RSV disease burden estimation: methodological considerations

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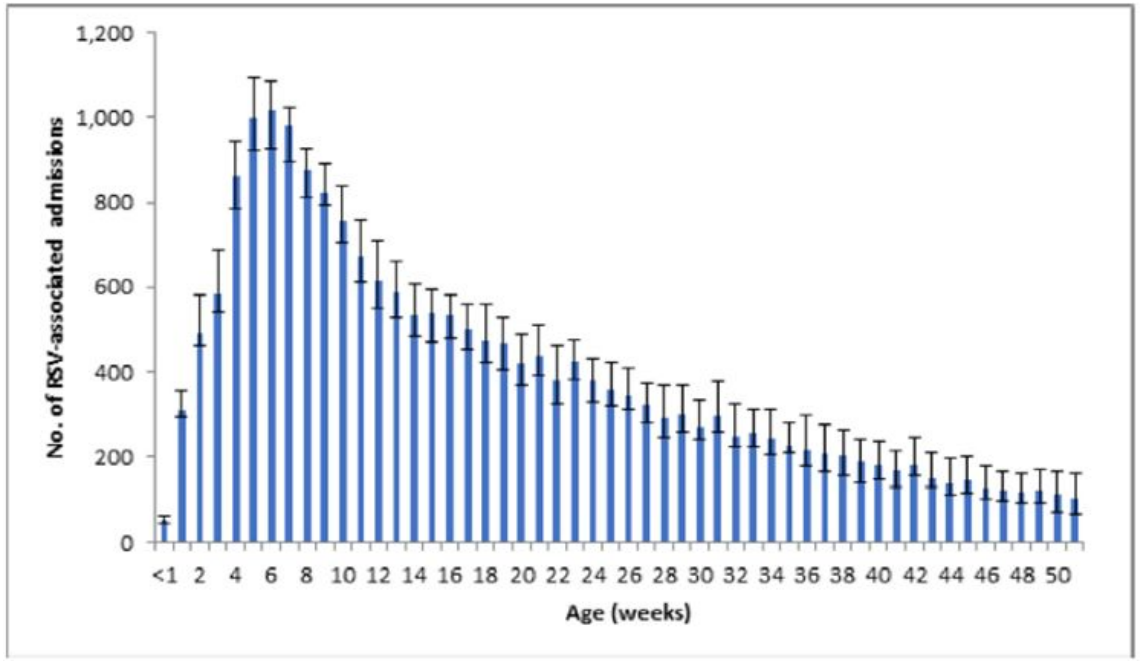
Definitions

- Acute lower respiratory infection (ALRI)
  - Community setting: WHO IMCI definition – cough or difficulty breathing with increased respiratory rate for age (e.g. >=50bpm for 2-<12m)
  - Hospital setting: physician-confirmed diagnosis of ALRI (pneumonia or bronchiolitis)
- RSV-associated ALRI: ALRI with laboratory-confirmed RSV
- RSV-attributable ALRI: ALRI causally attributable to RSV

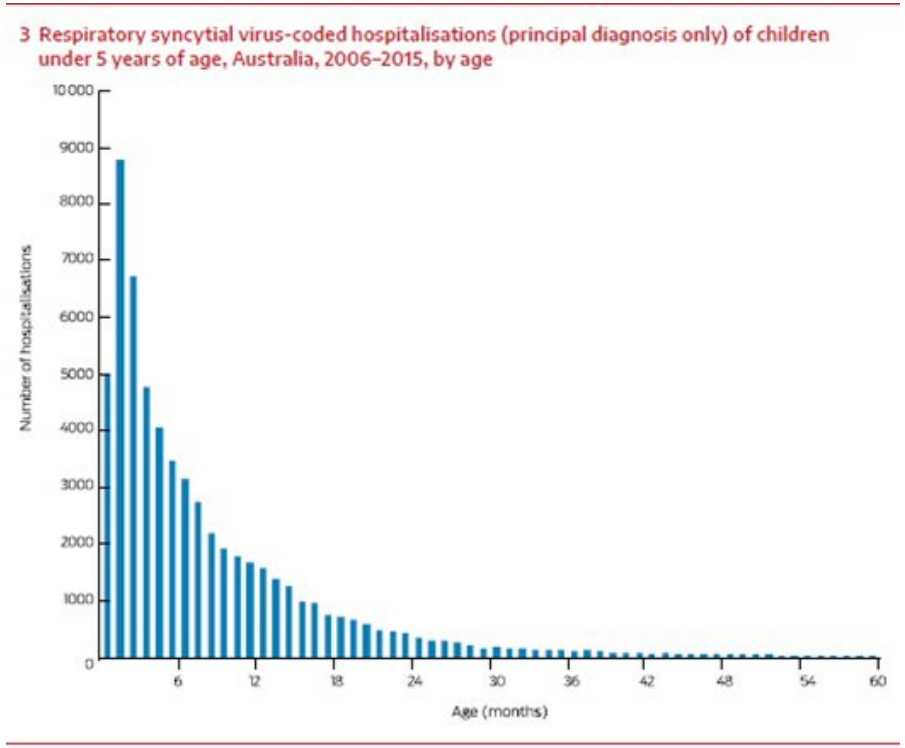
Age is the predominant risk factor

England (2010-12)



