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# BMJ Open

## Impact and cost-effectiveness of potential interventions against infant respiratory syncytial virus (RSV) in low- and middle-income countries

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3 1 **Impact and cost-effectiveness of potential interventions against infant respiratory syncytial virus**  
4  
5 2 **(RSV) in low- and middle-income countries**  
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34 16 **Running title:**

35 Infant RSV interventions in LMIC  
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## 18 Abstract

19 *Background.* Interventions to prevent childhood respiratory syncytial virus (RSV) disease are limited and  
20 costly. New interventions are in advanced stages of development and could be available for soon. We  
21 evaluate the potential impact and cost-effectiveness of two such interventions—a maternal vaccine and a  
22 monoclonal antibody (mAb).

23 *Methods.* Using a static population-based cohort model, we evaluate impact and cost-effectiveness of  
24 RSV interventions across 131 low- and middle-income countries, from a health systems perspective. The  
25 assumed baseline efficacy and duration of protection were higher for the mAb compared to the maternal  
26 vaccine. Both interventions were evaluated at US\$3 and \$5 per dose for Gavi and non-Gavi countries,  
27 respectively. A range of input values were considered to explore uncertainty.

28 *Results.* Under baseline assumptions, maternal vaccine and mAbs were projected to avert 25% and 55%  
29 of RSV-related deaths among infants younger than six months of age, respectively. The average  
30 incremental cost-effectiveness ratio per disability-adjusted life year averted was \$1,342 (range \$800 to  
31 \$1,866) for maternal RSV vaccine and \$431 (range \$167 to \$692) for mAbs. At a 50% gross domestic  
32 product per capita threshold, maternal vaccine and mAbs were cost-effective in 60 and 118 countries,  
33 respectively.

34 *Conclusions.* Both interventions are projected to be impactful and cost-effective in many countries, a  
35 finding that would be enhanced if country-specific Gavi co-financing to eligible countries were included.  
36 mAbs, with assumed higher efficacy and duration of protection, are expected to be more cost-effective  
37 than RSV maternal vaccines at similar prices. Final product characteristics will influence this finding.

38  
39 **Key words:** Respiratory syncytial virus (RSV); maternal RSV vaccine; RSV monoclonal antibody; health  
40 impact; cost-effectiveness.

#### 44 **Strengths and limitations of this study**

- 45 • This is one of the first studies to examine the potential impact and cost-effectiveness of maternal  
46 vaccines and monoclonal antibodies for RSV prevention, across 131 low-and middle-income  
47 countries.
- 48 • This study compares products with uncertain characteristics using the latest available data on  
49 vaccine characteristics, supplemented by the target product profile to inform the model  
50 parameters.
- 51 • A range of input values were considered to explore uncertainty, insights from which are useful to  
52 inform subsequent intervention development.
- 53 • Final product characteristics and product prices will determine the relative cost effectiveness of  
54 RSV interventions.

## 55 Introduction

56 Respiratory syncytial virus (RSV) is a common cause of acute lower respiratory illness (ALRI) among  
57 children younger than age five, causing between 41,000 and 118,000 child deaths per year globally [1,2].  
58 RSV disease is most severe among young infants, and the burden is highest in low- and middle-income  
59 countries (LMICs), where more than 99% of RSV deaths occur [2]. Emerging evidence indicates the  
60 unrecognized burden of RSV among children in low-resource settings is also significant, with up to 10%  
61 of young infant deaths attributable to RSV infection [3,4].

62 Existing RSV interventions are limited and cost prohibitive, even in high-income countries [5]. Several  
63 prophylactic interventions are currently under development [6,7]. Multiple maternal vaccine candidates  
64 designed to protect against RSV illness in young children are in relatively advanced stages of  
65 development and expected to be available for global use in the coming years [6]. Monoclonal antibodies  
66 (mAbs) are available and in use for high-risk babies in high-income countries, but more affordable mAbs  
67 are also in advanced stages of development [8]. Given the extent of the global RSV disease burden—  
68 especially in low-income countries (LICs)—and the lack of efficacious and cost-effective therapeutic  
69 options, these new interventions are expected to be included in Gavi, the Vaccine Alliance's, portfolio  
70 [9], subject to licensure, prequalification, and cost characteristics.

71 In this paper, we estimate the potential impact and cost-effectiveness of a maternal vaccine and a mAb,  
72 both designed to avert RSV disease burden in young infants in LMICs. We compare each intervention  
73 against a scenario of no intervention and against each other. Results from this study illustrate the potential  
74 benefits of these products and will help inform decisions around further development. This analysis will  
75 also inform global and LMIC decision-makers likely to face choices about whether and which  
76 interventions to introduce.

## 78 Methods

79 We examined the potential impact and cost-effectiveness of a single-dose RSV maternal vaccine  
80 administered to pregnant women at 24 to 36 weeks gestation, and of a single-dose mAb given to infants

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2  
3 81 directly at birth across 131 LMICs, compared to no intervention. Both interventions were evaluated  
4  
5 82 independently using a static cohort model. For maternal vaccine, infants born two weeks following  
6  
7 83 maternal immunization were considered as protected to allow time for immune transfer from mother to  
8  
9 84 children. All children receiving mAbs were considered protected immediately.  
10  
11 85 We examined the impact and cost of interventions from the health systems perspective over the period  
12  
13 86 2030 to 2039 (10 years), assuming nationwide introduction in 2030. Primary input values for a baseline  
14  
15 87 scenario are given in Table 1. Key model outputs include cases averted, severe cases averted,  
16  
17 88 hospitalizations averted, deaths averted, disability adjusted life years (DALYs) averted, and the  
18  
19 89 incremental cost per DALY averted due to RSV interventions. Given the inconsistent use of country-  
20  
21 90 specific cost-effectiveness thresholds across LMICs, we used a willingness-to-pay threshold of 0.5 times  
22  
23 91 the gross domestic product (GDP) per capita in each country [10]. Results are summarized by World  
24  
25 92 Health Organization (WHO) regions, World Bank income group, and Gavi eligibility to understand  
26  
27 93 impact by country group. All monetary units are adjusted to 2016 US dollars.

28  
29  
30  
31 94 [Insert Table 1 here: Key parameter values used for modeling]

### 32 95 *Disease burden*

33  
34  
35 96 Disease burden inputs including disease incidence, severe disease incidence, incidence of hospitalizations,  
36  
37 97 and mortality were derived from a comprehensive systematic review paper [2]. We combined country-  
38  
39 98 specific disease incidence estimates in children under five years of age with a representative developing-  
40  
41 99 country estimate to generate incidence by granular age band in each country. To generate incidence of  
42  
43 100 severe disease, hospitalization, and hospital mortality, we used developing-country estimates [2].  
44  
45 101 Estimated hospital deaths were adjusted by multiplying by 1.98 to account for community deaths and  
46  
47 102 influenza coinfection [2]. The actual values of disease burden inputs are given in Table 1.  
48  
49 103 Some RSV interventions under development have shown promising results in their ability to avert all-  
50  
51 104 cause lower respiratory tract infections (LRTIs) among children [11], in addition to RSV infection. Thus,  
52  
53 105 we also explored the potential impact of both RSV interventions on all-cause LRTI, based on emerging  
54  
55 106 burden data, using estimates from the Global Burden of Disease Study 2017 [12], and assuming a uniform



1  
2  
3 107 distribution of disease among children one to 12 months of age. Further, we assumed 11.5% of all-cause  
4  
5 108 LRTI cases would result in severe cases [13] and 40% of all severe cases would result in hospitalization.

6  
7 109 *Intervention introduction and coverage*

8  
9 110 The leading RSV intervention candidates could be available for use in the next five-to-eight years [7]. We  
10  
11 111 assumed both interventions would be available by 2030 and all countries would begin national  
12  
13 112 introduction in 2030.

14  
15 113 All pregnant women attending antenatal care (ANC) visits were assumed eligible to receive RSV  
16  
17 114 maternal vaccine. To project the number of pregnant women per country, we added country-specific  
18  
19 115 stillbirths to the United Nations Population Division annual birth projections [14]. We estimated maternal  
20  
21 116 vaccine coverage during the 24- to 36-week vaccination window by examining country-specific ANC  
22  
23 117 first-visit timing [15], country-specific ANC coverage [16], and the WHO's recommended ANC timing  
24  
25 118 based on the focused ANC model guideline [17]. Details on methods used in estimating maternal vaccine  
26  
27 119 coverage during ANC within a specific gestation window is described elsewhere [18].

28  
29 120 All live births were considered eligible for mAbs. All infants were assumed to be covered at the Bacillus  
30  
31 121 Calmette–Guérin (BCG) vaccine birth dose coverage levels adjusted to the timeliness of vaccine receipt.  
32  
33 122 Country's overall BCG coverage were derived from the most recent WHO/UNICEF estimates of national  
34  
35 123 immunization coverage [19]. Timeliness of BCG birth dose receipt was derived using the methods  
36  
37 124 described in the literature [20,21].

38  
39 125 Coverage levels for both interventions for each country are projected to improve by 3 percentage points  
40  
41 126 each year until coverage reaches 70%, and after that by 1 percentage point each year until reaching 95%  
42  
43 127 coverage. This projection was made to correspond with methods applied during the Gavi vaccine  
44  
45 128 investment strategy [9].

46  
47 129 *Intervention characteristics*

48  
49 130 Our analysis assumed a single dose maternal RSV vaccine would be given to pregnant women between  
50  
51 131 24 and 36 months of gestation, based on the WHO preferred product characteristics (PPCs) [22]. We  
52  
53 132 based vaccine efficacy and duration of protection on data from one of the first maternal vaccine candidate  
54  
55  
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1  
2  
3 133 Phase 3 clinical trials (Table 1) [11]. Given the uncertainty in vaccine characteristics, scenario analyses  
4  
5 134 included a range in efficacy (30% to 90%) and duration of protection afforded to infants (three to six  
6  
7 135 months).

8  
9 136 Our analysis assumed a single dose mAb would be given to newborns at birth, would have 60% to 70%  
10  
11 137 efficacy, and would offer protection for six months, based on the PPCs [23]. As with the maternal  
12  
13 138 vaccine, we varied efficacy and duration of protection in scenario analysis. We assumed neither  
14  
15 139 intervention contributed to herd immunity, and that efficacy did not wane during the period of protection.

#### 16 140 *Intervention price and delivery costs*

17  
18 141 For both interventions, we assumed a per-dose price of US\$3 in Gavi-eligible countries and per-dose  
19  
20 142 price of \$5 in LMICs not eligible for Gavi support. If Gavi decides to support RSV interventions once  
21  
22 143 they are available, Gavi-eligible countries would likely be able to access the interventions at varying  
23  
24 144 prices depending on their transition status [24]. We refrained from projecting individual country Gavi  
25  
26 145 eligibility or intervention prices due to significant uncertainty, and instead evaluated a range of  
27  
28 146 intervention prices in sensitivity analyses.

29  
30 147 Given the paucity of data on maternal immunization and mAb delivery costs in LMICs, we used delivery  
31  
32 148 costs estimates for other vaccines derived from the Immunization Costing Action Network (ICAN)  
33  
34 149 repository [25]. Unit costs of delivering RSV interventions were \$0.63 for LICs and \$1.73 for LMICs.  
35  
36 150 We accounted for vaccine/mAbs wastage at 5% and a buffer stock at 25% of demand in the introduction  
37  
38 151 year, and at 25% of the incremental demand in subsequent years.

#### 39 152 *Health service costs*

40  
41 153 Very few studies have analyzed the cost of managing RSV in children, especially in LMICs [26–31].  
42  
43 154 Hospitalization costs also vary widely. In Bangladesh, for example, hospitalization averages \$74, whereas  
44  
45 155 in China it averages \$662. Given limited RSV-specific information in LMICs, we used the average cost of  
46  
47 156 treating pneumonia in young children, identified in a systematic review [32] as \$53.26 and \$250.04 per  
48  
49 157 outpatient and inpatient episode, respectively. We assumed that severe cases seek inpatient care and non-  
50  
51 158 severe cases seek outpatient care.

### 159 *Cost-effectiveness analysis*

160 We calculated intervention costs by multiplying the number of doses (estimated number of pregnant  
161 women receiving vaccine for maternal vaccine and estimated number of live births for mAbs) with the  
162 unit cost of delivery and cost per dose. We estimated averted health care costs by multiplying the  
163 estimated number of non-severe/severe cases averted by the costs of an outpatient/inpatient episode.  
164 Vaccine impact was calculated by multiplying the respective disease burden in children born two weeks  
165 after maternal vaccination with vaccine efficacy. The mAb impact was calculated by multiplying disease  
166 burden with the BCG coverage estimates and mAb efficacy. We estimated health outcomes including  
167 severe/non-severe cases averted, hospitalizations averted, deaths averted, and DALYs averted for each  
168 country and year. Disability weights for non-severe and severe ALRI were used to compute DALYs [33].  
169 Further, we assumed duration of illness at five days for non-severe disease and 10 days for severe disease  
170 [34]. The length of a hospital stay for severe disease was assumed to be 6.4 days [32]. We also accounted  
171 for variation in health-seeking practices by using health care use data from children younger than five  
172 years receiving pneumonia care [35].  
173 We calculated incremental cost-effectiveness ratios (ICERs) for each country by dividing the net cost of  
174 intervention by the net DALYs averted by the intervention.

### 175 *Sensitivity analysis*

176 We conducted one-way sensitivity analysis by changing the values of key input parameters, including  
177 intervention efficacy, duration of protection, anticipated coverage, and intervention price. Alternate  
178 scenarios that changed one or more input parameters to evaluate results sensitivity were also considered.  
179 In an adjunct scenario, we evaluated how different interventions show impact on all-cause LRTI  
180 mortality, using the efficacy and duration of protection values as suggested by recent clinical trial data  
181 [11], and disease burden for all-cause LRTI from the 2017 Global Burden of Disease Study [12].

182

## 183 **Results**

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3 184 *Disease burden without interventions*  
4

5 185 Over the 10-year period, about 41.94 million non-severe cases, 15.28 million severe cases, 11.48 million  
6  
7 186 hospitalizations, and 504,963 thousand deaths among children younger than six months of age in 131  
8  
9 187 LMICs are projected (Table 3). Seventy-three Gavi-eligible countries accounted for 70% of the mortality  
10  
11 188 burden. Most deaths would occur in sub-Saharan Africa (36%, 47 countries), followed by South Asia  
12  
13 189 (26%, eight countries).

14  
15  
16 190 [Insert Table 2 here: Summary of disease burden, impact and cost-effectiveness ratios with and without  
17  
18 191 intervention (2030-2039), baseline scenario]  
19

20 192 *Expected health outcomes with intervention*  
21

22 193 RSV maternal vaccine, under the baseline scenario, has the potential to avert 2.97 million non-severe  
23  
24 194 cases, 2.63 million severe cases, 2.03 million hospitalizations, 126,552 deaths, and 3.73 million DALYs  
25  
26 195 (discounted) among children younger than six months of age across all countries over 10 years (Table 2).  
27  
28 196 Globally, about 17% of severe RSV cases and 25% of RSV-related deaths among infants under six  
29  
30 197 months of age would be averted by RSV maternal vaccine, which is roughly 13 deaths averted per  
31  
32 198 100,000 vaccinated pregnant women.  
33

34  
35 199 An RSV mAb, under the baseline scenario, is expected to avert 19.47 million cases of non-severe disease,  
36  
37 200 7.18 million severe cases, 5.40 million hospitalizations, 276,933 deaths, and 8.19 million DALYs  
38  
39 201 (discounted) among children younger than six months of age across all countries over 10 years (Table 2).  
40  
41 202 Globally, about 55% of RSV deaths among infants younger than six months of age would be averted with  
42  
43 203 RSV mAbs—equivalent to approximately 28 averted deaths per 100,000 newborns receiving the  
44  
45 204 intervention.  
46

47 205 Under alternative scenarios using varying efficacy and duration of protection assumptions (minimum and  
48  
49 206 maximum scenarios), the RSV maternal vaccine is estimated to avert between 84,934 and 356,346 deaths  
50  
51 207 over 10 years; and the RSV mAb is expected to avert roughly 84, 864 and 356, 057 deaths. Assuming  
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53 208 both interventions are able to affect all-cause LRTI, as suggested by recent clinical trial data [11], either  
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209 intervention is projected to avert roughly 1.05 million LRTI deaths (29% of all LRTI deaths) among  
210 children younger than six months of age in LMICs.

### 211 *Cost-effectiveness of interventions*

212 The average annual cost of vaccination programs across all countries for the duration of analysis was  
213 estimated to be about \$546.36 million and \$538.40 million for RSV maternal vaccine and mAbs,  
214 respectively. The economic benefits expressed in terms of cost-of-care averted was about \$602.10 million  
215 (maternal vaccine) and \$1.97 billion (mAbs) over the 10 years (see appendix Table 1).

216 For maternal RSV vaccine, the ICER per DALY averted is estimated at \$1,342 (\$1,073 across Gavi-  
217 eligible countries and \$1,681 across non-Gavi countries). Similarly, the ICER estimates for RSV mAbs is  
218 \$431 (\$315 across Gavi-eligible countries and \$577 across non-Gavi countries). It is important to note  
219 these ICERs reflect the full potential cost of either intervention. Countries eligible for Gavi support would  
220 be expected to pay a share of the prices used in this analysis, thus reducing the ICER from the country  
221 perspective.

