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MAJOR ARTICLE

Incidence of Respiratory Syncytial Virus Lower Respiratory Tract Infections During the First 2 Years of Life: A Prospective Study Across Diverse Global Settings

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(See the Editorial Commentary Storch, on pages 367–9.)

Background. The true burden of lower respiratory tract infections (LRTIs) due to respiratory syncytial virus (RSV) remains unclear. This study aimed to provide more robust, multinational data on RSV-LRTI incidence and burden in the first 2 years of life.

Methods. This prospective, observational cohort study was conducted in Argentina, Bangladesh, Canada, Finland, Honduras, South Africa, Thailand, and United States. Children were followed for 24 months from birth. Suspected LRTIs were detected via active (through regular contacts) and passive surveillance. RSV and other viruses were detected from nasopharyngeal swabs using PCR-based methods.

Results. Of 2401 children, 206 (8.6%) had 227 episodes of RSV-LRTI. Incidence rates (IRs) of first episode of RSV-LRTI were 7.35 (95% confidence interval [CI], 5.88–9.08), 5.50 (95% CI, 4.21–7.07), and 2.87 (95% CI, 2.18–3.70) cases/100 person-years in children aged 0–5, 6–11, and 12–23 months. IRs for RSV-LRTI, severe RSV-LRTI, and RSV hospitalization tended to be higher among 0–5 month olds and in lower-income settings. RSV was detected for 40% of LRTIs in 0–2 month olds and for approximately 20% of LRTIs in older children. Other viruses were codetected in 29.2% of RSV-positive nasopharyngeal swabs.

Conclusions. A substantial burden of RSV-LRTI was observed across diverse settings, impacting the youngest infants the most.

Clinical Trials Registration. NCT01995175.

Keywords. respiratory syncytial virus; respiratory tract infections; epidemiology; incidence; burden of disease; infants; young children.

LAY SUMMARY

Respiratory syncytial virus (RSV) is a common pathogen that causes respiratory illnesses. Although symptoms are usually mild, young children can have more serious diseases such as bronchiolitis and pneumonia. The number of children with RSV illnesses and the need for health care differ by country and are likely underestimated. In a study conducted in 8 countries, we followed 2401 children from birth to 2 years to determine the frequency of lower respiratory tract infections (LRTIs) and hospitalizations due to RSV. We found that 206 children had these infections. Approximately 7 in 100 children had an RSV-LRTI in the first 6 months of life. Furthermore, the youngest children had more serious symptoms and were hospitalized more often than children older than 6 months. While RSV-LRTI incidence and hospitalization rates varied among countries, they were higher in low- or middle-income countries or regions than in high-

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income countries. We found that approximately 1 in 3 children with RSV-LRTIs also had other viruses that could cause respiratory illness. These results show that children younger than 2 years are greatly affected by RSV, especially in low- and middle-income countries. Programs to prevent RSV infections in young children around the world would likely bring health benefits.

Lower respiratory tract infections (LRTIs) remain a leading cause of morbidity and mortality worldwide in children under 5 years of age [1, 2]. As of 2017, despite a 36.4% reduction in fatal cases since 2007, LRTIs accounted for >800 000 deaths in this age group, with most occurring during the first year of life. Children in low-income countries are disproportionately affected [1].

Human respiratory syncytial virus (RSV) is the most common cause of acute viral LRTIs among children under 5 years of age. A meta-analysis estimated an annual global burden of 33.1 million cases of RSV-LRTIs resulting in 3.2 million hospitalizations and 118 200 deaths in 2015 in this age group [3]. A substantial proportion of this burden occurred among children less than 6 months of age, accounting for approximately 5.6 million RSV-LRTI cases, 1.4 million hospitalizations, and 27 300 in-hospital deaths [3]. The global annual incidence of hospitalizations for RSV was estimated at 13.42/1000 children among children under 2 years of age and 20.01/1000 children among those under 6 months of age [4]. In the Pneumonia Etiology Research for Child Health Study, RSV was identified as the dominant pathogen isolated from children younger than 5 years hospitalized with severe pneumonia across multiple countries between 2011 and 2014 [5]. In 2017, RSV ranked second only to *Streptococcus pneumoniae* as a global leading cause of LRTI-associated deaths, accounting for 15% of LRTI deaths in children under 5 years of age [1]. Most children are infected during the first season when they are exposed to RSV. Severe disease is most likely during the first 6 months of life and in older adults [6–8], but symptomatic infections occur throughout life.

Current programs for RSV prevention target only the highest-risk populations, and there are no interventions for the general population, including infants [9]. Accurate epidemiologic data on RSV-associated disease burden are necessary to plan, implement, evaluate, and optimize newly emerging RSV prevention strategies. The burden of RSV-LRTI is globally recognized, but RSV infection is not notifiable worldwide and the reported incidence, morbidity, and mortality rates vary widely based on geography and from season to season. For instance, meta-estimates suggested that approximately 26% of children under 5 years with respiratory tract infections tested positive for RSV in the World Health Organization (WHO) Western Pacific Region (from studies covering 1991 to 2012) [10] and 46% tested RSV positive across the WHO European region (from 2004 to 2018) [11]. Important differences were noted by country, economic setting, and age group [3]. The wide variations in reported disease burden may be due to true geographical differences in incidence based on genetic, sociodemographic, or environmental factors, including access to care and diagnosis. The degree to which differences in study design (eg, retrospective vs prospective, passive vs active surveillance) and/or methodology contribute to the wide variations in reported disease burden remains unknown but must be considered.

To provide more robust, multinational data on the incidence of RSV-LRTIs and related hospitalizations, we performed a prospective birth cohort study to assess the burden of RSV-associated LRTIs in children living in 8 economically diverse countries across the globe from birth until 2 years of age.

METHODS

Study Design and Participants

Our prospective, observational cohort study was conducted at study sites located in Argentina, Bangladesh, Canada, Finland, Honduras, South Africa, Thailand, and the United States.

Infants were enrolled if their parent(s)/legally acceptable representative(s)(LARs) signed an informed consent before and within 5 working days after birth, and if a ≥3 mL cord blood sample was collected. Infants who had parent(s) under the legal consenting age, were born at gestational age of <28 weeks, who had any conditions expected to require postnatal hospitalization for >12 weeks, had a life expectancy of less than 5 years, or who had a confirmed/suspected immunosuppressive or immunodeficient condition were excluded.