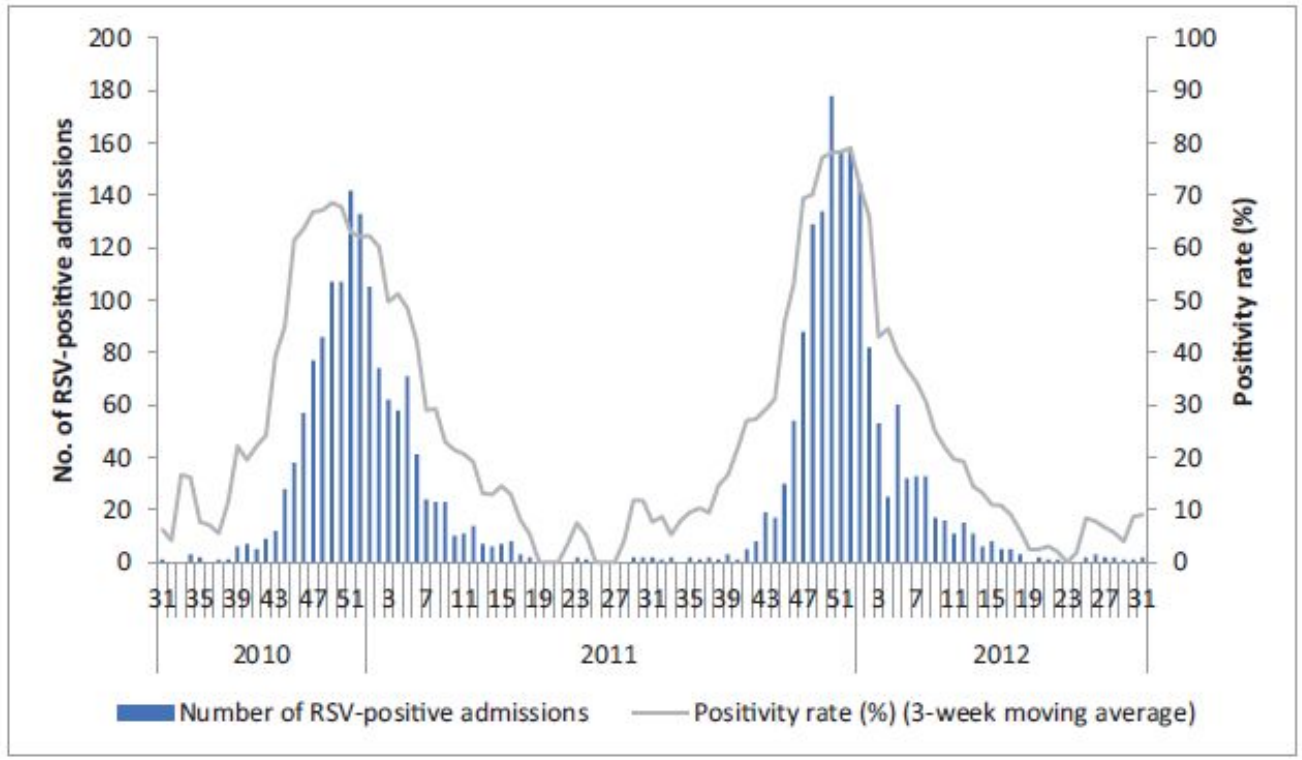
Reeves RM et al., J Infect 2019

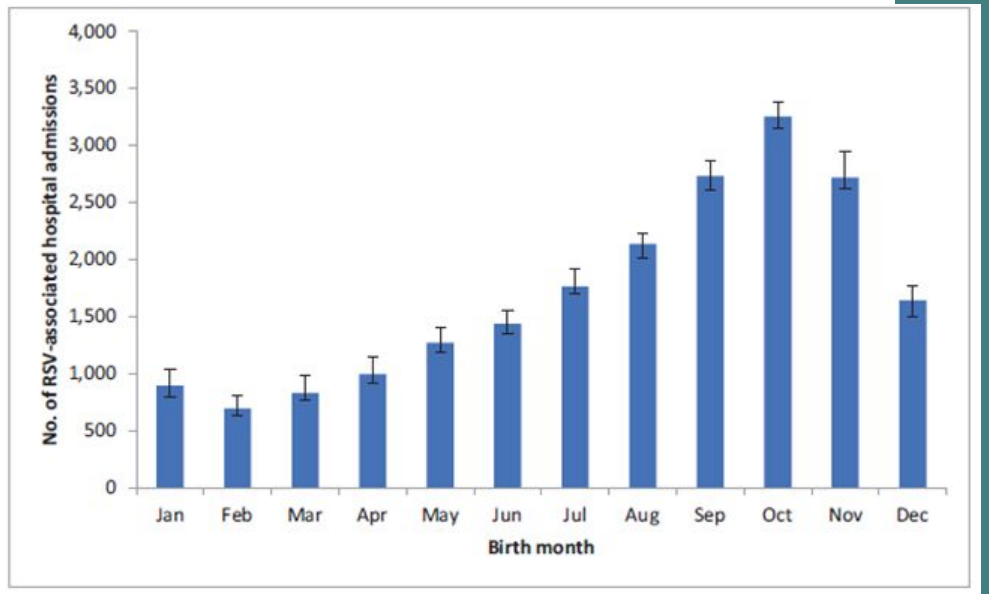
Australia (2006-15)



