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# Report of the WHO technical consultation on the evaluation of respiratory syncytial virus prevention cost effectiveness in low- and middle-income countries, April 7-8, 2022

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# Vaccine

## Report of the WHO technical consultation on the evaluation of respiratory syncytial virus prevention cost effectiveness in low- and middle-income countries, April 7-8, 2022 --Manuscript Draft--

<b>Manuscript Number:</b>	JVAC-D-23-01228R1
<b>Article Type:</b>	Conference Report
<b>Keywords:</b>	cost effectiveness; Global health; Monoclonal antibody; respiratory syncytial virus; vaccine
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<b>Abstract:</b>	<p>Policymakers often rely on impact and cost-effectiveness evaluations to inform decisions about the introduction of health interventions in low- and middle-income countries (LMICs); however, cost-effectiveness results for the same health intervention can differ by the choice of parameter inputs, modelling assumptions, and geography. Anticipating the near-term availability of new respiratory syncytial virus (RSV) prevention products, WHO convened a two-day virtual consultation in April 2022 with stakeholder groups and global experts in health economics, epidemiology, and vaccine implementation. The objective was to review methods, parameterization, and results of existing cost-effectiveness analyses for RSV prevention in LMICs; identify the most influential inputs and data limitations; and recommend and prioritize future data gathering and research to improve RSV prevention impact estimates in LMICs. Epidemiological parameters identified as both influential and uncertain were those associated with RSV hospitalization and death, specifically setting-specific hospitalization rates and RSV-attributable death rates. Influential economic parameters included product price, delivery costs, willingness-to-pay for health on the part of potential donors, and the cost of RSV-associated hospitalization. Some of the influential parameters identified at this meeting should be more precisely measured by further research. Other influential economic parameters that are highly uncertain may not be resolved, and it is appropriate to use sensitivity analyses to explore these within</p>

	cost-effectiveness evaluations. This report highlights the presentations and major discussions of the meeting.
<b>Suggested Reviewers:</b>	Meredith McMorrow bwe3@cdc.gov
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Dear Vaccine,

Attached please find a revision to manuscript (JVAC-D-23-01228) titled "Report of the WHO technical consultation on the evaluation of respiratory syncytial virus prevention cost effectiveness in low- and middle-income countries, April 7-8, 2022."

We have revised the manuscript to address peer-reviewer concerns. We have also lightly edited the document for sense and to update the evidence base.

We thank you for your review and the opportunity to submit it to your journal.

Thank you,

Justin R. Ortiz, MD, MS  
Professor  
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Scientist, Center for Vaccine Development and Global Health  
University of Maryland School of Medicine

Ms. Ref. No.: JVAC-D-23-01228

Title: Report of the WHO technical consultation on the evaluation of respiratory syncytial virus prevention cost effectiveness in low- and middle-income countries, April 7-8, 2022

Reviewers' comments:

#### REVIEWER 1 COMMENTS

**Reviewer 1 comment: Thank you for the opportunity to review Report of the WHO Consultation on the Evaluation of RSV Prevention Cost Effectiveness in Low- and Middle-Income Countries. The report is well written and will provide very useful information for those interested in designing cost effectiveness studies for RSV monoclonal antibodies and maternal RSV vaccination programs. The text is well organized, the figures and tables are useful in providing examples and baseline data.**

AUTHOR RESPONSE: We thank the reviewer for noting that manuscript was well written and will be useful.

**Reviewer 1 comment: P6 Line 143-144. Re affordability. What products are being referred to here? If referring to maternal vaccine and mAb no pricing is known so would suggest that the authors not state that they are unaffordable.**

AUTHOR RESPONSE: Prices in the US have been reported to be \$395-\$495 for nirsevimab, \$295 for maternal vaccine. The authors have heard of no commitments for tiered pricing on current products. The referenced sentence is supported by three WHO citations related to anticipated affordability of products.

**Reviewer 1 comment: P6 Line 147-148. Suggest delete word "also" from this sentence.**

AUTHOR RESPONSE: The suggested edit has been made.

**Reviewer 1 comment: P7 Line 169. Suggest a little more explanation re the Th2-biased response. Describe result of this response, as this statement doesn't express the gravity of this safety signal.**

AUTHOR RESPONSE: We have removed the statement related to the mechanism of the vaccine safety signal as it is not relevant to the current manuscript objectives.

**Reviewer 1 comment: P8 Line 196. Suggest removing "expected to have limited durations of protection".**

AUTHOR RESPONSE: We cite three WHO publications supporting this sentence. mAb and maternal vaccines are not anticipated to produce durable immune protection.

**Reviewer 1 comment: P8 Line 207. The morbidity data you describe are impressive for all infants (0-12 months) not only infants <6mos. Given data presented, it is justified to recommend prevention for all infants (0-12 months).**

AUTHOR RESPONSE: It was not in the scope of our meeting to make policy recommendations. We await the WHO Strategic Advisory Group of Experts on Immunization (SAGE) for prevention recommendations.

**Reviewer 1 comment: P10 Line 240. The authors might substitute AAP US-centric reference and make more generic comment here. Suggest: "Policy recommendation for palivizumab in most countries are limited to preterm infants and toddlers with congenital heart disease and chronic lung disease of prematurity. "**

AUTHOR RESPONSE: We removed the reference to AAP clinical guidelines.

**Reviewer 1 comment: P11 Line 255. Suggest adding birth dose as that is the most vulnerable time for protection. Suggest: "These drugs could be given at birth or during a routine childhood immunization visit."**

AUTHOR RESPONSE: Routine immunization timepoints include birth doses. We have edited the sentence to clarify this (with italicized text representing additions and strikethrough text representing deletions): "These drugs could be given *as a birth dose or during a later* routine childhood immunization ~~visit~~ *timepoint* either year-round or before the anticipated RSV season, and they are expected to provide protection through much, or all, of an RSV season..."

**Reviewer 1 comment: P11 Line 275. Please clarify by adding the efficacy of Pfizer maternal vax here. The overall efficacy against MALRI is low (~51-54%). It would be useful to describe modeled efficacy estimate against demonstrated efficacy.**

AUTHOR RESPONSE: We have added a parenthetical phrase indicating that vaccine efficacy against medically attended severe lower respiratory tract illness for 180 days after birth was 69.4%, an outcome that we think is most relevant to LMICs (with italicized text representing additions): "A Pfizer maternal RSV vaccine candidate has demonstrated higher efficacy (*vaccine efficacy against medically attended severe lower respiratory tract illness for 180 days after birth was 69.4%*) than modelled by the studies presented here..."

**Reviewer 1 comment: P12 Line 289. Tdap?**

AUTHOR RESPONSE: Tdap is not given as a birth dose in the EPI schedule. We maintain that the most relevant proxy for birth dose RSV mAb would be birth dose BCG or HepB, although neither is a perfect proxy.

**Reviewer 1 comment: P12+. General. Would it be of value to describe DALYs and note this measure as the preferential measure for the ICER?**

AUTHOR RESPONSE: We described DALYs and contextualized their interpretation in a subsequent paragraph (with italicized text representing additions): "*DALYs are a widely-used metric that combine years of life lost from mortality with years of healthy life lost from morbidity, and are a standard way to express health impact in cost-effectiveness studies as they can be compared across disease states and aetiologies.*"

**Reviewer 1 comment: P19 Line 446. It is true that delivery costs for maternal vaccines are unknown, however what might one learn from extant maternal vaccine programs (Tdap, hepatitis B) to apply to this scenario apart from the complexity of seasonal delivery. Would it be possible to make a comparison with other maternal vaccine programs here?**

AUTHOR RESPONSE: Maternal vaccine programs for Tdap and HepB are not widely used in LMICs and we are unaware of generalizable data from existing programs that are particularly helpful here. There are tetanus vaccination programs used as part of maternal neonatal tetanus elimination programs, but these are typically done through supplemental immunization activities that are different from the routine delivery anticipated for RSV vaccines.

**Reviewer 1 comment: P21 Line 501. Efficacy data for nirsevimab and Pfizer maternal vaccine are available and nirsevimab is authorized in EU.**

AUTHOR RESPONSE: We edited the sentence to acknowledge these data availabilities (with italicized text representing additions): "It is anticipated that *more product-specific characteristics data*, such as duration of protection and efficacy *from LMIC settings* will become available as field trials progress."

**Reviewer 1 comment: P22 Line 513 and 514. Suggest adding the word antibody after monoclonal or substituting with mAb. Best to be consistent with naming convention throughout document.**

AUTHOR RESPONSE: The suggested edit has been made.

**Reviewer 1 comment: Figure 2. Suggest that you "name" the ratio of out of hospital deaths/in hospital deaths so that this quantity might be conventionally named in future work.**

AUTHOR RESPONSE: We are unaware of a standard naming convention for the referenced statistic.

**Reviewer 1 comment: Figure 3. Suggest reducing range of X axis (-100 to +300).**

AUTHOR RESPONSE: We believe that by keeping the scale the same on the negative and positive sides, it allows better visualization of where the important factors are in sensitivity analyses.

### REVIEWER 3 COMMENTS

**Reviewer 3: The manuscript provides a report of a WHO technical group meeting on deliberations regarding the case and gaps to address the cost-effectiveness of RSV interventions, particularly maternal vaccination of pregnant women and long-acting monoclonal antibodies which have been recently licensed or will be licensed soon. The manuscript is well written and there are only minor suggestions.**

AUTHOR RESPONSE: We thank the reviewer for noting that the manuscript was well written.

**Reviewer 3: 1. Line 217- rather than the CHAMPS data providing a "conservative" estimate, it provides more specific evidence of the role of RSV in LRTI-associated deaths. Although it would yield a lower percentage of LRTI attributable to RSV, it does not indicate it's a more "conservative" estimate.**

AUTHOR RESPONSE: We removed the language regarding CHAMPS providing a "conservative" estimate.

**Reviewer 3: 2. Ln 232 - citing of the US indigenous population is using somewhat of an outlier, even in relation to LMIC type of setting, as this population has been shown to have much higher rates of infectious disease morbidity and mortality even for other diseases compared with sub-Saharan African and other settings. Suggest also comparing to the placebo arm of the maternal RSV study done by Novavax, which reports for LMIC.**

AUTHOR RESPONSE: The referenced data are factually correct and reflect the discussion at the meeting. We edited the line to provide additional context to these results (with indented text representing additions): "Incidence of RSV LRTI illnesses and hospitalizations during the first six months of life were appreciably lower in the systematic review (when restricted to LMICs) than in the placebo arm of an RSV mAb trial among US indigenous populations [28], *possibly reflecting lower testing rates and worse access to care in LMIC compared to the US, even in underserved populations.*"

**Reviewer 3: 3. Ln 245- agree not licensed at time of meeting, however, Nirsevimab is now licensed in EU (and soon elsewhere) and Pfizer pre-F maternal vaccine has a positive opinion and licensure is imminent, suggest reflecting as such.**

AUTHOR RESPONSE: We added a sentence at the end of the paragraph with updates of authorized RSV prevention products: "As of September 2023, extended half-life mAbs and maternal RSV vaccines have been authorized for use in some high-income countries in North America and Europe." We have also provided additional updates where appropriate throughout the manuscript.

**Reviewer 3: 4. Ln 273- would be useful to also indicate that duration of protection for maternal vaccination is a big unknown, as alluded to by studies on influenza vaccination of pregnant women where efficacy waned rapidly beyond two months of infant age.**

AUTHOR RESPONSE: We added a sentence noting that clinical outcomes were assessed for 6 months in the recent Pfizer vaccine trials (with italicized text representing additions): “A Pfizer maternal RSV vaccine candidate has demonstrated higher efficacy (*vaccine efficacy against medically attended severe lower respiratory tract illness for 180 days after birth was 69.4%*) than modelled by the studies presented here...”

**Reviewer 3: 5. Ln 276- can provide the recently published study on the Pfizer pre-F vaccine in pregnant women**

AUTHOR RESPONSE: We have made this edit as referenced above.

**Reviewer 3: 6. Ln 288- a birth dose of Nirsevimab is not necessarily a the best strategy for most settings where there is a strong seasonality to RSV epidemics, hence using BCG as a proxy would be misleading.**

AUTHOR RESPONSE: In response to a similar comment from Reviewer #1, we already highlight the programmatic challenges of seasonal vaccination in LMIC settings without programs for other seasonal vaccines. In response to the Reviewer #3 comment, we further elaborated on the existing EPI schedule and that seasonal campaign approaches may be programmatic challenging (with italicized text representing additions): “*Extended Programme on Immunization routine immunization contact also include visits around 6, 10 and 14 weeks, 9 months, and a timepoint during the second year of life. One of these timepoints could potentially be used for mAb delivery, seasonal campaign dosing approaches may be programmatic challenging in LMICs where this has not been done for other vaccines.*”

**Reviewer 3: 7. Ln 397- need to indicate, as alluded to by the previous paragraph related to CHAMPS data where there is granular interrogation of the cause of death, that these may be over-estimates based upon likelihood that RSV could have been incidental infection in some of the decedents where it was identified.**

AUTHOR RESPONSE: We have made this edit(with italicized text representing additions): “*These figures may be over-estimates based upon the possibility that RSV might not have been in the cause chain of death in some of the decedents where it was identified.*”

**Reviewer 3: 8. Not related to the article, however, it is striking that only a fraction of the participants in the workshop were actually from a LMIC country.**

AUTHOR RESPONSE: The reviewer comment is noted.



## Suggested Reviewers

### Suggested reviewers

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**Declaration of interests:**

- Meagan C. Fitzpatrick: received grants to her institution from the National Institutes of Health, National Science Foundation, World Health Organization, and Bill & Melinda Gates Foundation; consulting fees from Sanofi Pasteur and The Commonwealth Fund.
- Rachel S. Laufer: none to declare
- Ranju Baral: none to declare
- Amanda Driscoll: none to declare
- Danny Feikin : none to declare
- Jessica A. Fleming: none to declare
- Mark Jit: Mark Jit is an unpaid member of the Respiratory Syncytial Virus Consortium in Europe (RESCEU) and Preparing for RSV Immunisation and Surveillance in Europe (PROMISE). RESCEU and PROMISE have received funding from the Innovative Medicines Initiative 2 Joint Undertaking. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation program and the European Federation of Pharmaceutical Industries and Associations. Neither MJ nor his research group has received any forms of pecuniary or other support from the pharmaceutical industry.
- Sonnie Kim: none to declare
- Mihaly Koltai: none to declare
- You Li: Grants to his institutions from Wellcome Trust and GSK; personal fees from Pfizer, all outside the submitted work.
- Xiao Li: none to declare
- Harish Nair: Received funding from Innovative Medicines Initiative, National Institute of Health Research, Pfizer, and Icosavax; Consultancies from Sanofi, Pfizer, GSK, MSD, ReViral, Icosavax, Astra Zeneca, and Abbvie all outside submitted work.
- Kathleen M. Neuzil: Is a member of the WHO Strategic Advisory Group of Experts on Immunization.
- Clint Pecenka: none to declare
- Erin Sparrow: none to declare
- Padmini Srikantiah: none to declare
- Justin R. Ortiz: Grants to his institution from the National Science Foundation, Bill & Melinda Gates Foundation, Pfizer, NIH, and World Health Organization; consulting fees from Putnam and GSK; and participation on advisory boards for Pfizer, Seqirus, and Moderna, all outside the submitted work.

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1 **TITLE:** Report of the WHO technical consultation on the evaluation of respiratory syncytial virus  
2 prevention cost effectiveness in low- and middle-income countries, April 7-8, 2022

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**HIGHLIGHTS:**

- Respiratory syncytial virus (RSV) is an important pathogen globally.
- The burden of RSV illness is highest in low/middle-income countries (LMICs).
- In April 2022, WHO convened a meeting to discuss the economics of RSV prevention.
- We reviewed cost-effectiveness analyses of RSV prevention in LMICs.
- We provided recommendations for future data gathering to address data limitations.

[Click here to view linked References](#)

1 **TITLE:** Report of the WHO technical consultation on the evaluation of respiratory syncytial virus  
2 prevention cost effectiveness in low- and middle-income countries, April 7-8, 2022

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56 **HIGHLIGHTS:**

- 57 • Respiratory syncytial virus (RSV) is an important pathogen globally.  
58 • The burden of RSV illness is highest in low/middle-income countries (LMICs).  
59 • In April 2022, WHO convened a meeting to discuss the economics of RSV prevention.  
60 • We reviewed cost-effectiveness analyses of RSV prevention in LMICs.  
61 • We provided recommendations for future data gathering to address data limitations.  
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65 **ABSTRACT**

66 Policymakers often rely on impact and cost-effectiveness evaluations to inform decisions about the  
67 introduction of health interventions in low- and middle-income countries (LMICs); however, cost-  
68 effectiveness results for the same health intervention can differ by the choice of parameter inputs,  
69 modelling assumptions, and geography. Anticipating the near-term availability of new respiratory  
70 syncytial virus (RSV) prevention products, WHO convened a two-day virtual consultation in April 2022  
71 with stakeholder groups and global experts in health economics, epidemiology, and vaccine  
72 implementation. The objective was to review methods, parameterization, and results of existing cost-  
73 effectiveness analyses for RSV prevention in LMICs; identify the most influential inputs and data  
74 limitations; and recommend and prioritize future data gathering and research to improve RSV  
75 prevention impact estimates in LMICs. Epidemiological parameters identified as both influential and  
76 uncertain were those associated with RSV hospitalization and death, specifically setting-specific  
77 hospitalization rates and RSV-attributable death rates. Influential economic parameters included  
78 product price, delivery costs, willingness-to-pay for health on the part of potential donors, and the cost  
79 of RSV-associated hospitalization. Some of the influential parameters identified at this meeting should  
80 be more precisely measured by further research. Other influential economic parameters that are highly  
81 uncertain may not be resolved, and it is appropriate to use sensitivity analyses to explore these within  
82 cost-effectiveness evaluations. This report highlights the presentations and major discussions of the  
83 meeting.

84 **Keywords:** cost effectiveness; global health; monoclonal antibody; respiratory syncytial virus; vaccine

85 **Abbreviations:**

86 AAP = American Academy of Pediatrics

- 87 ANISA = Aetiology of Neonatal Infections in South Asia study
- 88 BCG = Bacille Calmette-Guérin vaccine
- 89 CFR = case fatality ratio
- 90 CHAMPS = Child Health and Mortality Prevention Surveillance Study
- 91 CHOICE = WHO Choosing Interventions that are Cost-Effective Programme
- 92 DALY = disability-adjusted life year
- 93 GBD = global burden of disease
- 94 GDP = gross domestic product
- 95 ICU = Intensive care unit
- 96 IHME = Institute for Health Metrics and Evaluation
- 97 LMIC = low- and middle-income countries
- 98 LRTI = lower respiratory tract illness
- 99 mAb = monoclonal antibody
- 100 RSV = respiratory syncytial virus
- 101 PAHO = Pan American Health Organization
- 102 PERCH = Pneumonia Etiology Research for Child Health project
- 103 SAGE = WHO Strategic Advisory Group of Experts on Immunization
- 104 US = United States
- 105 WHO = World Health Organization



106 **BACKGROUND**

107 Respiratory syncytial virus (RSV) is a leading cause of hospitalization in infants and young children due to  
108 lower respiratory tract illness (LRTI), including pneumonia and bronchiolitis; however, licensed  
109 preventive interventions and leading pipeline candidates are not anticipated to be affordable for low-  
110 income countries without subsidies; [1-3]. In 2016, recognizing the growing pipeline of RSV prevention  
111 products, the World Health Organization (WHO) Strategic Advisory Group of Experts on Immunization  
112 (SAGE) requested that preparations be made to support global policymaking for RSV preventive  
113 interventions [4]. To inform decisions about the introduction of RSV immunization products,  
114 policymakers in low- and middle-income countries (LMICs) will need to consider their impact and cost-  
115 effectiveness.

116 WHO convened an online meeting in April 2022 to review cost-effectiveness analyses for RSV  
117 prevention. The objectives of the meeting were the following: 1) to review objectives, methods, inputs,  
118 and results of cost-effectiveness analyses of RSV prevention for young children in LMICs; 2) to identify  
119 the most influential parameter inputs and data limitations for the cost-effectiveness analyses; and 3) to  
120 recommend and prioritize future data gathering and research to improve RSV prevention impact  
121 estimates in LMICs. Attendees included stakeholder groups and global experts in health economics,  
122 epidemiology, and vaccine implementation. The agenda and list of participants are in the Online  
123 Supplement.

124 **RSV DISEASE OVERVIEW**

125 RSV is a common respiratory virus that circulates in seasonal epidemics [5]. Its symptoms are usually  
126 mild and self-limited [6]. However, RSV can also cause severe disease. It is the most common cause of  
127 LRTI in young children globally [7], it can exacerbate chronic medical conditions, and it can cause acute

128 respiratory illness in older adults [8]. RSV transmission can occur by contact or inhalation of airborne  
129 virus. Most individuals have evidence of RSV infection by two years of age [6], however subsequent  
130 reinfection is possible [9]. Among children, the greatest risk of severe RSV disease occurs in infants <6  
131 months of age and in children with congenital heart disease or lung disease [6].