Children were enrolled between December 2013 and October 2015 and followed until 2 years of age for any potential LRTI using both active and passive surveillance. For active surveillance, study staff regularly contacted the children's parent(s)/LAR(s) to identify potential LRTI cases, at predefined intervals which were based on local settings and were more frequent in RSV transmission periods (up to 16 contacts/year for each child). For passive surveillance, the parent(s)/LAR(s) spontaneously reported any new or worsened RTI symptoms experienced by their child to study staff. Study visits with physical examinations occurred within 72 hours of all new or worsening potential LRTI cases identified by either active or passive means (Supplementary Material, Text 1).

A full list of the study objectives is presented in Supplementary Table 1. Here, we report the results on disease burden in terms of incidence rates of RSV-LRTI, severe RSV-LRTI, and RSV-associated hospitalization (coprimary objective), and data on the association of codetected viral pathogens with the incidence of LRTIs and/or severe LRTIs (tertiary objective), using the WHO case definitions [12]. The results of the other objectives will be reported elsewhere.

We conducted the study in accordance with the principles of Good Clinical Practice, the Declaration of Helsinki, and all

applicable regulatory requirements. The study protocol and subsequent amendments were approved by national regulatory authorities and institutional review boards/institutional ethics committees at each site. Corrective actions were implemented when deviations from these guidelines and regulations were detected. This was the case for one of the study sites in Argentina. Therefore, the data from that site were excluded from the analyses. The site would have contributed <2% of the study participants. The study is registered on ClinicalTrials.gov (NCT01995175) and a full protocol is available at http://www.gsk-studyregister.com (ID 200150).

Illness Assessments

At study visits to assess potential LRTIs the temperature, respiratory rate, and blood oxygen saturation (using pulse oximetry) were measured, and all clinical symptoms were recorded. Nasopharyngeal swab samples were collected at these visits and tested for a panel of respiratory viral pathogens. RSV subtypes were detected using reverse transcription-quantitative real-time polymerase chain reaction (RT-qPCR). The Luminex xTAG respiratory viral panel fast assay version 2 was used to detect 17 viral types and subtypes (Supplementary Material, Text 1).

Statistical Analyses

Sample size estimates were based on expected RSV-associated LRTI hospitalization rates as reported in previous studies [13–18]. Assuming a hospitalization rate of 20 cases per 1000 person-years, and an overall sample size of about 320 evaluable children by country, the 95% confidence interval (CI) around the point estimate of the RSV hospitalization rate was estimated to be 6.9–40.8 for the exact Poisson distribution and 0.0–51.7 for the normal approximation with design effect of 4.18 [19]. The RSV-LRTI incidence rate was expected to be approximately 8 times higher than the hospitalization rate [20]. Assuming a drop-out rate of approximately 20% over the 2-year follow-up period, the enrolment target was set at 400 children per country or 2400 overall. This number was considered sufficient for descriptive purposes.

All LRTI episodes were assessed by the investigators and classified by severity, using the WHO 2015 case definitions [12] as presented in Table 1. The RSV-LRTI incidence rates for first episodes of RSV-LRTI, severe RSV-LRTI, and RSV-associated hospitalization were calculated overall, by country, and by age group (0–5 months, 6–11 months, 12–23 months) with exact 95% CIs. Incidence rates were calculated by dividing the number of children with first episodes over the follow-up period by the total person-years and were expressed as cases/100 person-years. The person-time at risk was calculated as the time between the date of birth and the end of the at-risk period or the earliest of the following: date of first diagnosis of event, date when child reaches 2 years of age, date of last contact, or date of death. The date of last contact was defined as no contact by the child's parent(s)/LAR(s) over a period of 3 planned contacts and/or 2 months and after a final attempt has been made by mail; in this case, the child was censored at the time of last contact.

Table 1. Case Definitions (World Health Organization, 2015 [12])

RSV-LRTI	Child with history of cough or difficulty breathing; SpO_2 <95% or respiratory rate increase[a]; RT-qPCR-confirmed RSV detection
Severe RSV-LRTI	Child with RSV-LRTI; SpO_2 <93% or lower chest wall indrawing
RSV-LRTI hospitalization	Meeting the case definition of RSV-LRTI; associated with hospitalization
Severe RSV-LRTI hospitalization	Meeting the case definition of severe RSV-LRTI; associated with hospitalization
LRTI, all cause	Child with history of cough or difficulty breathing; SpO_2 <95% or respiratory rate increase[a]
Severe LRTI	Child with LRTI; SpO_2 <93% or lower chest wall indrawing

Abbreviations: LRTI, lower respiratory tract infection; RSV, respiratory syncytial virus; RT-qPCR, reverse transcription-quantitative polymerase chain reaction; SpO_2, saturation of peripheral oxygen.

[a]Respiratory rate increase defined by age as ≥60/minute (less than 2 months of age); ≥50/minute (between 2 and 11 months of age); ≥40/minute (12 to 24 months of age).

The analysis of other respiratory viruses and RSV infection during LRTIs was performed overall, by country, and by age group (0–2 months, 3–5 months, 6–11 months, 12–23 months) by calculating the number and percentage of cases for each virus type/subtype identified.

Analyses were performed in all children who met the study eligibility criteria and complied with passive surveillance reporting and examination visits in the timeframe stated in the protocol. All statistical analyses were performed using SAS version 9.4.

RESULTS

Demographics

Of 2402 children enrolled in the study, 2401 were included in the analyses and 2148 (89.5%) completed the study (Figure 1). The children's and mothers' characteristics varied slightly by country (Table 2). More than half (55.2%) of the mothers were between 28 and 37 years of age at delivery; 49.5% of them had higher education (university or postsecondary school). Overall, 38.2% of infants were born via caesarean delivery. Race distribution varied by country of origin. Most children were born after 37 weeks of gestation (92.5%), weighed over 2.5 kg at birth (91.7%), and had a 5-minute Apgar score of 7 or higher (98.1%). Overall, nearly two-thirds of the participants (62.9%) were born during the local RSV transmission period.