Saravanos GL et al., Med J Aust 2019

Relationship of birth month to RSV season





Reeves RM et al., J Infect 2019

Risk factors for RSV-ALRI

Risk factor	No. of studies	OR meta-estimate
Male sex	13	1.23 (1.19-1.28)
Maternal smoking during pregnancy	6	1.40 (1.32-1.48)
HIV-infected	4	3.74 (2.65-5.27)
Indoor air pollution	3	1.45 (1.10-1.90)
Low birth weight	3	2.07 (1.51-2.85)
Prematurity (<37wGA)	3	1.85 (1.74-1.97)
Sibling	3	1.93 (1.70-2.20)
Hemodynamically significant congenital heart disease	4	2.59 (1.07-6.26)
Bronchopulmonary dysplasia	3	1.19 (1.02-1.40)
Downs syndrome	3	3.10 (2.73-3.53)
Chronic disease	3	2.53 (2.28-2.80)

Deng S et al., RSVVW 2023

Risk factors for poor outcome in severe RSV

Poor outcome- prolonged LOS, O_2 supplementation, mechanical ventilation, ICU admission

Risk factor	#studies	OR (95% CI)
Comorbidity	5	2.69 (1.89-3.83)
Congenital heart disease	6	3.40 (2.14-5.40)
Prematurity <37wGA	6	1.75 (1.31-2.36)
Prematurity <32wGA	3	2.68 (1.43-5.04)
Age <3m	4*	4.91 (1.64-14.71)*
Age <6m	3	2.02 (1.73-2.35)

Shi T et al., J Infect Dis. 2022

Global estimates

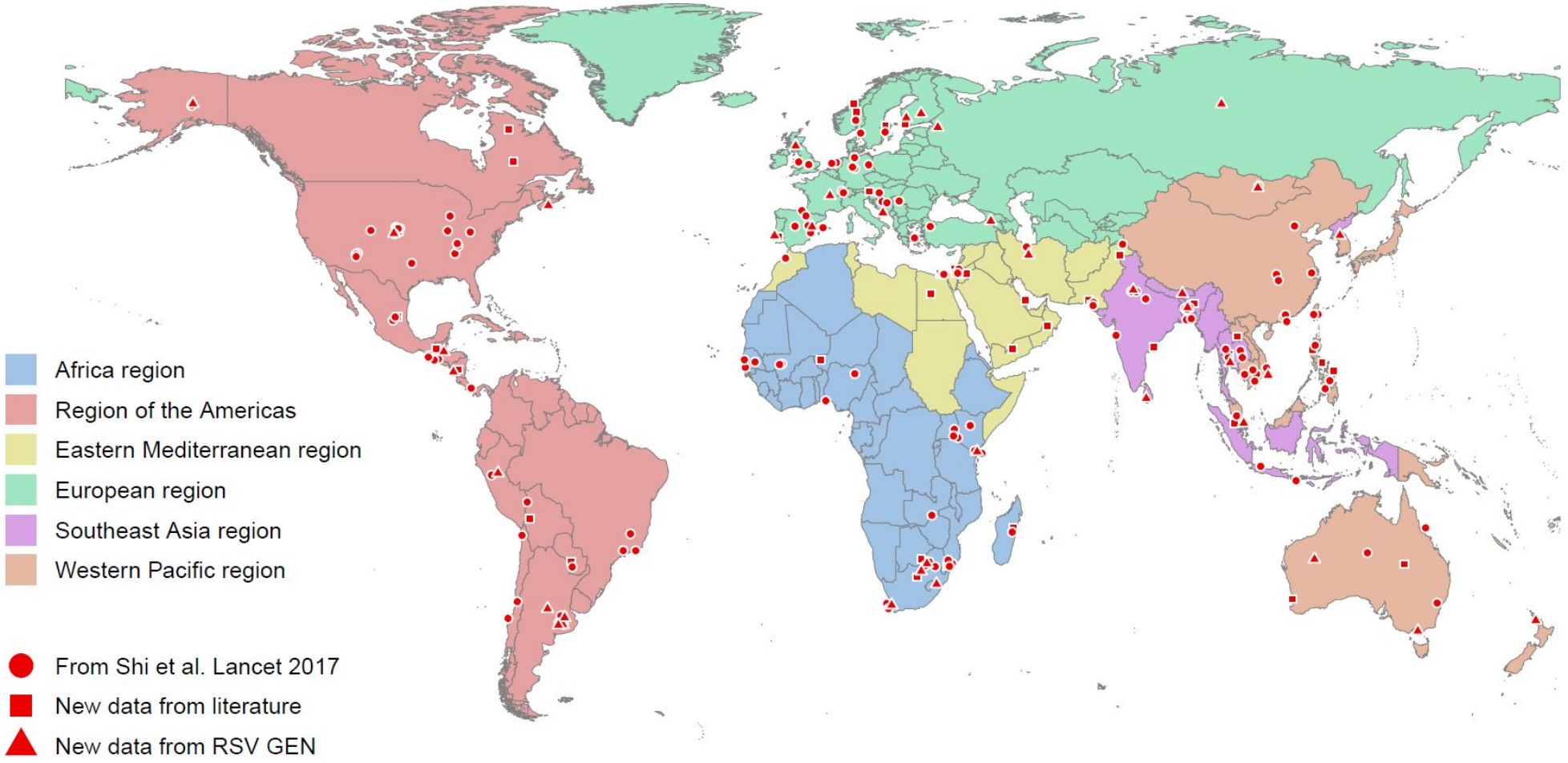
- Morbidity
  - Overall RSV-associated ALRI
    - <5y: 33.0M (25.4-44.6)
    - <6m: 6.6M (4.6-9.7)
  - RSV-associated ALRI hospitalisation
    - <5y: 3.6M (2.9-4.6)
    - <6m: 0.9M (0.5-1.9)
- Mortality
  - RSV-associated ALRI in-hospital deaths
    - <5y: 26.3K (15.1-49.1)
    - <6m: 13.3K (6.8-28.1)
  - Overall RSV-attributable deaths
    - <5y: 109.6K (97.2-124.9)
    - <6m: 45.7K (38.4-55.9)