222 Results from alternative scenarios with low and high efficacy and duration of protection assumptions  
223 show that costs per DALY averted across countries range from \$244 to \$1,982 (maternal vaccine) and  
224 \$239 to \$1,958 (mAbs). By reducing the intervention price to 50% of the baseline price (i.e., \$1.50 for  
225 Gavi-eligible countries and \$2.50 for non-Gavi countries), the average ICER per DALY averted would  
226 decline to \$781 (range \$45 to \$1,147) for the maternal vaccine and \$178 (range \$42 to \$1,132) for the  
227 mAb. Increasing the intervention price by 200% of the baseline price, the average ICER per DALY  
228 averted increases to \$2,465 (range \$642 to \$3,651) for the maternal vaccine and \$938 (range \$632 to  
229 \$3,610) for the mAbs.

230 When comparing ICERs against an individual country's income level at baseline, the maternal vaccine  
231 ICERs were less than 50% of the GDP per capita in 60 countries (12 Gavi and 48 non-Gavi), suggesting  
232 intervention cost-effectiveness in those countries. ICERs for RSV mAbs were below the 50% GDP per  
233 capita threshold in 118 countries (62 Gavi-eligible and all non-Gavi). For both interventions, countries  
234 with higher ICER to GDP per capita ratios are concentrated in sub-Saharan Africa and Asia (Figure 1).

235 Many of these countries remain eligible for Gavi support and are expected to pay lower intervention  
236 prices. As a result, the cost per DALY averted from the perspective of these countries is likely to be much  
237 more favorable than shown here. For example, if each of the original Gavi-eligible countries were  
238 responsible for half of the cost of the intervention (\$1.50), which is still a relatively high cost as the  
239 countries with the lowest GDP per capita would pay only a fraction of that price under Gavi's current co-  
240 financing model, then the ICER for the RSV maternal vaccine and mAb would fall below the 50% GDP  
241 per capita threshold in 46% (maternal vaccine) and 100% (mAb) of these countries. Further, maternal  
242 vaccine ICERs across countries at base price are roughly equivalent to the mAb ICER evaluated at 300%  
243 of the base price. Appendix Table 2 includes a comparison of ICERs as a share of country GDP for  
244 alternative intervention scenarios.

245 [Insert Figure 1 here: Incremental cost-effectiveness ratios as a percentage of national GDP per capita.]

246

## 247 Discussion

248 Both RSV interventions are projected to be impactful across all countries under baseline assumptions. A  
249 maternal vaccine is projected to avert 12.65 thousand deaths and mAbs roughly two times more (27.69  
250 thousand deaths averted) annually among children younger than six months of age. We note that our  
251 baseline assumptions for the maternal vaccine draw from a Phase 3 trial in which the primary endpoints  
252 were not met. As a result, maternal vaccine assumptions may be conservative compared to mAb  
253 assumptions, leading to lower overall impact of RSV maternal vaccines. Under alternative scenarios that  
254 consider both interventions with similar characteristics, we observe no substantial variation in impact.  
255 Under a minimal (30% efficacy and four months protection) and maximal (90% efficacy and six months  
256 protection) intervention characteristics scenario, both interventions are projected to avert roughly 84,900  
257 and 356,000 deaths among children younger than six months of age across 131 countries, suggesting that  
258 efficacy and duration of protection are primary parameters for determining impact, reinforced by a similar  
259 study [36].



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3 260 Unknowns around intervention delivery strategy and potential coverage implications create uncertainties;  
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5 261 this is especially true for a novel intervention like a maternal vaccine. To further understand the potential  
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7 262 implications of unknown parameters on a maternal vaccine impact, we evaluated the marginal gains in  
8  
9 263 impact by incrementally changing the parameter values to mimic those used in the mAb baseline scenario.  
10  
11 264 When changing maternal vaccine coverage assumptions to the mAb coverage values, the maternal  
12  
13 265 vaccine would prevent 22,000 additional deaths. Similarly, when changing both duration of protection  
14  
15 266 and efficacy for maternal vaccine at baseline to the mAb baseline equivalent, maternal vaccine would  
16  
17 267 avert an additional 150,000 deaths. As seen in Figure 2, the duration of protection is the most important  
18  
19 268 factor for increasing impact (109,000 additional deaths averted).

20 269 [Insert Figure 2 here: Impact of change in key input parameter values on deaths averted.]  
21  
22  
23  
24 270

25  
26 271 The cost per DALY averted under the baseline scenario for a maternal vaccine is more than three times  
27  
28 272 that for mAbs (\$1,342 versus \$431). This is mainly driven by the modest vaccine efficacy and assumed  
29  
30 273 duration of protection for the maternal vaccine as compared to mAbs. Under the maximum and minimum  
31  
32 274 scenarios with high and low vaccine efficacy and duration of protection assumptions, the difference in the  
33  
34 275 estimated ICERs between the two interventions is muted (Figure 3).

35 276 [Insert Figure 3 here: Average incremental cost-effectiveness ratios by country groups.]  
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40  
41 278 Though it didn't meet the primary endpoint, the recent Phase 3 maternal vaccine trial shows promising  
42  
43 279 impact on all-cause LRTI mortality [11]. If both future RSV interventions reduce all-cause LRTI  
44  
45 280 mortality, our adjunct scenario shows more pronounced impact by averting more than a million all-cause  
46  
47 281 LRTIs during the 10-year period. ICER estimates under this scenario were \$896 for the maternal vaccine  
48  
49 282 (range \$34 to \$7,602) and \$889 for the mAb (range \$33 to \$7,608) per DALY averted across all  
50  
51 283 countries, with 116 countries (69 Gavi-eligible and 47 non-Gavi countries) demonstrating ICERs less  
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53 284 than 50% of their respective GDP per capita. We refrained from directly comparing these estimates to  
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3 285 other scenarios as they use data sources [12] not comparable with the primary disease burden data [2]  
4  
5 286 used in other scenarios.  
6  
7 287 There are several additional limitations worth citing. There is a dearth of RSV disease burden data,  
8  
9 288 especially regarding the age distribution of disease in young infants in LMICs. Although we used the best  
10  
11 289 published estimates of RSV disease burden in children [2], the literature is expanding rapidly. For  
12  
13 290 example, studies from Zambia [37] and Argentina [38] highlight that community mortality and deaths  
14  
15 291 from RSV could be as high as 10% and 11% of all-cause deaths occurring among infants up to six months  
16  
17 292 of age. This highlights a large and underappreciated burden of RSV and would mean our estimates of  
18  
19 293 impact and effectiveness are conservative. Although we attempted to quantify the potential benefits of  
20  
21 294 RSV interventions with additional scenario analysis, lack of consistent input data coupled with poorly  
22  
23 295 established age distribution limits the comparability of our results across these scenarios. Collecting more  
24  
25 296 granular data on disease burden is critical to inform future studies [36].  
26  
27  
28 297 The products evaluated in this study are not yet available in the market so other key parameters are  
29  
30 298 unknown. We assumed the same price for both interventions, which may not hold, as historical evidence  
31  
32 299 suggests mAbs are likely to be more expensive to produce than a vaccine [5]. This could have  
33  
34 300 considerable impact on the ICERs and comparisons between products. Nonetheless, our analysis shows  
35  
36 301 that the mAb is more cost-effective than a maternal vaccine at baseline efficacy and duration of protection  
37  
38 302 values, until a mAb reaches approximately three times the baseline price assumption. Gavi evaluated both  
39  
40 303 interventions for inclusion in its 2018 Vaccine Investment Strategy in anticipation of the potential  
41  
42 304 benefits, and they are expected to be included in the Gavi portfolio, subject to licensure, prequalification,  
43  
44 305 and affordability. In that case, the eligible Gavi countries would benefit from a considerable subsidy for  
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46 306 access and affordability, especially the countries with the lowest GDPs per capita. Further, the <50% of  
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48 307 GDP per capita thresholds used in this paper are non-specific measures of cost-effectiveness, especially  
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50 308 when intervention prices to be paid by individual Gavi-supported countries are not yet known. Country-  
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52 309 specific thresholds are recommended [39] but often do not exist for most LMICs. In the absence of  
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3 310 country-specific thresholds, we used a conservative metric uniform across all countries to define cost-  
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5 311 effectiveness.  
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7 312 Lastly, RSV infection is seasonal in many countries. We did not consider seasonal delivery in this  
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9 313 analysis. Seasonal intervention could potentially be a more cost-effective yet feasible strategy [40],  
10  
11 314 especially when using mAbs to selectively immunize children before the start of the RSV season.  
12  
13 315 Delivering maternal vaccine seasonally to pregnant woman in LMICs may be more challenging due to the  
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15 316 lack of a defined maternal vaccine delivery strategy. Future research should explore the feasibility of  
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17 317 alternative delivery strategies.  
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## 22 319 **Conclusions**

23  
24 320 RSV interventions evaluated in this study are projected to be impactful and cost-effective across many  
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26 321 LMICs. Under the assumptions used, mAbs are comparatively more impactful and cost-effective than  
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28 322 RSV maternal vaccines. However, we reiterate the uncertainty around several critical parameters that  
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30 323 inform this finding. The emerging evidence of RSV's role in all LRTI deaths among young infants  
31  
32 324 suggests our analyses of RSV burden averted may prove conservative and enhance the attractiveness of  
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34 325 RSV interventions as important tools for curbing LRTI mortality in infants. As disease burden shifts  
35  
36 326 toward neonates and very young children, RSV maternal immunization and mAbs offer the opportunity to  
37  
38 327 protect young infants from disease.  
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336

### 337 **Author contributions**

338 CP, DH and RB conceptualized the study. RB and CP developed the model. RB performed the analysis.

339 RB and CP wrote the first draft of the paper. DH and KR reviewed and edited the manuscript.

340

### 341 **Declaration of interest statement**

342 All authors declare no conflict of interest.

343

### 344 **Patient and Public Involvement**

345 Patients were not included in this modeling study.

346

### 347 **Ethics approval**

348 Not required.

349

### 350 **Data sharing statement**

351 All relevant data is included in the manuscript including in the supplementary materials.

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**Tables**

Table 1. Input parameter values used for modeling.

Input	RSV maternal vaccine	RSV monoclonal antibody	Sources
<i>Intervention specific inputs</i>			
Target population	126 million (annual average number of pregnant women, between 2030 and 2039, across 131 countries)	124 million (annual average live births between 2030 and 2039 across 131 countries)	Birth estimates and population growth rate [41]; still birth rates [14]
Intervention schedule	Single dose vaccine given during weeks 24–36 of gestation, as a part of ANC	Single dose mAb given to newborn at birth	[22]; expert opinion
Efficacy against RSV endpoints	Baseline: cases = 40.9%; hospitalization = 41.7%; death = 59.6% Minimum scenario: 30% (for all endpoints) Maximum scenario: 90% (for all endpoints)	Baseline: cases = 60%; hospitalization = 60%; death = 70% Minimum scenario: 30% (for all endpoints) Maximum scenario: 90% (for all endpoints)	[11]; [22,23], expert opinion
Duration of protection against RSV <sup>+</sup>	Baseline: 3 months Minimum scenario: 4 months Maximum scenario: 6 months	Baseline: 6 months Minimum scenario: 4 months Maximum scenario: 6 months	[22,23] and expert opinion
Efficacy against all cause LRTI*	Cases = 25%; hospitalization = 25%; death = 39%	Cases = 25%; hospitalization = 25%; death = 39%	[11]; expert opinion
Duration of protection against all cause LRTI*	6 months	6 months	[11]; expert opinion
Intervention coverage	Derived from ANC coverage (average 84%, range: 40% to 96%, in 2030)	Derived from BCG coverage (average 82%, range: 48% to 98%, in 2030)	[15,17,19]
<i>Common to both interventions</i>			
<i>Disease burden</i>			
Incidence of RSV ALRI	Country-specific incidence for 0–5 years for envelope (35.3 to 65.6)		[2]
	Developing-country estimate by narrow age band for case distribution by age;		
	Annual incidence per 1,000 children		
	0–27 days	40.0	
	28–< 3 months	45.7	
	3–5 months	99.6	
	6–11 months	98.8	
12–23 months	79.1		
Rescaled to match country-specific incidence envelope			
Incidence of severe RSV ALRI	Developing-country estimates with uniform age distribution		[2]
	Annual incidence of severe RSV ALRI per 1,000 children		
	0–5 months	36.1	
	6–11 months	24.7	
	0–59 months	10.2	

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Hospital admissions for RSV-associated ALRI	Annual hospital admissions for RSV-associated ALRI per 1,000 children		[2]
	0–5 months	20.2	
	6–11 months	11	
Hospital case fatality	Hospital case fatality risk (%), by age group		[2]
	0–5 months	2.2	
	6–11 months	2.4	
RSV-ALRI mortality	Hospital deaths *2.2 ( <i>adjusted for community deaths</i> ) *0.9 ( <i>adjusted for influenza activities</i> )		[2]
Incidence of all-cause LRTI	Country-specific; By ages: early neonates (0–7 days), post neonates (7–28 days), late neonates (1–12 months); Burden for post neonates, uniformly distributed across ages by month		[12]
Incidence of severe LRTI	11.5% of all incidence resulting in severe cases		Assumed (based on the estimates used in [13])
Hospital admissions for LRTI	40% of all severe cases resulting in hospital admissions		Assumed
Mortality due to LRTI	Country specific, early neonates, post neonates, late neonates; burden for post neonates uniformly distributed across ages by month		[12]
Age distribution of LRTI	Assumes uniform distribution of burden across months by age		Assumed
<b>Costs</b>			
Intervention cost	\$3 per dose in Gavi countries; \$5 per dose in non-Gavi countries		Assumed
Intervention delivery costs	Mean incremental economic cost of delivery per dose: \$0.63 in LICs; \$1.73 in LMICs and UMICs		[25]
Treatment cost	Cost of managing severe pneumonia in LMICs (outpatients \$53; inpatients \$250)		[32]
Vaccine introduction dates	National introduction starting 2030		Product development timeline, assumed
<b>Other assumptions</b>			
DALY weights	Severe ALRI = 0.21; Non-severe ALRI = 0.053		[33]
Duration of illness	Severe ALRI = 10 days; Non-severe ALRI = 5 days		[34]
Length of hospital stay	Length of stay for severe pneumonia in LMICs, 6.4 days		[32]
Health care seeking	Health seeking for children with pneumonia, country specific		[35]

Abbreviations: ANC, antenatal care; BCG, Bacillus Calmette–Guérin; LIC, low-income country; LMIC, low- and middle-income country; LRTI, lower respiratory tract infection; mAb, monoclonal antibody; UMIC, upper-middle-income country; RSV, respiratory syncytial virus; WHO, World Health Organization; ALRI, acute lower respiratory illness; DALY, disability-adjusted life year; LMIC, low- and middle-income country; LRTI, lower respiratory tract infection; RSV, respiratory syncytial virus.

\*Duration of protection in the minimum scenario is higher than in the baseline scenario. For maternal vaccine baseline, we assume duration of protection data from a recent clinical trial that failed to meet the primary endpoint. Nonetheless, in anticipation that a successful product would likely have higher duration of protection than three months, we evaluate the minimum scenario at four months duration of protection.

\*Used in adjunct scenario only. The adjunct scenario evaluates intervention impact on all-cause LRTI mortality.

Table 2. Summary of disease burden, impact and cost effectiveness ratios, with and without intervention (2030–2039), baseline scenario.

