# THE LANCET **Infectious Diseases**

# **Supplementary appendix**

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Li Y, Hodgson D, Wang X, Atkins KE, Feikin DR, Nair H. Respiratory syncytial virus seasonality and prevention strategy planning for passive immunisation of infants in low-income and middle-income countries: a modelling study. *Lancet Infect Dis* 2021; published online May 6. https://doi.org/10.1016/ S1473-3099(20)30703-9.

# **Contents**





# <span id="page-3-0"></span>List of low and middle income countries (LMIC)

The list of low and middle income countries are extracted from the World Bank Classifications by Income.1

#### <span id="page-3-1"></span>Low-income economies



# <span id="page-3-2"></span>Lower-middle economies



# <span id="page-4-0"></span>Upper-middle economies



# <span id="page-5-0"></span>Detailed description of data included in the analysis

### <span id="page-5-1"></span>RSV activity data

Available RSV monthly activity data in LMICs were obtained from three sources, including systematic literature review, online datasets and RSV Global Epidemiology Network (RSV GEN), as detailed previously.<sup>2</sup> We updated the literature search to the end of 2019 using the previous search strategy<sup>2</sup> to capture new RSV studies published between  $1<sup>st</sup>$  January 2018 and 31<sup>st</sup> December 2019. The literature review update was conducted by YL and XW, independently. We revisited our previous RSV seasonality dataset<sup>2</sup> to identify any data records that had available RSV activity data for three or more consecutive years for the multi-year analysis of this study. Detailed selection criteria for RSV activity data are attached below.

### <span id="page-5-2"></span>Inclusion criteria

- Laboratory-confirmed cases
- Number of RSV positives cases aggregated at least on a monthly basis
- At least 25 RSV positive cases per year
- Data available for at least consecutive 12 months, or at least consecutive 36 months for multi-year analysis

### <span id="page-5-3"></span>Exclusion criteria

- RSV data from only patients with comorbidities
- RSV data from only hospital-acquired infections

### <span id="page-5-4"></span>Results of updated literature review

After removal of duplicates, a total of 3000 publications were screened by title and abstract, and subsequently 269 full-text articles were screened. A total of 16 studies<sup>3-18</sup> (including data from 11 countries of which 6 were new) had eligible RSV seasonality data for LMICs (PRISMA flowchart on Page 4). Details of these studies are presented below (Page 5).

The 16 new studies were assessed for data quality, and data were extracted as described previously.2



**PRISMA flowchart showing the search and selection of studies for the updated literature review**  (contextualising the previous published systematic review<sup>2</sup>). Other reasons for exclusion include subset of online reports (2), no full-text (1), outbreak investigation data only (1) and review (1).



#### **Summary of studies reporting RSV seasonality in LMICs from the literature update**

ARI = acute respiratory infection; SARI = severe acute respiratory infection; ILI = influenza-like illness; ALRI = acute lower respiratory infection; PCR =

polymerase chain reaction; NA = not available

### <span id="page-8-0"></span>RSV burden data

The RSV burden data among infants in LMICs (as one region) were obtained from our previously published RSV global burden estimates.<sup>19</sup> The data were available in the following age groups: <28 days, 1–<3 months, 3–<6 months, 6–<9 months and 9–<12 months; and by two outcomes: RSV-ALRI incidence rate in the community and RSV-ALRI hospitalisation rate. For the present study, we used the aggregated regional level percentage of RSV cases among infants <1y for each group as the model input (as shown in the table below).



#### **Model input of RSV incidence data**

For each outcome, the percentage results add up to 100% across age groups.

#### <span id="page-8-1"></span>RSV prophylactic coverage data

For monoclonal antibody immunisation, data on BCG and Hepatitis B vaccines coverage were included from the World Health Organization (WHO).<sup>20</sup> The average coverage between the two vaccines was calculated for each country. If coverage was missing for one vaccine for a country, then the coverage of the other vaccine was used.

As limited data were available on the maternal influenza vaccine coverage in LMICs, we used the WHO ANC4+ indicator for the maternal vaccine coverage, defined as the percentage of women aged 15-49 with a live birth who received antenatal care (ANC) four or more times.<sup>21</sup> WHO did not report a separate indicator for each of the ANC visits.