The average number of persons living in the household when children reached 3 months of age was 4.6. This average varied by country, ranging from 3.7 in Argentina to 6.1 in Bangladesh.

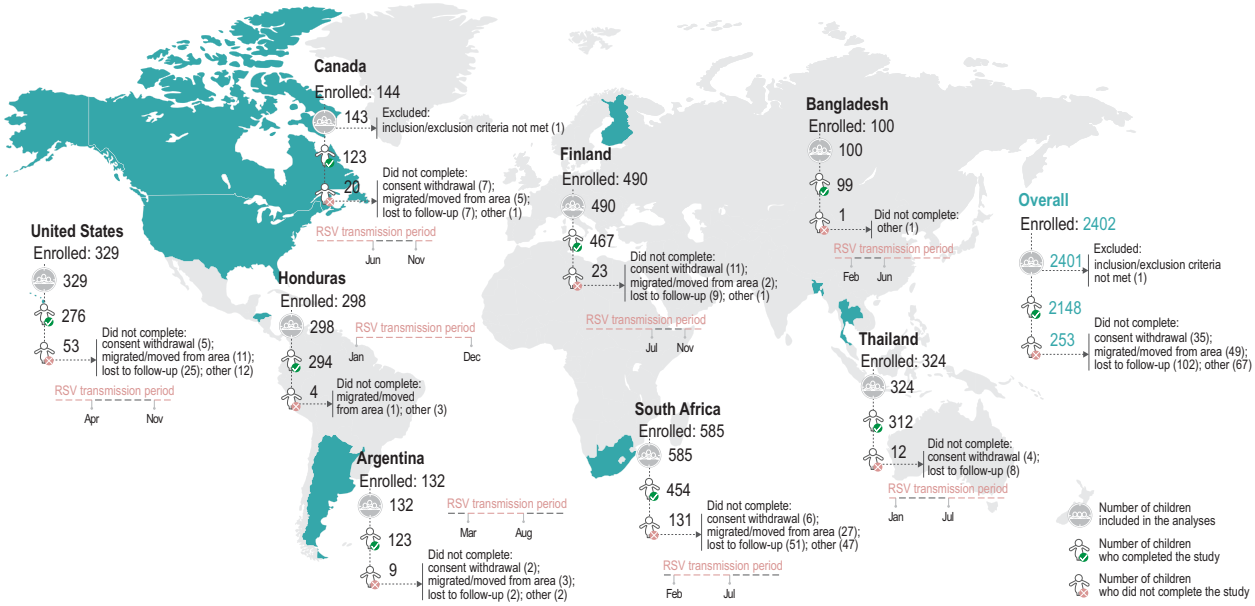

Figure 1. Participant flowchart and local RSV transmission period. The RSV transmission period in each country was defined based on the actual observed RSV season during the period of surveillance for each country. For countries such as Canada, the Unites States, and Finland, which had well-established RSV surveillance systems in place near the study sites, the actual reported RSV season start and stop dates (by month) were used to define the RSV transmission period. If the RSV season was longer in 1 year than the other and >5% of children for that country were exposed to the longer season, then the longer season was considered. In countries without a robust RSV surveillance system, the RSV transmission period was established through the identification of at least 1 RSV case in each month defined as being within the RSV season. In order for the month to be counted as within the RSV season for that country, the month had to be adjacent to at least 1 other month that similarly met the definition for being within the RSV season. Abbreviation: RSV, respiratory syncytial virus.

Overall Incidence of RSV-LRTIs and RSV-Associated Hospitalizations

Two-hundred-six (8.6%) children had 227 episodes of RSV-LRTI (per the WHO case definition) before the age of 2 years, with most episodes occurring during the first 6 months of life. Eighty-six children had their first RSV-LRTI episode at 0–5 months of age (with a higher proportion being affected at 3 to <4 months of age; Supplementary Figure 1), 61 children at 6–11 months of age, and 59 children at 12–23 months of age.

The incidence rate of first episode of RSV-LRTI was 7.35 cases/100 person-years (95% CI, 5.88–9.08) for children 0–5 months and 5.50 (95% CI, 4.21–7.07) in those aged 6–11 months; a lower incidence rate (2.87; 95% CI, 2.18–3.70) was observed during the second year of life (Figure 2 and Supplementary Table 2).

Sixty-nine (2.9%) children had 73 severe RSV-LRTIs, with 38, 16, and 15 participants having the first episode at 0–5, 6–11, and 12–23 months of age. The incidence rate of severe RSV-LRTI was higher in children 0–5 months (3.22 cases/100 person-years; 95% CI, 2.28–4.42) than in those 6–11 (1.40; 95% CI, 0.80–2.27) and 12–23 months of age (0.69; 95% CI, 0.39–1.14) (Figure 2 and Supplementary Table 2).

Of the 31 first-time hospitalizations with positive RSV detection (RSV hospitalizations), 22, 3, and 6 occurred in children 0–5, 6–11, and 12–23 months of age. Of these, 20 met the WHO case definition for LRTI or severe LRTI. Approximately 10% of all first RSV-LRTI cases were hospitalized and 5% were admitted in an intensive care unit. The highest incidence rate of RSV hospitalizations, RSV-LRTI hospitalizations, and severe RSV-LRTI hospitalizations occurred among children 0–5 months of age; rates were comparable between children 6–11 and 12–23 months of age (Supplementary Table 2).

When children were stratified by the amount of time spent in the local RSV transmission period during the first 6 months of life, the observed incidence rates were higher among infants with >3 months than those with ≤3 months in the RSV transmission period (10.63 vs 1.01 cases/100 person-years for RSV-LRTI, 4.73 vs 0.25 for severe RSV-LRTI, and 2.67 vs 0.25 for RSV hospitalization; Supplementary Table 3).

Incidence of RSV-LRTIs and RSV Hospitalizations, by Country

The incidence rates varied by country. The observed RSV-LRTI incidence rates were the highest in Bangladesh and Honduras and lowest in Finland (Figure 2 and Supplementary Table 2). The highest incidence rates for RSV hospitalization, RSV-LRTI hospitalization, and severe RSV-LRTI hospitalizations were observed in Bangladesh, overall (2.10, 2.10, and 1.03 cases/100 person-years, respectively) and in the 0–5-month age group (8.21, 8.21, and 4.06 cases/100 person-years, respectively).