132 As of September 2023, there are no licensed vaccines administered to children for RSV prevention [2].  
133 Clinical trials assessing pediatric RSV vaccine candidates in the 1960s were halted due to evidence of  
134 vaccine-associated enhanced disease[10, 11]. This safety signal slowed RSV vaccine development for  
135 decades. Since 1998, palivizumab, a humanized monoclonal antibody (mAb) directed against the F  
136 protein of RSV, has been licensed for use in young children at high risk for RSV disease [12]. The  
137 immunoprophylaxis is administered by monthly intramuscular injection throughout the RSV season [12].  
138 Palivizumab is too expensive for use in most LMICs. Acknowledging that RSV preventive interventions  
139 are an unmet global health need, biomedical research funders including the US National Institutes of  
140 Health and the Bill & Melinda Gates Foundation have made substantial investments in understanding  
141 and preventing RSV disease. There is now a robust research and development pipeline for RSV  
142 prevention products, including monoclonal antibody (mAb) immunoprophylaxis and vaccines in late-  
143 stage development. By May 2023, extended half-life mAb have achieved licensure in Europe [13, 14],  
144 maternal RSV vaccines are undergoing regulatory review [15], and RSV vaccines for older adults have  
145 achieved licensure in the United States [16].

146 While RSV prevention products are likely to become available first in high-income countries, efforts are  
147 underway to accelerate their availability and programmatic suitability in LMICs [1, 2]. A major  
148 requirement to justify funding is product cost-effectiveness, defined as the expenditure necessary to  
149 achieve a unit of health or other benefit. Cost-effectiveness is often an explicit part of decisions by  
150 regulatory bodies, countries, and donors about whether to adopt a health intervention. For instance,

151 SAGE includes cost-effectiveness as one of the criteria considered when deciding whether to  
152 recommend vaccines for use [17], recommendations which are regarded as authoritative by many  
153 countries. Gavi, the Vaccine Alliance, is a major donor supporting immunization efforts for LMICs and  
154 lists “Value for Health” among its own criteria when considering which products to financially support  
155 [18]. For Gavi-eligible countries, adoption of a vaccination program is often conditional on both a SAGE  
156 recommendation and Gavi support, with additional country-specific considerations regarding the cost-  
157 effectiveness of the new intervention relative to current and potential uses of the health budget [19].

## 158 **DISEASE BURDEN**

159 In 2022, researchers published an updated systematic analysis of global disease burden estimates for  
160 RSV acute LRTI in young children [20, 21]. The update included disease burden estimates within narrow  
161 age bands to facilitate impact modelling of potential RSV preventive interventions expected to have  
162 limited durations of protection [1-3]. Global and regional estimates of RSV community morbidity and  
163 hospitalization were presented, as well as RSV in-hospital and overall mortality burden from published  
164 and unpublished data, using a generalized linear mixed-effect modelling framework.

165 The research highlighted the substantial RSV morbidity and mortality burden in infants <6 months,  
166 accounting for 20% and 45% of RSV LRTI episodes and deaths in children <5 years, respectively. In LMICs,  
167 the RSV LRTI incidence rate was three times as high as that in high-income countries in the community  
168 whereas the RSV LRTI hospitalization rate was lower than that in high-income countries among infants  
169 <6 months, highlighting the limited access to healthcare in LMICs. This was further emphasized by  
170 estimates for the RSV community mortality burden, which showed that 82% of RSV-attributable deaths  
171 occurred out of hospital and the infant case fatality ratio (CFR) of RSV LRTI in the community could be as  
172 high as 6.6% in low-income countries. These findings suggest that RSV immunization programs targeting  
173 protection during the first six months of life could have a substantial effect on reducing severe RSV

174 disease burden. In LMICs, RSV immunization programs are likely to be even more impactful given that a  
175 considerable proportion of RSV morbidity and mortality was due to limited access to health-care  
176 services, and therefore these deaths could potentially only be averted through immunization programs.  
177 However, substantial year to year variability as well as intra- and inter-region variability in RSV morbidity  
178 and mortality (in a given year) were noted. In an attempt to attribute cause of death to the RSV related  
179 mortality estimate, two sets of estimates were presented – one where RSV was identified in the upper  
180 airway samples of a deceased child (RSV associated mortality); and the other where RSV was deemed to  
181 be in the causal chain based on the opinion of an expert adjudication panel, such as in CHAMPS (RSV  
182 attributable mortality) [22]. Although the most recent RSV mortality estimates incorporate more data on  
183 mortality than previous estimates, more data are needed to better characterize RSV mortality,  
184 particularly in community settings.

185 During the WHO meeting, RSV LRTI morbidity and mortality incidence estimates from the systematic  
186 review were compared with estimates determined by other high-quality studies, including mAb and  
187 vaccine trials and large, multi-country observational studies (Table 1). Estimates of several RSV LRTI  
188 epidemiologic parameters from the systematic analysis were similar to placebo arms in RSV intervention  
189 field trials, including RSV LRTI incidence in the first 3 and 6 months of life, and severe and hospitalized  
190 RSV LRTI incidence in first 3 months of life [23, 24]. Severe RSV LRTI incidence estimates from the first  
191 two months of life were comparable to the findings of the Aetiology of Neonatal Infections in South Asia  
192 (ANISA) observational cohort study [25]. In-hospital CFR estimates for RSV LRTI among children <5 years  
193 of age were similar to the Pneumonia Etiology Research for Child Health (PERCH) case control study [26,  
194 27]. Incidence of RSV LRTI illnesses and hospitalizations during the first six months of life were  
195 appreciably lower in the systematic review (when restricted to LMICs) than in the placebo arm of an RSV  
196 mAb trial among US indigenous populations [28], possibly reflecting lower testing rates and worse  
197 access to care in LMIC compared to the US, even in underserved populations. The systematic review

198 estimated much higher RSV LRTI morbidity and mortality during early childhood than the Institute for  
199 Health Metrics and Evaluation (IHME) Global Burden of Disease estimates in 2016 (33 million episodes  
200 and 101,000 deaths in review compared to 11 million cases and 41,000 deaths by IHME) [29].

## 201 **PREVENTIVE INTERVENTIONS**

202 Palivizumab, a humanized monoclonal antibody (mAb) directed against the F protein of RSV, is licensed  
203 for use in young children at high risk for RSV disease [12]. The immunoprophylaxis is administered by  
204 intramuscular injection monthly throughout the RSV season [12]. The utility of palivizumab is limited by  
205 its narrow clinical indication and high price [1-3]. Safe and effective next-generation RSV preventive  
206 interventions that provide increased duration of protection are a critical unmet global health need [1, 2].

207 At the time of the WHO meeting, there were no licensed next-generation RSV prevention products,  
208 although some leading candidates were expected to seek regulatory approval soon. PATH tracks the  
209 clinical development landscape of RSV prevention including development stages, target populations,  
210 and relevant publications (Figure 1) [13, 30]. There are three general classes of RSV preventive  
211 interventions under development for infant protection: extended half-life mAbs, vaccines for use during  
212 pregnancy to protect infants through transplacental antibody transfer, and pediatric vaccines. As of  
213 September 2023, extended half-life mAbs and maternal RSV vaccines have been authorized for use in  
214 some high-income countries in North America and Europe [14, 31] [32-34].

215 Extended half-life mAbs are the first of next-generation RSV prevention products to achieve licensure.  
216 Unlike palivizumab, pipeline immunoprophylaxis drugs have an engineered Fc domain with half-life  
217 extension crystallizable fragment domain M252Y/S254T/T256E (YTE) mutation, extending circulation to  
218 about 70 days, 3-fold that for palivizumab [35]. These drugs could be given as a birth dose or during a  
219 later routine childhood immunization timepoint either year-round or before the anticipated RSV season,

220 and they are expected to provide protection through much, or all, of an RSV season [1]. The leading  
221 extended half-life mAb candidate, nirsevimab, received market authorization throughout the European  
222 Union in November 2022 [14, 36]. In a phase three randomized controlled trial among infants born at  
223 gestational age of at least 35 weeks, nirsevimab had an efficacy of 74.5% (95%CI: 49.6%-87.1%)  
224 compared to placebo against medically attended RSV LRTI [23]. Similar results were seen in a study of  
225 nirsevimab among infants born between 29 and 35 weeks of gestation [24], and nirsevimab protection  
226 was comparable to palivizumab among infants with chronic heart or lung disease [37]. Other extended  
227 half-life mAbs are under development, including a product by the Bill and Melinda Gates Medical  
228 Research Institute with a primary aim for use in LMICs [35].

229 RSV vaccines for use during pregnancy, like influenza and Tdap vaccines, have been developed for  
230 administration during routine prenatal care visits with the primary goal of providing newborns with  
231 maternal antibodies against RSV during the first months of life [2]. Maternal vaccines provide protection  
232 at the time of birth, unlike pediatric vaccines, and are expected to have lower manufacturing costs than  
233 extended half-life mAbs. The exact duration of protection of maternal RSV vaccination is not established,  
234 but it is expected to be less than 6 months, as is seen with maternal influenza and pertussis vaccination  
235 [2, 3]. The optimal timing of maternal vaccination is unclear. Current products target vaccination during  
236 the late second or third trimester of pregnancy, providing a narrow time window for optimal product  
237 delivery [13, 38]. When vaccination does not occur during the third trimester for full term children, or  
238 when children are born preterm, product efficacy may be decreased. Further, maternal vaccination  
239 platforms will need considerable strengthening before high coverage can be achieved in many LMICs  
240 [39]. A Pfizer maternal RSV vaccine candidate has demonstrated higher efficacy (vaccine efficacy against  
241 medically attended severe lower respiratory tract illness for 180 days after birth was 69.4%) than  
242 modelled by the studies presented here [40]; the results of this trial had not been available at the time  
243 of the meeting and the models relied on efficacy results from older trials (see detailed description

244 below). Other vaccine candidates are also in human trials [13]. Pediatric RSV vaccines are in  
245 development as well; however, they are not as advanced in clinical development as the other categories  
246 [13], and they were not discussed in detail during the meeting.

247 Despite the limited data on product effectiveness, duration of protection, and prevention coverage,  
248 performance goals do exist to inform health economic analyses of RSV prevention. Most notably, WHO  
249 has developed Preferred Product Characteristics for RSV maternal vaccines, infant mAbs, and pediatric  
250 vaccines [1, 2]. Preferred Product Characteristics describe WHO preferences regarding indications,  
251 target groups, immunization strategies, and clinical data for assessment of safety and efficacy. These  
252 preferences are shaped by the global unmet public health need in a WHO priority disease area. Other  
253 relevant national public health program indicators, such as immunization coverage and antenatal care  
254 visit timing and coverage can help estimate RSV product coverage, though they are not wholly  
255 interchangeable [41, 42]. The most relevant proxy for birth dose mAb coverage would be coverage for  
256 existing birth dose vaccines, including Bacille Calmette-Guérin (BCG) or Hepatitis B virus. Extended  
257 Programme on Immunization routine immunization contact also include visits around 6, 10 and 14  
258 weeks, 9 months, and a timepoint during the second year of life. One of these timepoints could  
259 potentially be used for mAb delivery, seasonal campaign dosing approaches may be programmatically  
260 challenging in LMICs where this has not been done for other vaccines. National coverage estimates for  
261 routine immunization during pregnancy are limited, so modelers are more likely to use antenatal care  
262 coverage estimates as a proxy for maternal RSV vaccination coverage [43].

263 While the efficacy and duration of protection may not be equivalent across classes of RSV preventive  
264 interventions, more product-specific clinical data are anticipated in the next few years to inform  
265 estimates of prevention impact in LMICs. Beyond decision making, supporting product delivery—  
266 including platforms, logistics, training, and monitoring—will be required for successful introduction,

267 uptake, and ultimately coverage. Finally, product acceptability is a critical input and may differ between  
268 interventions, location, and across time.

## 269 **COST-EFFECTIVENESS STUDIES IN LMICS**

270 At the WHO-sponsored meeting, four cost-effectiveness studies for RSV prevention in LMICs were  
271 reviewed—one each considering cost-effectiveness for 72 Gavi-eligible countries [44], 131 LMICs [45],  
272 and Mali [46], and a joint analysis for Kenya and South Africa [47] (Table 2). These studies all used static  
273 models to estimate RSV LRTI health outcomes and costs. The ages of children varied from the first six  
274 months to the first five years of life. Each measured health impact in disability adjusted life-years  
275 (DALYs) and costs in US dollars with a discount rate of 3% applied to future health and economic  
276 outcomes. DALYs are a widely-used metric that combine years of life lost from mortality with years of  
277 healthy life lost from morbidity and they are a standard way to express health impact in cost-  
278 effectiveness studies as they can be compared across disease states and etiologies.

279 While each study examined the expected health and economic impact of extended half-life mAb and  
280 RSV maternal vaccine, they used different assumptions regarding intervention efficacy, duration of  
281 protection, and product cost. In general, extended half-life mAbs are estimated to have lower  
282 incremental cost-effectiveness ratios (indicating higher value for money) than equally priced RSV  
283 maternal vaccine. As the price of mAb rises relative to maternal vaccine, maternal vaccine becomes  
284 increasingly more favorable. Seasonal administration of mAb limited to the months of highest RSV risk  
285 also improves the value for money compared to year-round administration. A seasonal strategy is  
286 advised by the PPC in settings where the RSV season is clearly defined [1]. Only the Mali study  
287 considered a seasonal program, which contributed to the more favorable cost-effectiveness ratio for  
288 mAb in that analysis.



289 Data from Kenya and South Africa reveal that RSV LRTI incidence and death are concentrated among  
290 infants in the first three months of life [47], whereas in Mali RSV LRTI incidence was greatest in the  
291 fourth and fifth months of life [46]. For this reason, cost-effectiveness estimates for maternal vaccine  
292 aimed at protection during early infancy were more favorable in Kenya and South Africa compared to  
293 Mali. Whether these differences in age distribution of early RSV disease are due to true differences in  
294 epidemiology, health care utilization or in surveillance approaches is not clear. However, the impact of  
295 this discrepancy on intervention cost-effectiveness highlights the importance of robust estimates of  
296 early-life RSV epidemiology and health-care utilization within regions and countries. Additionally, as  
297 deaths are the largest driver of DALYs averted, RSV case fatality rates in the hospital and in the  
298 community are critically important inputs. Both large multi-country studies applied an adjustment factor  
299 of 2.2 to all country-specific inpatient case fatality rates to estimate the rate of community deaths [44,  
300 45, 48]. In the Kenya and Mali analyses, deaths in the community accounted for approximately 3/4 of all  
301 RSV-associated deaths, whereas in South Africa they made up about a quarter (Figure 2) [47]. It is  
302 possible that these studies have underestimated the total number of RSV associated deaths, as the 2022  
303 systematic review of RSV LRTI burden estimates suggests approximately four community deaths for each  
304 in-hospital death in low-income countries [7].

305 Assessing model sensitivity to either different assumptions or changing conditions is critical to  
306 understanding the decision space, or in other words, which model changes might lead to a different  
307 policy choice. Univariate sensitivity analyses, in which individual parameters are varied incrementally  
308 above and below a point estimate, can identify which parameters most influence model output. Another  
309 important analysis tool for decision models is the Expected Value of Partially Perfect Information, which  
310 calculates the amount that key stakeholders would be willing to spend to gain an exact estimate for a  
311 specific influential parameter. The Expected Value of Partially Perfect Information is calculated as the  
312 difference in the monetary value of health gain associated with a decision made using the currently

313 available information and when the choice is made based on perfect information without uncertainty  
314 [49]. Among the studies presented at the meeting which assessed parameter influence, the authors  
315 identified rates of illness, hospitalization, and death due to RSV as the most influential (Figure 3).  
316 Identifying influential parameters can help to determine target areas for funding further research and  
317 data collection, especially when expensive trials and observational studies are involved.

## 318 **KEY PARAMETERS FOR RSV PREVENTION COST-EFFECTIVENESS**

### 319 **Cost of Care**

320 Few primary data collection studies have been done on the cost of facility treatment specifically for RSV,  
321 with general pneumonia costs often used as proxies [50]. Additionally, there is a paucity of data  
322 regarding intensive care unit (ICU) and ventilation costs among RSV patients. However, facility  
323 treatment costs for RSV may not be the most influential drivers of the cost-effectiveness of RSV  
324 interventions in low-resource settings, due to the often-low cost of care and healthcare utilization [44].  
325 Most of the economic benefits from RSV interventions derive from the value of prevented mortality  
326 (DALYs averted), which may be relatively higher in such settings partly because of low healthcare access.  
327 Rates of facility treatment may grow over time if countries are able to invest more in healthcare systems  
328 as a whole. Under these conditions, the costs averted by preventive RSV interventions will increase; this  
329 may even make RSV interventions net cost saving as suggested by the cost-effectiveness results for  
330 South Africa [47].

331 RSV preventive interventions may also achieve broader cost savings apart from direct healthcare  
332 expenditures, which are less commonly measured. Costs for out-of-pocket payments, transport,  
333 accommodation, and lost productivity may fall on households of infants with RSV illness; these were  
334 measured in a study of RSV hospitalization in Malawi [51]. Studies in high-income countries suggest that

335 the productivity costs can last well beyond the acute episode itself [52]. RSV illness has been associated  
336 with long-term sequelae such as wheezing and asthma [53]; if these can be prevented by vaccination or  
337 mAbs then the long-term medical and productivity cost savings may be substantial. Antibiotics are often  
338 inappropriately prescribed to treat respiratory illness associated with RSV [54]. Hence RSV preventive  
339 interventions may reduce both the costs of antibiotic prescribing and the long-term costs and health  
340 losses associated with the loss of antibiotic efficacy due to overuse. The studies discussed at the meeting  
341 did not include these cost elements, and therefore are likely underestimating the full societal value of  
342 RSV interventions.

### 343 **Age specific CFR of RSV LRTI**

344 Because mortality is a primary driver of the cost-effectiveness ratio for RSV preventative interventions in  
345 LMICs, it is critical that it be estimated as accurately as possible. Despite progress in updating global RSV  
346 mortality estimates using rigorous methodology [20], the number of studies directly measuring RSV  
347 deaths in LMICs remain few and are faced with several inherent challenges. Three such challenges  
348 include (1) estimating the proportion of deaths with RSV detected that are caused by RSV, i.e.,  
349 differentiating RSV-attributable from RSV-associated deaths; (2) estimating the number of deaths in  
350 LMICs that occur outside of health facilities; and (3) estimating the out-of-facility RSV CFR, which likely is  
351 higher than the in-hospital CFR.

352 The presence of RSV in a deceased child, identified through antemortem or post-mortem sampling (i.e.,  
353 an RSV-associated death), does not always indicate that the death was attributable to the RSV infection.  
354 Using RSV-associated deaths to estimate CFR can therefore lead to over-estimates of the mortality that  
355 could be prevented by RSV-targeted interventions, and therefore an inaccurate cost-effectiveness  
356 assessment. Conversely, RSV could be in the causal chain leading to death and no longer be detectable  
357 once samples are obtained, leading to under-estimation of its role. Differentiating RSV-associated from

358 RSV-attributable illness and death can be complicated, as multiple pathogens are often detected from  
359 the same LRTI episode [55]. Although there is compelling evidence that RSV is causally associated with  
360 LRTI episodes when it is detected in a child with LRTI, it is not clear that detecting RSV in fatal cases is  
361 similarly predictive of death caused by RSV [55, 56]. This is highlighted by the Child Health and Mortality  
362 Prevention Surveillance Study (CHAMPS), a multi-site study where expert panels determine cause of  
363 death from post-mortem specimens, verbal autopsy and antemortem clinical records. In pooled cases  
364 from CHAMPS sites representing seven countries, RSV was determined to be in the causal chain leading  
365 to death in 24 cases among 67 where it was detected (36%), with considerable variation by age group  
366 and study site [57]. The implication is that mortality could have been prevented by RSV-targeted  
367 intervention in only 1/3 of these RSV-associated deaths.

368 A second major challenge is estimating the proportion of RSV deaths in children that occur outside of  
369 health care facilities. This is a particularly important consideration for low resource setting with a high  
370 burden of deaths from all causes, including RSV, in the community. Community mortality studies in  
371 infants <6 months document a high proportion of RSV deaths occurring in the community, ranging from  
372 29% in Karachi, Pakistan to 70% in Lusaka, Zambia to 75% in rural Maharashtra, India [58-60]. These  
373 figures may be over-estimates based upon the possibility that RSV might not have been in the cause  
374 chain of death in some of the decedents where it was identified.

375 A third challenge is estimating the CFR for RSV illness that occurs in the community. In Maharashtra,  
376 community and in-hospital CFRs were directly compared for the same cohort of children <6 months [59].  
377 In this cohort, community RSV CFR was 2.5 times greater than the in-hospital RSV CFR (3/52 [7.1%] vs.  
378 1/36 [2.8%]). Although limited by small numbers, this study demonstrates that applying in-hospital RSV  
379 CFR to community incidence may underestimate community mortality.

380 The methodologic, logistic, and ethical barriers to generating accurate RSV-attributable mortality  
381 estimates and CFRs in low resource settings are significant. These inputs will therefore be most reliably  
382 generated with post-introduction studies of RSV vaccines or mAbs [61].

### 383 **RSV intervention product pricing and delivery costs**

384 Immunization program costs are comprised of commodity costs and delivery (i.e., administration) costs.  
385 To date, there are limited data to directly inform the costs of RSV intervention programs, as only limited  
386 interventions are available. Commodity prices are not yet known, and delivery costs are only now  
387 beginning to be assessed. However, some information can be inferred from other vaccines and  
388 associated delivery costs. Broadly speaking, RSV vaccine commodity costs are likely to depend on the  
389 complexity of developing and manufacturing the product, market size and makeup (i.e., potential for  
390 different market segments), number and location of suppliers, country income level or ability to pay,  
391 donor support, and time since the intervention has entered the market. These commodity costs are thus  
392 linked to supplier-related costs and other market factors that will also influence prices. Delivery costs  
393 are likely to be influenced by country income level, delivery strategy and ability to leverage other  
394 program activities. These factors can help interpret data from other vaccines that might serve as proxies  
395 as RSV specific information is forthcoming.