#### <span id="page-8-2"></span>Efficacy data

We used the ResVax efficacy data from its phase 3 clinical trial results among third-trimester pregnant women: 39·4% (95% CI: 5·3–61·2) for medically significant RSV-ALRI and 44·4% (95% CI: 19·6–61·5) for RSV-ALRI hospitalisation by day 90 after birth.<sup>22</sup> We used the Nirsevimab efficacy data from its phase 2b clinical trial results among healthy preterm infants: 70·1% (95% CI: 52·3–81·2) for medically attended RSV-ALRI and 78·4% (95% CI: 51·9–80·3) for RSV-ALRI hospitalisation by day 150 after inoculation.<sup>23</sup>

# <span id="page-9-0"></span>Details on the candidate seasonal approaches

### <span id="page-9-1"></span>mAb

- Seasonal approach A: mAb being administered in each epidemic month
- Seasonal approach B: mAb being administered in each month if there are two or more epidemic months among that month and the following two months (i.e. three months in total), allowing advanced administration by up to one month
- Seasonal approach C: mAb being administered in each month if there are two or more epidemic months among that month and the following three months (i.e. four months in total), allowing advanced administration by up to two months
- Seasonal approach D: mAb being administered in each month if there are two or more epidemic months among that month and the following four months (i.e. five months in total), allowing advanced administration by up to three months

### <span id="page-9-2"></span>Maternal vaccine

- Seasonal approach A: maternal vaccine being administered to pregnant woman whose expected date of delivery is in an epidemic month
- Seasonal approach B: maternal vaccine being administered to pregnant woman if there are two or more epidemic months among the expected month of delivery and the following two months (i.e. three months in total), allowing advanced administration by up to one month

# <span id="page-10-0"></span>Mathematical modelling

### <span id="page-10-1"></span>Notation

For simplicity, we present here the calculations for a specific country and a specific RSV outcome.





### <span id="page-10-2"></span>Calculations related to the effectiveness and relative efficiency

We calculated the proportion of monthly of incidence for age group  $a$  among annual incidence in <6 month using the formula,

$$
p^{a,m} = \frac{Z^a A P P^m}{\sum_{a=1}^6 \sum_{m=1}^{12} Z^a A P P^m}
$$

For each candidate approach *c,* we determined whether each month and age group pair *(a,m)* is protected by the prophylactic treatment. If *(a,m)* is protected then it is a "benefit group", if it is not protected then it is a "non-benefit group". Therefore, by defining an indicator function **1**c(a,m) = 1 if *(a,m)* is a benefit group and 0 otherwise, we calculated the effectiveness of a candidate approach  $(I_c)$  with coverage  $c_c$  and efficacy  $e_c$  through the formulae,

$$
I_c^{max} = \sum_{a=1}^{6} \sum_{m=1}^{12} p^{a,m} \mathbf{1}_c(a,m)
$$

$$
I_c = I_c^{max} \boldsymbol{e}_c \boldsymbol{c}_c
$$

To determine the per-dose effectiveness for each candidate approach  $(D<sub>c</sub>)$ , we calculated the ratio of the effectiveness and the number of doses given, resulting in the formula,

$$
D_c = \frac{I_c}{\mu N_c}
$$

To determine the relative efficiency (*Rc*)*,* we calculated the ratio of the per-dose effectiveness between each candidate approach and the year-round approach. That is,

For 
$$
c = \{1, ..., 5\}
$$
,  $R_c = \frac{D_c}{D_5}$ , otherwise  $R_c = \frac{D_c}{D_8}$ 

#### <span id="page-11-0"></span>Calculations related to RSV-ALRI hospitalisations by birth month

To calculate the proportion of RSV-ALRI hospitalisations in <3m by birth month, *b*, we used the formula,

$$
p_b = \frac{\sum_{a=1}^{3} p^{a,[(b+a-1) \mod 12]+1}}{\sum_{a=1}^{3} \sum_{m=1}^{12} p^{a,m}}
$$

Where  $(b + a - 1)$  mod 12 is the value of  $(b + a + 1)$  modulus 12.

# <span id="page-12-0"></span>Summary of the base case values and the values for sensitivity

# analyses



# <span id="page-13-0"></span>Supplementary tables of results



### <span id="page-13-1"></span>Table S1. Effectiveness and relative efficiency for each mAb candidate approach

Results are presented as median (IQR) among the included countries. Seasonal approach A administers mAb in each epidemic month, while seasonal approaches B–D begin administration of mAb 1, 2 and 3 months prior to the onset of the first epidemic month, respectively.

# <span id="page-13-2"></span>Table S2. Effectiveness and relative efficiency for each maternal vaccine candidate approach



Results are presented as median (IQR) among the included countries. Seasonal approach A is designed to protect infants born in each epidemic month, while seasonal approach B protects infants whose first three months of life include at least two RSV epidemic months.



# <span id="page-14-0"></span>Table S3. Effectiveness and relative efficiency for each mAb candidate approach among countries with ≤5 epidemic months, with monthly efficacy decay rate of 0.8

Results are presented as median (IQR) among the included countries. Seasonal approach A administers mAb in each epidemic month, while seasonal approaches B–D begin administration of mAb 1, 2 and 3 months prior to the onset of the first epidemic month, respectively.