Li Y et al., Lancet 2022

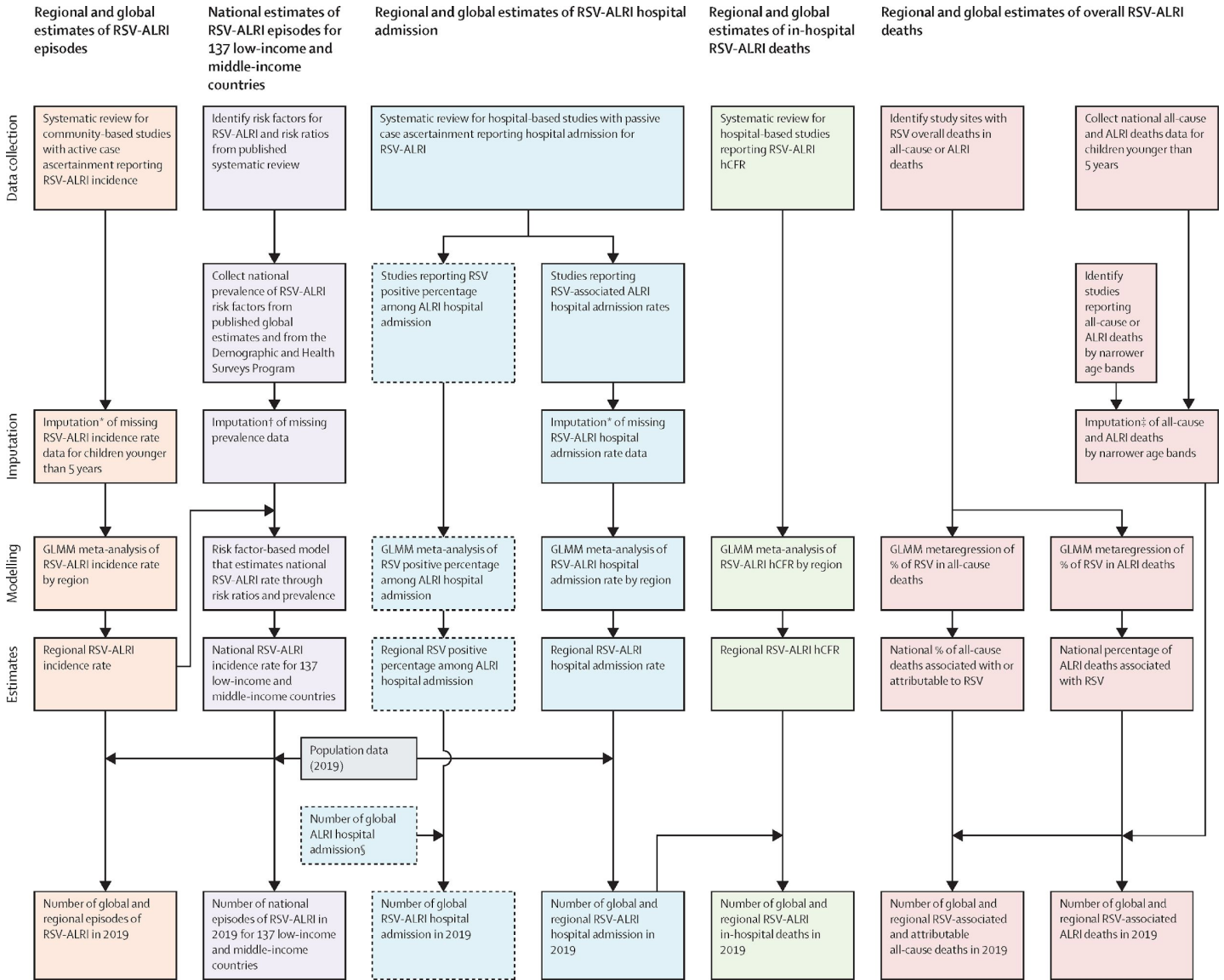
Overview of data (previous vs present)

- Systematic literature review
  - Years: 1995-2016 vs ~+2017-2020
  - Included articles: 250 vs ~+113
- RSV Global Epi Network (RSV GEN)
  - Included studies: 76 vs ~+40
- Data for RSV overall mortality are detailed separately