The highest percentage of hospitalized RSV-LRTI episodes was observed in Bangladesh: across all age categories, 20% of

Table 2. Characteristics of Children Included in the Analyses and Their Parents

Characteristic	Argentina N = 132	Bangladesh N = 100	Canada N = 143	Finland N = 490	Honduras N = 298	South Africa N = 585	Thailand N = 324	United States N = 329	Overall N = 2401
Age of mother at delivery, years, n (%)									
18–27	41 (31.1)	60 (60.0)	33 (23.1)	170 (34.7)	140 (47.0)	220 (37.6)	113 (34.9)	75 (22.8)	852 (35.5)
28–37	75 (56.8)	35 (35.0)	100 (69.9)	282 (57.6)	143 (48.0)	283 (48.4)	184 (56.8)	223 (67.8)	1325 (55.2)
≥38	16 (12.1)	5 (5.0)	10 (7.0)	38 (7.8)	15 (5.0)	82 (14.0)	27 (8.3)	31 (9.4)	224 (9.3)
Singleton or multiple pregnancy, n (%)									
Singleton	127 (96.2)	100 (100.0)	137 (95.8)	486 (99.2)	290 (97.3)	441 (75.4)	322 (99.4)	322 (97.9)	2225 (92.7)
Multiple	5 (3.8)	0 (0.0)	6 (4.2)	4 (0.8)	8 (2.7)	144 (24.6)	2 (0.6)	7 (2.1)	176 (7.3)
Caesarean delivery, n (%)									
Yes	94 (71.2)	0 (0.0)	40 (28.0)	106 (21.6)	156 (52.3)	312 (53.3)	144 (44.4)	64 (19.5)	916 (38.2)
No	38 (28.8)	100 (100.0)	103 (72.0)	384 (78.4)	142 (47.7)	273 (46.7)	180 (55.6)	265 (80.5)	1485 (61.8)
Gestational age at birth, weeks, n (%)									
<28	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
29–32	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	26 (4.4)	0 (0.0)	0 (0.0)	26 (1.1)
33–36	9 (6.8)	6 (6.0)	9 (6.3)	9 (1.8)	7 (2.3)	94 (16.1)	14 (4.3)	6 (1.8)	154 (6.4)
≥37	123 (93.2)	94 (94.0)	134 (93.7)	481 (98.2)	291 (97.7)	465 (79.5)	310 (95.7)	323 (98.2)	2221 (92.5)
Sex of newborn(s), n (%)									
Male	43 (32.6)	47 (47.0)	37 (25.9)	155 (31.6)	55 (18.5)	197 (33.7)	85 (26.2)	85 (25.8)	704 (29.3)
Female	38 (28.8)	52 (52.0)	45 (31.5)	144 (29.4)	43 (14.4)	208 (35.6)	82 (25.3)	117 (35.6)	729 (30.4)
Missing[a]	51 (38.6)	1 (1.0)	61 (42.7)	191 (39.0)	200 (67.1)	180 (30.8)	157 (48.5)	127 (38.6)	968 (40.3)
Born during RSV transmission period[b], n (%)									
Yes	112 (84.8)	100 (100.0)	84 (58.7)	427 (87.1)	298 (100.0)	238 (40.7)	212 (65.4)	40 (12.2)	1511 (62.9)
No	20 (15.2)	0 (0.0)	59 (41.3)	63 (12.9)	0 (0.0)	347 (59.3)	112 (34.6)	289 (87.8)	890 (37.1)
Predominant geographic ancestry, n (%)									
African heritage/African American	1 (0.8)	0 (0.0)	5 (3.5)	0 (0.0)	0 (0.0)	585 (100)	0 (0.0)	41 (12.5)	632 (26.3)
American Indian or Alaskan Native	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (1.8)	7 (0.3)
Asian[c]	0 (0.0)	100 (100)	3 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	324 (100)	18 (5.5)	445 (18.5)
Latino/ Mestizo	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	298 (100.0)	0 (0.0)	0 (0.0)	5 (1.5)	303 (12.6)
Native Hawaiian or other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.9)	3 (0.1)
White[d]	131 (99.2)	0 (0.0)	116 (81.1)	489 (99.8)	0 (0.0)	0 (0.0)	0 (0.0)	158 (48.0)	894 (37.2)
Other	0 (0.0)	0 (0.0)	18 (12.6)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	98 (29.8)	117 (4.9)
Length, cm, mean ± SD	49.2 ± 2.03	48.0 ± 1.96	51.3 ± 2.51	50.3 ± 1.97	49.2 ± 2.34	48.7 ± 4.33	50.0 ± 2.31	50.8 ± 2.61	49.7 ± 3.04
Birthweight, kg, n (%)									
<1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.0)
1–1.499	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	10 (1.7)	0 (0.0)	0 (0.0)	11 (0.5)
1.5–1.999	1 (0.8)	4 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)	22 (3.8)	3 (0.9)	3 (0.9)	33 (1.4)
2–2.499	2 (1.5)	17 (17.0)	2 (1.4)	6 (1.2)	16 (5.4)	90 (15.4)	11 (3.4)	6 (1.8)	150 (6.2)
≥2.5	129 (97.7)	78 (78.0)	141 (98.6)	484 (98.8)	282 (94.6)	457 (78.1)	310 (95.7)	320 (97.3)	2201 (91.7)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.9)	0 (0.0)	0 (0.0)	5 (0.2)
5-minute Apgar score, n (%)									
0–3	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)