## <span id="page-14-1"></span>Table S4. Effectiveness and relative efficiency for each maternal vaccine candidate approach in countries with ≤5 epidemic months, with monthly efficacy decay rate of 0.8



Results are presented as median (IQR) among the included countries. Seasonal approach A is designed to protect infants born in each epidemic month, while seasonal approach B protects infants whose first three months of life include at least two RSV epidemic months.

<span id="page-15-0"></span>Table S5. Year-to-year variations in relative effectiveness and relative efficiency for each monoclonal antibodies candidate approach in countries with ≤5 epidemic months



Results are presented as median (IQR) among all the study years. Seasonal approach A administers mAb in each epidemic month, while seasonal approaches B–D begin administration of mAb 1, 2 and 3 months prior to the onset of the first epidemic month, respectively.



# <span id="page-15-1"></span>Table S6. Year-to-year variations in the effectiveness and relative efficiency for each maternal vaccine candidate approach in countries with ≤5 epidemic months

Results are presented as median (IQR) among all the study years. Seasonal approach A is designed to protect infants born in each epidemic month, while seasonal approach B protects infants whose first three months of life include at least two RSV epidemic months.



<span id="page-16-0"></span>Table S7. Country-specific year-to-year variations in the effectiveness and relative efficiency for each monoclonal antibodies candidate approach











Countries are arranged by the duration of RSV epidemics from short (more seasonal) to long (less seasonal). Seasonal approach A administers mAb in each epidemic month, while seasonal approaches B–D begin administration of mAb 1, 2 and 3 months prior to the onset of the first epidemic month, respectively.



<span id="page-22-0"></span>Table S8. Country-specific year-to-year variations in the effectiveness and relative efficiency for each maternal vaccine candidate approach







Countries are arranged by the duration of RSV epidemics from short (more seasonal) to long (less seasonal). Seasonal approach A is designed to protect infants born in each epidemic month, while seasonal approach B protects infants whose first three months of life include at least two RSV epidemic months.

<span id="page-26-0"></span>Table S9. Year-to-year variations in relative effectiveness and relative efficiency for each monoclonal antibodies candidate approach in countries with ≤5 epidemic months, with a monthly efficacy decay rate of 0.8



Results are presented as median (IQR) among all the study years. Seasonal approach A administers mAb in each epidemic month, while seasonal approaches B–D begin administration of mAb 1, 2 and 3 months prior to the onset of the first epidemic month, respectively.

# <span id="page-26-1"></span>Table S10. Year-to-year variations in relative effectiveness and relative efficiency for each maternal vaccine candidate approach in countries with ≤5 epidemic months with a monthly efficacy decay rate of 0.8



Results are presented as median (IQR) among all the study years. Seasonal approach A is designed to protect infants born in each epidemic month, while seasonal approach B protects infants whose first three months of life include at least two RSV epidemic months.

# <span id="page-27-0"></span>Supplementary figures

<span id="page-27-1"></span>Figure S1. Schematic figure showing the workflow of the study



<span id="page-27-2"></span>Figure S2. RSV activity data availability in LMICs



LMIC: low and middle income countries. List of LMICs from the 2019 World Bank Income Classification.<sup>1</sup>



### <span id="page-28-0"></span>Figure S3. Month-by-month activity of RSV in LMICs.

AAP: annual average percentage. LMICs are arranged by latitude. The solid line denotes the equator and the dashed lines denote tropics of Cancer and Capricorn. The months 1 to 12 represent January to December.



# <span id="page-29-0"></span>Figure S4. Month-by-month activity of RSV in LMICs.

AP: annual percentage; LMICs are arranged by duration of average RSV seasonal epidemics. The months 1 to 12 represent January to December. Y-axis denotes the activity of each year with the annual average activity on the top.



#### Figure S5. Distribution of RSV-ALRI hospitalisation in infants <3m by birth month and by calendar month

<span id="page-30-0"></span>For each line, proportions of RSV-ALRI hospitalisation episodes add up to 100% across months. Countries are arranged by the duration of RSV epidemics (in months, shown next to country name).



### Figure S6. Distribution of RSV-ALRI in infants <3m by birth month and by calendar month

<span id="page-31-0"></span>For each line, proportions of RSV-ALRI episodes add up to 100% across months. Countries are arranged by the duration of RSV epidemics (in months, shown next to country name).



### <span id="page-32-0"></span>Figure S7. Dosing schedules for seasonal mAb programmes

Countries arranged by latitude. The solid line denotes the equator and the dashed lines denote tropics of Cancer and Capricorn. Shaded areas denote mAb administration months.



### <span id="page-33-0"></span>Figure S8. Dosing schedules for seasonal maternal vaccine programmes

Countries arranged by latitude. The solid line denotes the equator and the dashed lines denote tropics of Cancer and Capricorn. Shaded areas denote birth months considered for the maternal vaccine programme.