Overview of data



Overall approach to burden estimation

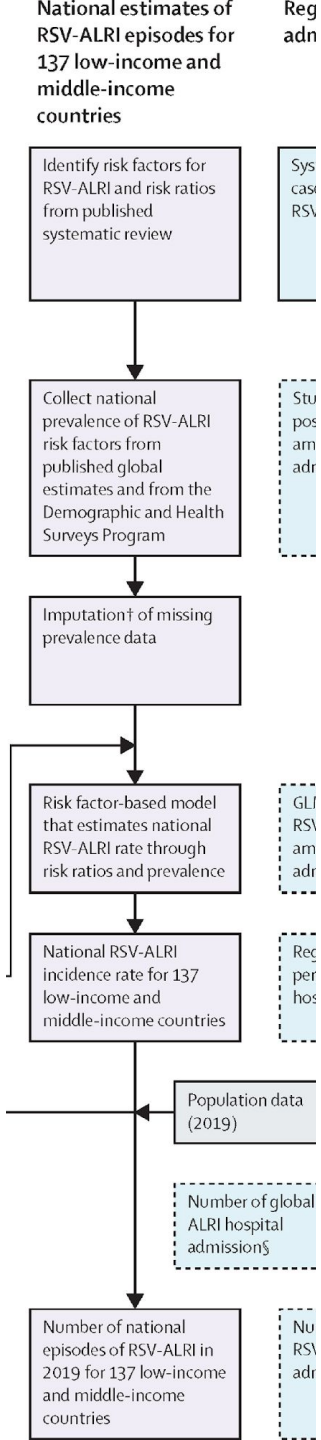


Li Y et al., Lancet 2022

Part 1: RSV morbidity

Method

- Generalised linear mixed effect (GLMM) meta-regression model
- Main outcomes
  - RSV-ALRI, severe RSV-ALRI (ALRI with chest wall indrawing)
  - RSV-ALRI hospital admission, severe RSV-ALRI hospital admission (with hypoxaemia)
- Regional estimates by country development status and by WB income region
- Main age groups of reporting
  - 0-<3m, 3-<6m, 0-<6m, 6-<12m, 12-<60m, 0-<60m
- Imputation
  - Multiple imputation reflecting uncertainty around imputation
  - For 0-<60m only, based on the meta estimates of incidence rate ratio between 0-<60m and 0-<12m / 0-<24m / 0-<36m


National estimates of RSV-ALRI episodes for 137 low-income and middle-income countries
Identify risk factors for RSV-ALRI and risk ratios from published systematic review
Collect national prevalence of RSV-ALRI risk factors from published global estimates and from the Demographic and Health Surveys Program
Imputation† of missing prevalence data
Risk factor-based model that estimates national RSV-ALRI rate through risk ratios and prevalence
National RSV-ALRI incidence rate for 137 low-income and middle-income countries
Population data (2019)
Number of global ALRI hospital admission§
Number of national episodes of RSV-ALRI in 2019 for 137 low-income and middle-income countries

Main sources of heterogeneity

- Study setting (e.g. urban, rural, SES grouping, etc.)
- Case definition
  - Community-based studies: e.g. cut-offs for respiratory rates
  - Hospital-based studies: variations related to clinical judgement
- RSV testing strategy
  - “Selection bias”: those tested for RSV vs not tested for RSV, challenging to account for statistically
  - Note: excluded studies that used “excess morbidity” modelling approach; e.g. Regression of aggregated ALRI counts with aggregated RSV counts / proportion, often from two separate populations.
- Health-care access and seeking behaviour
- …

Part 2: RSV in-hospital mortality

Method

- Three-step process
  - RSV-ALRI hospital admission rates from meta-analysis (Part 1)
  - RSV-ALRI in-hospital CFR from meta-analysis
  - To apply CFR to RSV-ALRI admissions for in-hospital mortality (UR estimated through 1000 MC samples of meta-estimates)
- GLMM (binomial-normal model) for metanalysis

ALRI in-hospital deaths attributable to RSV

- %ALRI in-hospital deaths attributable to RSV, AFE[m]
- AFE[c] = 90% (Shi et al. JoGH 2015)
- AFE[m] =

$$\frac{(RSV[+ve] * CFR[+ve] - (1 - AFE[c]) * RSV[+ve] * CFR[non\text{-}RSV\text{-}attributable])}{(RSV[+ve] * CFR[+ve])}$$

- If assuming CFR[non-RSV-attributable] = CFR[non-RSV+ve], then

AFE[m] =

$1 - (1 - AFE[c]) * CFR[non\text{-}RSV+ve]/CFR[RSV+ve]$

which is 2.0, estimated by meta-analysis.

- AFE[m] = 1 – (1 – 90%) * 2.0 = **80%**

Part 3: RSV overall mortality

New RSV community mortality data - 1

- CHAMPS
  - The Child Health and Mortality Prevention Surveillance
  - Seven countries from high child mortality settings: Bangladesh, Ethiopia, Kenya, Mali, Mozambique, Sierra Leone and South Africa
  - Collect standardised, population-based, longitudinal data on <5y mortality and stillbirths to improve accuracy of determining causes of death
  - RSV tested from both nasopharyngeal and lung samples (through minimally invasive tissue sampling [MITS])
  - Determination of Cause of Death (DeCoDe) panels to determine cause of deaths — e.g. being in the causal chain, contributing to the death, etc.

