization for RSV may reflect the most severe cases of
infection, it is well known that the decision to hospitalize is highly subjective. With increasing pressure on payers to reduce overall costs for payment, and the increasing costs of inpatient hospital charges to these payers, there has been a decrease in the rates of bronchiolitis-related infant hospitalization and emergency room visits, with, however, an increase in the overall total costs. Hence only about a quarter of the overall costs to society are reflected in RSV hospitalization, compared to about half of the direct costs.

**Reduction in Outpatient Medically Attended Lower Respiratory Tract Infections (MALRI)**

The term medically attended acute respiratory infections (MAARI) has been used in several database-related epidemiologic studies, influenza vaccine trials, or studies in preterm infants. These studies used clear definitions of ICD-9 codes or ICD – 10 or other criteria for searching databases, to define medically attended acute respiratory infections. Recently, the term outpatient MALRI was used in an attempt to capture the burden of acute respiratory illness that was primarily affecting the lower respiratory tract that was medically attended. The term “outpatient MALRI” has been used in recent epidemiologic studies of RSV and the Motavizumab trial in preterm infants. This trial defined outpatient MALRI as “any medical management in a physician’s office, clinic, or emergency department with a diagnosis of bronchiolitis or pneumonia or an LRI as determined by the presence of cough, retractions, rhonchi, wheezing, crackles, or rales associated with coryza, fever, or apnea”. In the latter 2 reports, RSV-related MAARI was defined as “any laboratory-documented RSV illness associated with an outpatient visit (upper or lower respiratory tract illness), ED visit or hospitalization. LRI was defined as pneumonia, bronchiolitis or wheezing”.

**PRO:** Outpatient MALRI, if taken in conjunction with RSV hospitalization and ER/Urgent care visits, would capture a majority of the overall medical impact of RSV, and will provide the best overall
impact of any intervention on a medically attended event.

**CON:** There are three major difficulties with use of this endpoint. The first is the fact that in different countries, and even within the same country, subjects utilize medical services differently, with use differing based on the payer.\textsuperscript{53,58} The second difficulty with this broad end point is that the number of outpatient visits determine this endpoint, and outpatient visits depend almost entirely on the care-seeking behavior of the population.\textsuperscript{64} Thus this endpoint may be viewed as too subjective and dependent on cultural differences between patients in different countries. For example, in some countries, parents may seek attention for mild disease in their children, while in others the norm would not be to seek medical attention early. The final difficulty with this end point is that the definitions of LRI vary quite a lot between the different studies. [Please see discussion below for the definition of LRI].

**Reduction in Hospitalization, Emergency Room or Urgent Care Center visits due to an RSV Respiratory Infection**

**PRO:** This endpoint captures medical attendance for the most severe forms an RSV lower respiratory tract infection. While there is still some degree of subjectivity in this endpoint, this is the most objective endpoint. This endpoint depends to a lesser degree on the care-seeking behavior of the infant’s parents, [as to where they are seen] than MALRI. This endpoint also captures between 50 and 75% of the overall medical costs associated with an RSV infection. In this era of disincentives for hospital admission, many hospitals are increasing the emergency room purview, with the addition of short care units and urgent care centers that take care of children for less than 24 hours. In the US, many of these children would have been admitted for management in the past. Another advantage of this endpoint is that, if all the data on emergency room visits, urgent care attendance, and hospitalization is captured concomitant with the identification of the presence of RSV in the respiratory tract of the infant, this data can be captured in a standardized manner over all study sites. In a randomization by site strategy,
differences in care-seeking behavior and reasons for hospital admission should also be equally distributed by placebo and active substance.

**CON:** There are different reasons for admissions of patients to the hospital, and this might bring some degree of variability into the endpoint, since this endpoint does not include LRI in the diagnosis. Additionally, there is no clear definition of a lower respiratory tract infection; however, if a clinical diagnosis of any lower respiratory tract infection is added in a per protocol analysis, this difficulty will be overcome. Another limitation is that visits for RSV upper respiratory tract infections will be lumped with lower respiratory tract infections to at least some degree. This may diminish the apparent efficacy of a compound in preventing LRI, which would be an important outcome to evaluate in any study.