Country group by	N	Disease burden without intervention				Burden averted and ICER with RSV maternal vaccine					Burden averted and ICER with RSV monoclonal antibody				
		Non-severe cases	Severe cases	Hospitalizations	Deaths	Non-severe cases	Severe cases	Hospitalizations	Deaths	ICER per DALY averted	Non-severe cases	Severe cases	Hospitalizations	Deaths	ICER per DALY averted
<b>Gavi status</b>															
Gavi	73	31,288,677	10,683,106	8,031,827	352,990	2,159,630	1,730,164	1,333,545	83,024	1,073	13,866,799	4,742,022	3,565,171	182,800	315
Non-Gavi	58	10,657,947	4,599,391	3,457,938	151,973	819,749	907,088	699,149	43,528	1,681	5,610,598	2,441,921	1,835,898	94,133	577
<b>World Bank income group</b>															
LIC	34	10,823,869	3,562,172	2,678,130	117,701	760,348	577,452	445,078	27,710	949	4,774,083	1,573,199	1,182,771	60,645	257
LMIC	46	22,502,889	7,872,029	5,918,389	260,107	1,559,549	1,292,990	996,588	62,046	1,311	10,083,892	3,536,660	2,658,950	136,334	428
UMIC	51	8,619,867	3,848,296	2,893,246	127,155	659,482	766,809	591,027	36,796	1,631	4,619,422	2,074,084	1,559,348	79,954	551
<b>WHO geographic region</b>															
EAP	20	5,313,235	3,097,972	2,329,133	102,363	314,036	582,849	449,238	27,969	1,411	2,570,416	1,558,912	1,172,029	60,094	479
ECA	20	2,609,512	633,363	476,178	20,928	244,307	125,417	96,666	6,018	1,425	1,398,536	337,329	253,612	13,004	437
LAC	23	2,583,464	1,024,279	770,079	33,844	209,296	204,837	157,881	9,829	1,507	1,349,631	536,105	403,057	20,666	507
MENA	13	2,907,732	1,058,521	795,823	34,976	222,211	192,789	148,594	9,251	1,566	1,468,837	535,629	402,699	20,648	532
SA	8	12,207,891	4,018,853	3,021,474	132,791	842,810	643,028	495,622	30,857	1,138	5,628,427	1,857,416	1,396,452	71,601	342
SSA	47	16,324,790	5,449,509	4,097,078	180,062	1,146,719	888,332	684,693	42,628	1,169	7,061,551	2,358,554	1,773,220	90,920	359
<b>Total</b>	<b>131</b>	<b>41,946,624</b>	<b>15,282,497</b>	<b>11,489,765</b>	<b>504,963</b>	<b>2,979,379</b>	<b>2,637,252</b>	<b>2,032,693</b>	<b>126,552</b>	<b>1,342</b>	<b>19,477,397</b>	<b>7,183,943</b>	<b>5,401,069</b>	<b>276,933</b>	<b>431</b>

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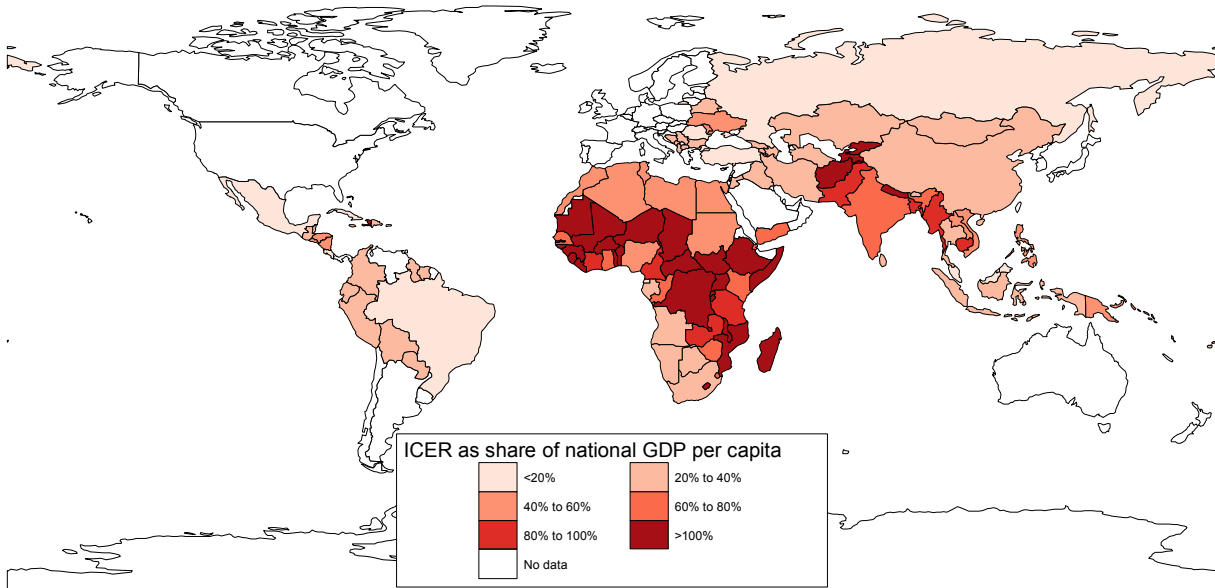
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Abbreviations: LIC, low-income country; LMIC, low- and middle-income country; RSV, respiratory syncytial virus; UMIC, upper-middle-income country; WHO, World Health Organization; EAP: East Asia & Pacific; ECA: Europe & Central Asia; LAC: Latin America & Caribbean; MENA: Middle East & North Africa; SA: South Asia; SSA: Sub-Saharan Africa.

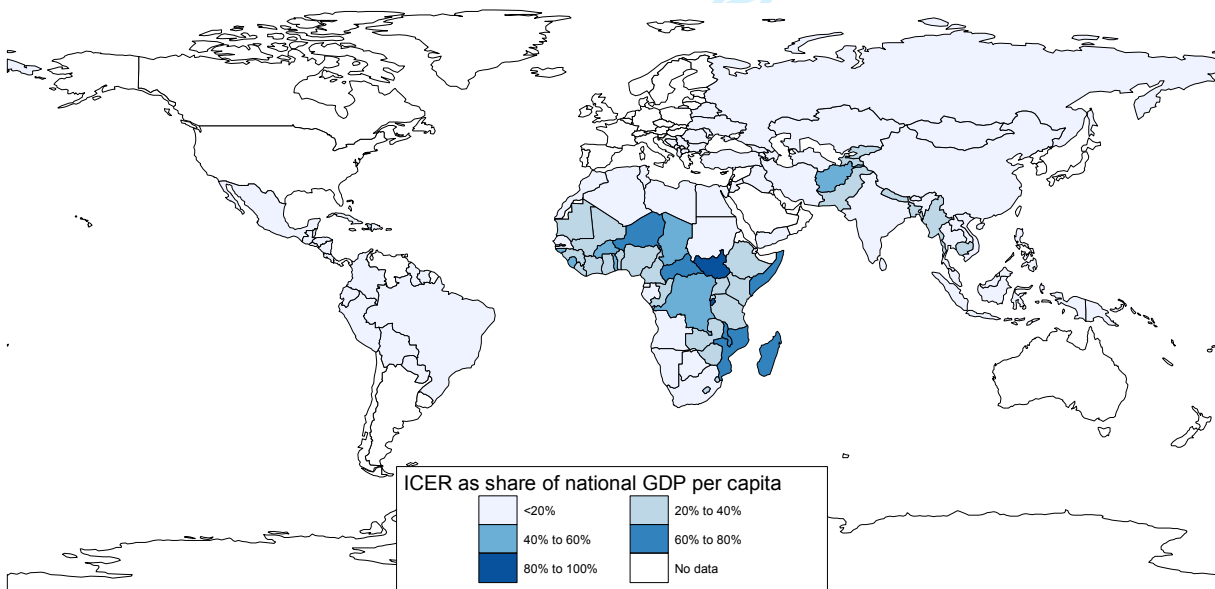
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Figures

Figure 1. Incremental cost-effectiveness ratios as a percentage of national GDP per capita.



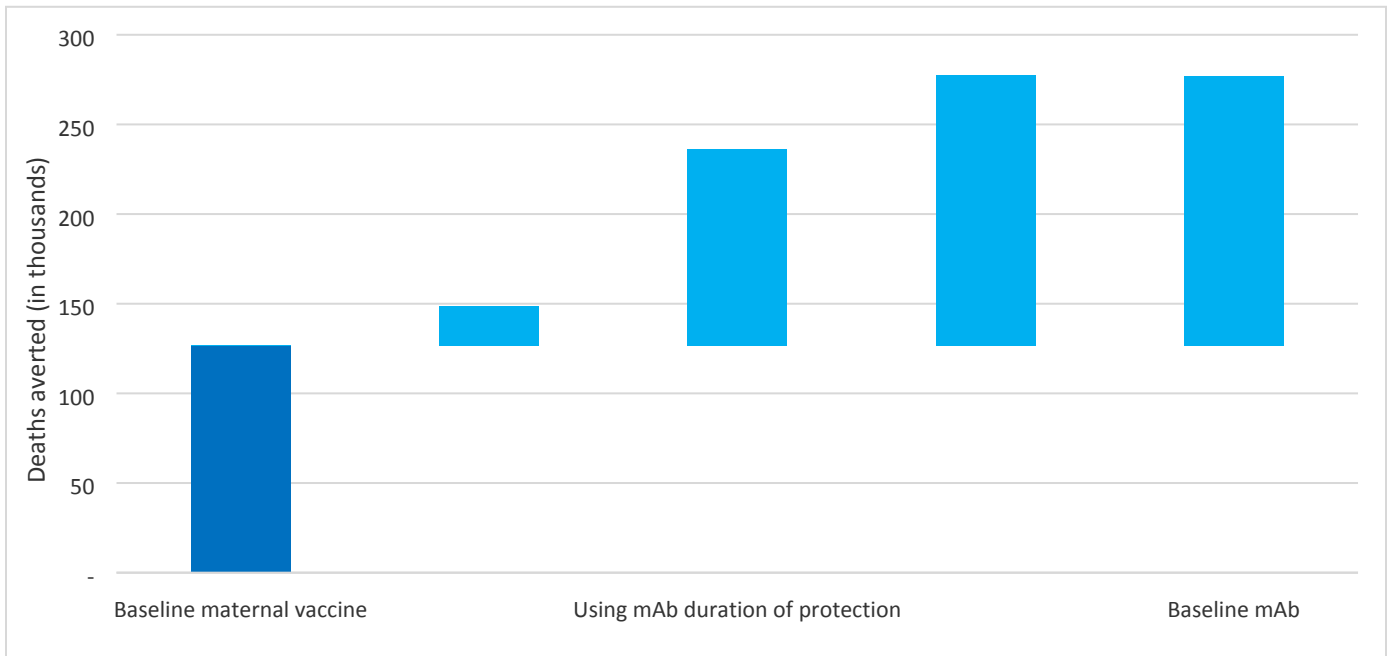
Panel a. Maternal vaccine



Panel b. Monoclonal antibody

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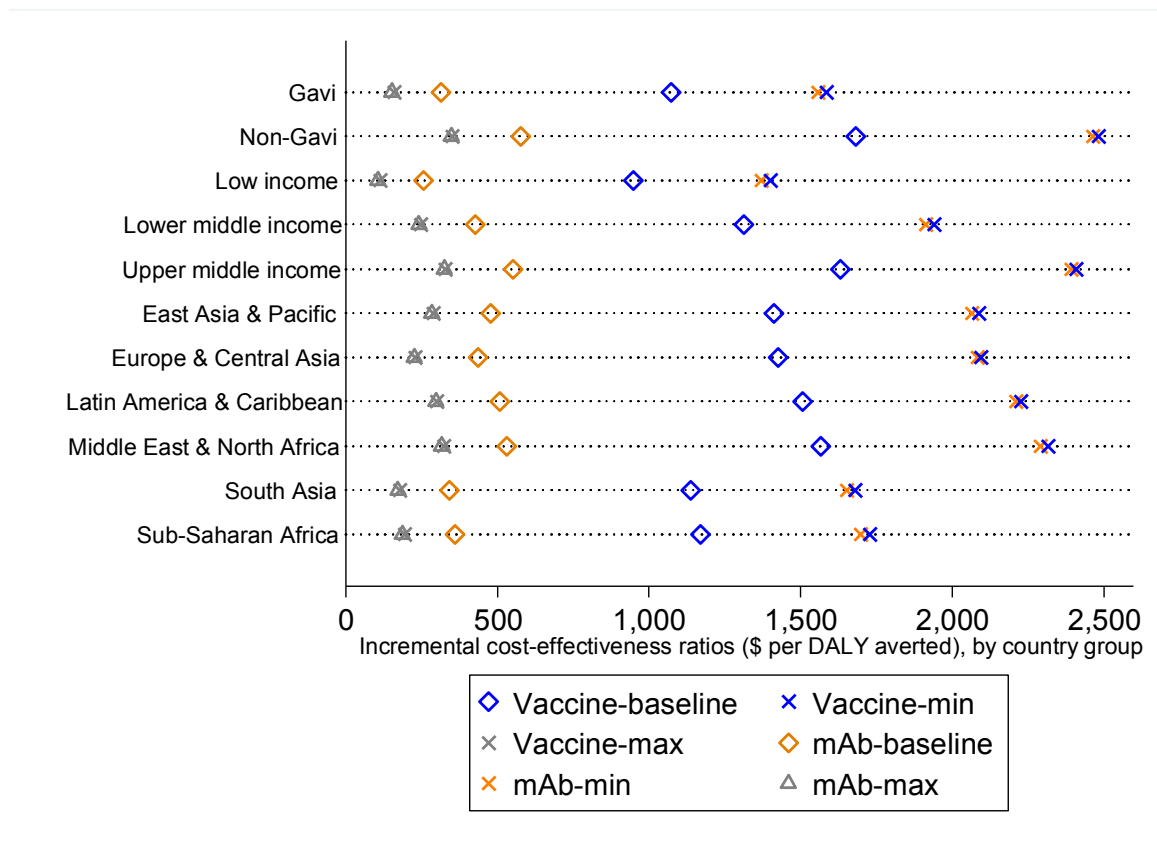
**Figure 2. Impact of change in key input parameter values on deaths averted.**



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Figure 3. Average incremental cost-effectiveness ratios by country groups.



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**Figure captions**

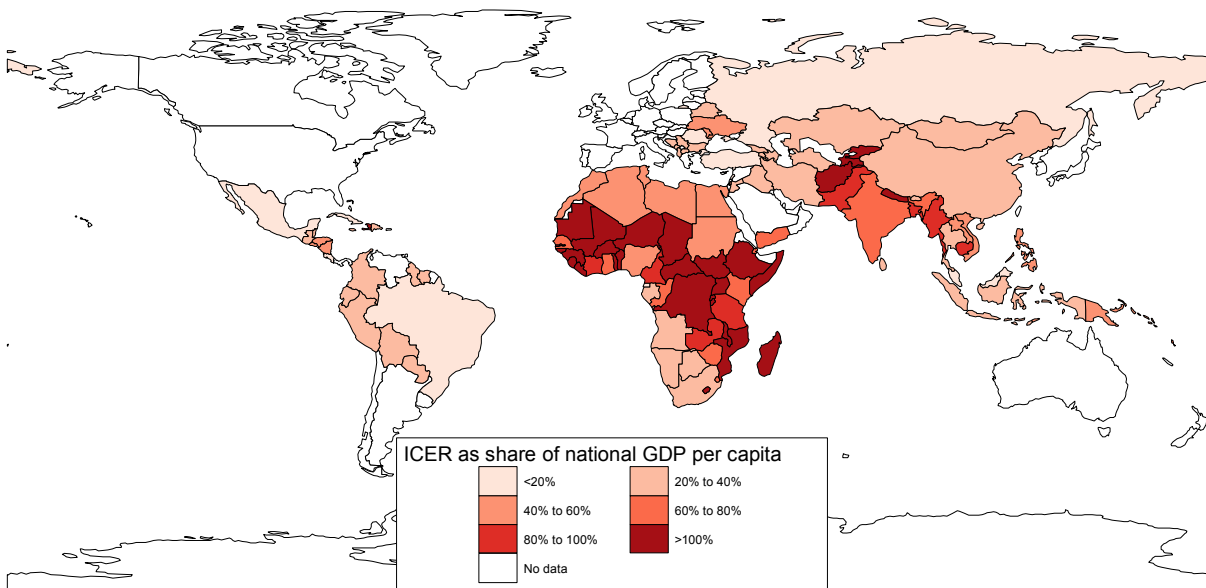
Figure 1. Incremental cost-effectiveness ratios as a percentage of national GDP per capita.

Figure 2. Impact of change in key input parameter values on deaths averted.

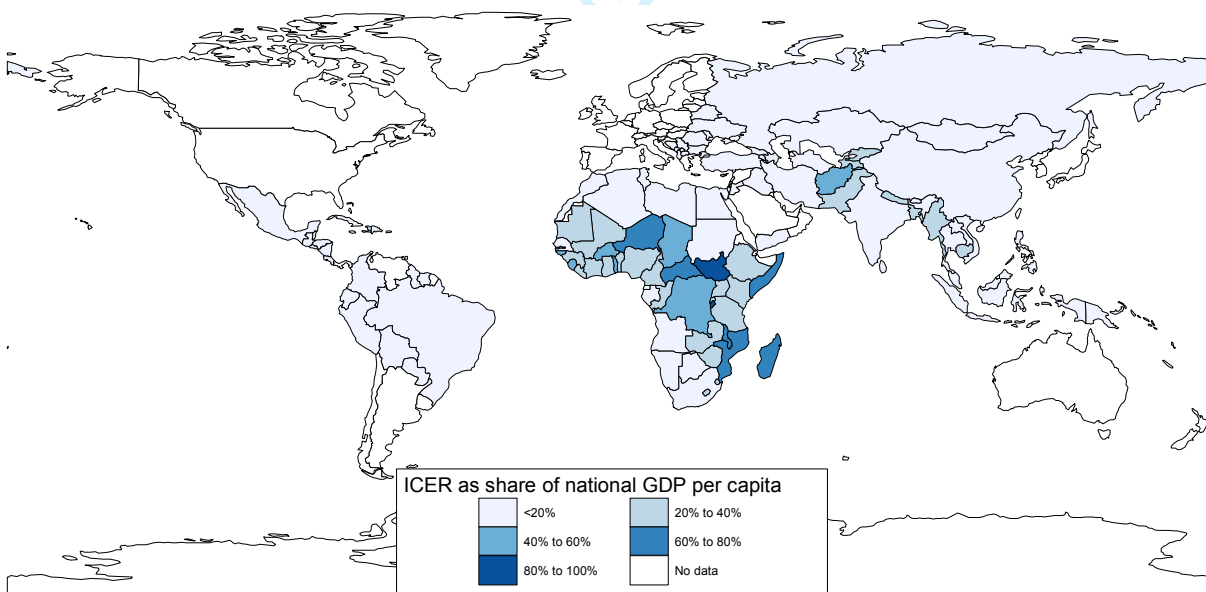
Figure 3. Average incremental cost-effectiveness ratios by country groups.