Taylor et al. Lancet GH 2020

New RSV community mortality data - 2

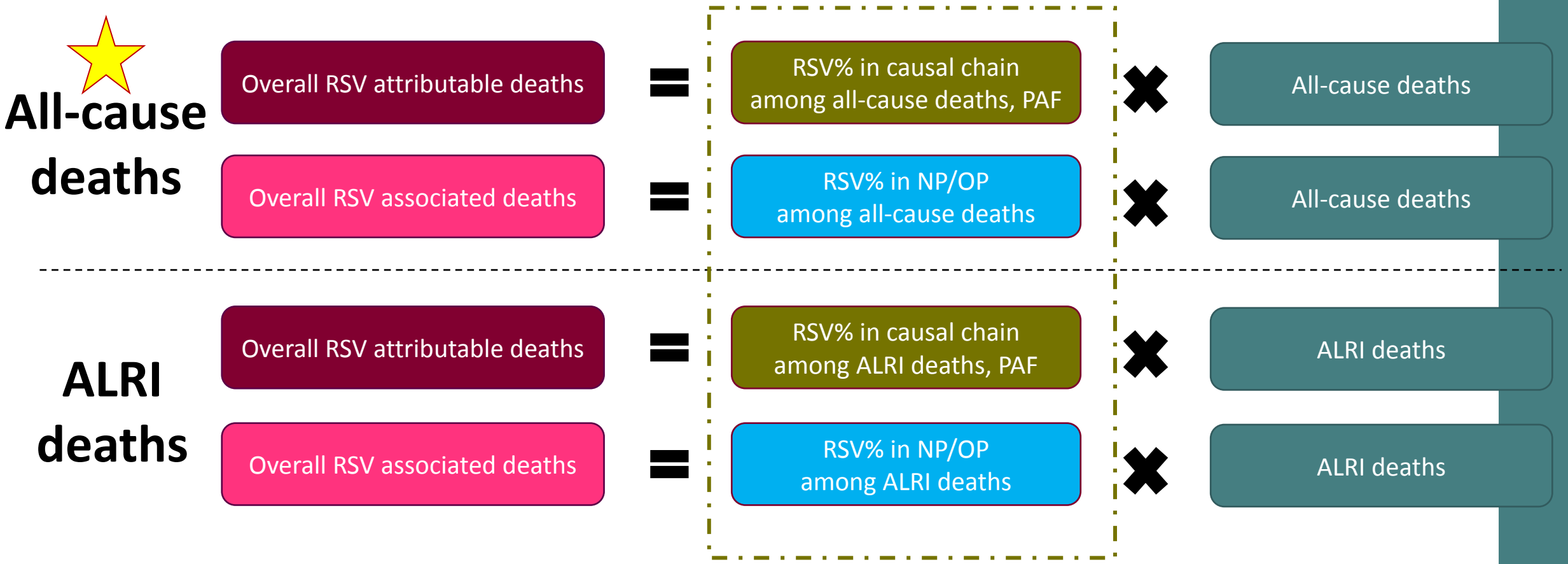
- Gates RSV community mortality studies
  - Argentina (<5y), India (<2y), Pakistan (<6m) and Zambia (<6m)
  - RSV tested in nasopharyngeal samples (all four sites) and lung (through MITS; Argentina only)
  - Cause of deaths determined by verbal autopsy (except for Argentina where cause of deaths determined by CoD panels

Data

- CHAMPS: seven countries
  - Bangladesh, Ethiopia, Kenya, Mali, Mozambique, Sierra Leone and South Africa
- Gates community mortality studies: four countries
  - Argentina, India, Pakistan and Zambia
- For ALRI deaths only — additional studies in three high-income countries, assuming that all deaths were captured in facility
  - Australia, New Zealand and Portugal
- For all-cause deaths only — one additional study (Li et al. JID 2020) on RSV-attributable mortality in <5y in Scotland
- To account for RSV seasonality, all study data had duration of multiplies of 12 months.
- Country-specific deaths “denominator” data (<5y)
  - All-cause: UNICEF (2019)
  - ALRI: McAllister et al. Lancet GH 2019 (the 2015 rate applied to the 2019 population)

The new model

- Based on proportion of RSV among ALRI/all-cause deaths



What do we know about RSV mortality in young children?

- RSV is the leading infectious cause of deaths in infants second only to malaria
- True RSV mortality in infants is unknown but estimated to be between 101,400 and 229,000 deaths in children <5 years world wide.
- 45% deaths occur in children <6 months and 20% in children 6-11 months
- RSV mortality in infants is rare in high income countries – >97% occurs in LMICs
- Care seeking, access to care, and quality of care in hospitals all have an impact on RSV mortality
- Most deaths can be averted by supportive management- supplemental oxygen and hydration