396 Product pricing for currently available vaccines can be assessed through several sources including the  
397 UNICEF and WHO websites [62, 63]. Data from UNICEF show that product prices can vary substantially  
398 by vaccine and may even differ substantially even within a single product. For example, average prices  
399 for measles vaccine, oral polio vaccine (OPV), or diphtheria-pertussis-tetanus vaccine may cost less than  
400 \$0.25 per dose. Other newer products or those with markets dominated by multinational producers  
401 such as human papillomavirus vaccine or pneumococcal conjugate vaccine may command higher prices.  
402 Prices can also vary depending on the procurement mechanism and country income level. Between

403 2018 and 2020, average country reported prices for Pevnar13 varied substantially. Countries eligible for  
404 Gavi support reported prices approximating \$3.50 per dose while countries procuring through the Pan  
405 American Health Organization (PAHO) revolving fund paid approximately four times this amount.  
406 Average reported prices were slightly higher than PAHO revolving fund prices for other lower- and  
407 upper-middle income countries [63]. On average, high-income countries reporting prices paid nine times  
408 the average price paid by countries eligible for Gavi support. Country income level and donor support  
409 are important factors influencing vaccine prices. While prices for RSV prevention interventions are not  
410 yet known, similar trends may be expected when these products come to market.

411 To date, there are no known studies assessing RSV intervention delivery costs, though several  
412 prospective studies are being initiated. As with product price, information can be gleaned from other  
413 vaccines to inform potential delivery costs. The Immunization Delivery Cost Catalogue and associated  
414 publications are a useful source of delivery cost data [64]. While delivery strategy, study method,  
415 country context and other factors limit direct comparability, most studies find that the economic cost to  
416 deliver a vaccine ranges from approximately \$0.50 to \$1.50 USD. However, costs for human  
417 papillomavirus vaccine delivery can be higher due to the potential for alternative delivery strategies to  
418 reach a different target population through unique contacts with recipients. Maternal immunization  
419 may also require alternative delivery strategies, unique contacts with recipients or seasonal delivery and  
420 thus may cost more to deliver. There are currently few empirical estimates of maternal immunization  
421 delivery costs in LMICs, though existing estimates broadly align with estimates for childhood vaccines  
422 [65].

423 Prospective RSV or maternal immunization delivery cost estimates will help inform our understanding of  
424 whether maternal immunization delivery costs will align with existing childhood vaccine delivery costs or  
425 if they may cost more due to distinct contacts with beneficiaries, alternative delivery strategies or

426 platforms, e.g., integration with antenatal care programs. There are no known estimates of mAb  
427 delivery costs in LMICs, but these costs may be similar to other childhood vaccines. Our knowledge of  
428 RSV intervention program costs is limited but expected to grow quickly as RSV preventive interventions  
429 become available and enter use.

#### 430 **Willingness to pay for health**

431 Once a cost-effectiveness ratio has been estimated, the result must then be interpreted for policy  
432 decisions. The amount of money that an entity will spend in order to achieve a unit of improved health  
433 for a given population under its remit is often referred to as the societal willingness to pay, or as the  
434 cost-effectiveness threshold [66]. The WHO Choosing Interventions that are Cost-Effective (CHOICE)  
435 Programme offers guidance for evaluating new interventions, centered on comparison with existing  
436 interventions and alternative spending choices. Under this framework, the maximum willingness-to-pay  
437 for health might be approximated as the highest cost-effectiveness ratio for a currently funded  
438 intervention that is deemed cost-effective, with the caveat that cost-effectiveness is not the sole  
439 consideration when selecting health programs [67]. Previous documents suggested designating “very  
440 cost-effective” and “cost-effective” interventions for a country based on per-capita gross domestic  
441 product (GDP) and three times that value, respectively [68]. These numbers were widely adopted as  
442 global norms in cost-effectiveness analyses [67], and have often been used as a decision rule, despite  
443 replacement with new guidance as well as evidence that these thresholds may be unrealistically high for  
444 LMICs [69].

445 The willingness to pay intersects with cost-effectiveness and policy decisions in ways that are both  
446 intuitive and not. Intuitively, as the willingness to pay rises, higher cost-effectiveness ratios become  
447 acceptable to payers. Interventions become more likely to be adopted, and higher prices better  
448 tolerated. When there are multiple payers, this general principle remains true, but each payer may end

449 up preferring different decisions or strategies. For instance, a donor generally will have a higher  
450 willingness or ability to pay for health than a recipient, by nature of their relationship. A donor who is  
451 subsidizing an intervention across multiple countries may also be less sensitive to the cost-effectiveness  
452 of the program in a single country, and willing to accept high cost-effectiveness ratios for some contexts  
453 when the overall value for health is favorable. Another aspect of the donor/recipient dynamic is that  
454 cost-sharing may lead to different cost-effectiveness ratios for each payer and potentially different  
455 policy preferences. For instance, under a donor model similar to that used by Gavi, combination  
456 strategies using both extended half-life mAb and pediatric vaccination have a lower cost-effectiveness  
457 ratio from a government payer perspective than a donor perspective in Mali [70]. However, if the donor  
458 willingness-to-pay is higher than that of the government, this combination strategy might be optimal  
459 from both perspectives [71].

#### 460 **Summary of the discussion about key parameters**

461 Objectives of the meeting included identifying the most influential parameter inputs and data  
462 limitations for the cost-effectiveness analyses and recommending and prioritizing future data gathering  
463 and research to improve estimates of the impact of RSV prevention in LMICs. Epidemiological  
464 parameters from the presented health economics studies identified as both influential and uncertain  
465 were those associated with RSV hospitalization and death, specifically setting-specific hospitalization  
466 rates and RSV-attributable death rates. Influential economic parameters included product price, delivery  
467 costs, willingness-to-pay for health on the part of potential donors, and the cost of RSV-associated  
468 hospitalization. Participants appraised the research presented in the meeting as being of high quality,  
469 with the caveats that the health economics studies used inputs for which there were limited empiric  
470 data. Public health donors and investigators should consider future research to develop more robust,  
471 precise measurements of the parameters identified by the meeting as influential and uncertain.



472 The most influential disease epidemiology data include incidence of severe and fatal RSV LRTI. These  
473 relatively rare endpoints are difficult to measure precisely with most observational study designs.  
474 Pooling data from multiple studies for meta-analysis is the most efficient way to address the issue of  
475 lack of power, and standardized case definitions and data collection procedures could facilitate these  
476 efforts. Further, vaccine or mAb probe design may be able to reveal the fraction of hospitalizations that  
477 are attributable to RSV and thus preventable through product use.

478 It is anticipated that more product-specific data, such as duration of protection and efficacy from LMIC  
479 settings will become available as field trials progress. Additional valuable data can be achieved from  
480 observational effectiveness studies. Standardization of case definitions, methodologies, data reporting  
481 can facilitate study-to-study comparisons and data pooling.

482 This meeting highlighted the limitations in the availability of general LRTI or RSV-specific medical care  
483 costs, as well as costs related to product delivery. More data collection from diverse locales would  
484 benefit impact models.

## 485 **DISCUSSION**

486 As RSV preventive interventions move through clinical development towards licensure, there is an  
487 urgent need to consider the suitability of these products for use in LMICs. Palivizumab is unsuitable due  
488 to its price point and the need for multiple doses. Products meeting WHO Preferred Product  
489 Characteristics would have lower barriers: a single-dose maternal vaccine, a two-dose pediatric series,  
490 or a birth dose mAb with extended half-life. For high-income countries where the short half-life  
491 monoclonal is currently used, the health economic case for next generation products may be  
492 straightforward. At a similar or lower price and with higher protection, these products can replace the  
493 short half-life mAb and could be offered to all infants. However, in LMICs the adoption of these

494 strategies represents a substantial financial outlay that may not be entirely offset by savings on medical  
495 care. The cost-effectiveness of these new strategies will be a critical consideration for public health  
496 policymakers aiming to maximize health with limited resources.

497 In convening this meeting, we aimed to illuminate the known drivers of cost-effectiveness for these  
498 interventions based on existing health economic models, and to highlight where insufficient knowledge  
499 contributes to uncertainty regarding the appropriate public health decision. We also sought to clarify  
500 the factors contributing to cross-country variability in parameter estimates. Finally, it was our goal to  
501 identify whether there was a clear need for future research to resolve these uncertainties.

502 The first major challenge is accurate determination of the health burden that could be alleviated by each  
503 prevention strategy. In most LMICs, RSV illness data remains scarce. Disease burden estimations often  
504 rely on sentinel sites or research studies to extrapolate information across broad geographic areas and  
505 populations. Complicating quantification, recent studies suggest that some proportion of deaths among  
506 RSV-positive infants which occur in a hospital setting are likely attributable to a different pathogen or  
507 cause, and therefore could not have been prevented by any of these RSV-specific preventative products  
508 [27]. As a further complication, evidence indicates that more RSV deaths than previously suspected  
509 occur in the community [7] and are not documented at a hospital setting. These biases pull the  
510 estimates of disease burden in opposing directions, adding considerable uncertainty.

511 The investment case for RSV preventive interventions also relies on economic inputs such as the costs  
512 for medically attended RSV illness. There may not be substantial uncertainty at the country level; for  
513 instance, assessment of RSV prevention in Mali using high-quality, setting-specific inputs found that  
514 even relatively wide ranges for medical costs did not lead to large changes in the economic case for RSV  
515 prevention [46]. However, variation across countries can dramatically change the decision space. In  
516 South Africa, for instance, greater healthcare utilization and higher costs for RSV illness leads to the

517 conclusion that RSV prevention strategies could be cost saving for that country [47]. International  
518 decision-making bodies and donors must be aware of these cross-country drivers, so that a less  
519 favorable cost-effectiveness ratio is not necessarily interpreted as due to a lower disease burden, but  
520 potentially to greater investment in, and access to, healthcare.

521 Changes across reasonable ranges for the product price and willingness-to-pay for health also influence  
522 whether these RSV prevention strategies would be considered favorable or unfavorable. As the vaccine-  
523 preventable mortality is lower for RSV than for other pathogens such as *Haemophilus influenzae* type B  
524 [72], acceptable prices for RSV preventive interventions are also lower than for these vaccines. It is not  
525 yet clear whether these lower prices are feasible for manufacturers, particularly for mAbs. Regarding the  
526 willingness-to-pay for health, WHO and other global bodies have moved away from single yardsticks for  
527 cost-effectiveness. The previous commonly used measures of one and three times the per-capita GDP  
528 per DALY averted may not reflect true budget constraints, which may cap the interventions that could  
529 efficiently be adopted at a lower range. For example, in the analysis of RSV prevention in Mali, the  
530 authors found that extended half-life monoclonals have an incremental cost-effectiveness ratio (ICER) of  
531 approximately US \$200 per DALY from the government perspective, which would generally be  
532 considered good value even with this new perspective [46]. However, the societal and donor ICERs are  
533 twice and three times higher, respectively. Although it is reasonable to expect that donors might be  
534 willing to pay for interventions that are not otherwise affordable, as that is the nature of donation, it is  
535 not clear whether donors value health at ICERs in these specific ranges.

## 536 **CONCLUSION**

537 RSV LRTI is a major cause of death and suffering among young children in LMICs. Prevention of RSV LRTI  
538 is a major unmet need in these settings. There is a robust pipeline of RSV preventive intervention  
539 candidates in clinical development, including an extended half-life mAb recently authorized for use in

540 Europe and a maternal vaccine undergoing regulatory review. Vaccine decision makers will need  
541 estimates of cost effectiveness to inform policies and implementation. These cost-effectiveness  
542 estimates will require data that are not routinely collected through public health practice nor in  
543 intervention efficacy studies. This meeting identified the most influential modelling parameters which  
544 could drive results about intervention cost effectiveness. Precise and high-quality estimates for these  
545 parameters will improve health and economic impact estimates of RSV prevention.

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549

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557 **REFERENCES**

- 558 [1] Sparrow E, Adetifa I, Chaiyakunapruk N, Cherian T, Fell DB, Graham BS, et al. WHO preferred product  
559 characteristics for monoclonal antibodies for passive immunization against respiratory syncytial virus  
560 (RSV) disease in infants - Key considerations for global use. *Vaccine*. 2022.
- 561 [2] Vekemans J, Moorthy V, Giersing B, Friede M, Hombach J, Arora N, et al. Respiratory syncytial virus  
562 vaccine research and development: World Health Organization technological roadmap and preferred  
563 product characteristics. *Vaccine*. 2019;37:7394-5.
- 564 [3] Fleming JA, Baral R, Higgins D, Khan S, Kochar S, Li Y, et al. Value profile for respiratory syncytial virus  
565 vaccines and monoclonal antibodies. *Vaccine*. 2023.
- 566 [4] Meeting of the Strategic Advisory Group of Experts on immunization, April 2016 - conclusions and  
567 recommendations. *Wkly Epidemiol Rec*. 2016;91:266-84.
- 568 [5] Li Y, Reeves RM, Wang X, Bassat Q, Brooks WA, Cohen C, et al. Global patterns in monthly activity of  
569 influenza virus, respiratory syncytial virus, parainfluenza virus, and metapneumovirus: a systematic  
570 analysis. *Lancet Glob Health*. 2019;7:e1031-e45.
- 571 [6] Centers for Disease Control and Prevention. RSV in Infants and Young Children. 2020.
- 572 [7] Li Y, Wang X, Blau DM, Caballero MT, Feikin DR, Gill CJ, et al. Global, regional, and national disease  
573 burden estimates of acute lower respiratory infections due to respiratory syncytial virus in children  
574 younger than 5 years in 2019: a systematic analysis. *Lancet*. 2022;399:2047-64.
- 575 [8] Nguyen-Van-Tam JS, O'Leary M, Martin ET, Heijnen E, Callendret B, Fleischhackl R, et al. Burden of  
576 respiratory syncytial virus infection in older and high-risk adults: a systematic review and meta-analysis  
577 of the evidence from developed countries. *Eur Respir Rev*. 2022;31.
- 578 [9] Hall CB, Walsh EE, Long CE, Schnabel KC. Immunity to and frequency of reinfection with respiratory  
579 syncytial virus. *J Infect Dis*. 1991;163:693-8.

580 [10] Aranda SS, Polack FP. Prevention of Pediatric Respiratory Syncytial Virus Lower Respiratory Tract  
581 Illness: Perspectives for the Next Decade. *Front Immunol.* 2019;10:1006.

582 [11] Ruckwardt TJ, Morabito KM, Graham BS. Immunological Lessons from Respiratory Syncytial Virus  
583 Vaccine Development. *Immunity.* 2019;51:429-42.

584 [12] American Academy of Pediatrics Committee on Infectious Diseases, Bronchiolitis Guidelines  
585 Committee,. Updated guidance for palivizumab prophylaxis among infants and young children at  
586 increased risk of hospitalization for respiratory syncytial virus infection. *Pediatrics.* 2014;134:415-20.

587 [13] PATH. RSV Vaccine and mAb Snapshot. 2023.

588 [14] European Medicines Agency. Beyfortus 2022.

589 [15] Pfizer. U.S. FDA Accepts Biologics License Application for Pfizer’s Respiratory Syncytial Virus  
590 Maternal Vaccine Candidate for Priority Review. 2023.

591 [16] Food and Drug Agency. FDA Approves First Respiratory Syncytial Virus (RSV) Vaccine. 2023.

592 [17] World Health Organization. Guidance for the Development of Evidence-based Vaccination-related  
593 Recommendations. 2017.

594 [18] Gavi The Vaccine Alliance. Vaccine investment strategy. 2022.

595 [19] Bertram MY, Edejer TTT. Introduction to the Special Issue on "The World Health Organization  
596 Choosing Interventions That Are Cost-Effective (WHO-CHOICE) Update". *Int J Health Policy Manag.*  
597 2021;10:670-2.

598 [20] Li Y, Wang X, Blau DM, Caballero MT, Feikin DR, Gill CJ, et al. Global, regional, and national disease  
599 burden estimates of acute lower respiratory infections due to respiratory syncytial virus in children  
600 younger than 5 years in 2019: a systematic analysis. *Lancet (London, England).* 2022;399:2047-64.

601 [21] Shi T, McAllister DA, O'Brien KL, Simoes EAF, Madhi SA, Gessner BD, et al. Global, regional, and  
602 national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus  
603 in young children in 2015: a systematic review and modelling study. *Lancet.* 2017;390:946-58.

604 [22] Madewell ZJ, Whitney CG, Velaphi S, Mutevedzi P, Mahtab S, Madhi SA, et al. Prioritizing Health  
605 Care Strategies to Reduce Childhood Mortality. *JAMA Netw Open*. 2022;5:e2237689.

606 [23] Hammitt LL, Dagan R, Yuan Y, Baca Cots M, Bosheva M, Madhi SA, et al. Nirsevimab for Prevention  
607 of RSV in Healthy Late-Preterm and Term Infants. *N Engl J Med*. 2022;386:837-46.

608 [24] Griffin MP, Yuan Y, Takas T, Domachowske JB, Madhi SA, Manzoni P, et al. Single-Dose Nirsevimab  
609 for Prevention of RSV in Preterm Infants. *N Engl J Med*. 2020;383:415-25.

610 [25] Saha SK, Schrag SJ, El Arifeen S, Mullany LC, Shahidul Islam M, Shang N, et al. Causes and incidence  
611 of community-acquired serious infections among young children in south Asia (ANISA): an observational  
612 cohort study. *Lancet*. 2018;392:145-59.

613 [26] Nair H. Global, regional and national disease burden estimates of acute lower respiratory infections  
614 due to respiratory syncytial virus in young children in 2015, 1995-2015 [dataset]. In: Edinburgh Uo,  
615 editor.: Usher Institute of Population Health Sciences and Informatics; 2016.

616 [27] Pneumonia Etiology Research for Child Health Study Group. Causes of severe pneumonia requiring  
617 hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-  
618 control study. *Lancet*. 2019;394:757-79.

619 [28] O'Brien KL, Chandran A, Weatherholtz R, Jafri HS, Griffin MP, Bellamy T, et al. Efficacy of  
620 motavizumab for the prevention of respiratory syncytial virus disease in healthy Native American  
621 infants: a phase 3 randomised double-blind placebo-controlled trial. *Lancet Infect Dis*. 2015;15:1398-  
622 408.

623 [29] Collaborators GBDLRI. Estimates of the global, regional, and national morbidity, mortality, and  
624 aetiologies of lower respiratory infections in 195 countries, 1990-2016: a systematic analysis for the  
625 Global Burden of Disease Study 2016. *Lancet Infect Dis*. 2018;18:1191-210.

626 [30] PATH. RSV Clinical Trial Tracker. 2022.

627 [31] Food and Drug Agency. FDA Approves New Drug to Prevent RSV in Babies and Toddlers. 2023.



628 [32] Boytchev H. FDA advisers back Pfizer's maternal RSV vaccine after voicing safety concerns. *BMJ*.  
629 2023;381:1187.

630 [33] Food and Drug Agency. FDA Approves First Vaccine for Pregnant Individuals to Prevent RSV in  
631 Infants. 2023.

632 [34] Pfizer. European Commission Approves Pfizer's ABRYOVO™ to Help Protect Infants through  
633 Maternal Immunization and Older Adults from RSV. 2023.

634 [35] Ananworanich J, Heaton PM. Bringing Preventive RSV Monoclonal Antibodies to Infants in Low- and  
635 Middle-Income Countries: Challenges and Opportunities. *Vaccines (Basel)*. 2021;9.

636 [36] Medicines & Healthcare products Regulatory Agency. Decision Cover Letter. 2022.

637 [37] Domachowske J, Madhi SA, Simoes EAF, Atanasova V, Cabanas F, Furuno K, et al. Safety of  
638 Nirsevimab for RSV in Infants with Heart or Lung Disease or Prematurity. *N Engl J Med*. 2022;386:892-4.

639 [38] Clinicaltrials.gov. A PHASE 2B PLACEBO-CONTROLLED, RANDOMIZED STUDY OF A RESPIRATORY  
640 SYNCYTIAL VIRUS (RSV) VACCINE IN PREGNANT WOMEN. 2023.

641 [39] Giles ML, Mantel C, Munoz FM, Moran A, Roos N, Yusuf N, et al. Vaccine implementation factors  
642 affecting maternal tetanus immunization in low- and middle-income countries: Results of the Maternal  
643 Immunization and Antenatal Care Situational Analysis (MIACSA) project. *Vaccine*. 2020;38:5268-77.

644 [40] Kampmann B, Madhi SA, Munjal I, Simoes EAF, Pahud BA, Llapur C, et al. Bivalent Prefusion F  
645 Vaccine in Pregnancy to Prevent RSV Illness in Infants. *N Engl J Med*. 2023;388:1451-64.

646 [41] World Health Organization. WHO and UNICEF estimates of national immunization coverage: 2019  
647 revision. 2019.

648 [42] UNICEF. Antenatal care. 2022.

649 [43] Baral R, Fleming J, Khan S, Higgins D, Hendrix N, Pecenka C. Inferring antenatal care visit timing in  
650 low- and middle-income countries: Methods to inform potential maternal vaccine coverage. *PLoS One*.  
651 2020;15:e0237718.

652 [44] Li X, Willem L, Antillon M, Bilcke J, Jit M, Beutels P. Health and economic burden of respiratory  
653 syncytial virus (RSV) disease and the cost-effectiveness of potential interventions against RSV among  
654 children under 5 years in 72 Gavi-eligible countries. *BMC Med.* 2020;18:82.

655 [45] Baral R, Higgins D, Regan K, Pecenka C. Impact and cost-effectiveness of potential interventions  
656 against infant respiratory syncytial virus (RSV) in 131 low-income and middle-income countries using a  
657 static cohort model. *BMJ Open.* 2021;11:e046563.