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**Figure 1. Incremental cost-effectiveness ratios as a percentage of national GDP per capita.**



**Panel a. Maternal vaccine**

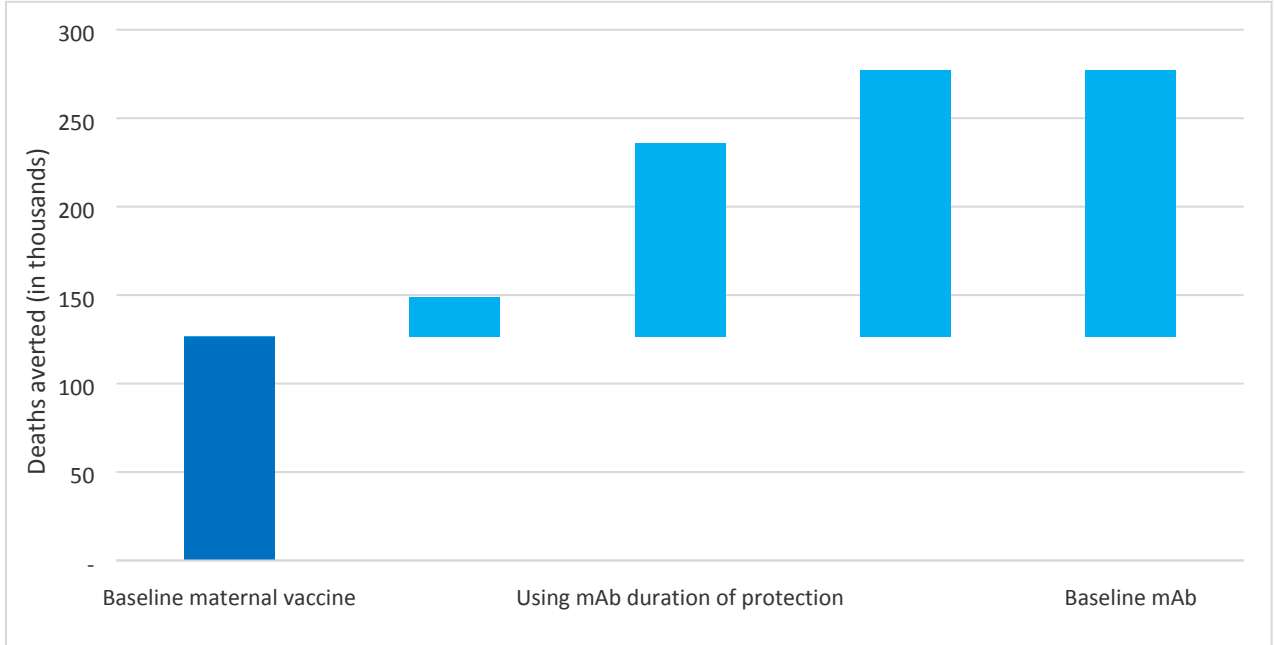


**Panel b. Monoclonal antibody**



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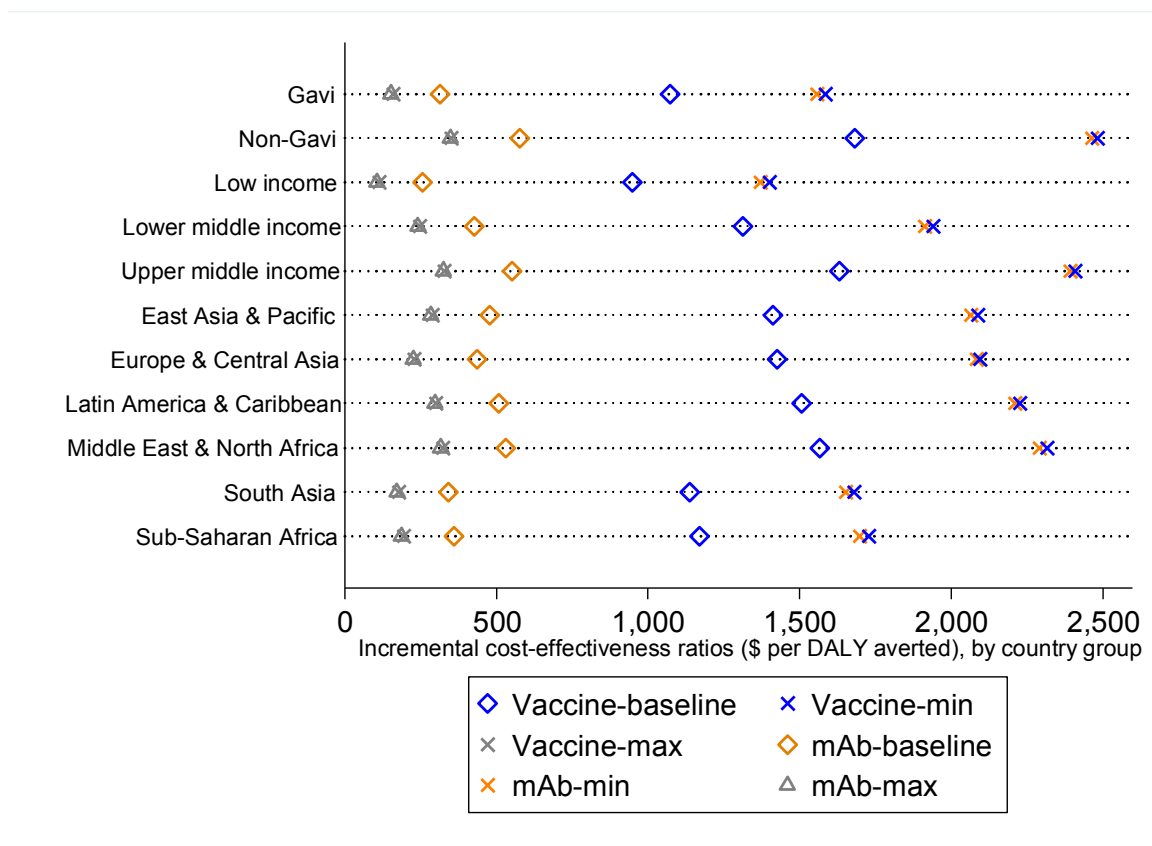
**Figure 2. Impact of change in key input parameter values on deaths averted.**



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**Figure 3. Average incremental cost-effectiveness ratios by country groups.**



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**Appendix Table 1. Cost of intervention and incremental cost-effectiveness ratios by country group (2030–2039).**

Country group by	Maternal vaccine			Monoclonal antibody		
	Health care cost averted	Cost of vaccination program	ICER per DALY averted	Health care cost averted	Cost of vaccination program	ICER per DALY averted
<b>Gavi status</b>						
Gavi (N=73)	397,985,940	3,065,106,927	1,073	1,311,275,193	3,028,242,872	315
Non-Gavi (N=58)	204,118,914	2,398,496,379	1,681	663,227,127	2,355,785,836	577
<b>World Bank Country income group</b>						
LIC (N=34)	131,178,798	886,636,675	949	420,421,498	867,885,189	257
LMIC (N=46)	299,612,949	2,557,430,903	1,311	995,875,548	2,522,516,388	428
UMIC (N=51)	171,313,107	2,019,535,727	1,631	558,205,274	1,993,627,132	551
<b>Geographic region</b>						
East Asia & Pacific (N=20)	124,384,911	1,411,293,535	1,411	392,896,831	1,380,338,857	479
Europe & Central Asia (N=20)	32,220,016	301,556,780	1,425	109,878,013	295,554,675	437
Latin America & Caribbean (N=23)	46,562,615	515,567,727	1,507	146,732,622	492,924,565	507
Middle East & North Africa (N=13)	45,216,714	496,642,134	1,566	154,303,356	504,915,613	532
South Asia (N=8)	155,092,982	1,187,286,456	1,138	558,355,660	1,236,166,379	342
Sub-Saharan Africa (N=47)	198,627,617	1,551,256,674	1,169	612,335,839	1,474,128,619	359
<b>Total (N=131)</b>	<b>602,104,854</b>	<b>5,463,603,306</b>	<b>1,342</b>	<b>1,974,502,320</b>	<b>5,384,028,709</b>	<b>431</b>

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Abbreviations: DALY, disability-adjusted life year; ICER, incremental cost-effectiveness ratio; LIC, low-income country; LMIC, low- and middle-income country; UMIC, upper-middle-income country.

**Appendix Table 2. Incremental cost-effectiveness ratio per disability-adjusted life year (DALY) averted as a percentage of gross domestic product (GDP) per capita across various scenarios.**

Scenarios	Maternal vaccine						Monoclonal antibody						
	Baseline	Baseline low price	Baseline high price	Minimum	Maximum	Adjunct	Baseline	Baseline low price	Baseline high price	Minimum	Maximum	Adjunct	
Efficacy (%)	Trial (40%–60%)	Trial (40%–60%)	Trial (40%–60%)	30	90	Trial (25%–39%)	60%–70%	60%–70%	60%–70%	30	90	Trial (25%–39%)	
Duration of Protection (months)	3	3	3	4	6	6	6	6	6	4	6	6	
Coverage (%)	1	1	1	1	1	1	4	4	4	4	4	4	
Intervention cost (Gavi/non-Gavi)	\$3/\$5	\$1.5/\$2.5	\$6/\$10	\$3/\$5	\$3/\$5	\$3/\$5	\$3/\$5	\$1.5/\$2.5	\$6/\$10	\$3/\$5	\$3/\$5	\$3/\$5	
Afghanistan	1	163%	82%	325%	240%	16%	7%	41%	5%	113%	23%	15%	7%
Albania		37%	21%	69%	55%	6%	17%	11%	4%	26%	55%	6%	17%
Algeria		43%	25%	79%	64%	10%	35%	15%	7%	31%	63%	9%	35%
Angola	1	36%	23%	63%	54%	7%	4%	12%	6%	24%	53%	7%	4%
Armenia	1	31%	20%	55%	47%	6%	14%	10%	5%	21%	47%	6%	14%
Azerbaijan	1	30%	19%	52%	44%	5%	2%	9%	4%	19%	44%	5%	2%
Bangladesh	1	83%	52%	145%	123%	15%	8%	27%	13%	55%	12%	15%	8%
Belarus		32%	18%	59%	46%	4%	105%	9%	3%	21%	4%	4%	104%
Belize		34%	20%	63%	51%	7%	12%	12%	5%	25%	50%	7%	12%
Benin	1	122%	63%	240%	181%	20%	11%	37%	11%	90%	17%	19%	11%
Bhutan	1	40%	25%	70%	59%	7%	8%	12%	6%	26%	58%	7%	8%
Bolivia	1	36%	23%	63%	54%	6%	7%	11%	5%	23%	53%	6%	7%
Bosnia & Herzegovina		33%	19%	61%	48%	5%	156%	10%	3%	23%	4%	5%	156%

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Botswana		26%	15%	47%	39%	7%	10%	10%	5%	19%	38%	7%	10%
Brazil		19%	11%	35%	28%	4%	11%	7%	3%	14%	28%	4%	11%
Bulgaria		22%	13%	40%	32%	4%	19%	7%	3%	15%	32%	4%	18%
Burkina Faso	1	158%	80%	315%	233%	17%	10%	43%	7%	114%	23%	17%	10%
Burundi	1	333%	168%	663%	490%	33%	27%	86%	12%	235%	48%	31%	27%
Cambodia	1	90%	56%	157%	133%	14%	7%	27%	12%	58%	13%	14%	7%
Cameroon	1	93%	59%	162%	139%	19%	11%	31%	16%	61%	13%	18%	11%
Cape Verde		56%	33%	102%	83%	13%	25%	20%	9%	40%	81%	12%	24%
C.A. Rep.	1	260%	133%	513%	386%	40%	9%	76%	20%	188%	37%	37%	9%
Chad	1	148%	76%	291%	220%	25%	7%	44%	13%	107%	21%	22%	7%
China		21%	12%	38%	31%	5%	13%	8%	4%	15%	31%	5%	13%
Colombia		28%	16%	51%	41%	6%	16%	10%	5%	21%	41%	6%	16%
Comoros	1	75%	38%	148%	111%	10%	9%	20%	4%	52%	10%	9%	9%
Congo	1	71%	45%	123%	106%	15%	14%	25%	13%	49%	10%	15%	14%
Costa Rica		14%	8%	26%	21%	3%	27%	5%	2%	10%	21%	3%	27%
Cuba	1	13%	8%	23%	18%	0%	22%	2%	0%	7%	19%	0%	22%
Côte d'Ivoire	1	86%	55%	150%	128%	16%	7%	28%	14%	57%	12%	16%	7%
N. Korea	1												
D. Rep. Congo	1	212%	109%	419%	314%	30%	14%	59%	14%	150%	36%	27%	13%
Djibouti	1	61%	38%	108%	90%	7%	11%	16%	5%	37%	88%	6%	11%
Dominican Republic		25%	14%	45%	37%	5%	8%	9%	4%	18%	36%	5%	8%
Ecuador		27%	16%	49%	40%	6%	10%	10%	5%	20%	40%	6%	10%
Egypt		50%	29%	92%	74%	11%	8%	18%	8%	37%	74%	11%	8%
El Salvador		44%	26%	81%	66%	9%	22%	15%	7%	32%	64%	9%	21%
Equatorial Guinea		20%	12%	37%	30%	5%	4%	7%	4%	15%	30%	5%	4%
Eritrea	1												
Ethiopia	1	127%	65%	251%	188%	18%	15%	37%	9%	93%	18%	17%	15%
Fiji		34%	20%	63%	51%	8%	9%	12%	6%	25%	50%	8%	9%
Gabon		26%	15%	47%	38%	5%	5%	9%	4%	18%	37%	5%	5%
Gambia	1	130%	65%	260%	191%	10%	19%	32%	3%	91%	19%	10%	18%
Georgia	1	30%	19%	53%	45%	5%	42%	9%	4%	20%	44%	5%	41%
Ghana	1	63%	40%	110%	94%	12%	11%	21%	10%	42%	9%	12%	11%

Grenada		17%	10%	31%	25%	4%	8%	6%	3%	12%	25%	4%	8%
Guatemala		40%	24%	74%	60%	9%	5%	15%	7%	30%	60%	9%	5%
Guinea	1	134%	68%	265%	199%	20%	8%	40%	10%	99%	199%	19%	8%
Guinea-Bissau	1	147%	75%	291%	218%	21%	20%	43%	10%	108%	218%	20%	19%
Guyana	1	25%	16%	44%	37%	3%	10%	7%	3%	15%	36%	3%	9%
Haiti	1	123%	62%	246%	181%	10%	8%	28%	1%	83%	171%	8%	8%
Honduras	1	47%	29%	82%	69%	7%	44%	14%	6%	30%	68%	7%	43%
India	1	65%	41%	114%	96%	9%	6%	19%	7%	41%	95%	8%	6%
Indonesia	1	32%	20%	57%	48%	5%	8%	10%	4%	21%	48%	5%	8%
Iran		32%	19%	59%	47%	7%	29%	11%	5%	23%	47%	7%	29%
Iraq		38%	22%	70%	56%	8%	18%	13%	6%	27%	55%	8%	18%
Jamaica		34%	20%	63%	51%	7%	36%	12%	5%	25%	50%	7%	35%
Jordan		41%	24%	74%	60%	8%	20%	13%	6%	29%	59%	8%	19%
Kazakhstan		22%	13%	41%	32%	4%	10%	7%	2%	15%	32%	3%	10%
Kenya	1	81%	51%	141%	120%	13%	8%	25%	11%	52%	111%	12%	8%
Kiribati	1	76%	48%	132%	113%	13%	23%	24%	12%	50%	111%	13%	23%
Kyrgyzstan	1	106%	67%	184%	157%	20%	34%	35%	17%	70%	156%	20%	33%
Lao PDR	1	51%	32%	88%	76%	10%	3%	16%	8%	33%	73%	9%	2%
Lebanon		19%	11%	34%	27%	4%	54%	6%	3%	13%	27%	4%	53%
Lesotho	1	121%	76%	211%	179%	19%	10%	36%	16%	76%	176%	18%	10%
Liberia	1	130%	66%	258%	192%	15%	17%	35%	7%	93%	180%	15%	16%
Libya		40%	24%	74%	60%	8%	109%	14%	6%	29%	59%	8%	108%
Madagascar	1	234%	120%	462%	346%	33%	14%	66%	16%	167%	331%	30%	14%
Malawi	1	307%	154%	614%	449%	21%	36%	70%	1%	207%	438%	18%	35%
Malaysia		17%	10%	32%	26%	4%	27%	6%	3%	13%	26%	4%	27%
Maldives		16%	9%	29%	23%	4%	52%	6%	3%	12%	23%	4%	52%
Mali	1	125%	65%	247%	186%	21%	12%	39%	11%	93%	186%	20%	12%
Mauritania	1	117%	74%	203%	174%	24%	15%	38%	19%	76%	165%	22%	15%
Mauritius		17%	10%	31%	25%	4%	18%	6%	3%	13%	25%	4%	18%
Mexico		20%	11%	36%	29%	4%	11%	7%	3%	14%	29%	4%	11%
Micronesia		55%	32%	100%	81%	13%	23%	20%	10%	40%	81%	13%	23%
Mongolia	1	33%	21%	57%	48%	6%	4%	11%	5%	21%	48%	6%	4%
Montenegro		23%	13%	42%	33%	3%	108%	7%	2%	15%	33%	3%	108%