#### Figure S9. Country-specific results of effectiveness and relative efficiency in averting RSV-ALRI for monoclonal antibodies

<span id="page-34-0"></span>Number after each country indicates duration of RSV epidemics (in months). Effectiveness is defined by annual proportion averted among infants under six months of age; relative efficiency is defined by the ratio between per-dose effectiveness of a seasonal approach and that of the year-round approach. Approaches in the upper right quadrant would be considered those with optimal effectiveness and relative efficiency.



### Figure S10. Country-specific results of effectiveness and relative efficiency in averting RSV-ALRI hospitalisation for maternal vaccine

<span id="page-35-0"></span>Number after each country indicates duration of RSV epidemics (in months). Effectiveness is defined by annual proportion averted among infants under six months of age; relative efficiency is defined by the ratio between per-dose effectiveness of a seasonal approach and that of the year-round approach. Approaches in the upper right quadrant would be considered those with optimal effectiveness and relative efficiency.



### Figure S11. Country-specific results of effectiveness and relative efficiency in averting RSV-ALRI for maternal vaccine

<span id="page-36-0"></span>Number after each country indicates duration of RSV epidemics (in months). Effectiveness is defined by annual proportion averted among infants under six months of age; relative efficiency is defined by the ratio between per-dose effectiveness of a seasonal approach and that of the year-round approach. Approaches in the upper right quadrant would be considered those with optimal effectiveness and relative efficiency.



# <span id="page-37-0"></span>Figure S12. Year-to-year variations of effectiveness and relative efficiency in averting RSV-ALRI hospitalisation for monoclonal antibodies

Countries are arranged by the duration of RSV epidemics (in months, shown next to country name). Each dot represents an approach in a single year. Effectiveness is defined by annual proportion averted among infants under six months of age; relative efficiency is defined by the ratio between per-dose effectiveness of a seasonal approach and that of the year-round approach. Approaches in the upper right quadrant would be considered those with optimal effectiveness and relative efficiency. Linear relationship between effectiveness and relative efficiency within each approach and country is due to the fact that relative efficiency is a function of effectiveness and number of dosing months; the latter is a constant for each approach and country. Degree of year-on-year variations can be reflected by the distance between dots of the same colour.



<span id="page-38-0"></span>Figure S13. Year-to-year variations of effectiveness and relative efficiency in averting RSV-ALRI for monoclonal antibodies

Countries are arranged by the duration of RSV epidemics (in months, shown next to country name). Each dot represents an approach in a single year. Effectiveness is defined by annual proportion averted among infants under six months of age; relative efficiency is defined by the ratio between per-dose effectiveness of a seasonal approach and that of the year-round approach. Approaches in the upper right quadrant would be considered those with optimal effectiveness and relative efficiency. Linear relationship between effectiveness and relative efficiency within each approach and country is due to the fact that relative efficiency is a function of effectiveness and number of dosing months; the latter is a constant for each approach and country. Degree of year-on-year variations can be reflected by the distance between dots of the same colour.



### <span id="page-39-0"></span>Figure S14. Year-to-year variations of effectiveness and relative efficiency in averting RSV-ALRI hospitalisation for maternal vaccine

Countries are arranged by the duration of RSV epidemics (in months, shown next to country name). Each dot represents an approach in a single year. Effectiveness is defined by annual proportion averted among infants under six months of age; relative efficiency is defined by the ratio between per-dose effectiveness of a seasonal approach and that of the year-round approach. Approaches in the upper right quadrant would be considered those with optimal effectiveness and relative efficiency. Linear relationship between effectiveness and relative efficiency within each approach and country is due to the fact that relative efficiency is a function of effectiveness and number of dosing months; the latter is a constant for each approach and country. Degree of year-on-year variations can be reflected by the distance between dots of the same colour.



# <span id="page-40-0"></span>Figure S15. Year-to-year variations of effectiveness and relative efficiency in averting RSV-ALRI for maternal vaccine

Proportion averted among <6m

Countries are arranged by the duration of RSV epidemics (in months, shown next to country name). Each dot represents an approach in a single year. Effectiveness is defined by annual proportion averted among infants under six months of age; relative efficiency is defined by the ratio between per-dose effectiveness of a seasonal approach and that of the year-round approach. Approaches in the upper right quadrant would be considered those with optimal effectiveness and relative efficiency. Linear relationship between effectiveness and relative efficiency within each approach and country is due to the fact that relative efficiency is a function of effectiveness and number of dosing months; the latter is a constant for each approach and country. Degree of year-on-year variations can be reflected by the distance between dots of the same colour.

# <span id="page-41-0"></span>GATHER checklist



**Checklist of information that should be included in new reports of global health estimates**





# <span id="page-43-0"></span>Reference

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