658 [46] Laufer RS, Driscoll AJ, Baral R, Buchwald AG, Campbell JD, Coulibaly F, et al. Cost-effectiveness of  
659 infant respiratory syncytial virus preventive interventions in Mali: A modeling study to inform policy and  
660 investment decisions. *Vaccine.* 2021;39:5037-45.

661 [47] Koltai M, Moyes J, Nyawanda B, Nyiro J, Munywoki PK, Tempia S, et al. Estimating the cost-  
662 effectiveness of maternal vaccination and monoclonal antibodies for respiratory syncytial virus in Kenya  
663 and South Africa. *BMC Med.* 2023;21:120.

664 [48] Shi T, McAllister DA, O'Brien KL, Simoes EAF, Madhi SA, Gessner BD, et al. Global, regional, and  
665 national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus  
666 in young children in 2015: a systematic review and modelling study. *Lancet.* 2017;390:946-58.

667 [49] York Health Economics Consortium. Expected Value of Partially Perfect Information (EVPPI).  
668 York2016.

669 [50] Zhang S, Sammon PM, King I, Andrade AL, Toscano CM, Araujo SN, et al. Cost of management of  
670 severe pneumonia in young children: systematic analysis. *J Glob Health.* 2016;6:010408.

671 [51] Baral R, Mambule I, Vodicka E, French N, Everett D, Pecenka C, et al. Estimating the Economic  
672 Impact of Respiratory Syncytial Virus and Other Acute Respiratory Infections Among Infants Receiving  
673 Care at a Referral Hospital in Malawi. *J Pediatric Infect Dis Soc.* 2020;9:738-45.

674 [52] Pokrzywinski RM, Swett LL, Pannaraj PS, Yi J, Pavilack MS, Kumar VR, et al. Impact of Respiratory  
675 Syncytial Virus-Confirmed Hospitalizations on Caregivers of US Preterm Infants. *Clin Pediatr (Phila)*.  
676 2019;58:837-50.

677 [53] Brunwasser SM, Snyder BM, Driscoll AJ, Fell DB, Savitz DA, Feikin DR, et al. Assessing the strength of  
678 evidence for a causal effect of respiratory syncytial virus lower respiratory tract infections on  
679 subsequent wheezing illness: a systematic review and meta-analysis. *Lancet Respir Med*. 2020;8:795-  
680 806.

681 [54] Fitzpatrick T, Malcolm W, McMenamin J, Reynolds A, Guttman A, Hardelid P. Community-Based  
682 Antibiotic Prescribing Attributable to Respiratory Syncytial Virus and Other Common Respiratory Viruses  
683 in Young Children: A Population-Based Time-series Study of Scottish Children. *Clin Infect Dis*.  
684 2021;72:2144-53.

685 [55] Causes of severe pneumonia requiring hospital admission in children without HIV infection from  
686 Africa and Asia: the PERCH multi-country case-control study. *Lancet (London, England)*. 2019;394:757-  
687 79.

688 [56] Shi T, McLean K, Campbell H, Nair H. Aetiological role of common respiratory viruses in acute lower  
689 respiratory infections in children under five years: A systematic review and meta-analysis. *Journal of*  
690 *global health*. 2015;5:010408.

691 [57] Blau DM, Baillie VL, Els T, Mahtab S, Mutevedzi P, Keita AM, et al. Deaths Attributed to Respiratory  
692 Syncytial Virus in Young Children in High-Mortality Rate Settings: Report from Child Health and Mortality  
693 Prevention Surveillance (CHAMPS). *Clinical infectious diseases : an official publication of the Infectious*  
694 *Diseases Society of America*. 2021;73:S218-s28.

695 [58] Gill CJ, Mwananyanda L, MacLeod WB, Kwenda G, Pieciak R, Mupila Z, et al. Infant deaths from  
696 respiratory syncytial virus in Lusaka, Zambia from the ZPRIME study: a 3-year, systematic, post-mortem  
697 surveillance project. *The Lancet Global health*. 2022;10:e269-e77.

698 [59] Simões EAF, Dani V, Potdar V, Crow R, Satav S, Chadha MS, et al. Mortality From Respiratory  
699 Syncytial Virus in Children Under 2 Years of Age: A Prospective Community Cohort Study in Rural  
700 Maharashtra, India. *Clinical infectious diseases : an official publication of the Infectious Diseases Society  
701 of America.* 2021;73:S193-s202.

702 [60] Kazi AM, Aguolu OG, Mughis W, Ahsan N, Jamal S, Khan A, et al. Respiratory Syncytial Virus-  
703 Associated Mortality Among Young Infants in Karachi, Pakistan: A Prospective Postmortem Surveillance  
704 Study. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.*  
705 2021;73:S203-s9.

706 [61] Feikin DR, Scott JA, Gessner BD. Use of vaccines as probes to define disease burden. *Lancet.*  
707 2014;383:1762-70.

708 [62] UNICEF. Vaccines pricing data. 2022.

709 [63] World Health Organization. MI4A Vaccine Purchase Database. 2022.

710 [64] Immunizationeconomics.org. Immunization Delivery Cost Catalogue. 2022.

711 [65] Procter SR, Salman O, Pecenka C, Gonçalves BP, Paul P, Hutubessy R, et al. A review of the costs of  
712 delivering maternal immunisation during pregnancy. *Vaccine.* 2020;38:6199-204.

713 [66] Bertram MY, Lauer JA, Stenberg K, Edejer TTT. Methods for the Economic Evaluation of Health Care  
714 Interventions for Priority Setting in the Health System: An Update From WHO CHOICE. *Int J Health Policy  
715 Manag.* 2021;10:673-7.

716 [67] Bertram MY, Lauer JA, De Joncheere K, Edejer T, Hutubessy R, Kieny MP, et al. Cost-effectiveness  
717 thresholds: pros and cons. *Bull World Health Organ.* 2016;94:925-30.

718 [68] Hutubessy R, Chisholm D, Edejer TT. Generalized cost-effectiveness analysis for national-level  
719 priority-setting in the health sector. *Cost Eff Resour Alloc.* 2003;1:8.

720 [69] Ochalek J, Lomas J, Claxton K. Estimating health opportunity costs in low-income and middle-  
721 income countries: a novel approach and evidence from cross-country data. *BMJ Glob Health*.  
722 2018;3:e000964.

723 [70] Laufer RS, Baral R, Buchwald AG, Campbell JD, Coulibaly F, Diallo F, et al. Optimizing next-  
724 generation RSV prevention in Mali: A cost-effectiveness analysis of pediatric vaccination, maternal  
725 vaccination, and extended half-life monoclonal antibody immunoprophylaxis. *PLOS Glob Public Health*.  
726 2023;3:e0001432.

727 [71] Morton A, Arulsevan A, Thomas R. Allocation rules for global donors. *J Health Econ*. 2018;58:67-75.

728 [72] World Health Organization. Haemophilus influenzae type b (Hib) meningitis in the pre-vaccine era :  
729 a global review of incidence, age distributions, and case-fatality rates. 2002.

730 [73] Madhi SA, Polack FP, Piedra PA, Munoz FM, Trenholme AA, Simoes EAF, et al. Respiratory Syncytial  
731 Virus Vaccination during Pregnancy and Effects in Infants. *N Engl J Med*. 2020;383:426-39.

732 [74] Baral R, Li X, Willem L, Antillon M, Vilajeliu A, Jit M, et al. The impact of maternal RSV vaccine to  
733 protect infants in Gavi-supported countries: Estimates from two models. *Vaccine*. 2020;38:5139-47.

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**Table 1. Comparison of RSV morbidity and mortality burden estimates between the 2022 RSV LRTI systematic review and other important studies<sup>a</sup>**

Parameter <sup>b</sup>	Study	Population	Definition and measure	Estimate (95% CI)
<b>RSV LRTI incidence in first six months of life</b>	Nirsevimab phase 3 trial [23]	Late preterm and term infants, <12 months at baseline (mostly ≤3 months), followed up to day 150 (control arm); 20 countries	RSV medically attended LRTI <sup>c</sup> ; annualized incidence rate (per 1000)	108 (80-147)
	2022 RSV LRTI systematic review [7]	<6m; global	RSV LRTI; annual incidence rate (per 1000)	96 (68-143)
<b>Hospitalized RSV LRTI incidence in first six months of life</b>	Nirsevimab phase 3 trial [23]	Late preterm and term infants, <12 months at baseline (mostly ≤3 months), followed up to day 150 (control arm); 20 countries	Hospitalized RSV LRTI; annualized hospitalization rate (per 1000)	32 (18-58)
	2022 RSV LRTI systematic review [7]	<6m; global	RSV LRTI hospitalization; annual hospitalization rate (per 1000)	20 (15-29)
<b>Severe RSV LRTI incidence in first three months of life</b>	ResVax phase 3 trial [73]	Newborns followed up to day 90 (control arm); 11 countries (mostly from South Africa and US)	RSV medically significant LRTI <sup>d</sup> ; annualized incidence rate (per 1000)	24 (18-34)
	2022 RSV LRTI systematic review [7]	<3m; global	RSV LRTI with chest wall indrawing; annual incidence rate (per 1000)	28 (13-68)
<b>Hospitalized RSV LRTI incidence in first three months of life</b>	ResVax phase 3 trial [73]	Newborns followed up to day 90 (control arm); 11 countries (mostly from South Africa and US)	Hospitalized RSV LRTI; annualized hospitalization rate (per 1000)	37 (28-48)
	2022 RSV LRTI systematic review [7]	<3m; global	RSV LRTI hospitalization; annual hospitalization rate (per 1000)	25 (18-37)
<b>RSV LRTI incidence in first three months of life</b>	ResVax phase 3 trial [73]	Newborns followed up to day 90 (control arm); 11 countries (mostly from South Africa and US)	RSV LRTI with severe hypoxemia <sup>e</sup> ; annualized hospitalization rate (per 1000)	10 (6-16)
	2022 RSV LRTI systematic review [7]	<3m; global	RSV LRTI hospitalization with hypoxemia; annual hospitalization rate (per 1000)	7 (4-16)
<b>RSV LRTI incidence in first six months of life in low-resource setting</b>	Motavizumab phase 3 trial [28]	Term infants ≤6 months at baseline (mean age: 2 months), followed up to day 150 (control arm); native American	RSV LRTI, inpatient and outpatient; annualized incidence rate (per 1000)	403 (368-441)
	2022 RSV LRTI systematic review [7]	<6m; low- and middle-income countries	RSV LRTI; annual incidence rate (per 1000)	104 (70-154)
<b>RSV LRTI hospitalization incidence in first six months of life in low-resource setting</b>	Motavizumab phase 3 trial [28]	Term infants ≤6 months at baseline (mean age: 2 months), followed up to day 150 (control arm); native American	RSV LRTI, inpatient only; annualized incidence rate (per 1000)	165 (140-194)
	2022 RSV LRTI systematic review [7]	<6m; low- and middle-income countries	RSV LRTI hospitalization; annual hospitalization rate (per 1000)	19 (13-29)

<b>RSV LRTI in-hospital case fatality ratios in early childhood in low-resource settings</b>	PERCH multi-country case-control study [26, 27]	Children aged 1-<60m; seven countries (mostly low-income)	RSV severe pneumonia in-hospital CFR (%)	2.2 (1.3-3.6)
	2022 RSV LRTI systematic review [7]	<60m; low-income countries	RSV LRTI in-hospital mortality; CFR (%)	1.4 (0.6-2.8)
<b>Severe RSV LRTI incidence in first three months of life in low-resource settings</b>	ANISA observational cohort study [25]	Newborns actively followed to day 59 through active community surveillance; Bangladesh, India, and Pakistan	Possible serious bacterial infection <sup>f</sup> ; annualized incidence rate (per 1000)	32 (29-38)
	2022 RSV LRTI systematic review [7]	<3m; lower-middle income countries	RSV LRTI with chest wall indrawing; annual incidence rate (per 1000)	46 (24-86)
<b>RSV LRTI incidence in early childhood</b>	IHME GBD 2016 [29]	All ages, <60 months reported as a separate age band; medical records based on clinical databases across the globe	RSV attributable LRTI morbidity; annual episodes in millions	11 (7-17)
	2022 RSV LRTI systematic review [7]	<60m; global	RSV LRTI; annual episodes in millions	33 (25-45)
<b>RSV LRTI mortality in early childhood</b>	IHME GBD 2016 [29]	All ages, <60 months reported as a separate age band; medical records based on clinical databases across the globe	RSV attributable LRTI mortality; annual deaths in thousands	41 (23-66)
	2022 RSV LRTI systematic review [7]	<60m; global	RSV-attributable deaths; annual deaths in thousands	101 (85-125)

737 Notes

- 738 a) Abbreviations: RSV = respiratory syncytial virus; LRTI = lower respiratory tract infection; CFR = case fatality ratio; PERCH = Pneumonia  
739 Etiology Research for Child Health (PERCH) case-control study; ANISA = Aetiology of Neonatal Infections in South Asia (ANISA)  
740 observational cohort study; IHME GBD = Institute for Health Metrics and Evaluation (IHME) Global Burden of Disease estimates.  
741 b) For each pair of comparison, the best comparable population and case definition from the present study was selected.  
742 c) Physical examination findings localizing to lower respiratory tract plus any of the following: 1) fast breathing ( $\geq 50$  breaths/minute in  
743 children aged 2-<6 months); 2) Hypoxemia ( $SpO_2 < 95\%$  at  $\leq 1800$  meters elevation); 3) clinical signs of severe respiratory diseases.  
744 d)  $\geq 1$  LRTI manifestation plus fast breathing ( $\geq 60$  breaths/minute in children aged  $> 2$  months); or hypoxemia ( $SpO_2 < 95\%$  at  $\leq 1800m$ ).  
745 e)  $SpO_2 < 92\%$  at  $\leq 1800$  meters or documented use of supplemental  $O_2$  or ventilation.  
746 f) Based on one of the following signs: fast breathing, hyperthermia, movement only with stimulation, convulsions, and poor feeding; fast  
747 breathing cannot be the only sign.

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**Table 2. Parameter inputs from RSV prevention cost-effectiveness analyses in low- and middle-income countries**

	Li et al 2020 [44]	Lafer et al 2021 [46]	Baral et al 2020 [74]	Koltai et al 2022 [47]
<b>Location</b>	72 Gavi-eligible countries	Mali	131 LMICs	Kenya and South Africa
<b>Model type</b>	static	static	static	static
<b>Age Inclusion (years)</b>	0-5	0-0.5	1	0-5
<b>Time horizon (years)</b>	5	0.5	10	5
<b>RSV incidence rate</b>	NA	age- and month-specific (mean = 53.7%)	NA	Age- and country-specific (monthly resolution under 1 year) of ARI and SARI, medically attended or not
<b>RSV LRTI incidence rate</b>	Age- and country-specific (monthly resolution under 1 year; country rates from 3.5-6.7%)	NA	age-specific (4% - 9.96%)	Age- and country-specific (monthly resolution under 1 year)
<b>RSV hospitalization incidence rate</b>	NA	NA	NA	Age- and country-specific rates of hospitalized and non-hospitalized SARIs
<b>Probability of LRTI given RSV</b>	NA	0.13	NA	NA
<b>Probability of inpatient care given RSV LRTI</b>	0.09	0.29	20.2 per 1000 for 0-5 months, 11 per 1000 for 6-11 months	Age-specific hospitalization rates (<1 year: 5-60 hospitalizations/1000 population)
<b>Hospital case fatality rate</b>	age-specific (0.045 - 0.006)	0.016	0.022 for 0-5 months, 0.024 for 6-11 months	Age-specific mortality rates (under 1 year: 25-150 deaths/100.000 population)
<b>Disability weight, severe RSV LRTI</b>	0.21	0.13	0.21	0.21
<b>Disability weight, moderate RSV LRTI</b>	0.053	0.05	0.053	0.053
<b>QALY loss, severe RSV LRTI</b>	NA	NA	NA	NA
<b>QALY loss, moderate RSV LRTI</b>	NA	NA	NA	NA
<b>Duration of illness (days)</b>	11.2	8.5	10 for severe RSV LRTI, 5 for moderate RSV LRTI	11.2
<b>Life expectancy (years)</b>	country-specific (50 - 80)	58	country-specific (50 - 80)	Kenya: 66.5, South Africa: 62.5
<b>Discount rate (%)</b>	3	3	3	3
<b>Currency</b>	2016 USD	2019 USD	2016 USD	2021 USD
<b>Willingness to pay threshold (USD per DALY averted)</b>	continuous (0 - 30000)	891	country-specific (130 - 4774)	not fixed
<b>WTP as a multiplier of country GDP per capita</b>	NA	1	0.5	NA



<b>Outpatient costs (USD)</b>	country-specific (0.13 - 91)	6.56	53	Kenya: 20.9 USD, RSA: 24.95 USD
<b>Inpatient costs (USD)</b>	country-specific (0.37 - 640)	118.57	250	Kenya: 102 USD for healthcare provider + 172 USD for household (out-of-pocket); RSA: 634-1002 USD for healthcare provider + 4-22 USD for household (out-of-pocket)
<b>ICU costs (USD)</b>	NA	NA	NA	NA
<b>Administration cost per dose (USD)</b>	included in intervention cost per dose	1.35	0.63 for LIC, 1.73 LMIC and UMIC	included in intervention cost per dose
<b>Cost per dose, short-acting mAb (USD)</b>	NA	3	NA	NA
<b>Cost per dose, long-acting mAb (USD)</b>	6 (tested value: 4 and 11)	3	3 for Gavi eligible, 5 for non-Gavi	Tested values: 6, 20, 60
<b>Cost per dose, maternal vaccine (USD)</b>	3	3	3 for Gavi eligible, 5 for non-Gavi	Tested values: 3, 10, 30
<b>Outcome efficacy protects against</b>	RSV LRTI cases	RSV cases	RSV LRTI cases	RSV LRTI, RSV LRTI with hospitalization, severe RSV LRTI (death)
<b>Efficacy, short-acting mAb (%)</b>	NA	78	NA	NA
<b>Efficacy, long-acting mAb (%)</b>	70 (tested value 50 and 90)	56	60-70	70.1%, 78.4%, 78.4% [no data for efficacy against deaths]
<b>Efficacy, maternal vaccine (%)</b>	70 (tested value 50 and 90)	70	40-60	39.4%, 44.4%, 48.3% (the efficacy figures were updated in the published version of the article, lowering the ICER values <b>[47]</b> )
<b>Efficacy, pediatric vaccine (%)</b>	NA	NA	NA	NA
<b>Duration of protection, short-acting mAb (months)</b>	NA	1	NA	NA
<b>Duration of protection, long-acting mAb (months)</b>	6 (tested value: 4 and 8)	5	6	5
<b>Duration of protection, maternal vaccine<sup>a</sup> (months)</b>	5-6 (tested value: 3 and 8)	3	3	3
<b>Coverage<sup>b</sup>, short-acting mAb (%)</b>	NA	77	NA	NA
<b>Coverage<sup>b</sup>, long-acting mAb (%)</b>	country-specific (52 - 99)	83	82	95%
<b>Coverage<sup>b</sup>, maternal vaccine (%)</b>	country-specific (52 - 99)	35.5	84	95%
<b>ICER<sup>c</sup>, short-acting mAb</b>	NA	4280	NA	NA
<b>ICER<sup>c</sup>, long-acting mAb</b>	country-specific (3152 - 7927)	1656	431	6 USD dose price: Kenya: 325 South Africa: cost-saving  60 USD dose price: Kenya: 6248

				South Africa: 5583 USD
<b>ICER<sup>c</sup>, maternal vaccine</b>	country-specific (1708 - 5663)	8020	1342	3 USD dose price: Kenya: 734 South Africa: cost-saving  30 USD dose price: Kenya: 10,186 South Africa: 10,099

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- Notes:
- a) Duration of protection for maternal vaccine begins at birth.
  - b) Coverage refers to percentage receiving intervention among those eligible
  - c) Units for ICERs are USD per DALY averted

**Figure 1. RSV Vaccine and mAb development pipeline**

Note: Adapted from the from PATH Clinical Trial Tracker (as of September 2023) [13, 30]

**Figure 2. Hospitalized SARI cases, in-hospital CFR values and the estimated ratio of out-of-hospital to in-hospital deaths in Kenya and South Africa**

Note: As the overwhelming majority of the RSV disease burden in children under the age of 1 in Kenya and South Africa is estimated to be due to RSV-associated deaths, the parameters that most strongly influence the burden reduction are the age-specific CFR of in-hospital and out-of-hospital severe cases and the efficacy and duration of RSV preventive interventions against severe RSV LRTI. More deaths within the window of effectiveness of the RSV preventive interventions will lead to a proportionally larger reduction in the total disease burden. A longer duration or higher efficacy of the effect against deaths will similarly lead to a proportionally larger reduction of the burden and thereby lower the DALYs averted, improving the cost-effectiveness of the interventions.

The dose price of RSV preventive interventions will scale the cost-effectiveness of the interventions linearly. Figure reproduced from a previous publication [47].

### **Figure 3. A) Univariate sensitivity analysis for Mali**

Note: A series of univariate sensitivity analyses were conducted to assess the parameters whose variance has the largest influence on cost-effectiveness estimates for Mali. The parameter with the largest influence on the ICER across interventions is the inpatient case fatality rate (>300%). Parameters with moderate (<60%) influence include the probability of being hospitalized with RSV LRTI, probability of LRTI given RSV, age-based RSV attack rates, intervention product efficacy, and inpatient care costs. As deaths have the largest impact on cost-effectiveness estimates, case fatality rates are critically important inputs to capture accurately. Figure reproduced from a previous publication [46].