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Morocco		58%	34%	106%	85%	12%	24%	20%	9%	41%	84%	12%	24%
Mozambique	1	245%	124%	487%	361%	28%	34%	67%	12%	177%	366%	27%	34%
Myanmar	1	98%	62%	169%	144%	18%	9%	32%	16%	64%	146%	18%	9%
Namibia		39%	23%	72%	58%	9%	7%	14%	6%	29%	58%	9%	7%
Nepal	1	109%	54%	221%	160%	3%	11%	23%	-2%	73%	159%	3%	11%
Nicaragua	1	52%	33%	91%	77%	8%	15%	16%	7%	33%	76%	8%	15%
Niger	1	266%	135%	529%	392%	29%	20%	68%	10%	185%	376%	26%	19%
Nigeria	1	63%	40%	109%	93%	14%	3%	21%	11%	42%	91%	13%	3%
Pakistan	1	86%	54%	151%	127%	13%	9%	24%	10%	52%	120%	11%	8%
Papua New Guinea	1	51%	33%	89%	76%	10%	8%	17%	8%	34%	75%	10%	8%
Paraguay		31%	18%	57%	46%	6%	23%	10%	5%	22%	45%	6%	23%
Peru		27%	16%	50%	40%	6%	9%	10%	5%	20%	40%	6%	9%
Philippines		58%	34%	106%	85%	12%	10%	20%	9%	42%	85%	12%	10%
Republic of Moldova	1	58%	37%	102%	86%	9%	12%	18%	8%	38%	86%	9%	12%
Romania		17%	10%	31%	25%	3%	7%	5%	2%	12%	25%	3%	7%
Russian Federation		19%	11%	35%	28%	3%	25%	6%	2%	13%	28%	3%	25%
Rwanda	1	127%	65%	252%	188%	15%	16%	34%	6%	90%	180%	14%	15%
Saint Lucia		18%	10%	33%	26%	4%	13%	6%	3%	13%	26%	4%	13%
St. Vincent & Grenad.		23%	14%	43%	35%	5%	11%	8%	4%	17%	35%	5%	11%
Samoa		45%	26%	81%	66%	11%	26%	16%	8%	33%	65%	11%	26%
S. Tome & Principe	1	68%	43%	118%	100%	11%	13%	20%	9%	43%	98%	10%	13%
Senegal	1	73%	37%	146%	108%	7%	10%	19%	3%	52%	102%	7%	10%
Serbia		29%	17%	55%	43%	4%	114%	8%	3%	20%	43%	4%	113%
Sierra Leone	1	194%	97%	388%	285%	15%	11%	47%	3%	134%	280%	14%	10%
Solomon Islands	1	60%	38%	105%	89%	11%	15%	19%	9%	38%	86%	10%	15%
Somalia	1	217%	113%	425%	323%	41%	17%	69%	23%	161%	316%	38%	16%
South Africa		33%	19%	61%	49%	7%	8%	11%	5%	24%	48%	7%	7%
South Sudan	1	396%	196%	797%	580%	20%	14%	85%	-4%	264%	569%	17%	14%
Sri Lanka	1	30%	19%	52%	44%	6%	67%	10%	5%	20%	44%	6%	66%



State of Palestine		59%	35%	108%	89%	16%	124%	23%	12%	45%	88%	16%	123%
Sudan	1	51%	32%	89%	75%	9%	9%	16%	8%	33%	74%	9%	9%
Suriname		30%	18%	55%	44%	7%	10%	11%	5%	22%	44%	6%	10%
Swaziland		64%	38%	117%	95%	14%	7%	23%	11%	47%	95%	14%	7%
Syria													
Macedonia		31%	18%	57%	45%	4%	45%	9%	3%	21%	45%	4%	44%
Tajikistan	1	116%	60%	230%	172%	16%	7%	34%	8%	85%	172%	16%	7%
Thailand		28%	16%	51%	41%	6%	32%	10%	5%	20%	41%	6%	32%
Timor-Leste	1	60%	38%	104%	89%	11%	7%	19%	9%	38%	86%	10%	7%
Togo	1	162%	82%	321%	239%	19%	22%	44%	8%	115%	239%	18%	21%
Tonga		47%	28%	86%	70%	11%	24%	17%	8%	35%	69%	11%	23%
Tunisia		46%	27%	84%	68%	10%	83%	16%	8%	33%	67%	10%	83%
Turkey		15%	9%	27%	22%	3%	25%	5%	2%	11%	22%	3%	25%
Turkmenistan		27%	16%	50%	40%	5%	4%	9%	4%	19%	40%	5%	4%
Uganda	1	157%	78%	315%	230%	9%	29%	35%	0%	105%	229%	8%	29%
Ukraine	1	52%	33%	90%	76%	8%	89%	16%	7%	33%	76%	8%	89%
Tanzania	1	103%	52%	203%	151%	12%	10%	27%	5%	72%	149%	11%	10%
Uzbekistan	1	56%	35%	97%	83%	10%	5%	18%	9%	37%	82%	10%	5%
Vanuatu		62%	37%	113%	92%	15%	10%	23%	11%	46%	91%	15%	10%
Venezuela													
Viet Nam	1	51%	32%	89%	75%	9%	21%	16%	8%	34%	75%	9%	21%
Yemen	1	69%	35%	137%	102%	10%	13%	20%	5%	50%	109%	9%	13%
Zambia	1	99%	62%	173%	146%	15%	11%	29%	13%	62%	149%	14%	11%
Zimbabwe	1	74%	37%	146%	109%	9%	5%	21%	4%	54%	109%	9%	5%

Note: Country by Gavi status (Gavi country = 1). Current GDP values were not available for 4 countries (Venezuela, Syria, Eretria, North Korea) and were excluded from the analysis.

\*Negative cost-effectiveness ratio implies cost savings.

Cells in green indicate lower ICER to GDP ratio and cells in red indicate higher ICER to GDP ratio.



**Additional file 1**

EVEREST Statement: Checklist for health economics paper

	<b>Study section</b>	<b>Additional remarks</b>
<b>Study design</b>		
(1) The research question is stated	Introduction	
(2) The economic importance of the research question is stated	Introduction	
(3) The viewpoint(s) of the analysis are clearly stated and justified	Methods; Discussion	
(4) The rationale for choosing the alternative programmes or interventions compared is stated	Introduction; Methods	
(5) The alternatives being compared are clearly described	Methods	
(6) The form of economic evaluation used is stated	Introduction; Methods	
(7) The choice of form of economic evaluation is justified in relation to the questions addressed	Introduction; Discussion	
<b>Data collection</b>		
(8) The source(s) of effectiveness estimates used are stated	Methods- Assumptions used in the model; Table 1	
(9) Details of the design and results of effectiveness study are given (if based on single study)	N/A	Data derived from peer reviewed literature, Target product profile
(10) Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	N/A	
(11) The primary outcome measure(s) for the economic evaluation are clearly stated	Methods	
(12) Methods to value health states and other benefits are stated	N/A	
(13) Details of the subjects from whom valuations were obtained are given	N/A	
(14) Productivity changes (if included) are reported separately	N/A	
(15) The relevance of productivity changes to the study question is discussed	N/A	
(16) Quantities of resources are reported separately from their unit costs	Methods- Assumptions used in the model; Table 1	

(17) Methods for the estimation of quantities and unit costs are described	Methods- Assumptions used in the model; Table 1	
(18) Currency and price data are recorded	Methods-Cost calculations; Tables 1- 5	
(19) Details of currency of price adjustments for inflation or currency conversion are given	N/A	As the study is looking for relative cost
(20) Details of any model used are given	Methods	
(21) The choice of model used and the key parameters on which it is based are justified	Methods	
<b>Analysis and interpretation of results</b>		
(22) Time horizon of costs and benefits is stated	Methods	
(23) The discount rate(s) is stated	N/A	
(24) The choice of rate(s) is justified	N/A	
(25) An explanation is given if costs or benefits are not discounted	N/A	
(26) Details of statistical tests and confidence intervals are given for stochastic data	N/A	
(27) The approach to sensitivity analysis is given	Methods- Sensitivity analysis	
(28) The choice of variables for sensitivity analysis is justified	Methods; Discussion	
(29) The ranges over which the variables are varied are stated	Table 1	
(30) Relevant alternatives are compared	Methods	
(31) Incremental analysis is reported	Methods; Table 2; Figures 1, 2, 3	
(32) Major outcomes are presented in a disaggregated as well as aggregated form	Table 2; Appendix Tables 1 and 2	
(33) The answer to the study question is given	Results, Discussion; Conclusion	
(34) Conclusions follow from the data reported	Discussion; Conclusion	
(35) Conclusions are accompanied by the appropriate caveats	Discussion; Conclusion	

# BMJ Open

## Impact and cost-effectiveness of potential interventions against infant respiratory syncytial virus (RSV) in 131 low- and middle-income countries using a static cohort model

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3 1 **Impact and cost-effectiveness of potential interventions against infant respiratory syncytial virus**  
4  
5 2 **(RSV) in 131 low- and middle-income countries using a static cohort model**  
6  
7 3

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16 **Running title:**

17 Infant RSV interventions in LMIC

**Abstract**

*Objectives.* Interventions to prevent childhood respiratory syncytial virus (RSV) disease are limited and costly. New interventions are in advanced stages of development and could be available soon. This study aims to evaluate the potential impact and cost-effectiveness of two interventions to prevent childhood RSV—a maternal vaccine and a monoclonal antibody (mAb).

*Design.* Using a static population-based cohort model, we evaluate impact and cost-effectiveness of RSV interventions, from a health systems perspective. The assumed baseline efficacy and duration of protection were higher for the mAb (60-70% efficacy, protection 6 months) compared to the maternal vaccine (40-60% efficacy, protection 3 months). Both interventions were evaluated at US\$3 and \$5 per dose for Gavi and non-Gavi countries, respectively. A range of input values were considered to explore uncertainty.

*Settings.* 131 low- and middle-income countries.

*Participants.* Pregnant women and live birth cohorts.

*Interventions.* Maternal vaccine given to pregnant women and monoclonal antibody given to young infants.

*Primary and secondary outcome measures.* Disability adjusted life years averted, severe case averted, deaths averted, incremental cost effectiveness ratios.

*Results.* Under baseline assumptions, maternal vaccine and mAbs were projected to avert 25% and 55% of RSV-related deaths among infants younger than six months of age, respectively. The average incremental cost-effectiveness ratio per disability-adjusted life year averted was \$1,342 (range \$800 to \$1,866) for maternal RSV vaccine and \$431 (range \$167 to \$692) for mAbs. At a 50% gross domestic product per capita threshold, maternal vaccine and mAbs were cost-effective in 60 and 118 countries, respectively.

*Conclusions.* Both interventions are projected to be impactful and cost-effective in many countries, a finding that would be enhanced if country-specific Gavi co-financing to eligible countries were included.

1  
2  
3 43 mAbs, with assumed higher efficacy and duration of protection, are expected to be more cost-effective  
4  
5 44 than RSV maternal vaccines at similar prices. Final product characteristics will influence this finding.  
6  
7 45

8  
9 46 **Key words:** Respiratory syncytial virus (RSV); maternal RSV vaccine; RSV monoclonal antibody; health  
10  
11 47 impact; cost-effectiveness.  
12  
13 48

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15 50

16 51

### 17 52 **Strengths and limitations of this study**

- 18 53 • This is one of the first studies to examine the potential impact and cost-effectiveness of maternal  
19 54 vaccines and monoclonal antibodies for RSV prevention, across 131 low-and middle-income  
20 55 countries.
- 21 56 • This study compares products with uncertain characteristics using the latest available data on  
22 57 vaccine characteristics, supplemented by the target product profile to inform the model  
23 58 parameters.
- 24 59 • A range of input values were considered to explore uncertainty, insights from which are useful to  
25 60 inform subsequent intervention development.
- 26 61 • Final product characteristics and product prices will determine the relative cost-effectiveness of  
27 62 RSV interventions.

## 62 Introduction

63 Respiratory syncytial virus (RSV) is a common cause of acute lower respiratory illness (ALRI) among  
64 children younger than age five, causing between 41,000 and 118,000 child deaths per year globally [1,2].  
65 RSV disease is most severe among young infants, and the burden is highest in low- and middle-income  
66 countries (LMICs), where more than 99% of RSV deaths occur [2]. Emerging evidence indicates the  
67 unrecognized burden of RSV among children in low-resource settings is also significant, with up to 10%  
68 of young infant deaths attributable to RSV infection [3,4].  
69 Existing RSV interventions are limited and cost prohibitive, even in high-income countries [5]. Several  
70 prophylactic interventions are currently under development [6,7]. Multiple maternal vaccine candidates  
71 designed to protect against RSV illness in infants are in relatively advanced stages of development and  
72 expected to be available for global use in the coming years [6]. Monoclonal antibodies (mAbs) are  
73 available and in use for high-risk babies in high-income countries. However, the available mAbs are not  
74 only expensive but require multiple doses during the RSV season. Long lasting more affordable mAbs  
75 that are easier to deliver in low resource settings are in advanced stages of development [8]. Given the  
76 extent of the global RSV disease burden—especially in low-income countries (LICs)—and the lack of  
77 efficacious and cost-effective therapeutic options, these new interventions are expected to be included in  
78 Gavi, the Vaccine Alliance's, portfolio [9], subject to licensure, prequalification, and cost characteristics.  
79 In this paper, we estimate the potential impact and cost-effectiveness of a maternal vaccine and a mAb,  
80 both designed to avert RSV disease burden in young infants in LMICs. We compare each intervention  
81 against a scenario of no intervention and against each other. Results from this study illustrate the potential  
82 benefits of these products and will help inform decisions around further development. This analysis will  
83 also inform global and LMIC decision-makers likely to face choices about whether and which  
84 interventions to introduce.

## 86 Methods



87 We examined the potential impact and cost-effectiveness of a single-dose RSV maternal vaccine  
 88 administered to pregnant women at 24 to 36 weeks gestation, and of a single-dose mAb given to infants  
 89 directly at birth across 131 LMICs, compared to no intervention. Both interventions were evaluated  
 90 independently using a static cohort model. For maternal vaccine, infants born two weeks following  
 91 maternal immunization were considered as protected to allow time for immune transfer from mother to  
 92 children. All children receiving mAbs were considered protected immediately.

93 We examined the impact and cost of interventions from the health systems perspective over the period  
 94 2030 to 2039 (10 years), assuming nationwide introduction in 2030. Primary input values for a baseline  
 95 scenario are given in Table 1. Key model outputs include cases averted, severe cases averted,  
 96 hospitalizations averted, deaths averted, disability adjusted life years (DALYs) averted, and the  
 97 incremental cost per DALY averted due to RSV interventions. Given the inconsistent use of country-  
 98 specific cost-effectiveness thresholds across LMICs, we used a willingness-to-pay threshold of 0.5 times  
 99 the gross domestic product (GDP) per capita in each country [10]. Results are summarized by World  
 100 Health Organization (WHO) regions, World Bank income group, and Gavi eligibility to understand  
 101 impact by country group. All monetary units are adjusted to 2016 US dollars.

102 Table 1. Key input parameter values used for modeling.

Input	RSV maternal vaccine	RSV monoclonal antibody	Sources
<i>Intervention specific inputs</i>			
Target population	126 million (annual average number of pregnant women, between 2030 and 2039, across 131 countries)	124 million (annual average live births between 2030 and 2039, across 131 countries)	Birth estimates and population growth rate [11]; still birth rates [12]
Intervention schedule	Single dose vaccine given during weeks 24–36 of gestation, as a part of ANC	Single dose mAb given to newborn at birth	[13, 14]; expert opinion
Efficacy against RSV endpoints	Baseline: cases = 40.9%; hospitalization = 41.7%; death = 59.6% Minimum scenario: 30% (for all endpoints) Maximum scenario: 90% (for all endpoints)	Baseline: cases = 60%; hospitalization = 60%; death = 70% Minimum scenario: 30% (for all endpoints) Maximum scenario: 90% (for all endpoints)	[13,15,16], expert opinion
Duration of protection against RSV <sup>+</sup>	Baseline: 3 months Minimum scenario: 4 months Maximum scenario: 6 months	Baseline: 6 months Minimum scenario: 4 months Maximum scenario: 6 months	[13, 16] and expert opinion
Efficacy against all cause LRTI*	Cases = 25%; hospitalization = 25%; death = 39%	Cases = 25%; hospitalization = 25%; death = 39%	[15]; expert opinion
Duration of protection against all cause LRTI*	6 months	6 months	[15]; expert opinion

Intervention coverage	Derived from ANC coverage (average 84%, range: 40% to 96%, in 2030)	Derived from BCG coverage (average 82%, range: 48% to 98%, in 2030)	[17, 18, 19, 20]
<b>Common to both interventions</b>			
<b>Disease burden</b>			
Incidence of RSV ALRI	Country-specific incidence for 0–5 years for envelope (35.3 to 65.6). Developing-country estimate by narrow age band for case distribution by age; Annual incidence per 1,000 children 0–27 days 40.0 28–< 3 months 45.7 3–5 months 99.6 6–11 months 98.8 12–23 months 79.1 <i>Rescaled to match country-specific incidence envelope.</i>		[2]
Incidence of severe RSV ALRI	Developing-country estimates with uniform age distribution Annual incidence of severe RSV ALRI per 1,000 children 0–5 months 36.1 6–11 months 24.7 0–59 months 10.2		[2]
Hospital admissions for RSV-associated ALRI	Annual hospital admissions for RSV-associated ALRI per 1,000 children 0–5 months 20.2 6–11 months 11		[2]
Hospital case fatality	Hospital case fatality risk (%), by age group 0–5 months 2.2 6–11 months 2.4		[2]
RSV-ALRI mortality	Hospital deaths *2.2 ( <i>adjusted for community deaths</i> ) *0.9 ( <i>adjusted for influenza activities</i> )		[2]
Incidence of all-cause LRTI	Country-specific; By ages: early neonates (0–7 days), post neonates (7–28 days), late neonates (1–12 months); Burden for post neonates, uniformly distributed across ages by month		[21]
Incidence of severe LRTI	11.5% of all incidence resulting in severe cases		Assumed (based on the estimates used in [22])
Hospital admissions for LRTI	40% of all severe cases resulting in hospital admissions		Assumed
Mortality due to LRTI	Country specific, early neonates, post neonates, late neonates; burden for post neonates uniformly distributed across ages by month		[21]
Age distribution of LRTI	Assumes uniform distribution of burden across months by age		Assumed
<b>Costs</b>			
Intervention cost	\$3 per dose in Gavi countries; \$5 per dose in non-Gavi countries		Assumed
Intervention delivery costs	Mean incremental economic cost of delivery per dose: \$0.63 in LICs; \$1.73 in LMICs and UMICs		[23]
Treatment cost	Cost of managing severe pneumonia in LMICs (outpatients \$53; inpatients \$250)		[24]
Vaccine introduction dates	National introduction starting 2030		Product development timeline, assumed
<b>Other assumptions</b>			
DALY weights	Severe ALRI = 0.21; Non-severe ALRI = 0.053		[25]
Duration of illness	Severe ALRI = 10 days; Non-severe ALRI = 5 days		[26]
Length of hospital stay	Length of stay for severe pneumonia in LMICs, 6.4 days		[24]
Health care seeking	Health seeking for children with pneumonia, country specific		[27]

Abbreviations: ANC, antenatal care; BCG, Bacillus Calmette–Guérin; LIC, low-income country; LMIC, low- and middle-income country; LRTI, lower respiratory tract infection; mAb, monoclonal antibody; UMIC, upper-middle-income country; RSV, respiratory syncytial virus; WHO, World Health Organization; ALRI, acute lower respiratory illness; DALY, disability-adjusted life year; LMIC, low- and middle-income country; LRTI, lower respiratory tract infection; RSV, respiratory syncytial virus.