Table 2. Continued

Characteristic	Argentina N = 132	Bangladesh N = 100	Canada N = 143	Finland N = 490	Honduras N = 298	South Africa N = 585	Thailand N = 324	United States N = 329	Overall N = 2401
4–6	0 (0.0)	0 (0.0)	3 (2.1)	9 (1.8)	1 (0.3)	7 (1.2)	2 (0.6)	2 (0.6)	24 (1.0)
≥7	132 (100.0)	100 (100.0)	140 (97.9)	480 (98.0)	296 (99.3)	560 (95.7)	322 (99.4)	325 (98.8)	2355 (98.1)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	18 (3.1)	0 (0.0)	2 (0.6)	21 (0.9)
Breastfeeding, n (%)									
Yes	123 (93.2)	99 (99.0)	104 (72.7)	399 (81.4)	283 (95.0)	376 (64.3)	285 (88.0)	251 (76.3)	1920 (80.0)
No	8 (6.1)	0 (0.0)	39 (27.3)	85 (17.3)	14 (4.7)	192 (32.8)	38 (11.7)	73 (22.2)	449 (18.7)
Missing	1 (0.8)	1 (1.0)	0 (0.0)	6 (1.2)	1 (0.3)	17 (2.9)	1 (0.3)	5 (1.5)	32 (1.3)
Mother with higher/university education, n (%)									
Yes	61 (46.2)	14 (14.0)	123 (86.0)	328 (66.9)	26 (8.7)	90 (15.4)	269 (83.0)	277 (84.2)	1188 (49.5)
No	71 (53.8)	86 (86.0)	20 (14.0)	162 (33.1)	272 (91.3)	495 (84.6)	55 (17.0)	52 (15.8)	1213 (50.5)
Father with higher/university education, n (%)									
Yes	41 (31.1)	12 (12.0)	106 (74.1)	236 (48.2)	28 (9.4)	109 (18.6)	261 (80.6)	255 (77.5)	1048 (43.6)
No	91 (68.9)	88 (88.0)	37 (25.9)	254 (51.8)	270 (90.6)	476 (81.4)	63 (19.4)	74 (22.5)	1353 (56.4)
Number of people living in the household at month 3, n (%)									
1–3	61 (46.2)	5 (5.0)	68 (47.6)	214 (43.7)	52 (17.4)	115 (19.7)	73 (22.5)	89 (27.1)	677 (28.2)
4–6	64 (48.5)	60 (60.0)	70 (49.0)	254 (51.8)	201 (67.4)	283 (48.4)	208 (64.2)	201 (61.1)	1341 (55.9)
≥7	2 (1.5)	34 (34.0)	3 (2.1)	10 (2.0)	44 (14.8)	145 (24.8)	42 (13.0)	23 (7.0)	303 (12.6)
Mean No. (±SD)	3.7 (0.87)	6.1 (2.20)	3.8 (0.97)	3.9 (1.15)	4.9 (1.60)	5.4 (2.44)	4.8 (1.78)	4.3 (1.33)	4.6 (1.85)
Daily smoking environment at month 3, n (%)									
Yes	21 (15.9)	38 (38.0)	15 (10.5)	114 (23.3)	8 (2.7)	173 (29.6)	137 (42.3)	16 (4.9)	522 (21.7)
No	106 (80.3)	61 (61.0)	126 (88.1)	364 (74.3)	289 (97.0)	371 (63.4)	186 (57.4)	297 (90.3)	1800 (75.0)
Missing	5 (3.8)	1 (1.0)	2 (1.4)	12 (2.4)	1 (0.3)	41 (7.0)	1 (0.3)	16 (4.9)	79 (3.3)

The RSV transmission period in each country was defined based on the actual observed RSV season during the period of RSV surveillance for each country. For countries such as Canada, the United States, and Finland, which had well-established RSV surveillance systems in place in locations near the study sites during the study, the actual reported RSV season start and stop dates (by month) were used to define the RSV transmission period. If the RSV season was longer in 1 year than the other and >5% of children for that country were exposed to the longer season, then the longer season was used in the definition of the RSV transmission period for that country. In countries where a robust RSV surveillance system could not be identified, the RSV transmission period was established through the identification of at least 1 RSV case in each month defined as being within the RSV season. In order for the month to be counted as within the RSV season for that country, the month had to be adjacent to at least 1 other month that similarly met the definition for being within the RSV season.

Abbreviations: N, number of children in each country/overall; n (%), number (percentage) of children in a given category; RSV, respiratory syncytial virus; SD, standard deviation.

[a]The sex of 40.3% of children was not collected at birth as the question was omitted from the electronic case report form in the primary study; data were subsequently collected in an extension study, but sex remained missing for children who did not participate in the extension study.

[b]RSV transmission period was March to August for Argentina, June to February for Bangladesh, November to June for Canada, November to July for Finland, February to July for South Africa, July to January for Thailand, November to April for United States, and all year round for Honduras.

[c]Asian ancestry includes Central/South Asian, East Asian, Japanese, and South-East Asian heritage.

[d]White ancestry includes Arabic/North African and Caucasian/European heritage.