**Figure 4. Expected Value of Partially Perfect Information for Senegal (high incidence), Vietnam (low incidence), and Angola**

Note: In Figure 4, three examples are presented to demonstrate the influential factors. The age-specific RSV hospitalization probability is the most influential factor for all countries. RSV incidence rate, hospital case-fatality ratio and community case-fatality ratio are also top influential factors. A few countries (like Angola) show that cost of outpatient care is an influential factor at low willingness-to-pay level (<1000 USD per DALY averted), because the cost of outpatient care is higher and more uncertain compared to other countries. However, at higher WTP levels, the top-ranking influential factors are the same as the other countries. Figure reproduced from a previous publication [44].

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4 1 **TITLE:** Report of the WHO technical consultation on the evaluation of respiratory syncytial virus  
5 2 prevention cost effectiveness in low- and middle-income countries, April 7-8, 2022  
6 3

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**HIGHLIGHTS:**

- Respiratory syncytial virus (RSV) is an important pathogen globally.
- The burden of RSV illness is highest in low/middle-income countries (LMICs).
- In April 2022, WHO convened a meeting to discuss the economics of RSV prevention.
- We reviewed cost-effectiveness analyses of RSV prevention in LMICs.
- We provided recommendations for future data gathering to address data limitations.



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**65 ABSTRACT**

66 Policymakers often rely on impact and cost-effectiveness evaluations to inform decisions about the  
67 introduction of health interventions in low- and middle-income countries (LMICs); however, cost-  
68 effectiveness results for the same health intervention can differ by the choice of parameter inputs,  
69 modelling assumptions, and geography. Anticipating the near-term availability of new respiratory  
70 syncytial virus (RSV) prevention products, WHO convened a two-day virtual consultation in April 2022  
71 with stakeholder groups and global experts in health economics, epidemiology, and vaccine  
72 implementation. The objective was to review methods, parameterization, and results of existing cost-  
73 effectiveness analyses for RSV prevention in LMICs; identify the most influential inputs and data  
74 limitations; and recommend and prioritize future data gathering and research to improve RSV  
75 prevention impact estimates in LMICs. Epidemiological parameters identified as both influential and  
76 uncertain were those associated with RSV hospitalization and death, specifically setting-specific  
77 hospitalization rates and RSV-attributable death rates. Influential economic parameters included  
78 product price, delivery costs, willingness-to-pay for health on the part of potential donors, and the cost  
79 of RSV-associated hospitalization. Some of the influential parameters identified at this meeting should  
80 be more precisely measured by further research. Other influential economic parameters that are highly  
81 uncertain may not be resolved, and it is appropriate to use sensitivity analyses to explore these within  
82 cost-effectiveness evaluations. This report highlights the presentations and major discussions of the  
83 meeting.

84  
85 **Keywords:** cost effectiveness; global health; monoclonal antibody; respiratory syncytial virus; vaccine

86 **Abbreviations:**

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4 87 AAP = American Academy of Pediatrics  
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6 88 ANISA = Aetiology of Neonatal Infections in South Asia study  
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8  
9 89 BCG = Bacille Calmette-Guérin vaccine  
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11 90 CFR = case fatality ratio  
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14 91 CHAMPS = Child Health and Mortality Prevention Surveillance Study  
15  
16 92 CHOICE = WHO Choosing Interventions that are Cost-Effective Programme  
17  
18 93 DALY = disability-adjusted life year  
19  
20  
21 94 GBD = global burden of disease  
22  
23 95 GDP = gross domestic product  
24  
25 96 ICU = Intensive care unit  
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27  
28 97 IHME = Institute for Health Metrics and Evaluation  
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30 98 LMIC = low- and middle-income countries  
31  
32  
33 99 LRTI = lower respiratory tract illness  
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35 100 mAb = monoclonal antibody  
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37 101 RSV = respiratory syncytial virus  
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40 102 PAHO = Pan American Health Organization  
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42 103 PERCH = Pneumonia Etiology Research for Child Health project  
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44 104 SAGE = WHO Strategic Advisory Group of Experts on Immunization  
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47 105 US = United States  
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107 **BACKGROUND**

108 Respiratory syncytial virus (RSV) is a leading cause of hospitalization in infants and young children due to  
109 lower respiratory tract illness (LRTI), including pneumonia and bronchiolitis; however, ~~the available~~  
110 ~~RSV licensed~~ preventive ~~products~~~~interventions and leading pipeline candidates~~ are ~~unaffordable~~~~not~~  
111 ~~anticipated to be affordable~~ for ~~most low- and middle-~~income countries (~~LMICs~~)~~without subsidies~~; [1-3].

112 In 2016, recognizing the growing pipeline of RSV prevention products, the World Health Organization  
113 (WHO) Strategic Advisory Group of Experts on Immunization (SAGE) requested that preparations be  
114 made to support global policymaking for RSV preventive interventions [4]. ~~To inform decisions about the~~  
115 ~~introduction of RSV immunization products, policymakers in LMICs will also need to consider their~~  
116 ~~impact and cost-effectiveness.~~ [4]. To inform decisions about the introduction of RSV immunization  
117 products, policymakers in low- and middle-income countries (LMICs) will need to consider their impact  
118 and cost-effectiveness.

119 WHO convened an online meeting in April 2022 to review cost-effectiveness analyses for RSV  
120 prevention. The objectives of the meeting were the following: 1) to review objectives, methods, inputs,  
121 and results of cost-effectiveness analyses of RSV prevention for young children in LMICs; 2) to identify  
122 the most influential parameter inputs and data limitations for the cost-effectiveness analyses; and 3) to  
123 recommend and prioritize future data gathering and research to improve RSV prevention impact  
124 estimates in LMICs. Attendees included stakeholder groups and global experts in health economics,  
125 epidemiology, and vaccine implementation. The agenda and list of participants are in the Online  
126 Supplement.

127 **RSV DISEASE OVERVIEW**

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128 RSV is a common respiratory virus that circulates in seasonal epidemics [5]. Its symptoms are usually  
129 mild and self-limited [6]-[6]. However, RSV can also cause severe disease. It is the most common cause  
130 of LRTI in young children globally [7], it can exacerbate chronic medical conditions, and it can cause  
131 acute respiratory illness in older adults [8]. RSV transmission can occur by contact or inhalation of  
132 airborne virus. Most individuals have evidence of RSV infection by two years of age [6], however  
133 subsequent reinfection is possible [9]-[9]. Among children, the greatest risk of severe RSV disease occurs  
134 in infants <6 months of age and in children with congenital heart disease or lung disease [6].

135 As of ~~May~~September 2023, there are no licensed vaccines administered to children for RSV prevention  
136 ~~in children~~ [2]. Clinical trials assessing pediatric RSV vaccine candidates in the 1960s were halted due to  
137 evidence of vaccine-associated enhanced disease, ~~subsequently found to be associated with the~~  
138 ~~formalin inactivation process prompting poorly neutralizing antibodies and a Th2-biased response~~ [10,  
139 11]. This safety signal slowed RSV vaccine development for decades. Since 1998, palivizumab, a  
140 humanized monoclonal antibody (mAb) directed against the F protein of RSV, has been licensed for use  
141 in young children at high risk for RSV disease [12]. The immunoprophylaxis is administered by monthly  
142 intramuscular injection throughout the RSV season [12]. Palivizumab is too expensive for use in most  
143 LMICs. Acknowledging that RSV preventive interventions are an unmet global health need, biomedical  
144 research funders including the US National Institutes of Health and the Bill & Melinda Gates Foundation  
145 have made substantial investments in understanding and preventing RSV disease. There is now a robust  
146 research and development pipeline for RSV prevention products, including monoclonal antibody (mAb)  
147 immunoprophylaxis and vaccines in late-stage development. By May 2023, extended half-life mAb have  
148 achieved licensure in Europe [13, 14], maternal RSV vaccines are undergoing regulatory review [15], and  
149 RSV vaccines for older adults have achieved licensure in the United States [16]-[16].

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150 While RSV prevention products are likely to become available first in high-income countries, efforts are  
151 underway to accelerate their availability and programmatic suitability in LMICs [1, 2]. A major  
152 requirement to justify funding is product cost-effectiveness, defined as the expenditure necessary to  
153 achieve a unit of health or other benefit. Cost-effectiveness is often an explicit part of decisions by  
154 regulatory bodies, countries, and donors about whether to adopt a health intervention. For instance,  
155 SAGE includes cost-effectiveness as one of the criteria considered when deciding whether to  
156 recommend vaccines for use [17], recommendations which are regarded as authoritative by many  
157 countries. Gavi, the Vaccine Alliance, is a major donor supporting immunization efforts for LMICs and  
158 lists “Value for Health” among its own criteria when considering which products to financially support  
159 [18]-[18]. For Gavi-eligible countries, adoption of a vaccination program is often conditional on both a  
160 SAGE recommendation and Gavi support, with additional country-specific considerations regarding the  
161 cost-effectiveness of the new intervention relative to current and potential uses of the health budget  
162 [19].

163 **DISEASE BURDEN**

164 In 2022, researchers published an updated systematic analysis of global disease burden estimates for  
165 RSV acute LRTI in young children [20, 21]. The update included disease burden estimates within narrow  
166 age bands to facilitate impact modelling of potential RSV preventive interventions expected to have  
167 limited durations of protection- [1-3]. Global and regional estimates of RSV community morbidity and  
168 hospitalization were presented, as well as RSV in-hospital and overall mortality burden from published  
169 and unpublished data, using a generalized linear mixed-effect modelling framework.

170 The research highlighted the substantial RSV morbidity and mortality burden in infants <6 months,  
171 accounting for 20% and 45% of RSV LRTI episodes and deaths in children <5 years, respectively. In LMICs,  
172 the RSV LRTI incidence rate was three times as high as that in high-income countries in the community

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173 whereas the RSV LRTI hospitalization rate was lower than that in high-income countries among infants  
174 <6 months, highlighting the limited access to healthcare in LMICs. This was further emphasized by  
175 estimates for the RSV community mortality burden, which showed that 82% of RSV-attributable deaths  
176 occurred out of hospital and the infant case fatality ratio (CFR) of RSV LRTI in the community could be as  
177 high as 6.6% in low-income countries. These findings suggest that RSV immunization programs targeting  
178 protection during the first six months of life could have a substantial effect on reducing severe RSV  
179 disease burden. In LMICs, RSV immunization programs are likely to be even more impactful given that a  
180 considerable proportion of RSV morbidity and mortality was due to limited access to health-care  
181 services, and therefore these deaths could potentially only be averted through immunization programs.  
182 However, substantial year to year variability as well as intra- and inter-region variability in RSV morbidity  
183 and mortality (in a given year) were noted. In an attempt to attribute cause of death to the RSV related  
184 mortality estimate, two sets of estimates were presented – one where RSV was identified in the upper  
185 airway samples of a deceased child (RSV associated mortality); and the other where RSV was deemed to  
186 be in the causal chain based on the opinion of an expert adjudication panel, such as in CHAMPS (RSV  
187 attributable mortality). ~~The latter estimates are more conservative and consistent with estimates~~  
188 ~~reported for previous years (e.g., 2015)]~~ [22]. Although the most recent RSV mortality estimates  
189 incorporate more data on mortality than previous estimates, more data are needed to better  
190 characterize RSV mortality, particularly in community settings.

191 During the WHO meeting, RSV LRTI morbidity and mortality incidence estimates from the systematic  
192 review were compared with estimates determined by other high-quality studies, including mAb and  
193 vaccine trials and large, multi-country observational studies (Table 1). Estimates of several RSV LRTI  
194 epidemiologic parameters from the systematic analysis were similar to placebo arms in RSV intervention  
195 field trials, including RSV LRTI incidence in the first 3 and 6 months of life, and severe and hospitalized  
196 RSV LRTI incidence in first 3 months of life [23, 24]. Severe RSV LRTI incidence estimates from the first

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197 two months of life were comparable to the findings of the Aetiology of Neonatal Infections in South Asia  
198 (ANISA) observational cohort study [25]. In-hospital CFR estimates for RSV LRTI among children <5 years  
199 of age were similar to the Pneumonia Etiology Research for Child Health (PERCH) case control study [26,  
200 27]. Incidence of RSV LRTI illnesses and hospitalizations during the first six months of life were  
201 appreciably lower in the systematic review (when restricted to LMICs) than in the placebo arm of an RSV  
202 mAb trial among US indigenous populations [28], possibly reflecting lower testing rates and worse  
203 access to care in LMIC compared to the US, even in underserved populations. The systematic review  
204 estimated much higher RSV LRTI morbidity and mortality during early childhood than the Institute for  
205 Health Metrics and Evaluation (IHME) Global Burden of Disease estimates in 2016 (33 million episodes  
206 and 101,000 deaths in review compared to 11 million cases and 41,000 deaths by IHME) [29].

**PREVENTIVE INTERVENTIONS**

208 Palivizumab, a humanized monoclonal antibody (mAb) directed against the F protein of RSV, is licensed  
209 for use in young children at high risk for RSV disease [12]. The immunoprophylaxis is administered by  
210 intramuscular injection monthly throughout the RSV season [12]. The utility of palivizumab is limited by  
211 its narrow clinical indication and high price. ~~The American Academy of Pediatrics (AAP) recommends~~  
212 ~~that palivizumab administration be limited to children born at less than 29 weeks of gestation or those~~  
213 ~~with hemodynamically significant congenital heart disease and chronic lung disease of prematurity~~ [1-3].  
214 Safe and effective next-generation RSV preventive interventions that provide increased duration of  
215 protection are a critical unmet global health need [1, 2].

216 At the time of the WHO meeting, there were no licensed next-generation RSV prevention products,  
217 although some leading candidates were expected to seek regulatory approval soon. ~~PATH tracks the~~  
218 ~~clinical development landscape of RSV prevention including development stages, target populations,~~  
219 ~~and relevant publications (Figure 1)~~ [13, 30]. ~~There are three general classes of RSV preventive~~

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~~220 interventions under development for infant protection: extended half-life mAbs, vaccines for use during~~  
~~221 pregnancy to protect infants through transplacental antibody transfer, and pediatric vaccines. PATH~~  
~~222 tracks the clinical development landscape of RSV prevention including development stages, target~~  
~~223 populations, and relevant publications (Figure 1) [13, 30]. There are three general classes of RSV~~  
~~224 preventive interventions under development for infant protection: extended half-life mAbs, vaccines for~~  
~~225 use during pregnancy to protect infants through transplacental antibody transfer, and pediatric~~  
~~226 vaccines. As of September 2023, extended half-life mAbs and maternal RSV vaccines have been~~  
~~227 authorized for use in some high-income countries in North America and Europe [14, 31] [32-34].~~

228 Extended half-life mAbs are the first of next-generation RSV prevention products to achieve ~~European~~  
229 ~~Union~~ licensure ~~and are pending FDA review in the United States~~. Unlike palivizumab, pipeline  
230 immunoprophylaxis drugs have an engineered Fc domain with half-life extension crystallizable fragment  
231 domain M252Y/S254T/T256E (YTE) mutation, extending circulation to about 70 days, 3-fold that for  
232 palivizumab [35]. ~~These drugs could be given during a routine childhood immunization visit [35]. These~~  
233 ~~drugs could be given as a birth dose or during a later routine childhood immunization timepoint~~ either  
234 year-round or before the anticipated RSV season, and they are expected to provide protection through  
235 much, or all, of an RSV season [1]. The leading extended half-life mAb candidate, nirsevimab, received  
236 market authorization throughout the European Union in ~~October 2022~~ [14, 36]. ~~November 2022~~ [14, 36].  
237 In a phase three randomized controlled trial among infants born at gestational age of at least 35 weeks,  
238 nirsevimab had an efficacy of 74.5% (95%CI: 49.6%-87.1%) compared to placebo against medically  
239 attended RSV LRTI [23]. Similar results were seen in a study of nirsevimab among infants born between  
240 29 and 35 weeks of gestation [24], and nirsevimab protection was comparable to palivizumab among  
241 infants with chronic heart or lung disease [37]. Other extended half-life mAbs are under development,  
242 including a product by the Bill and Melinda Gates Medical Research Institute with a primary aim for use  
243 in LMICs [35].



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244 RSV vaccines ~~are under development~~ for use during pregnancy. ~~Like, like~~ influenza and Tdap vaccines,  
245 ~~the anticipated~~have been developed for administration ~~of these would be~~ during routine prenatal care  
246 visits with the primary goal of providing newborns with maternal antibodies against RSV during the first  
247 months of life [2]. Maternal vaccines provide protection at the time of birth, unlike pediatric vaccines,  
248 and are expected to have lower manufacturing costs than extended half-life mAbs. The exact duration of  
249 protection of maternal RSV vaccination is not established, but it is expected to be less than 6 months, as  
250 is seen with maternal influenza and pertussis vaccination [2, 3]. The optimal timing of maternal  
251 vaccination is unclear. Current products target vaccination during the late second or third trimester of  
252 pregnancy, providing a narrow time window for optimal product delivery [13, 38]. ~~[13, 38].~~ When  
253 vaccination does not occur during the third trimester for full term children, or when children are born  
254 preterm, product efficacy may be decreased. Further, maternal vaccination platforms will need  
255 considerable strengthening before high coverage can be achieved in many LMICs [39]. A Pfizer maternal  
256 RSV vaccine candidate has demonstrated higher efficacy ~~than modeled~~(vaccine efficacy against  
257 medically attended severe lower respiratory tract illness for 180 days after birth was 69.4%) than  
258 modelled by the studies presented here [40]; the results of this trial had not been available at the time  
259 of the meeting and the models ~~rely~~relied on efficacy results from older trials. ~~(see detailed description~~  
260 below). Other vaccine candidates are also in human trials [13].  
261 [13]. Pediatric RSV vaccines are in development as well; however, they are not as advanced in clinical  
262 development as the other categories [13], and they were not discussed in detail during the meeting.  
263 Despite the limited data on product effectiveness, duration of protection, and prevention coverage,  
264 performance goals do exist to inform health economic analyses of RSV prevention. Most notably, WHO  
265 has developed Preferred Product Characteristics for RSV maternal vaccines, infant mAbs, and pediatric  
266 vaccines [1, 2]. Preferred Product Characteristics describe WHO preferences regarding indications,

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267 target groups, immunization strategies, and clinical data for assessment of safety and efficacy. These  
268 preferences are shaped by the global unmet public health need in a WHO priority disease area. Other  
269 relevant national public health program indicators, such as immunization coverage and antenatal care  
270 visit timing and coverage can help estimate RSV product coverage, though they are not wholly  
271 interchangeable [41, 42].[41, 42]. The most relevant proxy for birth dose mAb coverage would be  
272 coverage for existing birth dose vaccines, including Bacille Calmette-Guérin (BCG) or Hepatitis B virus.  
273 Extended Programme on Immunization routine immunization contact also include visits around 6, 10  
274 and 14 weeks, 9 months, and a timepoint during the second year of life. One of these timepoints could  
275 potentially be used for mAb delivery, seasonal campaign dosing approaches may be programmatically  
276 challenging in LMICs where this has not been done for other vaccines. National coverage estimates for  
277 routine immunization during pregnancy are limited, so modelers are more likely to use antenatal care  
278 coverage estimates as a proxy for maternal RSV vaccination coverage [43].

279 While the efficacy and duration of protection may not be equivalent across classes of RSV preventive  
280 interventions, more product-specific clinical data are anticipated in the next few years to inform  
281 estimates of prevention impact in LMICs. Beyond decision making, supporting product delivery—  
282 including platforms, logistics, training, and monitoring—will be required for successful introduction,  
283 uptake, and ultimately coverage. Finally, product acceptability is a critical input and may differ between  
284 interventions, location, and across time.

285 **COST-EFFECTIVENESS STUDIES IN LMICS**

286 At the WHO-sponsored meeting, four cost-effectiveness studies for RSV prevention in LMICs were  
287 reviewed—one each considering cost-effectiveness for 72 Gavi-eligible countries [44], 131 LMICs [45],  
288 and Mali [46], and a joint analysis for Kenya and South Africa [47] (Table 2). These studies all used static  
289 models to estimate RSV LRTI health outcomes and costs. The ages of children varied from the first six

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290 months to the first five years of life. Each measured health impact in disability adjusted life-years ~~and~~  
291 costs in US dollars with a discount rate for costs of 3% (DALYs) and costs in US dollars with a discount  
292 rate of 3% applied to future health and economic outcomes. DALYs are a widely-used metric that  
293 combine years of life lost from mortality with years of healthy life lost from morbidity and they are a  
294 standard way to express health impact in cost-effectiveness studies as they can be compared across  
295 disease states and etiologies.

296 While each study examined the expected health and economic impact of extended half-life mAb and  
297 RSV maternal vaccine, they used different assumptions regarding intervention efficacy, duration of  
298 protection, and product cost. In general, extended half-life mAbs are estimated to have lower  
299 incremental cost-effectiveness ratios (indicating higher value for money) than equally priced RSV  
300 maternal vaccine. As the price of mAb rises relative to maternal vaccine, maternal vaccine becomes  
301 increasingly more favorable. Seasonal administration of mAb limited to the months of highest RSV risk  
302 also improves the value for money compared to year-round administration. A seasonal strategy is  
303 advised by the PPC in settings where the RSV season is clearly defined [1]. Only the Mali study  
304 considered a seasonal program, which contributed to the more favorable cost-effectiveness ratio for  
305 mAb in that analysis.