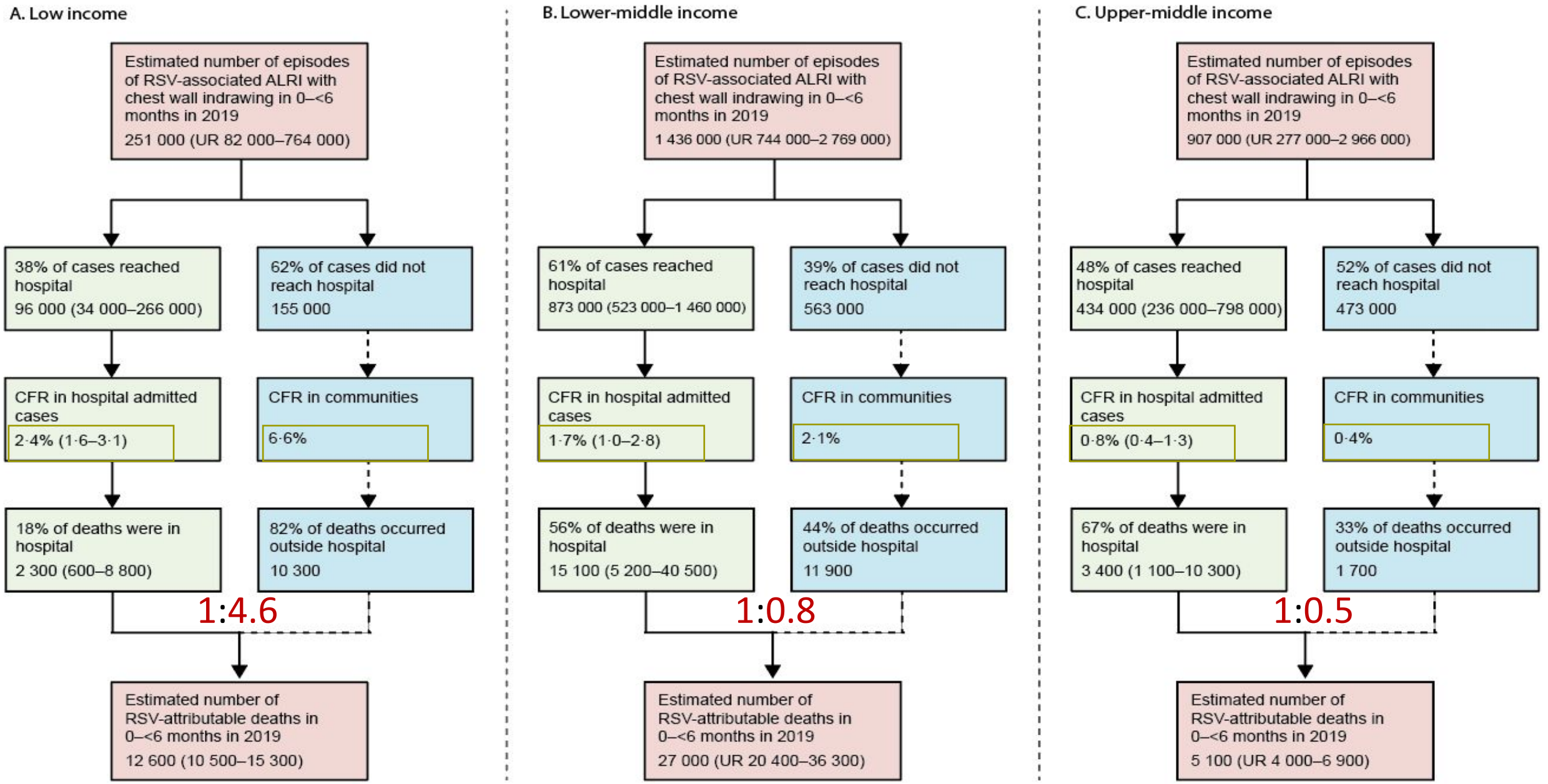
Li Y et al., Lancet 2022

Updated RSV child mortality estimates for 2019

- Utilised high quality data (including post-mortem sampling) in children dying from respiratory causes in hospital and home in LMICs.
- Analysis of Scottish national healthcare data suggests **children are at high risk of death within 1 month of RSV infection**.
- Re-confirms original estimate of **every 2 minutes 5 deaths from RSV worldwide**
- Every 1 in 50 deaths in <5y and 1 in 28 deaths in children <6 months due to RSV
- For every **1 child dying in hospital , 3 deaths occur at home**.