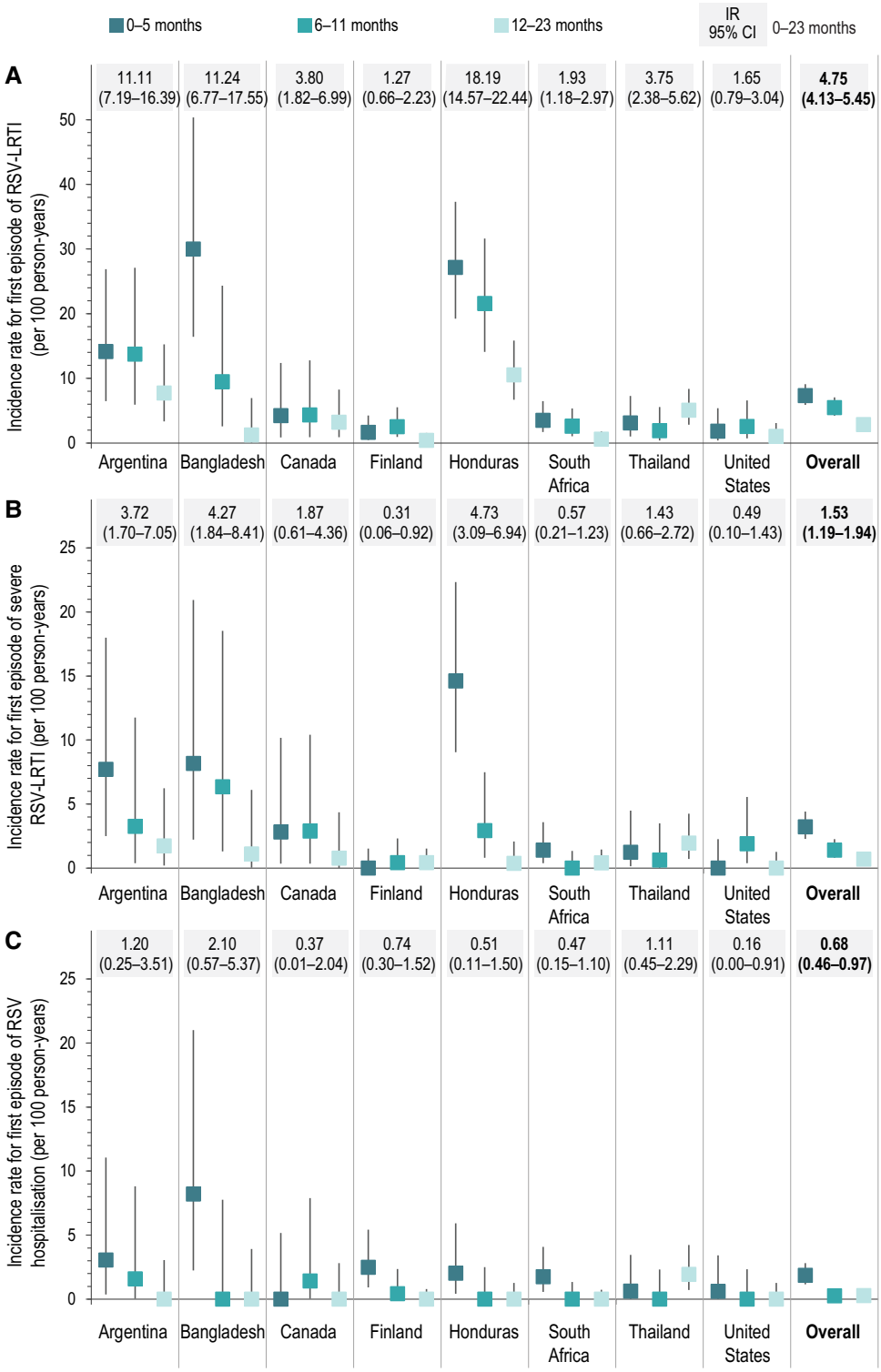

Figure 2. Incidence rate of first episode of RSV-LRTI (*A*), severe RSV-LRTI (*B*), and RSV hospitalization (*C*) by age group, overall, and by country. Error bars represent 95% CIs. Abbreviations: CI, confidence interval; IR, incidence rate (cases/100 person-years); LRTI, lower respiratory tract infection; RSV, respiratory syncytial virus.

all RSV-LRTI cases and 25% of severe RSV-LRTI cases required hospitalization (all without intensive care) (Supplementary Figure 2). No hospitalizations due to RSV-LRTI were observed in the US cohort.

RSV Detection and Viral Codetection in Children With LRTI

Of the 1012 LRTI episodes, 909 (89.8%) had 1 or more virus types/subtypes detected. Overall, approximately 22% of LRTIs involved RSV, with RSV-A detected for 94 episodes