306 Data from Kenya and South Africa reveal that RSV LRTI incidence and death are concentrated among  
307 infants in the first three months of life [47], whereas in Mali RSV LRTI incidence was greatest in the  
308 fourth and fifth months of life [46]. For this reason, cost-effectiveness estimates for maternal vaccine  
309 aimed at protection during early infancy were more favorable in Kenya and South Africa compared to  
310 Mali. Whether these differences in age distribution of early RSV disease are due to true differences in  
311 epidemiology, health care utilization or in surveillance approaches is not clear. However, the impact of  
312 this discrepancy on intervention cost-effectiveness highlights the importance of robust estimates of

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313 early-life RSV epidemiology and health-care utilization within regions and countries. Additionally, as  
314 deaths are the largest driver of ~~disability-adjusted life years (DALYs)~~, averted, RSV case fatality rates in  
315 the hospital and in the community are critically important inputs. Both large multi-country studies  
316 applied an adjustment factor of 2.2 to all country-specific inpatient case fatality rates to estimate the  
317 rate of community deaths [44, 45, 48]. In the Kenya and Mali analyses, deaths in the community  
318 accounted for approximately 3/4 of all RSV-associated deaths, whereas in South Africa they made up  
319 about a quarter (Figure 2) [47]. It is possible that these studies have underestimated the total number of  
320 RSV associated deaths, as the 2022 systematic review of RSV LRTI burden estimates suggests  
321 approximately four community deaths for each in-hospital death in low-income countries [7].

322 Assessing model sensitivity to either different assumptions or changing conditions is critical to  
323 understanding the decision space, or in other words, which model changes might lead to a different  
324 policy choice. Univariate sensitivity analyses, in which individual parameters are varied incrementally  
325 above and below a point estimate, can identify which parameters most influence model output. Another  
326 important analysis tool for decision models is the Expected Value of Partially Perfect Information, which  
327 calculates the amount that key stakeholders would be willing to spend to gain an exact estimate for a  
328 specific influential parameter. The Expected Value of Partially Perfect Information is calculated as the  
329 difference in the monetary value of health gain associated with a decision made using the currently  
330 available information and when the choice is made based on perfect information without uncertainty  
331 [49]-[49]. Among the studies presented at the meeting which assessed parameter influence, the authors  
332 identified rates of illness, hospitalization, and death due to RSV as the most influential (Figure 3).

333 Identifying influential parameters can help to determine target areas for funding further research and  
334 data collection, especially when expensive trials and observational studies are involved.

335 **KEY PARAMETERS FOR RSV PREVENTION COST-EFFECTIVENESS**

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**336 Cost of Care**

337 Few primary data collection studies have been done on the cost of facility treatment specifically for RSV,  
338 with general pneumonia costs often used as proxies [50]. Additionally, there is a paucity of data  
339 regarding intensive care unit (ICU) and ventilation costs among RSV patients. However, facility  
340 treatment costs for RSV may not be the most influential drivers of the cost-effectiveness of RSV  
341 interventions in low-resource settings, due to the often-low cost of care and healthcare utilization [44].  
342 Most of the economic benefits from RSV interventions derive from the value of prevented mortality  
343 (DALYs averted), which may be relatively higher in such settings partly because of low healthcare access.  
344 Rates of facility treatment may grow over time if countries are able to invest more in healthcare systems  
345 as a whole. Under these conditions, the costs averted by preventive RSV interventions will increase; this  
346 may even make RSV interventions net cost saving as suggested by the cost-effectiveness results for  
347 South Africa [47].  
348 RSV preventive interventions may also achieve broader cost savings apart from direct healthcare  
349 expenditures, which are less commonly measured. Costs for out-of-pocket payments, transport,  
350 accommodation, and lost productivity may fall on households of infants with RSV illness; these were  
351 measured in a study of RSV hospitalization in Malawi [51]. Studies in high-income countries suggest that  
352 the productivity costs can last well beyond the acute episode itself [52]. RSV illness has been associated  
353 with long-term sequelae such as wheezing and asthma [53]; if these can be prevented by vaccination or  
354 mAbs then the long-term medical and productivity cost savings may be substantial. Antibiotics are often  
355 inappropriately prescribed to treat respiratory illness associated with RSV [54]. Hence RSV preventive  
356 interventions may reduce both the costs of antibiotic prescribing and the long-term costs and health  
357 losses associated with the loss of antibiotic efficacy due to overuse. The studies discussed at the meeting

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358 did not include these cost elements, and therefore are likely underestimating the full societal value of  
359 RSV interventions.

**360 Age specific CFR of RSV LRTI**

361 Because mortality is a primary driver of the cost-effectiveness ratio for RSV preventative interventions in  
362 LMICs, it is critical that it be estimated as accurately as possible. Despite progress in updating global RSV  
363 mortality estimates using rigorous methodology [20], the number of studies directly measuring RSV  
364 deaths in LMICs remain few and are faced with several inherent challenges. Three such challenges  
365 include (1) estimating the proportion of deaths with RSV detected that are caused by RSV, i.e.,  
366 differentiating RSV-attributable from RSV-associated deaths; (2) estimating the number of deaths in  
367 LMICs that occur outside of health facilities; and (3) estimating the out-of-facility RSV CFR, which likely is  
368 higher than the in-hospital CFR.

369 The presence of RSV in a deceased child, identified through antemortem or post-mortem sampling (i.e.,  
370 an RSV-associated death), does not always indicate that the death was attributable to the RSV infection.  
371 Using RSV-associated deaths to estimate CFR can therefore lead to over-estimates of the mortality that  
372 could be prevented by RSV-targeted interventions, and therefore an inaccurate cost-effectiveness  
373 assessment. Conversely, RSV could be in the causal chain leading to death and no longer be detectable  
374 once samples are obtained, leading to under-estimation of its role. Differentiating RSV-associated from  
375 RSV-attributable illness and death can be complicated, as multiple pathogens are often detected from  
376 the same LRTI episode [55]. Although there is compelling evidence that RSV is causally associated with  
377 LRTI episodes when it is detected in a child with LRTI, it is not clear that detecting RSV in fatal cases is  
378 similarly predictive of death caused by RSV [55, 56]. This is highlighted by the Child Health and Mortality  
379 Prevention Surveillance Study (CHAMPS), a multi-site study where expert panels determine cause of  
380 death from post-mortem specimens, verbal autopsy and antemortem clinical records. In pooled cases

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381 from CHAMPS sites representing seven countries, RSV was determined to be in the causal chain leading  
382 to death in 24 cases among 67 where it was detected (36%), with considerable variation by age group  
383 and study site [57]. The implication is that mortality could have been prevented by RSV-targeted  
384 intervention in only 1/3 of these RSV-associated deaths.

385 A second major challenge is estimating the proportion of RSV deaths in children that occur outside of  
386 health care facilities. This is a particularly important consideration for low resource setting with a high  
387 burden of deaths from all causes, including RSV, in the community. Community mortality studies in  
388 infants <6 months document a high proportion of RSV deaths occurring in the community, ranging from  
389 29% in Karachi, Pakistan to 70% in Lusaka, Zambia to 75% in rural Maharashtra, India [58-60]. These  
390 figures may be over-estimates based upon the possibility that RSV might not have been in the cause  
391 chain of death in some of the decedents where it was identified.

392 A third challenge is estimating the CFR for RSV illness that occurs in the community. In Maharashtra,  
393 community and in-hospital CFRs were directly compared for the same cohort of children <6 months [59].  
394 In this cohort, community RSV CFR was 2.5 times greater than the in-hospital RSV CFR (3/52 [7.1%] vs.  
395 1/36 [2.8%]). Although limited by small numbers, this study demonstrates that applying in-hospital RSV  
396 CFR to community incidence may underestimate community mortality.

397 The methodologic, logistic, and ethical barriers to generating accurate RSV-attributable mortality  
398 estimates and CFRs in low resource settings are significant. These inputs will therefore be most reliably  
399 generated with post-introduction studies of RSV vaccines or mAbs [61].

400 **RSV intervention product pricing and delivery costs**

401 Immunization program costs are comprised of commodity costs and delivery (i.e., administration) costs.

402 To date, there are limited data to directly inform the costs of RSV intervention programs, as only limited

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403 interventions are available. Commodity prices are not yet known, and delivery costs are only now  
404 beginning to be assessed. However, some information can be inferred from other vaccines and  
405 associated delivery costs. Broadly speaking, RSV vaccine commodity costs are likely to depend on the  
406 complexity of developing and manufacturing the product, market size and makeup (i.e., potential for  
407 different market segments), number and location of suppliers, country income level or ability to pay,  
408 donor support, and time since the intervention has entered the market. These commodity costs are thus  
409 linked to supplier-related costs and other market factors that will also influence prices. Delivery costs  
410 are likely to be influenced by country income level, delivery strategy and ability to leverage other  
411 program activities. These factors can help interpret data from other vaccines that might serve as proxies  
412 as RSV specific information is forthcoming.

413 Product pricing for currently available vaccines can be assessed through several sources including the  
414 UNICEF and WHO websites [62, 63]-[62, 63]. Data from UNICEF show that product prices can vary  
415 substantially by vaccine and may even differ substantially even within a single product. For example,  
416 average prices for measles vaccine, oral polio vaccine (OPV), or diphtheria-pertussis-tetanus vaccine may  
417 cost less than \$0.25 per dose. Other newer products or those with markets dominated by multinational  
418 producers such as human papillomavirus vaccine or pneumococcal conjugate vaccine may command  
419 higher prices. Prices can also vary depending on the procurement mechanism and country income level.  
420 Between 2018 and 2020, average country reported prices for Prevnar13 varied substantially. Countries  
421 eligible for Gavi support reported prices approximating \$3.50 per dose while countries procuring  
422 through the Pan American Health Organization (PAHO) revolving fund paid approximately four times this  
423 amount. Average reported prices were slightly higher than PAHO revolving fund prices for other lower-  
424 and upper-middle income countries [63]-[63]. On average, high-income countries reporting prices paid  
425 nine times the average price paid by countries eligible for Gavi support. Country income level and donor



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4 426 support are important factors influencing vaccine prices. While prices for RSV prevention interventions  
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6 427 are not yet known, similar trends may be expected when these products come to market.  
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10 428 To date, there are no known studies assessing RSV intervention delivery costs, though several  
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12 429 prospective studies are being initiated. As with product price, information can be gleaned from other  
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14 430 vaccines to inform potential delivery costs. The Immunization Delivery Cost Catalogue and associated  
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17 431 publications are a useful source of delivery cost data [64]-[64]. While delivery strategy, study method,  
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19 432 country context and other factors limit direct comparability, most studies find that the economic cost to  
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22 433 deliver a vaccine ranges from approximately \$0.50 to \$1.50 USD. However, costs for human  
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24 434 papillomavirus vaccine delivery can be higher due to the potential for alternative delivery strategies to  
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26 435 reach a different target population through unique contacts with recipients. Maternal immunization  
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29 436 may also require alternative delivery strategies, unique contacts with recipients or seasonal delivery and  
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31 437 thus may cost more to deliver. There are currently few empirical estimates of maternal immunization  
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33 438 delivery costs in LMICs, though existing estimates broadly align with estimates for childhood vaccines  
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36 439 [65].  
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39 440 Prospective RSV or maternal immunization delivery cost estimates will help inform our understanding of  
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42 441 whether maternal immunization delivery costs will align with existing childhood vaccine delivery costs or  
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44 442 if they may cost more due to distinct contacts with beneficiaries, alternative delivery strategies or  
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46 443 platforms, e.g., integration with antenatal care programs. There are no known estimates of mAb  
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49 444 delivery costs in LMICs, but these costs may be similar to other childhood vaccines. Our knowledge of  
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51 445 RSV intervention program costs is limited but expected to grow quickly as RSV preventive interventions  
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54 446 become available and enter use.  
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57 447 **Willingness to pay for health**  
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448 Once a cost-effectiveness ratio has been estimated, the result must then be interpreted for policy  
449 decisions. The amount of money that an entity will spend in order to achieve a unit of improved health  
450 for a given population under its remit is often referred to as the societal willingness to pay, or as the  
451 cost-effectiveness threshold [66]-[66]. The WHO Choosing Interventions that are Cost-Effective (CHOICE)  
452 Programme offers guidance for evaluating new interventions, centered on comparison with existing  
453 interventions and alternative spending choices. Under this framework, the maximum willingness-to-pay  
454 for health might be approximated as the highest cost-effectiveness ratio for a currently funded  
455 intervention that is deemed cost-effective, with the caveat that cost-effectiveness is not the sole  
456 consideration when selecting health programs [67]-[67]. Previous documents suggested designating  
457 “very cost-effective” and “cost-effective” interventions for a country based on per-capita gross domestic  
458 product (GDP) and three times that value, respectively [68]-[68]. These numbers were widely adopted as  
459 global norms in cost-effectiveness analyses [67], and have often been used as a decision rule, despite  
460 replacement with new guidance as well as evidence that these thresholds may be unrealistically high for  
461 LMICs [69].

462 The willingness to pay intersects with cost-effectiveness and policy decisions in ways that are both  
463 intuitive and not. Intuitively, as the willingness to pay rises, higher cost-effectiveness ratios become  
464 acceptable to payers. Interventions become more likely to be adopted, and higher prices better  
465 tolerated. When there are multiple payers, this general principle remains true, but each payer may end  
466 up preferring different decisions or strategies. For instance, a donor generally will have a higher  
467 willingness or ability to pay for health than a recipient, by nature of their relationship. A donor who is  
468 subsidizing an intervention across multiple countries may also be less sensitive to the cost-effectiveness  
469 of the program in a single country, and willing to accept high cost-effectiveness ratios for some contexts  
470 when the overall value for health is favorable. Another aspect of the donor/recipient dynamic is that  
471 cost-sharing may lead to different cost-effectiveness ratios for each payer and potentially different

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472 policy preferences. For instance, under a donor model similar to that used by Gavi, combination  
473 strategies using both extended half-life mAb and pediatric vaccination have a lower cost-effectiveness  
474 ratio from a government payer perspective than a donor perspective in Mali [70]. However, if the donor  
475 willingness-to-pay is higher than that of the government, this combination strategy might be optimal  
476 from both perspectives [71].[\[71\]](#).

477 **Summary of the discussion about key parameters**

478 Objectives of the meeting included identifying the most influential parameter inputs and data  
479 limitations for the cost-effectiveness analyses and recommending and prioritizing future data gathering  
480 and research to improve estimates of the impact of RSV prevention in LMICs. Epidemiological  
481 parameters from the presented health economics studies identified as both influential and uncertain  
482 were those associated with RSV hospitalization and death, specifically setting-specific hospitalization  
483 rates and RSV-attributable death rates. Influential economic parameters included product price, delivery  
484 costs, willingness-to-pay for health on the part of potential donors, and the cost of RSV-associated  
485 hospitalization. Participants appraised the research presented in the meeting as being of high quality,  
486 with the caveats that the health economics studies used inputs for which there were limited empiric  
487 data. Public health donors and investigators should consider future research to develop more robust,  
488 precise measurements of the parameters identified by the meeting as influential and uncertain.

489 The most influential disease epidemiology data include incidence of severe and fatal RSV LRTI. These  
490 relatively rare endpoints are difficult to measure precisely with most observational study designs.  
491 Pooling data from multiple studies for meta-analysis is the most efficient way to address the issue of  
492 lack of power, and standardized case definitions and data collection procedures could facilitate these  
493 efforts. Further, vaccine or mAb probe design may be able to reveal the fraction of hospitalizations that  
494 are attributable to RSV and thus preventable through product use.

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495 It is anticipated that more product-specific characteristics data, such as duration of protection and  
496 efficacy from LMIC settings will become available as field trials progress. Additional valuable data can be  
497 achieved from observational effectiveness studies. Standardization of case definitions, methodologies,  
498 data reporting can facilitate study-to-study comparisons and data pooling.

499 This meeting highlighted the limitations in the availability of general LRTI or RSV-specific medical care  
500 costs, as well as costs related to product delivery. More data collection from diverse locales would  
501 benefit impact models.

502 **DISCUSSION**

503 As RSV preventive interventions move through clinical development towards licensure, there is an  
504 urgent need to consider the suitability of these products for use in LMICs. Palivizumab is unsuitable due  
505 to its price point and the need for multiple doses. Products meeting WHO Preferred Product  
506 Characteristics would have lower barriers: a single-dose maternal vaccine, a two-dose pediatric series,  
507 or a birth dose monoclonal mAb with extended half-life. For high-income countries where the short half-  
508 life monoclonal is currently used, the health economic case for next generation products may be  
509 straightforward. At a similar or lower price and with higher protection, these products can replace the  
510 short half-life mAb and could be offered to all infants. However, in LMICs the adoption of these  
511 strategies represents a substantial financial outlay that may not be entirely offset by savings on medical  
512 care. The cost-effectiveness of these new strategies will be a critical consideration for public health  
513 policymakers aiming to maximize health with limited resources.

514 In convening this meeting, we aimed to illuminate the known drivers of cost-effectiveness for these  
515 interventions based on existing health economic models, and to highlight where insufficient knowledge  
516 contributes to uncertainty regarding the appropriate public health decision. We also sought to clarify

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4 517 the factors contributing to cross-country variability in parameter estimates. Finally, it was our goal to  
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6 518 identify whether there was a clear need for future research to resolve these uncertainties.  
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10 519 The first major challenge is accurate determination of the health burden that could be alleviated by each  
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12 520 prevention strategy. In most LMICs, RSV illness data remains scarce. Disease burden estimations often  
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14 521 rely on sentinel sites or research studies to extrapolate information across broad geographic areas and  
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16 522 populations. Complicating quantification, recent studies suggest that ~~many~~some proportion of deaths  
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18 523 among RSV-positive infants which occur in a hospital setting are likely attributable to a different  
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20 524 pathogen or cause, and therefore could not have been prevented by any of these RSV-specific  
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22 525 preventative products [27]. As a further complication, evidence indicates that more RSV deaths than  
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24 526 previously suspected occur in the community [7] and are not documented at a hospital setting. These  
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26 527 biases pull the estimates of disease burden in opposing directions, adding considerable uncertainty.  
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32 528 The investment case for RSV preventive interventions also relies on economic inputs such as the costs  
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34 529 for medically attended RSV illness. There may not be substantial uncertainty at the country level; for  
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36 530 instance, assessment of RSV prevention in Mali using high-quality, setting-specific inputs found that  
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38 531 even relatively wide ranges for medical costs did not lead to large changes in the economic case for RSV  
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40 532 prevention [46]. However, variation across countries can dramatically change the decision space. In  
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42 533 South Africa, for instance, greater healthcare utilization and higher costs for RSV illness leads to the  
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44 534 conclusion that RSV prevention strategies could be cost saving for that country [47]. International  
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46 535 decision-making bodies and donors must be aware of these cross-country drivers, so that a less  
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48 536 favorable cost-effectiveness ratio is not necessarily interpreted as due to a lower disease burden, but  
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50 537 potentially to greater investment in, and access to, healthcare.  
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57 538 Changes across reasonable ranges for the product price and willingness-to-pay for health also influence  
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59 539 whether these RSV prevention strategies would be considered favorable or unfavorable. As the vaccine-

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540 preventable mortality is lower for RSV than for other pathogens such as *Haemophilus influenzae* type B  
541 [72], acceptable prices for RSV preventive interventions are also lower than for these vaccines. It is not  
542 yet clear whether these lower prices are feasible for manufacturers, particularly for mAbs. Regarding the  
543 willingness-to-pay for health, WHO and other global bodies have moved away from single yardsticks for  
544 cost-effectiveness. The previous commonly used measures of one and three times the per-capita GDP  
545 per DALY averted may not reflect true budget constraints, which may cap the interventions that could  
546 efficiently be adopted at a lower range. For example, in the analysis of RSV prevention in Mali, the  
547 authors found that extended half-life monoclonals have an incremental cost-effectiveness ratio (ICER) of  
548 approximately US \$200 per DALY from the government perspective, which would generally be  
549 considered good value even with this new perspective [46]. However, the societal and donor ICERs are  
550 twice and three times higher, respectively. Although it is reasonable to expect that donors might be  
551 willing to pay for interventions that are not otherwise affordable, as that is the nature of donation, it is  
552 not clear whether donors value health at ICERs in these specific ranges.

553 **CONCLUSION**

554 RSV LRTI is a major cause of death and suffering among young children in LMICs. Prevention of RSV LRTI  
555 is a major unmet need in these settings. There is a robust pipeline of RSV preventive intervention  
556 candidates in clinical development, including an extended half-life mAb recently authorized for use in  
557 Europe and a maternal vaccine undergoing regulatory review. Vaccine decision makers will need  
558 estimates of cost effectiveness to inform policies and implementation. These cost-effectiveness  
559 estimates will require data that are not routinely collected through public health practice nor in  
560 intervention efficacy studies. This meeting identified the most influential modelling parameters which  
561 could drive results about intervention cost effectiveness. Precise and high-quality estimates for these  
562 parameters will improve health and economic impact estimates of RSV prevention.

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**574 REFERENCES**

575 [1] Sparrow E, Adetifa I, Chaiyakunapruk N, Cherian T, Fell DB, Graham BS, et al. WHO preferred product  
576 characteristics for monoclonal antibodies for passive immunization against respiratory syncytial virus  
577 (RSV) disease in infants - Key considerations for global use. *Vaccine*. 2022.

578 [2] Vekemans J, Moorthy V, Giersing B, Friede M, Hombach J, Arora N, et al. Respiratory syncytial virus  
579 vaccine research and development: World Health Organization technological roadmap and preferred  
580 product characteristics. *Vaccine*. 2019;37:7394-5.

581 [3] Fleming JA, Baral R, Higgins D, Khan S, Kochar S, Li Y, et al. Value profile for respiratory syncytial virus  
582 vaccines and monoclonal antibodies. *Vaccine*. 2023.

583 [4] Meeting of the Strategic Advisory Group of Experts on immunization, April 2016 - conclusions and  
584 recommendations. *Wkly Epidemiol Rec*. 2016;91:266-84.