Li Y and Nair H et al., Lancet 2022

Substantial community mortality burden



RSV mortality in community vs hospital

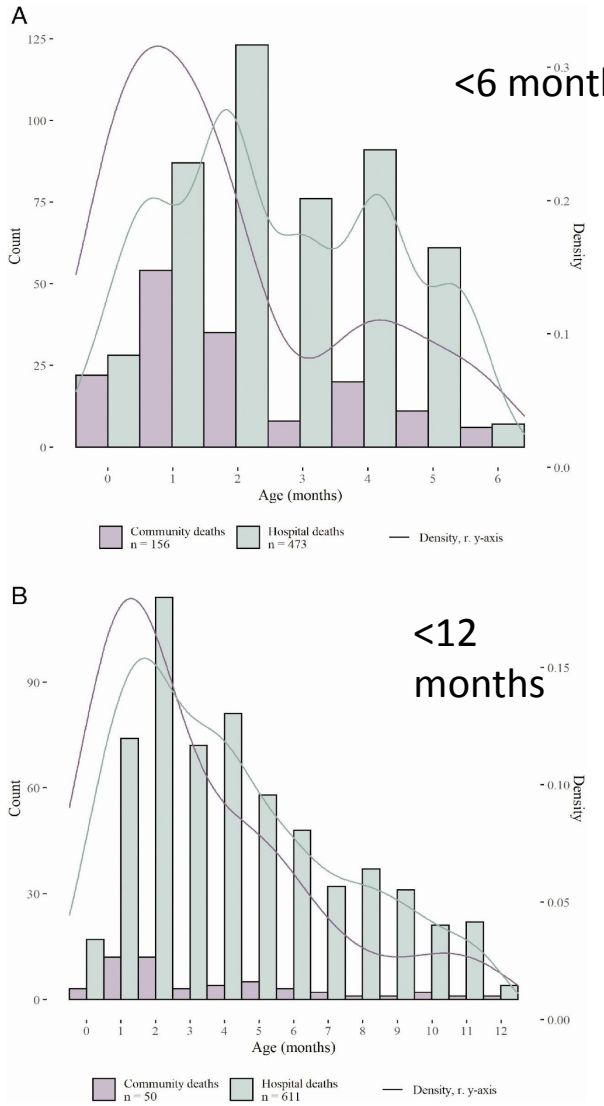


Table 2. Clinical Characteristics of Children Under 12 Months Who Died with Respiratory Syncytial Virus In-Hospital Versus in the Community in Lower-Middle-Income Countries and Upper-Middle-Income Countries, Excluding Deaths From Studies Recruiting Only Those Under 6 Months

Clinical Characteristics	All Deaths (n = 661)	Community (n = 50)	In-Hospital (n = 611)	*P*
Sex, male, % (n/N)	56 (369/661)	56 (28/50)	56 (341/611)	NS
Age at death, months, median (IQR)	4.0 (2.0-6.0)	2.1 (1.3-5.0)	4.0 (2.0-6.1)	.02
Neonatal deaths, % (n/N)	7 (47/661)	14 (7/50)	7 (40/611)	NS
Deaths <6 months, % (n/N)	70 (461/661)	80 (40/50)	69 (421/611)	NS
Comorbidity, % (n/N)	45 (250/561)	28 (10/36)	46 (240/525)	.04
Prematurity, % (n/N)	28 (101/356)	24 (9/37)	29 (92/319)	NS
Gestational age, weeks, mean (SD, n)	36.6 (3.5, 195)	38.4 (2.5, 27)	36.3 (3.5, 168)	.01
Birth weight, kg, median (IQR, n)	2.8 (2.2-3.2, 208)	3.0 (2.5-3.3, 30)	2.8 (2.2-3.2, 178)	NS
Month and year of death, minimum–maximum	July 1995–February 2021	February 2009–February 2020	July 1995–February 2021	…
Not immunized, % (n/N)	13 (33/258)	19 (5/27)	12 (28/231)	NS
Other children in household, % (n/N)	73 (160/220)	90 (19/21)	71 (141/199)	NS
Mother uneducated, % (n/N)	12 (19/155)	8 (2/25)	13 (17/130)	NS
Father uneducated, % (n/N)	7 (6/81)	5 (1/21)	8 (5/60)	NS

P values are provided for the comparison between community and in-hospital deaths. Abbreviations: IQR, interquartile range; NS, not significant; SD, standard deviation.

Mazur NI et al. Clin Infect Dis. 2021;73(Suppl_3):S229-S237

Case fatality ratios in hospital vs community

HOSPITAL

Age group	Low income	Lower middle income	Upper middle income	High income
0-2 months	2.6 (1.8-3.6)	1.8 (0.8-3.6)	0.7 (0.4-1.4)	<0.05 (<0.05-0.3)
3-5 months	2.2 (1.5-3.3)	1.0 (0.4-2.5)	0.7 (0.3-1.7)	<0.05 (<0.05-0.1)
6-11 months	1.8 (0.9-3.4)	0.8 (0.3-2.1)	0.4 (0.2-1.2)	0.1 (<0.05-0.3)
12-60 months	1.6 (0.4-5.7)	0.8 (0.3-1.9)	0.1 (<0.05-0.8)	0.2 (0.1-0.4)

COMMUNITY

Location	Deaths 0-2 months	3-5 months
Melghat, India	9.1% (2/22)	3.3(1/30)

Li Y et al., Lancet 2022
Simoes E et al., Clin Infect Dis. 2021

Risk factors for RSV mortality

- Pre-maturity (<37w GA) – 3.81 (95% CI 1.68-8.63)
- Co-morbidity – 59.83 (13.25- 270.43); 14.87 (1.3-164.6)
- Congenital heart disease – 3.57 (1.71-7.44)
- Age 0-8 weeks – 5.24 (1.56-33.14)
- Poverty / overcrowding – 2.00 (1.22-3.27); 17.09 (1.3-219.2)

Shi T et al., J Infect Dis. 2022; Forman LS et al., Clin Infect Dis 2021; Murphy C et al., Clin Infect Dis 2021; Caballero MT al., Clin Infect Dis 2021

Summary

- RSV deaths in community are younger, term born children
- Majority of RSV deaths in community have no underlying co-morbidity
- Case fatality due to RSV higher in LMICs – both in hospital as well as in community
- Estimating CFR due to RSV-ALRI in community is very challenging. Therefore, true mortality due to RSV remains unknown
- Vaccine probe / well-designed vaccine impact studies can uncover the true RSV mortality burden

Summary

- Age (0-8 weeks) is an important risk factor for RSV disease, poor outcome and death
- Age <6 months at peak RSV season at highest risk for RSV hospitalisation
- Pre-term babies (<37wGA), infants with underlying conditions, congenital heart disease at high risk of RSV disease, poor outcome and death
- Poverty and overcrowding shown to be associated with RSV mortality outside hospital (Zambia and Argentina)