\*Duration of protection in the minimum scenario is higher than in the baseline scenario. For maternal vaccine baseline, we assume duration of protection data from a recent clinical trial that failed to meet the primary endpoint. Nonetheless, in

1  
2  
3 110 anticipation that a successful product would likely have higher duration of protection than three months, we evaluate the  
4 111 minimum scenario at four months duration of protection.

5 112 \*Used in adjunct scenario only. The adjunct scenario evaluates intervention impact on all-cause LRTI mortality.  
6 113

### 7 8 114 *Disease burden*

9  
10 115 Disease burden inputs including disease incidence, severe disease incidence, incidence of hospitalizations,  
11  
12 116 and mortality were derived from a comprehensive systematic review paper [2]. We combined country-  
13  
14 117 specific disease incidence estimates in children under five years of age with a representative developing-  
15  
16 118 country estimate to generate incidence by granular age band in each country. To generate incidence of  
17  
18 119 severe disease, hospitalization, and hospital mortality, we used developing-country estimates [2].

19  
20 120 Estimated hospital deaths were adjusted by multiplying by 1.98 to account for community deaths and  
21  
22 121 influenza coinfection [2]. The actual values of disease burden inputs are given in Table 1.

23  
24 122 Some RSV interventions under development have shown promising results in their ability to avert all-  
25  
26 123 cause lower respiratory tract infections (LRTIs) among children [15], in addition to RSV infection. Thus,  
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28 124 we also explored the potential impact of both RSV interventions on all-cause LRTI, based on emerging  
29  
30 125 burden data, using estimates from the Global Burden of Disease Study 2017 [21], and assuming a uniform  
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32 126 distribution of disease among children one to 12 months of age. Further, we assumed 11.5% of all-cause  
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34 127 LRTI cases would result in severe cases [22] and 40% of all severe cases would result in hospitalization.  
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### 37 128 *Intervention introduction and coverage*

38  
39 129 The leading RSV intervention candidates could be available for use in the next five-to-eight years [7]. We  
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41 130 assumed both interventions would be available by 2030 and all countries would begin national  
42  
43 131 introduction in 2030.

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45 132 All pregnant women attending antenatal care (ANC) visits were assumed eligible to receive RSV  
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47 133 maternal vaccine. To project the number of pregnant women per country, we added country-specific  
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49 134 stillbirths [12] to the United Nations Population Division annual birth projections [11]. We estimated  
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51 135 maternal vaccine coverage during the 24- to 36-week vaccination window by examining country-specific  
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53 136 ANC first-visit timing [17], country-specific ANC coverage [18], and the WHO's recommended ANC  
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3 137 timing based on the focused ANC model guideline [19]. Details on methods used in estimating maternal  
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5 138 vaccine coverage during ANC within a specific gestation window is described elsewhere [28].  
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7 139 All live births were considered eligible for mAbs. All infants were assumed to be covered at the Bacillus  
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9 140 Calmette–Guérin (BCG) vaccine birth dose coverage levels adjusted to the timeliness of vaccine receipt.  
10  
11 141 Country’s overall BCG coverage were derived from the most recent WHO/UNICEF estimates of national  
12  
13 142 immunization coverage [20]. Timeliness of BCG birth dose receipt was derived using the methods  
14  
15 143 described in the literature [29,30].  
16  
17 144 Coverage levels for both interventions for each country are projected to improve by 3 percentage points  
18  
19 145 each year until coverage reaches 70%, and after that by 1 percentage point each year until reaching 95%  
20  
21 146 coverage. This projection was made to correspond with methods applied during the Gavi vaccine  
22  
23 147 investment strategy [9].

#### 24 148 *Intervention characteristics*

25  
26 149 Our analysis assumed a single dose maternal RSV vaccine would be given to pregnant women between  
27  
28 150 24 and 36 months of gestation, inferred based on the WHO preferred product characteristics (PPCs) [13]  
29  
30 151 and other ongoing clinical trials [14]. We based vaccine efficacy and duration of protection on data from  
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32 152 one of the first maternal vaccine candidate Phase 3 clinical trials (Table 1) [15]. Other maternal vaccines  
33  
34 153 are in clinical development which may have improved efficacy. Given the uncertainty in vaccine  
35  
36 154 characteristics, scenario analyses included a range in efficacy (30% to 90%) and duration of protection  
37  
38 155 afforded to infants (three to six months).

39 156 Our analysis assumed a single dose mAb would be given to newborns at birth, would have 60% to 70%  
40  
41 157 efficacy, and would offer protection for six months, inferred based on the PPCs [16] and other studies [31,  
42  
43 158 32]. As with the maternal vaccine, we varied efficacy and duration of protection in scenario analysis. We  
44  
45 159 assumed neither intervention contributed to herd immunity, and that efficacy did not wane during the  
46  
47 160 period of protection.

#### 48 161 *Intervention price and delivery costs*

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3 162 For both interventions, we assumed a per-dose price of US\$3 in Gavi-eligible countries and per-dose  
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5 163 price of \$5 in LMICs not eligible for Gavi support. Traditionally mAbs are more expensive to produce  
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7 164 than a vaccine and will likely have higher market price than a vaccine. If Gavi decides to support RSV  
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9 165 interventions once they are available, Gavi-eligible countries would likely be able to access the  
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11 166 interventions at varying prices depending on their transition status [33]. We refrained from projecting  
12  
13 167 individual country Gavi eligibility or intervention prices due to significant uncertainty, and instead  
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15 168 evaluated a range of intervention prices in sensitivity analyses.  
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18 169 Given the paucity of data on maternal immunization and mAb delivery costs in LMICs, we used delivery  
19  
20 170 costs estimates for other vaccines derived from the Immunization Costing Action Network (ICAN)  
21  
22 171 repository [23]. Unit costs of delivering RSV interventions were \$0.63 for LICs and \$1.73 for LMICs.  
23  
24 172 We accounted for vaccine/mAbs wastage at 5% and a buffer stock at 25% of demand in the introduction  
25  
26 173 year, and at 25% of the incremental demand in subsequent years.

#### 28 174 *Health service costs*

30 175 Very few studies have analyzed the cost of managing RSV in children, especially in LMICs [34–39].  
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33 176 Hospitalization costs also vary widely. In Bangladesh, for example, hospitalization averages \$74, whereas  
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35 177 in China it averages \$662. Given limited RSV-specific information in LMICs, we used the average cost of  
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37 178 treating pneumonia in young children, identified in a systematic review [24] as \$53.26 and \$250.04 per  
38  
39 179 outpatient and inpatient episode, respectively. We assumed that severe cases seek inpatient care and non-  
40  
41 180 severe cases seek outpatient care.

#### 43 181 *Cost-effectiveness analysis*

45 182 We calculated intervention costs by multiplying the number of doses (estimated number of pregnant  
46  
47 183 women receiving vaccine for maternal vaccine and estimated number of live births for mAbs) with the  
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49 184 unit cost of delivery and cost per dose. We estimated averted health care costs by multiplying the  
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51 185 estimated number of non-severe/severe cases averted by the costs of an outpatient/inpatient episode.  
52  
53 186 Vaccine impact was calculated by multiplying the respective disease burden in children born two weeks  
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55 187 after maternal vaccination with vaccine efficacy. The mAb impact was calculated by multiplying disease

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3 188 burden with the BCG coverage estimates and mAb efficacy. We estimated health outcomes including  
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5 189 severe/non-severe cases averted, hospitalizations averted, deaths averted, and DALYs averted for each  
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7 190 country and year. Disability weights for non-severe and severe ALRI were used to compute DALYs [25].  
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9 191 Further, we assumed duration of illness at five days for non-severe disease and 10 days for severe disease  
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11 192 [26]. The length of a hospital stay for severe disease was assumed to be 6.4 days [24]. Both undiscounted  
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13 193 and discounted DALYs (at 3% discount rate) were generated for the analysis. We also accounted for  
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15 194 variation in health-seeking practices by using health care use data from children younger than five years  
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17 195 receiving pneumonia care [27].  
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19 196 We calculated incremental cost-effectiveness ratios (ICERs) for each country by dividing the net cost of  
20  
21 197 intervention by the net DALYs averted by the intervention.  
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#### 24 198 *Sensitivity analysis*

25  
26 199 We conducted one-way sensitivity analysis by changing the values of key input parameters, including  
27  
28 200 intervention efficacy, duration of protection, anticipated coverage, and intervention price. Alternate  
29  
30 201 scenarios that changed one or more input parameters to evaluate results sensitivity were also considered.  
31  
32 202 In an adjunct scenario, we evaluated how different interventions show impact on all-cause LRTI  
33  
34 203 mortality, using the efficacy and duration of protection values as suggested by recent clinical trial data  
35  
36 204 [15], and disease burden for all-cause LRTI from the 2017 Global Burden of Disease Study [21].  
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### 40 41 206 **Patient and Public Involvement**

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43 207 Patients were not included in this modeling study.  
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### 47 48 209 **Results**

#### 49 210 *Disease burden without interventions*

50  
51 211 Over the 10-year period, about 41.94 million non-severe cases, 15.28 million severe cases, 11.48 million  
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53 212 hospitalizations, and 504,963 thousand deaths among children younger than six months of age in 131  
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3 213 LMICs are projected (Table 2). Seventy-three Gavi-eligible countries accounted for 70% of the mortality  
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5 214 burden. Most deaths would occur in sub-Saharan Africa (36%, 47 countries), followed by South Asia  
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7 215 (26%, eight countries).  
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218 Table 2. Summary of disease burden, impact and cost effectiveness ratios, with and without intervention (2030–2039), baseline scenario.

Country group by	N	Disease burden without intervention				Burden averted and ICER with RSV maternal vaccine				Burden averted and ICER with RSV monoclonal antibody					
		Non-severe cases	Severe cases	Hospitalizations	Deaths	Non-severe cases	Severe cases	Hospitalizations	Deaths	ICER per DALY averted	Non-severe cases	Severe cases	Hospitalizations	Deaths	ICER per DALY averted
<b>Gavi status</b>															
Gavi	73	31,288,677	10,683,106	8,031,827	352,990	2,159,630	1,730,164	1,333,545	83,024	1,073	13,866,799	4,742,022	3,565,171	182,800	315
Non-Gavi	58	10,657,947	4,599,391	3,457,938	151,973	819,749	907,088	699,149	43,528	1,681	5,610,598	2,441,921	1,835,898	94,133	577
<b>World Bank income group</b>															
LIC	34	10,823,869	3,562,172	2,678,130	117,701	760,348	577,452	445,078	27,710	949	4,774,083	1,573,199	1,182,771	60,645	257
LMIC	46	22,502,889	7,872,029	5,918,389	260,107	1,559,549	1,292,990	996,588	62,046	1,311	10,083,892	3,536,660	2,658,950	136,334	428
UMIC	51	8,619,867	3,848,296	2,893,246	127,155	659,482	766,809	591,027	36,796	1,631	4,619,422	2,074,084	1,559,348	79,954	551
<b>WHO geographic region</b>															
EAP	20	5,313,235	3,097,972	2,329,133	102,363	314,036	582,849	449,238	27,969	1,411	2,570,416	1,558,912	1,172,029	60,094	479
ECA	20	2,609,512	633,363	476,178	20,928	244,307	125,417	96,666	6,018	1,425	1,398,536	337,329	253,612	13,004	437
LAC	23	2,583,464	1,024,279	770,079	33,844	209,296	204,837	157,881	9,829	1,507	1,349,631	536,105	403,057	20,666	507
MENA	13	2,907,732	1,058,521	795,823	34,976	222,211	192,789	148,594	9,251	1,566	1,468,837	535,629	402,699	20,648	532
SA	8	12,207,891	4,018,853	3,021,474	132,791	842,810	643,028	495,622	30,857	1,138	5,628,427	1,857,416	1,396,452	71,601	342
SSA	47	16,324,790	5,449,509	4,097,078	180,062	1,146,719	888,332	684,693	42,628	1,169	7,061,551	2,358,554	1,773,220	90,920	359
<b>Total</b>	<b>131</b>	<b>41,946,624</b>	<b>15,282,497</b>	<b>11,489,765</b>	<b>504,963</b>	<b>2,979,379</b>	<b>2,637,252</b>	<b>2,032,693</b>	<b>126,552</b>	<b>1,342</b>	<b>19,477,397</b>	<b>7,183,943</b>	<b>5,401,069</b>	<b>276,933</b>	<b>431</b>



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3 219 Abbreviations: LIC, low-income country; LMIC, low- and middle-income country; RSV, respiratory syncytial virus; UMIC, upper-middle-income country; WHO, World Health  
4 220 Organization; EAP: East Asia & Pacific; ECA: Europe & Central Asia; LAC: Latin America & Caribbean; MENA: Middle East & North Africa; SA: South Asia; SSA: Sub-  
5 221 Saharan Africa.

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222 *Expected health outcomes with intervention*

223 RSV maternal vaccine, under the baseline scenario, has the potential to avert 2.97 million non-severe  
224 cases, 2.63 million severe cases, 2.03 million hospitalizations, 126,552 deaths, and 3.73 million DALYs  
225 (discounted) among children younger than six months of age across all countries over 10 years (Table 2).  
226 Globally, about 17% of severe RSV cases and 25% of RSV-related deaths among infants under six  
227 months of age would be averted by RSV maternal vaccine, which is roughly 13 deaths averted per  
228 100,000 vaccinated pregnant women.

229 An RSV mAb, under the baseline scenario, is expected to avert 19.47 million cases of non-severe disease,  
230 7.18 million severe cases, 5.40 million hospitalizations, 276,933 deaths, and 8.19 million DALYs  
231 (discounted) among children younger than six months of age across all countries over 10 years (Table 2).  
232 Globally, about 55% of RSV deaths among infants younger than six months of age would be averted with  
233 RSV mAbs—equivalent to approximately 28 averted deaths per 100,000 newborns receiving the  
234 intervention.

235 Under alternative scenarios using varying efficacy and duration of protection assumptions (minimum and  
236 maximum scenarios), the RSV maternal vaccine is estimated to avert between 84,934 and 356,346 deaths  
237 over 10 years; and the RSV mAb is expected to avert roughly 84,864 and 356,057 deaths. Assuming  
238 both interventions are able to affect all-cause LRTI, as suggested by recent clinical trial data [15], either  
239 intervention is projected to avert roughly 1.05 million LRTI deaths (29% of all LRTI deaths) among  
240 children younger than six months of age in LMICs.

241 *Cost-effectiveness of interventions*

242 The average annual cost of vaccination programs across all countries for the duration of analysis was  
243 estimated to be about \$546.36 million and \$538.40 million for RSV maternal vaccine and mAbs,  
244 respectively. The economic benefits expressed in terms of cost-of-care averted was about \$602.10 million  
245 (maternal vaccine) and \$1.97 billion (mAbs) over the 10 years (see appendix Table 1).

246 For maternal RSV vaccine, the ICER per DALY averted is estimated at \$1,342 (\$1,073 across Gavi-  
247 eligible countries and \$1,681 across non-Gavi countries). Similarly, the ICER estimates for RSV mAbs is

248 \$431 (\$315 across Gavi-eligible countries and \$577 across non-Gavi countries). It is important to note  
249 these ICERs reflect the full potential cost of either intervention. Countries eligible for Gavi support would  
250 be expected to pay a share of the prices used in this analysis, thus reducing the ICER from the country  
251 perspective.