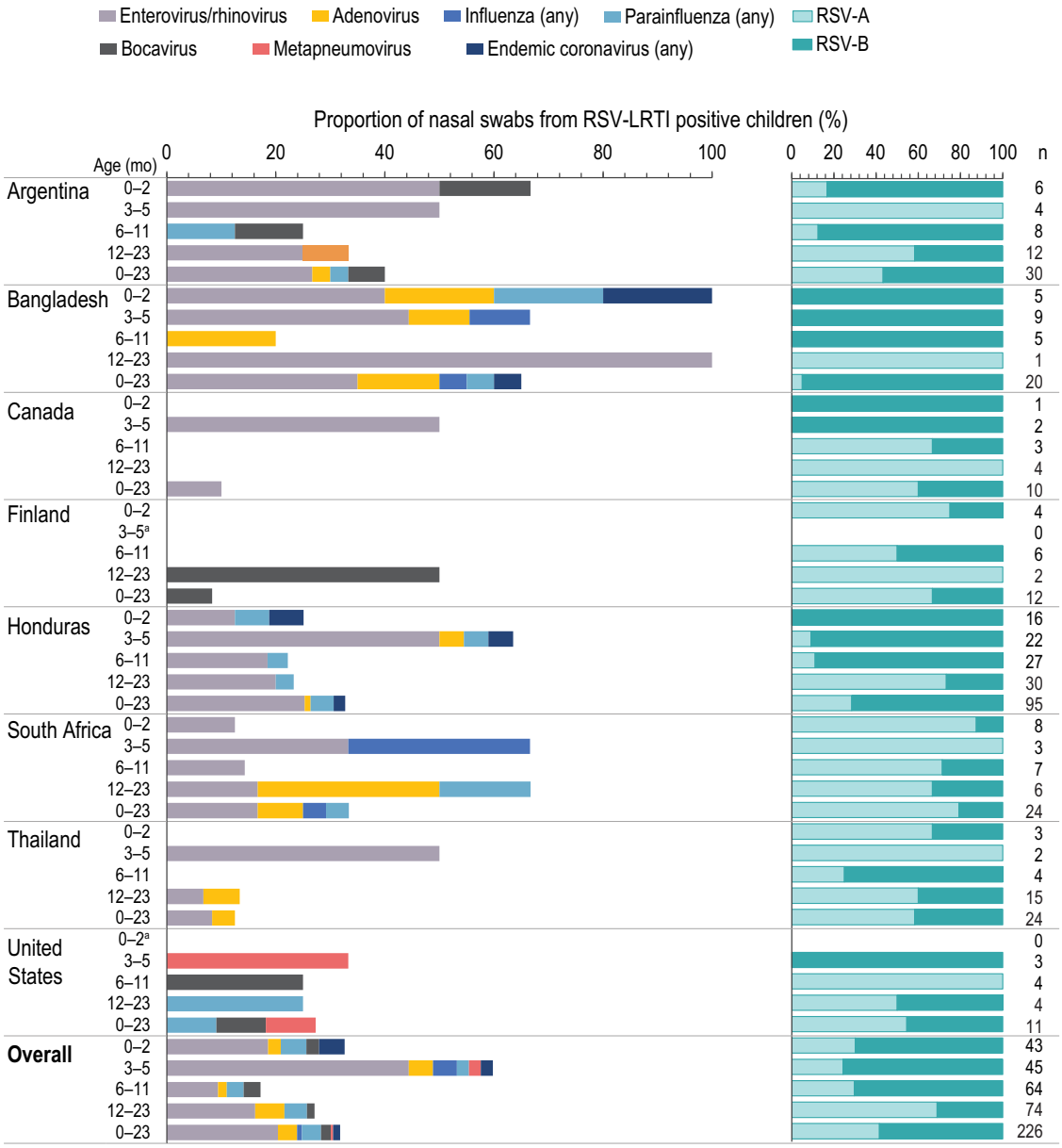

Figure 3. Virus codetection in laboratory-confirmed RSV-LRTI cases (left) and according to RSV subtype (right), by age group, overall, and by country. Abbreviations: LRTI, lower respiratory tract infection; RSV, respiratory syncytial virus. [a]No LRTIs were observed in these age groups.

and RSV-B for 132 episodes (Supplementary Table 4). In 0 to 2-month-old children, RSV was identified in approximately 40% (43/110) of all LRTIs and 47% (21/45) of severe LRTIs. After 2 months of age, the percentage of LRTIs with RSV detected were approximately 20% of all LRTIs and 24% of severe LRTIs. Of 260 severe LRTIs occurring in 259 children, approximately 28% involved RSV (27 RSV-A episodes and 46 RSV-B episodes).

One or more additional virus types were detected in 29.2% of all nasopharyngeal swab samples from children with LRTIs positive for the detection of RSV. Enteroviruses/rhinoviruses were the most commonly identified viruses codetected in cases of RSV-LRTI and severe RSV-LRTI. Human metapneumovirus (hMPV) was not detected for cases in infants <3 months of age (Figure 3 and Supplementary Table 5).

DISCUSSION

This is one of the largest prospective studies to date that evaluates disease burden of RSV-LRTI across diverse global settings. Our results support true regional variations in disease burden. RSV-LRTIs, severe RSV-LRTIs, and RSV

hospitalizations were detected in all 8 countries, but incidence rates varied largely from one country to another.

In most countries, RSV-LRTI incidence was consistently highest in infants less than 6 months of age with an observed stepwise decline among those aged 6–11 and 12–23 months. This trend was less obvious in children enrolled from high-income countries such as Canada, Finland, and the United States. Overall, our results are similar to global estimates reported from meta-analyses of RSV disease epidemiology [3, 4]. The differences observed across age groups were even greater for severe RSV-LRTI and RSV-associated hospitalizations, where the incidences were 4.7 and 4.9 times higher in the 0–5 months versus the 11–23 months age group. It should be noted, however, that the proportion of children with RSV-LRTI cases in the 6–23 age group was comparable to that observed for infants aged 0–5 months, indicating that a substantial burden of RSV-LRTI continues well beyond the first 6 months of life. Overall, higher incidence rates for RSV-LRTI and severe RSV-LRTI were observed in Honduras, Bangladesh, and Argentina, consistent with previous estimations of a higher burden of disease in low- and middle-income settings [3]. However, other factors that can at least partially contribute to differences in incidence rates across countries, such as the length of the RSV transmission period (and therefore of exposure to the virus), cannot be excluded. For instance, the RSV transmission period is all year round in Honduras and 9 months (from June to February) in Bangladesh. Of note, in Finland, a high-income country where we observed 9 continuous months of RSV activity, the observed incidence rates for RSV-LRTI were considerably lower. The timing of onset, peak, and duration of local RSV seasons are known to vary with altitude, climate, and across geographic locations [21, 22], and this may also contribute to the heterogeneity of the results across countries. Our finding that RSV-related hospitalization rates differ substantially from one country to another is consistent with previous reports [3]. Variation in medical practice could account for different hospitalization rates; we noted that among children with the same RSV-LRTI severity level hospitalization rates varied by country.

As expected, we observed incidence rates for RSV-LRTI, severe RSV-LRTI, and RSV hospitalizations that were considerably higher in children with >3 months exposure to the local RSV transmission period than in those with ≤ 3 months of exposure during the first 6 months of life. Children with a longer period of RSV exposure would have a higher likelihood of infection. While annual seasonal outbreaks of infection are expected, their timing, duration, severity, and impact on birth cohorts cannot be predicted with a high level of precision [22], so focusing prevention interventions only toward historical RSV seasons could leave a substantial proportion of the population at risk.

The results of our study highlight the high burden of RSV-associated illness in infants and the urgent need for global prevention strategies targeting young children. Palivizumab, a humanized monoclonal antibody (mAb), has been shown to reduce RSV severity and RSV-associated hospitalizations when administered monthly to infants born prematurely, or with congenital heart disease and chronic lung disease. However, its administration is limited to the highest-risk subgroups of those infants, and the associated high cost further restricts its availability and use to high-income settings [23, 24]. The single-dose nirsevimab (a modified mAb with extended half-life) has also shown promising results in reducing the incidence of RSV-LRTI and related hospitalization in infants [25, 26]. The observed peak in RSV-LRTI incidence during the first 6 months of life is likely related, at least in part, to the known decline in protective natural maternal antibodies that occurs after birth. Therefore, passive immunity through maternal vaccination during pregnancy or via the administration of long-acting mAbs has the potential to prevent a significant burden of disease among young infants. Several vaccines designed with the goal of boosting RSV antibodies during pregnancy are under development, with 2 candidates having reached phase 3 clinical trials [27–29]. However, antibodies derived from maternal immunization decrease during infancy, with low levels anticipated after the first 6 months of life. The present study indicates that there is also a substantial burden of RSV disease beyond 6 months up to 2 years of age, which could be addressed by infant immunization.