**Secondary endpoints considered:**

**Reduction in RSV Lower Respiratory Tract Infection (LRIs)**

**PRO:** RSV lower respiratory tract infection is one of the most severe manifestations of RSV infection in infants; therefore, demonstrating a reduction in RSV LRIs is a highly clinically meaningful endpoint. The major impact should be on preventing the more severe manifestations of RSV LRI, including hypoxemia, and visits to a physician’s office, an urgent care facility, an emergency department or a hospital. In addition to a standardized definition of RSV LRI, if a severity score were used, a real clinical impact might be able to be demonstrated, which would favorably impact payers decision-making.

**CON:** The use of RSV LRIs as a primary endpoint (but not as a secondary outcome) has several limitations. The definition of what constitutes an RSV LRI could vary in different countries. A physician visit for an LRI might not be considered clinically relevant in one country as opposed to another. Thus for cross-continental studies, regulatory agencies might not agree on the definition of RSV LRI. In addition, this is a very broad category that payers might not accept as a reason to provide a preventive therapy.
Finally, capturing LRI in a systematic manner at physician’s offices in many countries would introduce uncertainty into the endpoint. Given these many caveats, the group opined that while reducing RSV LRI, was an important goal of any preventive treatment, it would not be a primary endpoint that would be viewed as important either from the physician, payer or regulatory viewpoint. Finally, while prophylaxis might reduce RSV-related hospitalization, emergency room or urgent care center visits, its impact on RSV LRI might be more difficult to demonstrate because of the potential difficulty in LRI recognition.

There was, however, group consensus that reducing RSV LRI would be an important secondary endpoint to show biologic plausibility. This data is collected at any contact with a health care provider, regardless of whether it is at a healthcare provider's office, an urgent care center, an emergency room or a hospital. A standardized definition of severe RSV LRI was proposed based on the WHO definitions. The WHO defines severe pneumonia as the presence of lower chest wall in-drawing or hypoxemia (SpO₂ ≤ 90% on room air) in a child under five years of age, with cough or difficulty breathing. The pneumonia is considered to be very severe if there are general danger signs [altered sensorium, convulsions, difficulty feeding or vomiting all feeds]67,68. Thus in a child under five years of age, with cough or difficult breathing a definition of LRI could be - the presence of lower chest wall in-drawing or hypoxemia (SpO₂ ≤ 95% on room air at sea level, ≤ 92% on room air at altitude > 1800m, or ≤ 5% or lower in children with CLD or CHD with chronic underlying hypoxemia. (The hypoxemia definitions proposed here account for living at altitude and underlying CLD or CHD). The advantage of using these simplified guidelines is that they can be taught to any level of health worker [as is being done around the world with WHO-based child health programs]69-73 and standardized materials are available. In addition, there is no dependence on auscultation and the inherent difficulties with interpretation of breath sounds.

An alternative definition of LRI is a modification the previous definition used in the motavizumab study. It is known that retractions are a poorly defined clinical sign,71 and indeed the WHO uses lower
chest wall in-drawing for its definition of severe pneumonia. In addition, rhonchi refers to sounds produced in the bronchus and the trachea and is considered a sound due to thick mucus, which does not necessarily imply a lower respiratory tract infection.74 Hence in a child under five years of age, with cough OR difficult breathing an alternative definition of LRI could be the presence of lower chest wall in-drawing, OR wheezing OR crackles OR hypoxemia ($\text{SpO}_2 < 95\%$ on room air at sea level, $< 92\%$ on room air at altitude $> 1800\text{m}$, or $< 5\%$ or lower in children with CLD or CHD with chronic underlying hypoxemia).

Given the difficulties of standardizing recognition of the clinical signs of lower chest wall in-drawing, OR wheezing OR crackles, an alternative more objective definition of LRI was proposed as hypoxemia ($\text{SpO}_2 < 95\%$ on room air at sea level, $< 92\%$ on room air at altitude $> 1800\text{m}$, or $< 5\%$ or lower in children with CLD or CHD with chronic underlying hypoxemia) in a child under five years of age, with cough OR difficult breathing.

An RSV infection will be considered positive with the detection of RSV in nasal secretions obtained + 72 hours of the clinical definition for an LRI being made, as determined by cell culture RSV RNA using an FDA approved or a qualified RSV RT-PCR test.

Consistent measures and standardized methods for collection of signs and symptoms and criteria for obtaining an RSV swab should be implemented across sites.