252 Results from alternative scenarios with low and high efficacy and duration of protection assumptions  
253 show that costs per DALY averted across countries range from \$244 to \$1,982 (maternal vaccine) and  
254 \$239 to \$1,958 (mAbs). By reducing the intervention price to 50% of the baseline price (i.e., \$1.50 for  
255 Gavi-eligible countries and \$2.50 for non-Gavi countries), the average ICER per DALY averted would  
256 decline to \$781 (range \$45 to \$1,147) for the maternal vaccine and \$178 (range \$42 to \$1,132) for the  
257 mAb. Increasing the intervention price by 200% of the baseline price, the average ICER per DALY  
258 averted increases to \$2,465 (range \$642 to \$3,651) for the maternal vaccine and \$938 (range \$632 to  
259 \$3,610) for the mAbs.

260 When comparing ICERs against an individual country's income level at baseline, the maternal vaccine  
261 ICERs were less than 50% of the GDP per capita in 60 countries (12 Gavi and 48 non-Gavi), suggesting  
262 intervention cost-effectiveness in those countries. ICERs for RSV mAbs were below the 50% GDP per  
263 capita threshold in 118 countries (62 Gavi-eligible and all non-Gavi). For both interventions, countries  
264 with higher ICER to GDP per capita ratios are concentrated in sub-Saharan Africa and Asia (Figures 1  
265 and 2). Many of these countries remain eligible for Gavi support and are expected to pay lower  
266 intervention prices. As a result, the cost per DALY averted from the perspective of these countries is  
267 likely to be much more favorable than shown here. For example, if each of the original Gavi-eligible  
268 countries were responsible for half of the cost of the intervention (\$1.50), which is still a relatively high  
269 cost as the countries with the lowest GDP per capita would pay only a fraction of that price under Gavi's  
270 current co-financing model, then the ICER for the RSV maternal vaccine and mAb would fall below the  
271 50% GDP per capita threshold in 46% (maternal vaccine) and 100% (mAb) of these countries. Further,  
272 maternal vaccine ICERs across countries at base price are roughly equivalent to the mAb ICER evaluated

273 at 300% of the base price. Appendix Table 2 includes a comparison of ICERs as a share of country GDP  
274 for alternative intervention scenarios.

275 [Insert Figure 1 here: Incremental cost-effectiveness ratios as a percentage of national GDP per capita,  
276 maternal vaccine]

277 [Insert Figure 2 here: Incremental cost-effectiveness ratios as a percentage of national GDP per capita,  
278 monoclonal antibody]

279

## 280 Discussion

281 Both RSV interventions are projected to be impactful across all countries under baseline assumptions. A  
282 maternal vaccine is projected to avert 12.65 thousand deaths and mAbs roughly two times more (27.69  
283 thousand deaths averted) annually among children younger than six months of age. We note that our  
284 baseline assumptions for the maternal vaccine draw from a Phase 3 trial in which the primary endpoints  
285 were not met. As a result, maternal vaccine assumptions may be conservative compared to mAb  
286 assumptions, leading to lower overall impact of RSV maternal vaccines. Under alternative scenarios that  
287 consider both interventions with similar characteristics, we observe no substantial variation in impact.  
288 Under a minimal (30% efficacy and four months protection) and maximal (90% efficacy and six months  
289 protection) intervention characteristics scenario, both interventions are projected to avert roughly 84,900  
290 and 356,000 deaths among children younger than six months of age across 131 countries, suggesting that  
291 efficacy and duration of protection are primary parameters for determining impact, reinforced by a similar  
292 study [32].

293 Unknowns around intervention delivery strategy and potential coverage implications create uncertainties;  
294 this is especially true for a novel intervention like a maternal vaccine. To further understand the potential  
295 implications of unknown parameters on a maternal vaccine impact, we evaluated the marginal gains in  
296 impact by incrementally changing the parameter values to mimic those used in the mAb baseline scenario.  
297 When changing maternal vaccine coverage assumptions to the mAb coverage values, the maternal

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2  
3 298 vaccine would prevent 22,000 additional deaths. Similarly, when changing both duration of protection  
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5 299 and efficacy for maternal vaccine at baseline to the mAb baseline equivalent, maternal vaccine would  
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7 300 avert an additional 150,000 deaths. As seen in Figure 3, the duration of protection is the most important  
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9 301 factor for increasing impact (109,000 additional deaths averted).

10  
11 302 [Insert Figure 3 here: Impact of change in key input parameter values on deaths averted.]  
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14 303  
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16 304 The cost per DALY averted under the baseline scenario for a maternal vaccine is more than three times  
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18 305 that for mAbs (\$1,342 versus \$431). This is mainly driven by the modest vaccine efficacy and assumed  
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20 306 duration of protection for the maternal vaccine as compared to mAbs. Under the maximum and minimum  
21  
22 307 scenarios with high and low vaccine efficacy and duration of protection assumptions, the difference in the  
23  
24 308 estimated ICERs between the two interventions is muted (Figure 4).  
25

26 309 [Insert Figure 4 here: Average incremental cost-effectiveness ratios by country groups.]  
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31 311 Though it didn't meet the primary endpoint, the recent Phase 3 maternal vaccine trial shows promising  
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33 312 impact on all-cause LRTI mortality [15]. If both future RSV interventions reduce all-cause LRTI  
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35 313 mortality, our adjunct scenario shows more pronounced impact by averting more than a million all-cause  
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37 314 LRTIs during the 10-year period. ICER estimates under this scenario were \$896 for the maternal vaccine  
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39 315 (range \$34 to \$7,602) and \$889 for the mAb (range \$33 to \$7,608) per DALY averted across all  
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41 316 countries, with 116 countries (69 Gavi-eligible and 47 non-Gavi countries) demonstrating ICERs less  
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43 317 than 50% of their respective GDP per capita. We refrained from directly comparing these estimates to  
44  
45 318 other scenarios as they use data sources [21] not comparable with the primary disease burden data [2]  
46  
47 319 used in other scenarios.

48  
49 320 There are several additional limitations worth citing. There is a dearth of RSV disease burden data,  
50  
51 321 especially regarding the age distribution of disease in young infants in LMICs. Although we used the best  
52  
53 322 published estimates of RSV disease burden in children [2], the literature is expanding rapidly. For  
54  
55 323 example, studies from Zambia [40] and Argentina [41] highlight that community mortality and deaths  
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3 324 from RSV could be as high as 10% and 11% of all-cause deaths occurring among infants up to six months  
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5 325 of age. This highlights a large and underappreciated burden of RSV and would mean our estimates of  
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7 326 impact and effectiveness are conservative. Although we attempted to quantify the potential benefits of  
8  
9 327 RSV interventions with additional scenario analysis, lack of consistent input data coupled with poorly  
10  
11 328 established age distribution limits the comparability of our results across these scenarios. Collecting more  
12  
13 329 granular data on disease burden is critical to inform future studies [32].

14  
15 330 The products evaluated in this study are not yet available in the market so other key parameters are  
16  
17 331 unknown. We assumed the same price for both interventions, which may not hold, as historical evidence  
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19 332 suggests mAbs are likely to be more expensive to produce than a vaccine [5]. This could have  
20  
21 333 considerable impact on the ICERs and comparisons between products. Nonetheless, our analysis shows  
22  
23 334 that the mAb is more cost-effective than a maternal vaccine at baseline efficacy and duration of protection  
24  
25 335 values, until a mAb reaches approximately three times the baseline price assumption. Gavi evaluated both  
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27 336 interventions for inclusion in its 2018 Vaccine Investment Strategy in anticipation of the potential  
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29 337 benefits, and they are expected to be included in the Gavi portfolio, subject to licensure, prequalification,  
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31 338 and affordability. In that case, the eligible Gavi countries would benefit from a considerable subsidy for  
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33 339 access and affordability, especially the countries with the lowest GDPs per capita. Further, the <50% of  
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35 340 GDP per capita thresholds used in this paper are non-specific measures of cost-effectiveness, especially  
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37 341 when intervention prices to be paid by individual Gavi-supported countries are not yet known. Country-  
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39 342 specific thresholds are recommended [42] but often do not exist for most LMICs. In the absence of  
40  
41 343 country-specific thresholds, we used a conservative metric uniform across all countries to define cost-  
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43 344 effectiveness.

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45 345 Lastly, RSV infection is seasonal in many countries. We did not consider seasonal delivery in this  
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47 346 analysis. Seasonal intervention could potentially be a more cost-effective yet feasible strategy [31],  
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49 347 especially when using mAbs to selectively immunize children before the start of the RSV season.

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51 348 Delivering maternal vaccine seasonally to pregnant woman in LMICs may be more challenging due to the  
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349 lack of a defined maternal vaccine delivery strategy. Future research should explore the feasibility of  
350 alternative delivery strategies.

351

## 352 **Conclusions**

353 RSV interventions evaluated in this study are projected to be impactful and cost-effective across many  
354 LMICs. Under the assumptions used, mAbs are comparatively more impactful and cost-effective than  
355 RSV maternal vaccines. However, we reiterate the uncertainty around several critical parameters that  
356 inform this finding. The emerging evidence of RSV's role in all LRTI deaths among young infants  
357 suggests our analyses of RSV burden averted may prove conservative and enhance the attractiveness of  
358 RSV interventions as important tools for curbing LRTI mortality in infants. As disease burden shifts  
359 toward neonates and very young children, RSV maternal immunization and mAbs offer the opportunity to  
360 protect young infants from disease. As RSV interventions complete clinical development and the  
361 intervention characteristics and market prices becomes more definitive, future analysis will provide  
362 additional clarity on the anticipated health and economic impacts of these interventions.

363

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368

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371

## 372 **Author contributions**



373 CP, DH and RB conceptualized the study. RB and CP developed the model. RB performed the analysis.

374 RB and CP wrote the first draft of the paper. DH and KR reviewed and edited the manuscript.

375

### 376 **Declaration of interest statement**

377 All authors declare no conflict of interest.

378

### 379 **Ethics approval**

380 Not required.

381

### 382 **Data sharing statement**

383 All data relevant to the study are included in the article or uploaded as supplementary

384 information.

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3 **518 Figure captions**  
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5 519 Figure 1. Incremental cost-effectiveness ratios as a percentage of national GDP per capita, maternal  
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15 523 Figure 3. Impact of change in key input parameter values on deaths averted.  
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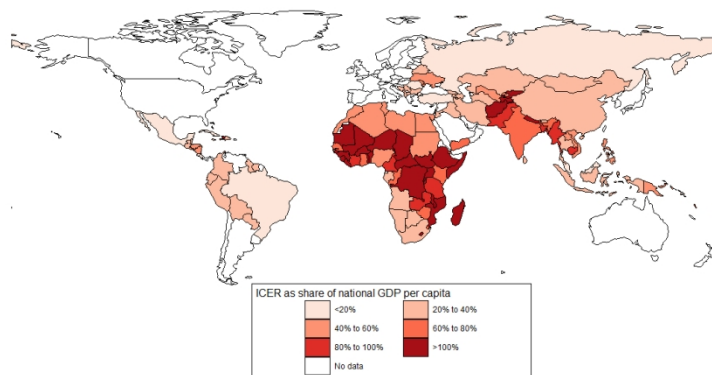


Figure 1: Incremental cost-effectiveness ratios as a percentage of national GDP per capita, maternal vaccine.

524x202mm (72 x 72 DPI)

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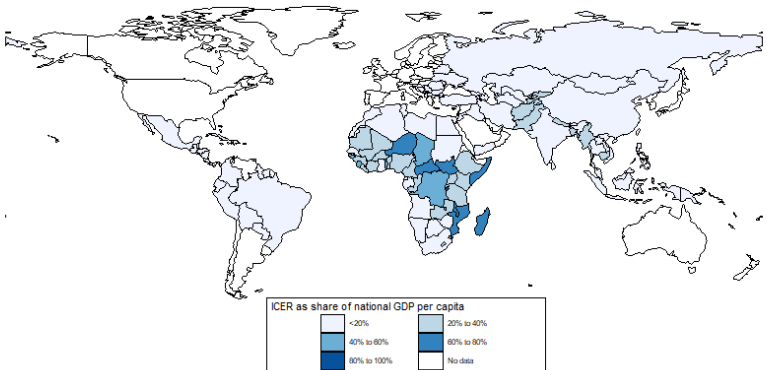


Figure 2: Incremental cost-effectiveness ratios as a percentage of national GDP per capita, monoclonal antibody.

358x138mm (72 x 72 DPI)



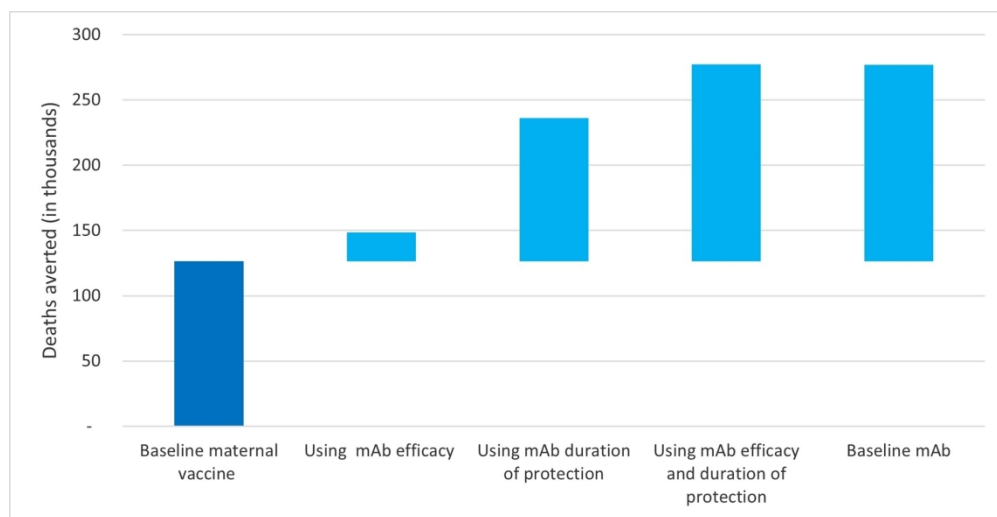


Figure 3. Impact of change in key input parameter values on deaths averted.

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Figure 3. Average incremental cost-effectiveness ratios by country groups.

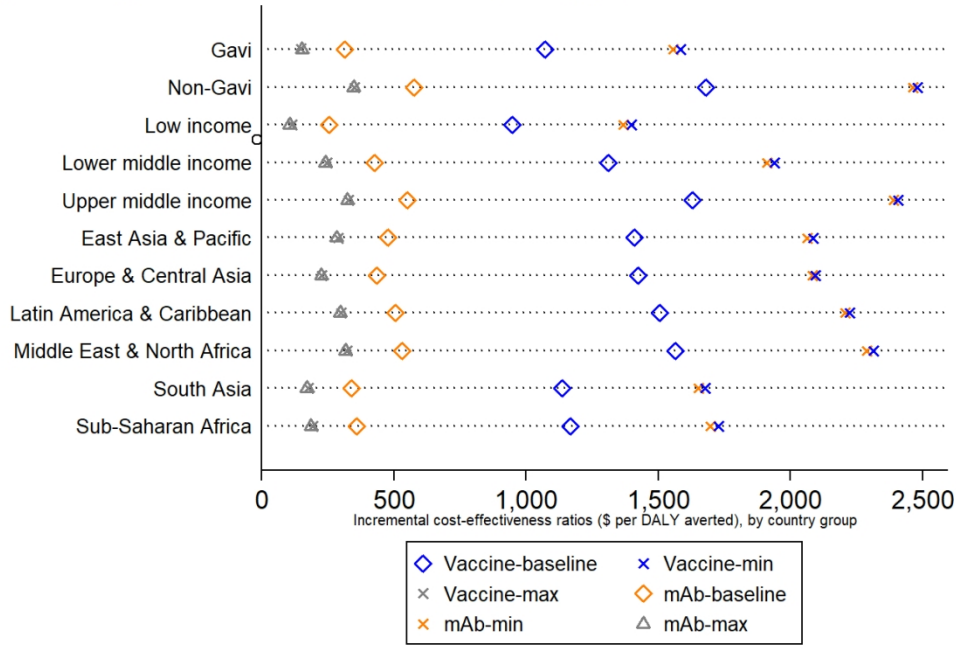


Figure 4 here: Average incremental cost-effectiveness ratios by country groups.

473x344mm (72 x 72 DPI)

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**Appendix Table 1. Cost of intervention and incremental cost-effectiveness ratios by country group (2030–2039).**

Country group by	Maternal vaccine			Monoclonal antibody		
	Health care cost averted	Cost of vaccination program	ICER per DALY averted	Health care cost averted	Cost of vaccination program	ICER per DALY averted
<b>Gavi status</b>						
Gavi (N=73)	397,985,940	3,065,106,927	1,073	1,311,275,193	3,028,242,872	315
Non-Gavi (N=58)	204,118,914	2,398,496,379	1,681	663,227,127	2,355,785,836	577
<b>World Bank Country income group</b>						
LIC (N=34)	131,178,798	886,636,675	949	420,421,498	867,885,189	257
LMIC (N=46)	299,612,949	2,557,430,903	1,311	995,875,548	2,522,516,388	428
UMIC (N=51)	171,313,107	2,019,535,727	1,631	558,205,274	1,993,627,132	551
<b>Geographic region</b>						
East Asia & Pacific (N=20)	124,384,911	1,411,293,535	1,411	392,896,831	1,380,338,857	479
Europe & Central Asia (N=20)	32,220,016	301,556,780	1,425	109,878,013	295,554,675	437
Latin America & Caribbean (N=23)	46,562,615	515,567,727	1,507	146,732,622	492,924,565	507
Middle East & North Africa (N=13)	45,216,714	496,642,134	1,566	154,303,356	504,915,613	532
South Asia (N=8)	155,092,982	1,187,286,456	1,138	558,355,660	1,236,166,379	342
Sub-Saharan Africa (N=47)	198,627,617	1,551,256,674	1,169	612,335,839	1,474,128,619	359
<b>Total (N=131)</b>	<b>602,104,854</b>	<b>5,463,603,306</b>	<b>1,342</b>	<b>1,974,502,320</b>	<b>5,384,028,709</b>	<b>431</b>

Abbreviations: DALY, disability-adjusted life year; ICER, incremental cost-effectiveness ratio; LIC, low-income country; LMIC, low- and middle-income country; UMIC, upper-middle-income country.