585 [5] Li Y, Reeves RM, Wang X, Bassat Q, Brooks WA, Cohen C, et al. Global patterns in monthly activity of  
586 influenza virus, respiratory syncytial virus, parainfluenza virus, and metapneumovirus: a systematic  
587 analysis. *Lancet Glob Health*. 2019;7:e1031-e45.

588 [6] Centers for Disease Control and Prevention. RSV in Infants and Young Children. 2020.

589 [7] Li Y, Wang X, Blau DM, Caballero MT, Feikin DR, Gill CJ, et al. Global, regional, and national disease  
590 burden estimates of acute lower respiratory infections due to respiratory syncytial virus in children  
591 younger than 5 years in 2019: a systematic analysis. *Lancet*. 2022;399:2047-64.

592 [8] Nguyen-Van-Tam JS, O'Leary M, Martin ET, Heijnen E, Callendret B, Fleischhackl R, et al. Burden of  
593 respiratory syncytial virus infection in older and high-risk adults: a systematic review and meta-analysis  
594 of the evidence from developed countries. *Eur Respir Rev*. 2022;31.

595 [9] Hall CB, Walsh EE, Long CE, Schnabel KC. Immunity to and frequency of reinfection with respiratory  
596 syncytial virus. *J Infect Dis*. 1991;163:693-8.



1  
2  
3  
4 597 [10] Aranda SS, Polack FP. Prevention of Pediatric Respiratory Syncytial Virus Lower Respiratory Tract  
5  
6 598 Illness: Perspectives for the Next Decade. *Front Immunol.* 2019;10:1006.  
7  
8  
9 599 [11] Ruckwardt TJ, Morabito KM, Graham BS. Immunological Lessons from Respiratory Syncytial Virus  
10  
11 600 Vaccine Development. *Immunity.* 2019;51:429-42.  
12  
13  
14 601 [12] American Academy of Pediatrics Committee on Infectious Diseases, Bronchiolitis Guidelines  
15  
16 602 Committee,. Updated guidance for palivizumab prophylaxis among infants and young children at  
17  
18 603 increased risk of hospitalization for respiratory syncytial virus infection. *Pediatrics.* 2014;134:415-20.  
19  
20  
21 604 [13] PATH. RSV Vaccine and mAb Snapshot. 2023.  
22  
23 605 [14] European Medicines Agency. Beyfortus 2022.  
24  
25 606 [15] Pfizer. U.S. FDA Accepts Biologics License Application for Pfizer’s Respiratory Syncytial Virus  
26  
27 607 Maternal Vaccine Candidate for Priority Review. 2023.  
28  
29  
30 608 [16] Food and Drug Agency. FDA Approves First Respiratory Syncytial Virus (RSV) Vaccine. 2023.  
31  
32  
33 609 [17] World Health Organization. Guidance for the Development of Evidence-based Vaccination-related  
34  
35 610 Recommendations. 2017.  
36  
37 611 [18] Gavi The Vaccine Alliance. Vaccine investment strategy. 2022.  
38  
39  
40 612 [19] Bertram MY, Edejer TTT. Introduction to the Special Issue on "The World Health Organization  
41  
42 613 Choosing Interventions That Are Cost-Effective (WHO-CHOICE) Update". *Int J Health Policy Manag.*  
43  
44 614 2021;10:670-2.  
45  
46  
47 615 [20] Li Y, Wang X, Blau DM, Caballero MT, Feikin DR, Gill CJ, et al. Global, regional, and national disease  
48  
49 616 burden estimates of acute lower respiratory infections due to respiratory syncytial virus in children  
50  
51 617 younger than 5 years in 2019: a systematic analysis. *Lancet (London, England).* 2022;399:2047-64.  
52  
53  
54 618 [21] Shi T, McAllister DA, O'Brien KL, Simoes EAF, Madhi SA, Gessner BD, et al. Global, regional, and  
55  
56 619 national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus  
57  
58 620 in young children in 2015: a systematic review and modelling study. *Lancet.* 2017;390:946-58.  
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[22] Madewell ZJ, Whitney CG, Velaphi S, Mutevedzi P, Mahtab S, Madhi SA, et al. Prioritizing Health Care Strategies to Reduce Childhood Mortality. *JAMA Netw Open*. 2022;5:e2237689.

[23] Hammitt LL, Dagan R, Yuan Y, Baca Cots M, Bosheva M, Madhi SA, et al. Nirsevimab for Prevention of RSV in Healthy Late-Preterm and Term Infants. *N Engl J Med*. 2022;386:837-46.

[24] Griffin MP, Yuan Y, Takas T, Domachowske JB, Madhi SA, Manzoni P, et al. Single-Dose Nirsevimab for Prevention of RSV in Preterm Infants. *N Engl J Med*. 2020;383:415-25.

[25] Saha SK, Schrag SJ, El Arifeen S, Mullany LC, Shahidul Islam M, Shang N, et al. Causes and incidence of community-acquired serious infections among young children in south Asia (ANISA): an observational cohort study. *Lancet*. 2018;392:145-59.

[26] Nair H. Global, regional and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015, 1995-2015 [dataset]. In: Edinburgh Uo, editor.: Usher Institute of Population Health Sciences and Informatics; 2016.

[27] Pneumonia Etiology Research for Child Health Study Group. Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study. *Lancet*. 2019;394:757-79.

[28] O'Brien KL, Chandran A, Weatherholtz R, Jafri HS, Griffin MP, Bellamy T, et al. Efficacy of motavizumab for the prevention of respiratory syncytial virus disease in healthy Native American infants: a phase 3 randomised double-blind placebo-controlled trial. *Lancet Infect Dis*. 2015;15:1398-408.

[29] Collaborators GBDLRI. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory infections in 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Infect Dis*. 2018;18:1191-210.

[30] PATH. RSV Clinical Trial Tracker. 2022.

[31] Food and Drug Agency. FDA Approves New Drug to Prevent RSV in Babies and Toddlers. 2023.

1  
2  
3  
4 645 [32] Boytchev H. FDA advisers back Pfizer's maternal RSV vaccine after voicing safety concerns. BMJ.  
5  
6 646 2023;381:1187.  
7  
8  
9 647 [33] Food and Drug Agency. FDA Approves First Vaccine for Pregnant Individuals to Prevent RSV in  
10  
11 648 Infants. 2023.  
12  
13  
14 649 [34] Pfizer. European Commission Approves Pfizer's ABRYOVO™ to Help Protect Infants through  
15  
16 650 Maternal Immunization and Older Adults from RSV. 2023.  
17  
18 651 [35] Ananworanich J, Heaton PM. Bringing Preventive RSV Monoclonal Antibodies to Infants in Low- and  
19  
20 652 Middle-Income Countries: Challenges and Opportunities. Vaccines (Basel). 2021;9.  
21  
22  
23 653 [36] Medicines & Healthcare products Regulatory Agency. Decision Cover Letter. 2022.  
24  
25 654 [37] Domachowske J, Madhi SA, Simoes EAF, Atanasova V, Cabanas F, Furuno K, et al. Safety of  
26  
27 655 Nirsevimab for RSV in Infants with Heart or Lung Disease or Prematurity. N Engl J Med. 2022;386:892-4.  
28  
29  
30 656 [38] Clinicaltrials.gov. A phase 2b placebo-controlled, randomized study of a respiratory syncytial virus  
31  
32 657 (RSV) vaccine in pregnant women. 2023.  
33  
34  
35 658 [39] Giles ML, Mantel C, Munoz FM, Moran A, Roos N, Yusuf N, et al. Vaccine implementation factors  
36  
37 659 affecting maternal tetanus immunization in low- and middle-income countries: Results of the Maternal  
38  
39 660 Immunization and Antenatal Care Situational Analysis (MIACSA) project. Vaccine. 2020;38:5268-77.  
40  
41  
42 661 [40] Kampmann B, Madhi SA, Munjal I, Simoes EAF, Pahud BA, Llapur C, et al. Bivalent Prefusion F  
43  
44 662 Vaccine in Pregnancy to Prevent RSV Illness in Infants. N Engl J Med. 2023;388:1451-64.  
45  
46  
47 663 [41] World Health Organization. WHO and UNICEF estimates of national immunization coverage: 2019  
48  
49 664 revision. 2019.  
50  
51  
52 665 [42] UNICEF. Antenatal care. 2022.  
53  
54 666 [43] Baral R, Fleming J, Khan S, Higgins D, Hendrix N, Pecenka C. Inferring antenatal care visit timing in  
55  
56 667 low- and middle-income countries: Methods to inform potential maternal vaccine coverage. PLoS One.  
57  
58 668 2020;15:e0237718.  
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669 [44] Li X, Willem L, Antillon M, Bilcke J, Jit M, Beutels P. Health and economic burden of respiratory  
670 syncytial virus (RSV) disease and the cost-effectiveness of potential interventions against RSV among  
671 children under 5 years in 72 Gavi-eligible countries. BMC Med. 2020;18:82.

672 [45] Baral R, Higgins D, Regan K, Pecenka C. Impact and cost-effectiveness of potential interventions  
673 against infant respiratory syncytial virus (RSV) in 131 low-income and middle-income countries using a  
674 static cohort model. BMJ Open. 2021;11:e046563.

675 [46] Laufer RS, Driscoll AJ, Baral R, Buchwald AG, Campbell JD, Coulibaly F, et al. Cost-effectiveness of  
676 infant respiratory syncytial virus preventive interventions in Mali: A modeling study to inform policy and  
677 investment decisions. Vaccine. 2021;39:5037-45.

678 [47] Koltai M, Moyes J, Nyawanda B, Nyiro J, Munywoki PK, Tempia S, et al. Estimating the cost-  
679 effectiveness of maternal vaccination and monoclonal antibodies for respiratory syncytial virus in Kenya  
680 and South Africa. BMC Med. 2023;21:120.

681 [48] Shi T, McAllister DA, O'Brien KL, Simoes EAF, Madhi SA, Gessner BD, et al. Global, regional, and  
682 national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus  
683 in young children in 2015: a systematic review and modelling study. Lancet. 2017;390:946-58.

684 [49] York Health Economics Consortium. Expected Value of Partially Perfect Information (EVPPI).  
685 York2016.

686 [50] Zhang S, Sammon PM, King I, Andrade AL, Toscano CM, Araujo SN, et al. Cost of management of  
687 severe pneumonia in young children: systematic analysis. J Glob Health. 2016;6:010408.

688 [51] Baral R, Mambule I, Vodicka E, French N, Everett D, Pecenka C, et al. Estimating the Economic  
689 Impact of Respiratory Syncytial Virus and Other Acute Respiratory Infections Among Infants Receiving  
690 Care at a Referral Hospital in Malawi. J Pediatric Infect Dis Soc. 2020;9:738-45.

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[52] Pokrzywinski RM, Swett LL, Pannaraj PS, Yi J, Pavilack MS, Kumar VR, et al. Impact of Respiratory Syncytial Virus-Confirmed Hospitalizations on Caregivers of US Preterm Infants. *Clin Pediatr (Phila)*. 2019;58:837-50.

[53] Brunwasser SM, Snyder BM, Driscoll AJ, Fell DB, Savitz DA, Feikin DR, et al. Assessing the strength of evidence for a causal effect of respiratory syncytial virus lower respiratory tract infections on subsequent wheezing illness: a systematic review and meta-analysis. *Lancet Respir Med*. 2020;8:795-806.

[54] Fitzpatrick T, Malcolm W, McMenamin J, Reynolds A, Guttmann A, Hardelid P. Community-Based Antibiotic Prescribing Attributable to Respiratory Syncytial Virus and Other Common Respiratory Viruses in Young Children: A Population-Based Time-series Study of Scottish Children. *Clin Infect Dis*. 2021;72:2144-53.

[55] Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study. *Lancet (London, England)*. 2019;394:757-79.

[56] Shi T, McLean K, Campbell H, Nair H. Aetiological role of common respiratory viruses in acute lower respiratory infections in children under five years: A systematic review and meta-analysis. *Journal of global health*. 2015;5:010408.

[57] Blau DM, Baillie VL, Els T, Mahtab S, Mutevedzi P, Keita AM, et al. Deaths Attributed to Respiratory Syncytial Virus in Young Children in High-Mortality Rate Settings: Report from Child Health and Mortality Prevention Surveillance (CHAMPS). *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2021;73:S218-s28.

[58] Gill CJ, Mwananyanda L, MacLeod WB, Kwenda G, Pieciak R, Mupila Z, et al. Infant deaths from respiratory syncytial virus in Lusaka, Zambia from the ZPRIME study: a 3-year, systematic, post-mortem surveillance project. *The Lancet Global health*. 2022;10:e269-e77.

1  
2  
3  
4 715 [59] Simões EAF, Dani V, Potdar V, Crow R, Satav S, Chadha MS, et al. Mortality From Respiratory  
5  
6 716 Syncytial Virus in Children Under 2 Years of Age: A Prospective Community Cohort Study in Rural  
7  
8 717 Maharashtra, India. *Clinical infectious diseases : an official publication of the Infectious Diseases Society*  
9  
10 of America. 2021;73:S193-s202.  
11  
12 718  
13 [60] Kazi AM, Aguolu OG, Mughis W, Ahsan N, Jamal S, Khan A, et al. Respiratory Syncytial Virus-  
14 719  
15 Associated Mortality Among Young Infants in Karachi, Pakistan: A Prospective Postmortem Surveillance  
16 720  
17 Study. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.*  
18 721  
19 2021;73:S203-s9.  
20 722  
21 [61] Feikin DR, Scott JA, Gessner BD. Use of vaccines as probes to define disease burden. *Lancet.*  
22 723  
23 2014;383:1762-70.  
24 724  
25 [62] UNICEF. Vaccines pricing data. 2022.  
26 725  
27 [63] World Health Organization. MI4A Vaccine Purchase Database. 2022.  
28 726  
29 [64] Immunizationeconomics.org. Immunization Delivery Cost Catalogue. 2022.  
30 727  
31 [65] Procter SR, Salman O, Pecenka C, Gonçalves BP, Paul P, Hutubessy R, et al. A review of the costs of  
32 728  
33 delivering maternal immunisation during pregnancy. *Vaccine.* 2020;38:6199-204.  
34 729  
35 [66] Bertram MY, Lauer JA, Stenberg K, Edejer TTT. Methods for the Economic Evaluation of Health Care  
36 730  
37 Interventions for Priority Setting in the Health System: An Update From WHO CHOICE. *Int J Health Policy*  
38 731  
39 *Manag.* 2021;10:673-7.  
40 732  
41 [67] Bertram MY, Lauer JA, De Joncheere K, Edejer T, Hutubessy R, Kieny MP, et al. Cost-effectiveness  
42 733  
43 thresholds: pros and cons. *Bull World Health Organ.* 2016;94:925-30.  
44 734  
45 [68] Hutubessy R, Chisholm D, Edejer TT. Generalized cost-effectiveness analysis for national-level  
46 735  
47 priority-setting in the health sector. *Cost Eff Resour Alloc.* 2003;1:8.  
48 736  
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737 [69] Ochalek J, Lomas J, Claxton K. Estimating health opportunity costs in low-income and middle-  
738 income countries: a novel approach and evidence from cross-country data. *BMJ Glob Health*.  
739 2018;3:e000964.

740 [70] Laufer RS, Baral R, Buchwald AG, Campbell JD, Coulibaly F, Diallo F, et al. Optimizing next-  
741 generation RSV prevention in Mali: A cost-effectiveness analysis of pediatric vaccination, maternal  
742 vaccination, and extended half-life monoclonal antibody immunoprophylaxis. *PLOS Glob Public Health*.  
743 2023;3:e0001432.

744 [71] Morton A, Arulsevan A, Thomas R. Allocation rules for global donors. *J Health Econ*. 2018;58:67-75.

745 [72] World Health Organization. Haemophilus influenzae type b (Hib) meningitis in the pre-vaccine era :  
746 a global review of incidence, age distributions, and case-fatality rates. 2002.

747 [73] Madhi SA, Polack FP, Piedra PA, Munoz FM, Trenholme AA, Simoes EAF, et al. Respiratory Syncytial  
748 Virus Vaccination during Pregnancy and Effects in Infants. *N Engl J Med*. 2020;383:426-39.

749 [74] Baral R, Li X, Willem L, Antillon M, Vilajeliu A, Jit M, et al. The impact of maternal RSV vaccine to  
750 protect infants in Gavi-supported countries: Estimates from two models. *Vaccine*. 2020;38:5139-47.

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752 **Table 1. Comparison of RSV morbidity and mortality burden estimates between the 2022 RSV LRTI systematic review and other important**  
753 **studies<sup>a</sup>**

Parameter <sup>b</sup>	Study	Population	Definition and measure	Estimate (95% CI)
<b>RSV LRTI incidence in first six months of life</b>	Nirsevimab phase 3 trial [23]	Late preterm and term infants, <12 months at baseline (mostly ≤3 months), followed up to day 150 (control arm); 20 countries	RSV medically attended LRTI <sup>c</sup> ; annualized incidence rate (per 1000)	108 (80-147)
	2022 RSV LRTI systematic review [7]	<6m; global	RSV LRTI; annual incidence rate (per 1000)	96 (68-143)
<b>Hospitalized RSV LRTI incidence in first six months of life</b>	Nirsevimab phase 3 trial [23]	Late preterm and term infants, <12 months at baseline (mostly ≤3 months), followed up to day 150 (control arm); 20 countries	Hospitalized RSV LRTI; annualized hospitalization rate (per 1000)	32 (18-58)
	2022 RSV LRTI systematic review [7]	<6m; global	RSV LRTI hospitalization; annual hospitalization rate (per 1000)	20 (15-29)
<b>Severe RSV LRTI incidence in first three months of life</b>	ResVax phase 3 trial [73]	Newborns followed up to day 90 (control arm); 11 countries (mostly from South Africa and US)	RSV medically significant LRTI <sup>d</sup> ; annualized incidence rate (per 1000)	24 (18-34)
	2022 RSV LRTI systematic review [7]	<3m; global	RSV LRTI with chest wall indrawing; annual incidence rate (per 1000)	28 (13-68)
<b>Hospitalized RSV LRTI incidence in first three months of life</b>	ResVax phase 3 trial [73]	Newborns followed up to day 90 (control arm); 11 countries (mostly from South Africa and US)	Hospitalized RSV LRTI; annualized hospitalization rate (per 1000)	37 (28-48)
	2022 RSV LRTI systematic review [7]	<3m; global	RSV LRTI hospitalization; annual hospitalization rate (per 1000)	25 (18-37)
<b>RSV LRTI incidence in first three months of life</b>	ResVax phase 3 trial [73]	Newborns followed up to day 90 (control arm); 11 countries (mostly from South Africa and US)	RSV LRTI with severe hypoxemia <sup>e</sup> ; annualized hospitalization rate (per 1000)	10 (6-16)
	2022 RSV LRTI systematic review [7]	<3m; global	RSV LRTI hospitalization with hypoxemia; annual hospitalization rate (per 1000)	7 (4-16)
<b>RSV LRTI incidence in first six months of life in low-resource setting</b>	Motavizumab phase 3 trial [28]	Term infants ≤6 months at baseline (mean age: 2 months), followed up to day 150 (control arm); native American	RSV LRTI, inpatient and outpatient; annualized incidence rate (per 1000)	403 (368-441)
	2022 RSV LRTI systematic review [7]	<6m; low- and middle-income countries	RSV LRTI; annual incidence rate (per 1000)	104 (70-154)
<b>RSV LRTI hospitalization incidence in first six months of life in low-resource setting</b>	Motavizumab phase 3 trial [28]	Term infants ≤6 months at baseline (mean age: 2 months), followed up to day 150 (control arm); native American	RSV LRTI, inpatient only; annualized incidence rate (per 1000)	165 (140-194)
	2022 RSV LRTI systematic review [7]	<6m; low- and middle-income countries	RSV LRTI hospitalization; annual hospitalization rate (per 1000)	19 (13-29)



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<b>RSV LRTI in-hospital case fatality ratios in early childhood in low-resource settings</b>	PERCH multi-country case-control study [26, 27]	Children aged 1-<60m; seven countries (mostly low-income)	RSV severe pneumonia in-hospital CFR (%)	2.2 (1.3-3.6)
	2022 RSV LRTI systematic review [7]	<60m; low-income countries	RSV LRTI in-hospital mortality; CFR (%)	1.4 (0.6-2.8)
<b>Severe RSV LRTI incidence in first three months of life in low-resource settings</b>	ANISA observational cohort study [25]	Newborns actively followed to day 59 through active community surveillance; Bangladesh, India, and Pakistan	Possible serious bacterial infection <sup>f</sup> ; annualized incidence rate (per 1000)	32 (29-38)
	2022 RSV LRTI systematic review [7]	<3m; lower-middle income countries	RSV LRTI with chest wall indrawing; annual incidence rate (per 1000)	46 (24-86)
<b>RSV LRTI incidence in early childhood</b>	IHME GBD 2016 [29]	All ages, <60 months reported as a separate age band; medical records based on clinical databases across the globe	RSV attributable LRTI morbidity; annual episodes in millions	11 (7-17)
	2022 RSV LRTI systematic review [7]	<60m; global	RSV LRTI; annual episodes in millions	33 (25-45)
<b>RSV LRTI mortality in early childhood</b>	IHME GBD 2016 [29]	All ages, <60 months reported as a separate age band; medical records based on clinical databases across the globe	RSV attributable LRTI mortality; annual deaths in thousands	41 (23-66)
	2022 RSV LRTI systematic review [7]	<60m; global	RSV-attributable deaths; annual deaths in thousands	101 (85-125)

Notes

- a) Abbreviations: RSV = respiratory syncytial virus; LRTI = lower respiratory tract infection; CFR = case fatality ratio; PERCH = Pneumonia Etiology Research for Child Health (PERCH) case-control study; ANISA = Aetiology of Neonatal Infections in South Asia (ANISA) observational cohort study; IHME GBD = Institute for Health Metrics and Evaluation (IHME) Global Burden of Disease estimates.
- b) For each pair of comparison, the best comparable population and case definition from the present study was selected.
- c) Physical examination findings localizing to lower respiratory tract plus any of the following: 1) fast breathing ( $\geq 50$  breaths/minute in children aged 2-<6 months); 2) Hypoxemia ( $SpO_2 < 95\%$  at  $\leq 1800$  meters elevation); 3) clinical signs of severe respiratory diseases.
- d)  $\geq 1$  LRTI manifestation plus fast breathing ( $\geq 60$  breaths/minute in children aged >2 months); or hypoxemia ( $SpO_2 < 95\%$  at  $\leq 1800m$ ).
- e)  $SpO_2 < 92\%$  at  $\leq 1800$  meters or documented use of supplemental  $O_2$  or ventilation.
- f) Based on one of the following signs: fast breathing, hyperthermia, movement only with stimulation, convulsions, and poor feeding; fast breathing cannot be the only sign.