**Reduction of Recurrent Wheezing or Asthma**

**PRO:** Impacts on long-term outcomes after RSV infection have the potential to change the cost-effectiveness of a treatment, so follow-up of treated patients is important. Specifically, long-term outcomes in treatment studies have been reported in studies linking RSV LRTI in infants with subsequent increased healthcare utilization and cost, reduced quality of life, recurrent wheezing during childhood, and asthma.75,76 As noted previously, preventing RSV with RSV-IVIG34 or palivizumab35–38 resulted in
significant improvements in both respiratory outcomes as well as lung function studies up to 10 years later.\textsuperscript{34} Different definitions of recurrent wheezing or asthma have been used in different studies. Thus the following have all been used in various seminal asthma studies: physician attended wheeze,\textsuperscript{35-37,77} parent report by phone questionnaire,\textsuperscript{77,78} and physician diagnosis of asthma.\textsuperscript{79,80} Parent report each year has been used in longitudinal studies,\textsuperscript{78-80} which may be more feasible.

\textit{CON}: Most long-term follow-up studies encounter difficulty in patient retention, and studies carry on for a long time. The need for long-term follow up makes the study difficult, and might negatively influence recruitment at the outset. Long-term follow-up studies could therefore be done either on a subset of the population that agrees after the primary studies are over, or as new studies themselves. The cost of long-term follow-up studies, depending on the complexity, would be a consideration.

\textbf{Costs Prevented}

\textit{Pro}: Obtaining an estimate of the direct and indirect costs of an RSV infection in a standardized manner is an important outcome. This is especially true because of the changing climate for the management of RSV disease. An estimation of the costs prevented will be an important secondary endpoint to collect, especially if the trial is conducted in many countries. Clearly, the direct costs prevented by an intervention would be of value to payers [whether they be insurance companies or governments for socialized programs]. The indirect costs of an RSV infection to society are relevant to policymakers as well as government. Clearly knowing the attributable reduction in the various primary and secondary endpoints, and the costs prevented, would be important in generating cost-effectiveness data.

\textit{Con}: Since studies will be presumably conducted in many countries in the Americas, Europe and Australia, there are quite different costs involved. Data could be quite variable because collecting cost
data is not standardized across countries. Additionally, it will be much more difficult to get costing data from countries where medicine is socialized. In North America, depending on the country, different states might have quite different methods for paying healthcare providers. For example, getting cost data from HMOs could be quite different from getting data from Medicaid-covered patients in the U.S.

Finally, it is often very difficult to get real cost data, and in some areas charges might be the only option available. Therefore the analysis of this data could be quite complicated, and perhaps difficult to generalize. In addition, if data on indirect costs are collected, there might be reticence on the part of some parents and caregivers to participate in the study. This could bias the generalizability of the results, and would make recruiting patients into any study more difficult.
Summary of consensus:

There was group consensus that a clinically relevant **primary endpoint** should be: Reduction in *Hospitalization, Emergency Room or Urgent Care Center visits due to an RSV Respiratory Infection*

There was group consensus that relevant **secondary endpoints** should include:

1. **Reduction in RSV LRI.** This was defined as either a) the presence of lower chest wall in-drawing, OR wheezing OR crackles OR hypoxemia (SpO2 < 95% on room air at sea level, < 92% on room air at altitude > 1800m, or ≤ 5% or lower in children with CLD or CHD with chronic underlying hypoxemia) in a child under five years of age, with cough OR difficult breathing AND a positive RSV test on upper or lower respiratory secretions + 72 hours of the clinical definition for an LRI being made, or b) the presence hypoxemia (SpO2 < 95% on room air at sea level, < 92% on room air at altitude > 1800m, or ≤ 5% or lower in children with CLD or CHD with chronic underlying hypoxemia) in a child under five years of age, with cough OR difficult breathing AND a positive RSV test on upper or lower respiratory secretions + 72 hours of the clinical definition for an LRI.

   Since agreement was not unanimous on which of these definitions were superior, as there were no trials to support either definition, and the majority preferred the former, it was suggested that the primary definition for RSV LRI be the former (a) and a sensitivity analysis be done using the latter (b), since it is embedded in the former definition. Clearly reducing RSV LRI using definition (a) would be less specific but potentially identify a larger population attributable reduction in RSV LRI and using definition (b) would be more specific but potentially identify a smaller population attributable reduction in RSV LRI.

2. **Reduction of Recurrent wheezing or asthma**
3. Costs prevented

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