**Appendix Table 2. Incremental cost-effectiveness ratio per disability-adjusted life year (DALY) averted as a percentage of gross domestic product (GDP) per capita across various scenarios.**

Scenarios		Maternal vaccine					Monoclonal antibody						
		Baseline	Baseline low price	Baseline high price	Minimum	Maximum	Adjuvant	Baseline	Baseline low price	Baseline high price	Minimum	Maximum	Adjuvant
Efficacy (%)		Trial (40%–60%)	Trial (40%–60%)	Trial (40%–60%)	30	90	Trial (25%–39%)	60%–70%	60%–70%	60%–70%	30	90	Trial (25%–39%)
Duration of Protection (months)		3	3	3	4	6	6	6	6	6	4	6	6
Intervention cost (Gavi/non-Gavi)		\$3/\$5	\$1.5/\$2.5	\$6/\$10	\$3/\$5	\$3/\$5	\$3/\$5	\$3/\$5	\$1.5/\$2.5	\$6/\$10	\$3/\$5	\$3/\$5	\$3/\$5
Afghanistan	1	163%	82%	325%	240%	16%	7%	41%	5%	113%	23%	15%	7%
Albania		37%	21%	69%	55%	6%	17%	11%	4%	26%	55%	6%	17%
Algeria		43%	25%	79%	64%	10%	35%	15%	7%	31%	63%	9%	35%
Angola	1	36%	23%	63%	54%	7%	4%	12%	6%	24%	53%	7%	4%
Armenia	1	31%	20%	55%	47%	6%	14%	10%	5%	21%	47%	6%	14%
Azerbaijan	1	30%	19%	52%	44%	5%	2%	9%	4%	19%	44%	5%	2%
Bangladesh	1	83%	52%	145%	123%	15%	8%	27%	13%	55%	12%	15%	8%
Belarus		32%	18%	59%	46%	4%	105%	9%	3%	21%	46%	4%	104%
Belize		34%	20%	63%	51%	7%	12%	12%	5%	25%	50%	7%	12%
Benin	1	122%	63%	240%	181%	20%	11%	37%	11%	90%	17%	19%	11%
Bhutan	1	40%	25%	70%	59%	7%	8%	12%	6%	26%	58%	7%	8%
Bolivia	1	36%	23%	63%	54%	6%	7%	11%	5%	23%	53%	6%	7%
Bosnia & Herzegovina		33%	19%	61%	48%	5%	156%	10%	3%	23%	48%	5%	156%
Botswana		26%	15%	47%	39%	7%	10%	10%	5%	19%	38%	7%	10%

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Brazil		19%	11%	35%	28%	4%	11%	7%	3%	14%	28%	4%	11%
Bulgaria		22%	13%	40%	32%	4%	19%	7%	3%	15%	32%	4%	18%
Burkina Faso	1	158%	80%	315%	233%	17%	10%	43%	7%	114%	232%	17%	10%
Burundi	1	333%	168%	663%	490%	33%	27%	86%	12%	235%	484%	31%	27%
Cambodia	1	90%	56%	157%	133%	14%	7%	27%	12%	58%	132%	14%	7%
Cameroon	1	93%	59%	162%	139%	19%	11%	31%	16%	61%	134%	18%	11%
Cape Verde		56%	33%	102%	83%	13%	25%	20%	9%	40%	81%	12%	24%
C.A. Rep.	1	260%	133%	513%	386%	40%	9%	76%	20%	188%	372%	37%	9%
Chad	1	148%	76%	291%	220%	25%	7%	44%	13%	107%	211%	22%	7%
China		21%	12%	38%	31%	5%	13%	8%	4%	15%	31%	5%	13%
Colombia		28%	16%	51%	41%	6%	16%	10%	5%	21%	41%	6%	16%
Comoros	1	75%	38%	148%	111%	10%	9%	20%	4%	52%	102%	9%	9%
Congo	1	71%	45%	123%	106%	15%	14%	25%	13%	49%	100%	15%	14%
Costa Rica		14%	8%	26%	21%	3%	27%	5%	2%	10%	21%	3%	27%
Cuba	1	13%	8%	23%	18%	0%	22%	2%	0%	7%	19%	0%	22%
Côte d'Ivoire	1	86%	55%	150%	128%	16%	7%	28%	14%	57%	122%	16%	7%
N. Korea	1												
D. Rep. Congo	1	212%	109%	419%	314%	30%	14%	59%	14%	150%	302%	27%	13%
Djibouti	1	61%	38%	108%	90%	7%	11%	16%	5%	37%	88%	6%	11%
Dominican Republic		25%	14%	45%	37%	5%	8%	9%	4%	18%	36%	5%	8%
Ecuador		27%	16%	49%	40%	6%	10%	10%	5%	20%	40%	6%	10%
Egypt		50%	29%	92%	74%	11%	8%	18%	8%	37%	74%	11%	8%
El Salvador		44%	26%	81%	66%	9%	22%	15%	7%	32%	64%	9%	21%
Equatorial Guinea		20%	12%	37%	30%	5%	4%	7%	4%	15%	30%	5%	4%
Eritrea	1												
Ethiopia	1	127%	65%	251%	188%	18%	15%	37%	9%	93%	182%	17%	15%
Fiji		34%	20%	63%	51%	8%	9%	12%	6%	25%	50%	8%	9%
Gabon		26%	15%	47%	38%	5%	5%	9%	4%	18%	37%	5%	5%
Gambia	1	130%	65%	260%	191%	10%	19%	32%	3%	91%	192%	10%	18%
Georgia	1	30%	19%	53%	45%	5%	42%	9%	4%	20%	44%	5%	41%

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Grenada		17%	10%	31%	25%	4%	8%	6%	3%	12%	25%	4%	8%
Guatemala		40%	24%	74%	60%	9%	5%	15%	7%	30%	60%	9%	5%
Guinea	1	134%	68%	265%	199%	20%	8%	40%	10%	99%	19%	19%	8%
Guinea-Bissau	1	147%	75%	291%	218%	21%	20%	43%	10%	108%	21%	20%	19%
Guyana	1	25%	16%	44%	37%	3%	10%	7%	3%	15%	36%	3%	9%
Haiti	1	123%	62%	246%	181%	10%	8%	28%	1%	83%	17%	8%	8%
Honduras	1	47%	29%	82%	69%	7%	44%	14%	6%	30%	68%	7%	43%
India	1	65%	41%	114%	96%	9%	6%	19%	7%	41%	95%	8%	6%
Indonesia	1	32%	20%	57%	48%	5%	8%	10%	4%	21%	48%	5%	8%
Iran		32%	19%	59%	47%	7%	29%	11%	5%	23%	47%	7%	29%
Iraq		38%	22%	70%	56%	8%	18%	13%	6%	27%	55%	8%	18%
Jamaica		34%	20%	63%	51%	7%	36%	12%	5%	25%	50%	7%	35%
Jordan		41%	24%	74%	60%	8%	20%	13%	6%	29%	59%	8%	19%
Kazakhstan		22%	13%	41%	32%	4%	10%	7%	2%	15%	32%	3%	10%
Kenya	1	81%	51%	141%	120%	13%	8%	25%	11%	52%	11%	12%	8%
Kiribati	1	76%	48%	132%	113%	13%	23%	24%	12%	50%	11%	13%	23%
Kyrgyzstan	1	106%	67%	184%	157%	20%	34%	35%	17%	70%	15%	20%	33%
Lao PDR	1	51%	32%	88%	76%	10%	3%	16%	8%	33%	73%	9%	2%
Lebanon		19%	11%	34%	27%	4%	54%	6%	3%	13%	27%	4%	53%
Lesotho	1	121%	76%	211%	179%	19%	10%	36%	16%	76%	17%	18%	10%
Liberia	1	130%	66%	258%	192%	15%	17%	35%	7%	93%	18%	15%	16%
Libya		40%	24%	74%	60%	8%	109%	14%	6%	29%	59%	8%	108%
Madagascar	1	234%	120%	462%	346%	33%	14%	66%	16%	167%	33%	30%	14%
Malawi	1	307%	154%	614%	449%	21%	36%	70%	1%	207%	43%	18%	35%
Malaysia		17%	10%	32%	26%	4%	27%	6%	3%	13%	26%	4%	27%
Maldives		16%	9%	29%	23%	4%	52%	6%	3%	12%	23%	4%	52%
Mali	1	125%	65%	247%	186%	21%	12%	39%	11%	93%	18%	20%	12%
Mauritania	1	117%	74%	203%	174%	24%	15%	38%	19%	76%	16%	22%	15%
Mauritius		17%	10%	31%	25%	4%	18%	6%	3%	13%	25%	4%	18%
Mexico		20%	11%	36%	29%	4%	11%	7%	3%	14%	29%	4%	11%
Micronesia		55%	32%	100%	81%	13%	23%	20%	10%	40%	81%	13%	23%
Mongolia	1	33%	21%	57%	48%	6%	4%	11%	5%	21%	48%	6%	4%

Montenegro		23%	13%	42%	33%	3%	108%	7%	2%	15%	33%	3%	108%
Morocco		58%	34%	106%	85%	12%	24%	20%	9%	41%	84%	12%	24%
Mozambique	1	245%	124%	487%	361%	28%	34%	67%	12%	177%	366%	27%	34%
Myanmar	1	98%	62%	169%	144%	18%	9%	32%	16%	64%	144%	18%	9%
Namibia		39%	23%	72%	58%	9%	7%	14%	6%	29%	58%	9%	7%
Nepal	1	109%	54%	221%	160%	3%	11%	23%	-2%	73%	156%	3%	11%
Nicaragua	1	52%	33%	91%	77%	8%	15%	16%	7%	33%	76%	8%	15%
Niger	1	266%	135%	529%	392%	29%	20%	68%	10%	185%	379%	26%	19%
Nigeria	1	63%	40%	109%	93%	14%	3%	21%	11%	42%	91%	13%	3%
Pakistan	1	86%	54%	151%	127%	13%	9%	24%	10%	52%	126%	11%	8%
Papua New Guinea	1	51%	33%	89%	76%	10%	8%	17%	8%	34%	75%	10%	8%
Paraguay		31%	18%	57%	46%	6%	23%	10%	5%	22%	45%	6%	23%
Peru		27%	16%	50%	40%	6%	9%	10%	5%	20%	40%	6%	9%
Philippines		58%	34%	106%	85%	12%	10%	20%	9%	42%	85%	12%	10%
Republic of Moldova	1	58%	37%	102%	86%	9%	12%	18%	8%	38%	86%	9%	12%
Romania		17%	10%	31%	25%	3%	7%	5%	2%	12%	25%	3%	7%
Russian Federation		19%	11%	35%	28%	3%	25%	6%	2%	13%	28%	3%	25%
Rwanda	1	127%	65%	252%	188%	15%	16%	34%	6%	90%	183%	14%	15%
Saint Lucia		18%	10%	33%	26%	4%	13%	6%	3%	13%	26%	4%	13%
St. Vincent & Grenad.		23%	14%	43%	35%	5%	11%	8%	4%	17%	35%	5%	11%
Samoa		45%	26%	81%	66%	11%	26%	16%	8%	33%	65%	11%	26%
S. Tome & Principe	1	68%	43%	118%	100%	11%	13%	20%	9%	43%	98%	10%	13%
Senegal	1	73%	37%	146%	108%	7%	10%	19%	3%	52%	109%	7%	10%
Serbia		29%	17%	55%	43%	4%	114%	8%	3%	20%	43%	4%	113%
Sierra Leone	1	194%	97%	388%	285%	15%	11%	47%	3%	134%	289%	14%	10%
Solomon Islands	1	60%	38%	105%	89%	11%	15%	19%	9%	38%	86%	10%	15%
Somalia	1	217%	113%	425%	323%	41%	17%	69%	23%	161%	316%	38%	16%

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South Africa		33%	19%	61%	49%	7%	8%	11%	5%	24%	48%	7%	7%
South Sudan	1	396%	196%	797%	580%	20%	14%	85%	-4%	264%	56%	17%	14%
Sri Lanka	1	30%	19%	52%	44%	6%	67%	10%	5%	20%	44%	6%	66%
State of Palestine		59%	35%	108%	89%	16%	124%	23%	12%	45%	88%	16%	123%
Sudan	1	51%	32%	89%	75%	9%	9%	16%	8%	33%	74%	9%	9%
Suriname		30%	18%	55%	44%	7%	10%	11%	5%	22%	44%	6%	10%
Swaziland		64%	38%	117%	95%	14%	7%	23%	11%	47%	95%	14%	7%
Syria													
Macedonia		31%	18%	57%	45%	4%	45%	9%	3%	21%	45%	4%	44%
Tajikistan	1	116%	60%	230%	172%	16%	7%	34%	8%	85%	17%	16%	7%
Thailand		28%	16%	51%	41%	6%	32%	10%	5%	20%	41%	6%	32%
Timor-Leste	1	60%	38%	104%	89%	11%	7%	19%	9%	38%	86%	10%	7%
Togo	1	162%	82%	321%	239%	19%	22%	44%	8%	115%	23%	18%	21%
Tonga		47%	28%	86%	70%	11%	24%	17%	8%	35%	69%	11%	23%
Tunisia		46%	27%	84%	68%	10%	83%	16%	8%	33%	67%	10%	83%
Turkey		15%	9%	27%	22%	3%	25%	5%	2%	11%	22%	3%	25%
Turkmenistan		27%	16%	50%	40%	5%	4%	9%	4%	19%	40%	5%	4%
Uganda	1	157%	78%	315%	230%	9%	29%	35%	0%	105%	22%	8%	29%
Ukraine	1	52%	33%	90%	76%	8%	89%	16%	7%	33%	76%	8%	89%
Tanzania	1	103%	52%	203%	151%	12%	10%	27%	5%	72%	14%	11%	10%
Uzbekistan	1	56%	35%	97%	83%	10%	5%	18%	9%	37%	82%	10%	5%
Vanuatu		62%	37%	113%	92%	15%	10%	23%	11%	46%	91%	15%	10%
Venezuela													
Viet Nam	1	51%	32%	89%	75%	9%	21%	16%	8%	34%	75%	9%	21%
Yemen	1	69%	35%	137%	102%	10%	13%	20%	5%	50%	10%	9%	13%
Zambia	1	99%	62%	173%	146%	15%	11%	29%	13%	62%	14%	14%	11%
Zimbabwe	1	74%	37%	146%	109%	9%	5%	21%	4%	54%	10%	9%	5%

Note: Country by Gavi status (Gavi country = 1). Current GDP values were not available for 4 countries (Venezuela, Syria, Eretria, North Korea)

and were excluded from the analysis.

\*Negative cost-effectiveness ratio implies cost savings.



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Cells in green indicate lower ICER to GDP ratio and cells in red indicate higher ICER to GDP ratio.

For peer review only

**CHEERS Checklist****Items to include when reporting economic evaluations of health interventions**

The **ISPOR CHEERS Task Force Report**, *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force*, provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: <http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp>

Section/item	Item No	Recommendation	Reported on page No/line No
<b>Title and abstract</b>			
Title	1	Identify the study as an economic evaluation or use more specific terms such as “cost-effectiveness analysis”, and describe the interventions compared.	1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	2
<b>Introduction</b>			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	4
<b>Methods</b>			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	5, 7
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	5
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	5
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	5
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	5
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	10
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	5
Measurement of effectiveness	11a	<i>Single study-based estimates:</i> Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	NA



1		11b	<i>Synthesis-based estimates:</i> Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	9
2				NA
3				
4	Measurement and	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	
5	valuation of preference			
6	based outcomes			
7				
8	Estimating resources	13a	<i>Single study-based economic evaluation:</i> Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	NA
9	and costs			
10				
11		13b	<i>Model-based economic evaluation:</i> Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	9,10
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16	Currency, price date,	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	5
17	and conversion			
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28	Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	5
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32	Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	7-9
33				
34	Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	9-10
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42	<b>Results</b>			
43	Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	12-14
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49	Incremental costs and	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	13-14
50	outcomes			
51				
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54	Characterising	20a	<i>Single study-based economic evaluation:</i> Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact	NA
55	uncertainty			
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1		of methodological assumptions (such as discount rate, study perspective).	
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4	20b	<i>Model-based economic evaluation</i> : Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	14-16
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6			
7	Characterising heterogeneity	21	
8		If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	Figures 3-4, Appendix table 2
9			
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13	<b>Discussion</b>		
14	Study findings, limitations, generalisability, and current knowledge	22	
15		Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	15-17
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19	<b>Other</b>		
20	Source of funding	23	
21		Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	18
22			
23			
24	Conflicts of interest	24	
25		Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	19
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For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

The **ISPOR CHEERS Task Force Report** provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: <http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp>

The citation for the CHEERS Task Force Report is:

Husereau D, Drummond M, Petrou S, et al. Consolidated health economic evaluation reporting standards (CHEERS)—Explanation and elaboration: A report of the ISPOR health economic evaluations publication guidelines good reporting practices task force. *Value Health* 2013;16:231-50.