766 **Table 2. Parameter inputs from RSV prevention cost-effectiveness analyses in low- and middle-income**  
 767 **countries**

	Li et al 2020 [44]	Lafer et al 2021 [46]	Baral et al 2020 [74]	Koltai et al 2022 [47]
<b>Location</b>	72 Gavi-eligible countries	Mali	131 LMICs	Kenya and South Africa
<b>Model type</b>	static	static	static	static
<b>Age Inclusion (years)</b>	0-5	0-0.5	1	0-5
<b>Time horizon (years)</b>	5	0.5	10	5
<b>RSV incidence rate</b>	NA	age- and month-specific (mean = 53.7%)	NA	Age- and country-specific (monthly resolution under 1 year) of ARI and SARI, medically attended or not
<b>RSV LRTI incidence rate</b>	Age- and country-specific (monthly resolution under 1 year; country rates from 3.5-6.7%)	NA	age-specific (4% - 9.96%)	Age- and country-specific (monthly resolution under 1 year)
<b>RSV hospitalization incidence rate</b>	NA	NA	NA	Age- and country-specific rates of hospitalized and non-hospitalized SARIs
<b>Probability of LRTI given RSV</b>	NA	0.13	NA	NA
<b>Probability of inpatient care given RSV LRTI</b>	0.09	0.29	20.2 per 1000 for 0-5 months, 11 per 1000 for 6-11 months	Age-specific hospitalization rates (<1 year: 5-60 hospitalizations/1000 population)
<b>Hospital case fatality rate</b>	age-specific (0.045 - 0.006)	0.016	0.022 for 0-5 months, 0.024 for 6-11 months	Age-specific mortality rates (under 1 year: 25-150 deaths/100.000 population)
<b>Disability weight, severe RSV LRTI</b>	0.21	0.13	0.21	0.21
<b>Disability weight, moderate RSV LRTI</b>	0.053	0.05	0.053	0.053
<b>QALY loss, severe RSV LRTI</b>	NA	NA	NA	NA
<b>QALY loss, moderate RSV LRTI</b>	NA	NA	NA	NA
<b>Duration of illness (days)</b>	11.2	8.5	10 for severe RSV LRTI, 5 for moderate RSV LRTI	11.2
<b>Life expectancy (years)</b>	country-specific (50 - 80)	58	country-specific (50 - 80)	Kenya: 66.5, South Africa: 62.5
<b>Discount rate (%)</b>	3	3	3	3
<b>Currency</b>	2016 USD	2019 USD	2016 USD	2021 USD
<b>Willingness to pay threshold (USD per DALY averted)</b>	continuous (0 - 30000)	891	country-specific (130 - 4774)	not fixed
<b>WTP as a multiplier of country GDP per capita</b>	NA	1	0.5	NA

<b>Outpatient costs (USD)</b>	country-specific (0.13 - 91)	6.56	53	Kenya: 20.9 USD, RSA: 24.95 USD
<b>Inpatient costs (USD)</b>	country-specific (0.37 - 640)	118.57	250	Kenya: 102 USD for healthcare provider + 172 USD for household (out-of-pocket); RSA: 634-1002 USD for healthcare provider + 4-22 USD for household (out-of-pocket)
<b>ICU costs (USD)</b>	NA	NA	NA	NA
<b>Administration cost per dose (USD)</b>	included in intervention cost per dose	1.35	0.63 for LIC, 1.73 LMIC and UMIC	included in intervention cost per dose
<b>Cost per dose, short-acting mAb (USD)</b>	NA	3	NA	NA
<b>Cost per dose, long-acting mAb (USD)</b>	6 (tested value: 4 and 11)	3	3 for Gavi eligible, 5 for non-Gavi	Tested values: 6, 20, 60
<b>Cost per dose, maternal vaccine (USD)</b>	3	3	3 for Gavi eligible, 5 for non-Gavi	Tested values: 3, 10, 30
<b>Cost per dose, pediatric vaccine (USD)</b>	NA	NA	NA	NA
<b>Outcome efficacy protects against</b>	RSV LRTI cases	RSV cases	RSV LRTI cases	RSV LRTI, RSV LRTI with hospitalization, severe RSV LRTI (death)
<b>Efficacy, short-acting mAb (%)</b>	NA	78	NA	NA
<b>Efficacy, long-acting mAb (%)</b>	70 (tested value 50 and 90)	56	60-70	70.1%, 78.4%, 78.4% [no data for efficacy against deaths]
<b>Efficacy, maternal vaccine (%)</b>	70 (tested value 50 and 90)	70	40-60	39.4%, 44.4%, 48.3% <a href="#">(the efficacy figures were updated in the published version of the article, lowering the ICER values [47])</a>
<b>Efficacy, pediatric vaccine (%)</b>	NA	NA	NA	NA
<b>Duration of protection, short-acting mAb (months)</b>	NA	1	NA	NA
<b>Duration of protection, long-acting mAb (months)</b>	6 (tested value: 4 and 8)	5	6	5
<b>Duration of protection, maternal vaccine<sup>a</sup> (months)</b>	5 6 (tested value: 3 and 8)	3	3	3
<b>Duration of protection, pediatric vaccine (months)</b>	NA	NA	NA	NA
<b>Coverage<sup>b</sup>, short-acting mAb (%)</b>	NA	77	NA	NA
<b>Coverage<sup>b</sup>, long-acting mAb (%)</b>	country-specific (52 - 99)	83	82	95%
<b>Coverage<sup>b</sup>, maternal vaccine (%)</b>	country-specific (52 - 99)	35.5	84	95%
<b>Coverage<sup>b</sup>, pediatric vaccine (%)</b>	NA	NA	NA	NA
<b>ICER/ICER<sup>c</sup>, short-acting mAb</b>	NA	4280	NA	NA

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<del>ICER</del> <b>ICER</b> , long-acting mAb	country-specific (3152 - 7927)	1656	431	<del>At 6 USD, dose price:</del> Kenya: <del>142 USD undiscounted DALYs,</del> 325 <del>USD discounted DALYs;</del> South Africa: cost-saving <del>at the</del> <del>lowest dose price</del> <del>At</del>  60 USD, <del>dose price:</del> Kenya: <del>2748;</del> 6248 South Africa: <del>4694</del> 5583 USD (undiscounted)
<del>ICER</del> <b>ICER</b> , maternal vaccine	country-specific (1708 - 5663)	8020	1342	<del>At 3 USD, dose price:</del> Kenya: <del>321 USD undiscounted DALYs,</del> 734 <del>discounted DALYs;</del> South Africa: cost-saving <del>at the</del> <del>lowest dose price</del> <del>At</del>  30 USD, <del>dose price:</del> Kenya: <del>4525;</del> 10,186 South Africa: <del>2641 USD</del> (undiscounted)10,099
<del>ICER</del> <b>ICER</b> , pediatric vaccine	NA	NA	NA	NA

Notes:

- a) Duration of protection for maternal vaccine begins at birth.
- b) Coverage refers to percentage receiving intervention among those eligible
- c) Units for ICERs are USD per DALY averted

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**Figure 1. RSV Vaccine and mAb development pipeline**

Note: Adapted from the from PATH Clinical Trial Tracker (as of June 2023) [13, 30]

Note: Adapted from the from PATH Clinical Trial Tracker (as of September 2023) [13, 30]

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4 **Figure 2. Hospitalized SARI cases, in-hospital CFR values and the estimated ratio of out-of-hospital to**  
5 **in-hospital deaths in Kenya and South Africa**  
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8 Note: As the overwhelming majority of the RSV disease burden in children under the age of 1 in Kenya  
9 and South Africa is estimated to be due to RSV-associated deaths, the parameters that most strongly  
10 influence the burden reduction are the age-specific CFR of in-hospital and out-of-hospital severe cases  
11 and the efficacy and duration of RSV preventive interventions against severe RSV LRTI. More deaths  
12 within the window of effectiveness of the RSV preventive interventions will lead to a proportionally  
13 larger reduction in the total disease burden. A longer duration or higher efficacy of the effect against  
14 deaths will similarly lead to a proportionally larger reduction of the burden and thereby lower the DALYs  
15 averted, improving the cost-effectiveness of the interventions.  
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17 The dose price of RSV preventive interventions will scale the cost-effectiveness of the interventions  
18 linearly. Figure reproduced from a previous publication [47].  
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4 **Figure 3. A) Univariate sensitivity analysis for Mali**  
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7 Note: A series of univariate sensitivity analyses were conducted to assess the parameters whose  
8 variance has the largest influence on cost-effectiveness estimates for Mali. The parameter with the  
9 largest influence on the ICER across interventions is the inpatient case fatality rate (>300%). Parameters  
10 with moderate (<60%) influence include the probability of being hospitalized with RSV LRTI, probability  
11 of LRTI given RSV, age-based RSV attack rates, intervention product efficacy, and inpatient care costs. As  
12 deaths have the largest impact on cost-effectiveness estimates, case fatality rates are critically  
13 important inputs to capture accurately. Figure reproduced from a previous publication [46].  
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4 **Figure 4. Expected Value of Partially Perfect Information for Senegal (high incidence), Vietnam (low**  
5 **incidence), and Angola**  
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8 Note: In Figure 4, three examples are presented to demonstrate the influential factors. The age-specific  
9 RSV hospitalization probability is the most influential factor for all countries. RSV incidence rate, hospital  
10 case-fatality ratio and community case-fatality ratio are also top influential factors. A few countries (like  
11 Angola) show that cost of outpatient care is an influential factor at low willingness-to-pay level (<1000  
12 USD per DALY averted), because the cost of outpatient care is higher and more uncertain compared to  
13 other countries. However, at higher WTP levels, the top-ranking influential factors are the same as the  
14 other countries. Figure reproduced from a previous publication [44].  
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TARGET INDICATION: P = PEDIATRIC M = MATERNAL E = ELDERLY

	▶ PHASE 1	▶ PHASE 2	▶ PHASE 3	▶ MARKET APPROVED
<b>LIVE-ATTENUATED/ CHIMERIC</b>	<div data-bbox="504 377 735 549">Blue Lake PIV5/RSV</div> <div data-bbox="749 377 980 549">Codagenix,<sup>P</sup> LID/NIAID/NIH RSV</div> <div data-bbox="994 377 1225 549">Intravacc<sup>P</sup> RSV-ΔG</div> <div data-bbox="504 571 735 743">Pontificia<sup>P</sup> Universidad Catolica de Chile BCG/RSV</div> <div data-bbox="749 571 980 743">SIPL,<sup>P</sup> St. Jude Hospital SeV/RSV</div>	<div data-bbox="1254 377 1485 549">Meissa<sup>P</sup> Vaccines RSV</div> <div data-bbox="1499 377 1730 549">Sanofi,<sup>P</sup> LID/NIAID/NIH RSV</div>		
<b>PROTEIN-BASED</b> • PARTICLE • SUBUNIT	<div data-bbox="504 808 735 980">Icosavax<sup>E</sup> RSV/hMPV VLP</div> <div data-bbox="749 808 980 980">Immunovaccine,<sup>E</sup> VIB RSV SH Protein</div> <div data-bbox="994 808 1225 980">NIH/<sup>E M</sup> NIAID/VRC RSV F Protein</div> <div data-bbox="504 1002 735 1175">Virometix VLP</div>	<div data-bbox="1254 808 1485 980">Advaccine<sup>P E</sup> Biotechnology RSV G Protein</div> <div data-bbox="1499 808 1730 980">Daiichi<sup>E</sup> Sankyo Protein ?</div>	<div data-bbox="1773 808 2004 980">Pfizer<sup>M</sup> RSV F Protein</div>	<div data-bbox="2292 808 2523 980">GlaxoSmithKline<sup>E</sup> RSV F Protein</div> <div data-bbox="2537 808 2768 980">Pfizer<sup>E</sup> RSV F Protein</div>
<b>NUCLEIC ACID</b>	<div data-bbox="504 1228 735 1401">Moderna<sup>M P</sup> RNA</div> <div data-bbox="749 1228 980 1401">Sanofi<sup>E</sup> RNA</div>		<div data-bbox="1773 1228 2004 1401">Moderna<sup>E</sup> RNA</div>	
<b>RECOMBINANT VECTORS</b>		<div data-bbox="1254 1455 1485 1627">Janssen<sup>P</sup> Pharmaceutical Adenovirus</div>	<div data-bbox="1773 1455 2004 1627">Bavarian<sup>E</sup> Nordic MVA</div>	
<b>IMMUNO-PROPHYLAXIS</b>	<div data-bbox="504 1681 735 1854">Gates MRI<sup>P</sup> Anti-F mAb</div> <div data-bbox="749 1681 980 1854">Trinomab<sup>P</sup> Biotechnology Anti-F mAb</div>		<div data-bbox="1773 1681 2004 1854">Merck<sup>P</sup> Anti-F mAb</div>	<div data-bbox="2292 1681 2523 1854">Astra Zeneca,<sup>P</sup> Sanofi Nirsevimab</div> <div data-bbox="2537 1681 2768 1854">Astra<sup>P</sup> Zeneca Palivizumab</div>
<b>UPDATED: June 2, 2023</b>	<div data-bbox="749 1897 951 2015">Indicates Change</div>			

Figure 2

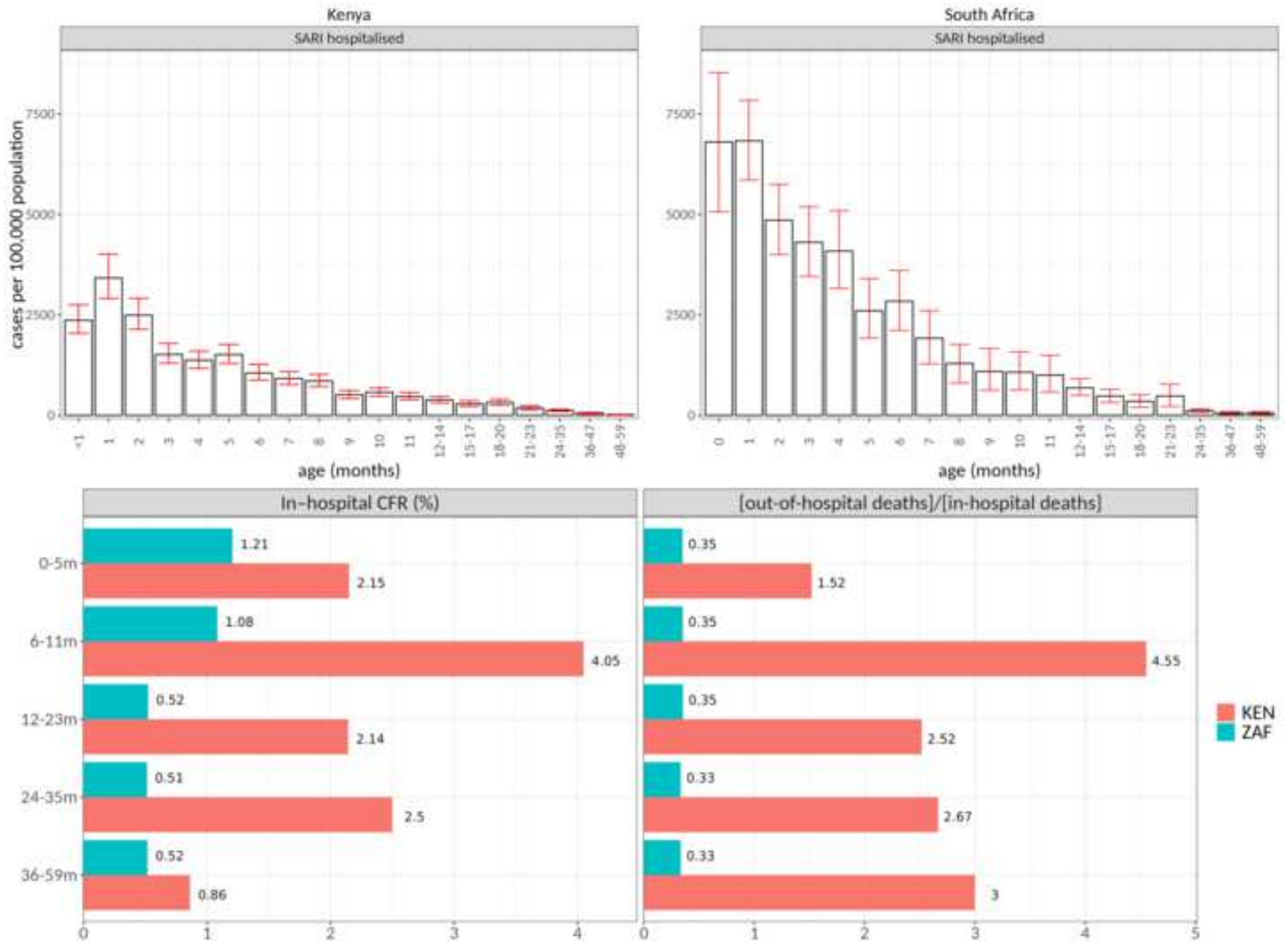


Figure 3

Short-acting mAb

Long-acting mAb

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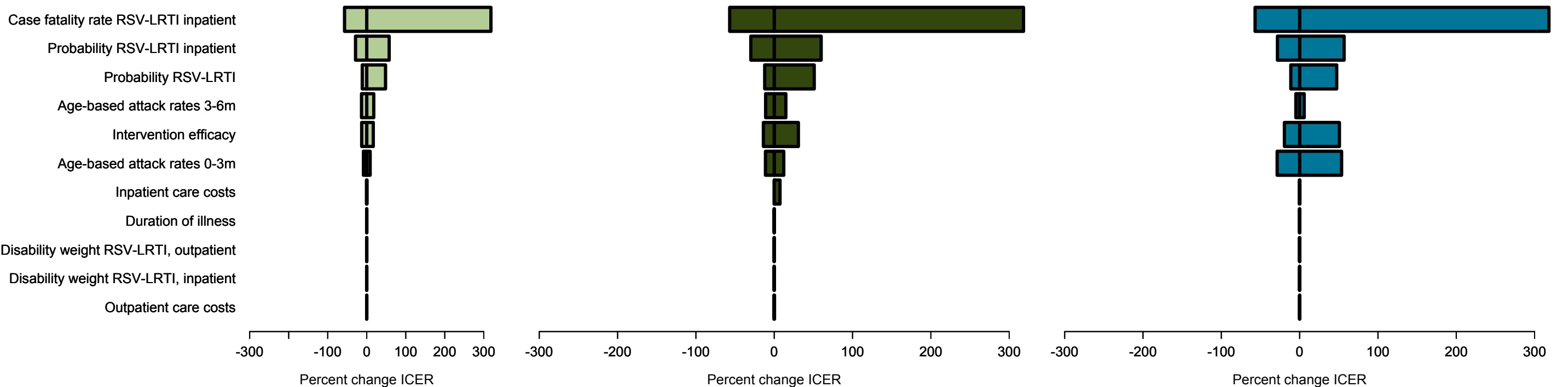
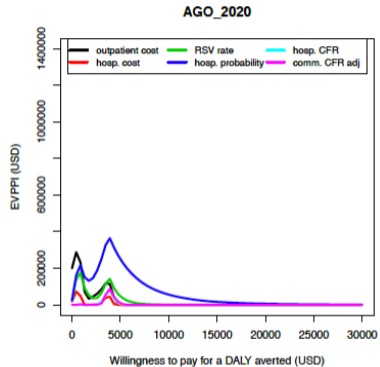
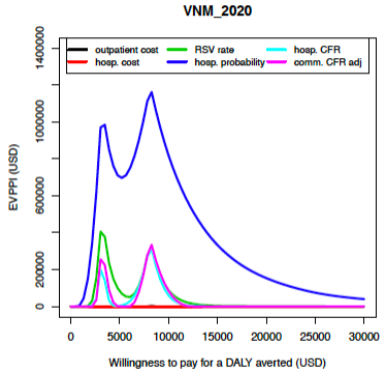
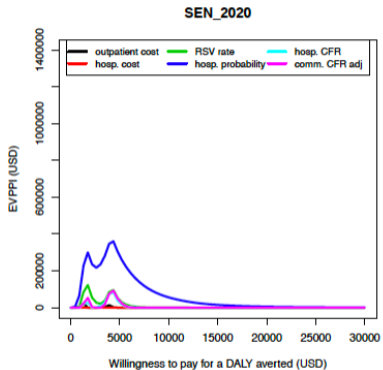


Figure 4  
(a) Senegal (highest incidence)

(b) Vietnam (lowest incidence)  
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(c) Angola  
Figure 4 





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**Supplemental Files**

WHO RSV Health Economics Meeting Supplement  
2023\_06\_24.docx