Among PCR-confirmed RSV-LRTIs in our cohort, detection of a second virus was observed in approximately 30% of episodes, with the enterovirus/rhinovirus type being the most commonly codetected, consistent with previous reports [30–32]. A recent meta-analysis indicated that codetection of RSV with any other virus is not associated with increased clinical severity of RSV-LRTI compared to monoinfection, with the exception of hMPV. Codetection of RSV and hMPV has been shown to be associated with a higher risk of intensive care unit admission in children under 5 years of age [33]. In the current study, hMPV was only rarely detected in RSV-LRTIs, and was not codetected in samples collected from children with severe RSV-LRTI.

The transmission and seasonal pattern of respiratory viruses, including RSV, has been interrupted during the coronavirus disease 2019 (COVID-19) pandemic, likely due in part to implementation of nonpharmaceutical public health interventions (NPIs) [34, 35]. Reduced exposure to respiratory viruses leads to an increase in the overall proportion of young children who have not yet experienced their primary RSV infection, and therefore to RSV outbreaks upon reduction/elimination of NPIs, as predicted by an US modelling study [36]. Substantial outbreaks of off-season RSV infections with higher than typical peaks in some locations have already been reported in Japan [37], Switzerland [38], the United Kingdom [39], Australia

[40], the United States [41, 42], and other countries. This sharp increase in disease burden, together with the potential impact of global climate changes on RSV transmission [43], further underscores the need for RSV prevention strategies targeting children under 2 years of age.

This study is among the largest to date to employ a prospective design and consistent methodology (including active surveillance) to determine RSV-LRTI incidence internationally, across diverse global settings. The work has several limitations. First, results are only applicable to the countries/regions included; generalizing the findings to the global population should be done with caution, if at all. Moreover, the sample population participating in the study may not be fully representative of the general population of the country or region from which the children were enrolled. For instance, caesarean delivery rates in some countries were higher than recent regional and subregional estimations [44]. Second, cohort enrolments (and births) were not evenly distributed throughout the calendar year and thus some age groups may have had higher numbers of children exposed to RSV disease activity than others. Finally, although all study sites followed a standard protocol, there may have been subtle differences in case ascertainment and/or follow-up, including variations in the threshold for parents or study staff suspecting an LRTI leading to a participant illness visit for clinical assessment and nasopharyngeal swabs.

CONCLUSIONS

A substantial burden of RSV-LRTIs was observed across sites from all 8 countries, with particularly high incidence rates in the birth cohorts from Honduras, Bangladesh, and Argentina. Infants under 6 months of age had the highest incidence of RSV-LRTI, severe RSV-LRTI, and associated hospitalizations. Our results show that RSV is the most commonly detected virus in infants under 3 months of age diagnosed with severe LRTIs. The significant burden of RSV during infancy and up to 2 years of age underscores the global imperative to prioritize the development and implementation of safe and effective RSV preventive strategies.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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References

1. GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 2017; 282, causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the global burden of disease study 2017. Lancet **2018**; 392:1736–88.
2. World Health Organization. The global health observatory: causes of child death. http://www.who.int/data/gho/data/themes/topics/indicator-groups/indicator-group-details/GHO/causes-of-child-death. Accessed 21 July 2021.
3. Shi T, McAllister DA, O'Brien KL, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study. Lancet **2017**; 390:946–58.
4. Stein RT, Bont LJ, Zar H, et al. Respiratory syncytial virus hospitalization and mortality: systematic review and meta-analysis. Pediatr Pulmonol **2017**; 52:556–69.
5. Pneumonia Etiology Research for Child Health (PERCH) Study Group. Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study. Lancet **2019**; 394:757–79.
6. Shi T, Denouel A, Tietjen AK, et al. Global disease burden estimates of respiratory syncytial virus-associated acute respiratory infection in older adults in 2015: a systematic review and meta-analysis. J Infect Dis **2020**; 222:S577–83.
7. Shi T, Vennard S, Mahdy S, Nair H. Risk Factors for Poor Outcome or Death in Young Children With Respiratory Syncytial Virus–Associated Acute Lower Respiratory Tract Infection: A Systematic Review and Meta-Analysis. J Infect Dis **2022**; 226:S10–6.
8. Tin Tin Htar M, Yerramalla MS, Moïsi JC, Swerdlow DL. The burden of respiratory syncytial virus in adults: a systematic review and meta-analysis. Epidemiol Infect **2020**; 148:e48.
9. Domachowske J, Halczyn J, Bonville CA. Preventing pediatric respiratory syncytial virus infection. Pediatr Ann **2018**; 47:e371–6.
10. Pangesti KNA, El Ghany MA, Kesson AM, Hill-Cawthorne GA. Respiratory syncytial virus in the Western Pacific region: a systematic review and meta-analysis. J Glob Health **2019**; 9:020431.
11. Suleiman-Martos N, Caballero-Vázquez A, Gómez-Urquiza JL, Albendín-García L, Romero-Béjar JL, Cañadas-De la Fuente GA. Prevalence and risk factors of respiratory syncytial virus in children under 5 years of age in the WHO European region: a systematic review and meta-analysis. J Pers Med **2021**; 11:416.
12. Modjarrad K, Giersing B, Kaslow DC, Smith PG, Moorthy VS. WHO consultation on respiratory syncytial virus vaccine development report from a World Health Organization meeting held on 23–24 March 2015. Vaccine **2016**; 34:190–7.
13. Boyce TG, Mellen BG, Mitchel EF Jr, Wright PF, Griffin MR. Rates of hospitalization for respiratory syncytial virus infection among children in Medicaid. J Pediatr **2000**; 137:865–70.
14. Deshpande SA, Northern V. The clinical and health economic burden of respiratory syncytial virus disease among children under 2 years of age in a defined geographical area. Arch Dis Child **2003**; 88:1065–9.
15. Hall CB, Weinberg GA, Iwane MK, et al. The burden of respiratory syncytial virus infection in young children. N Engl J Med **2009**; 360:588–98.
16. Holman RC, Curns AT, Cheek JE, et al. Respiratory syncytial virus hospitalizations among American Indian and Alaska Native infants and the general United States infant population. Pediatrics **2004**; 114:e437–44.
17. Iwane MK, Edwards KM, Szilagyi PG, et al. Population-based surveillance for hospitalizations associated with respiratory syncytial virus, influenza virus, and parainfluenza viruses among young children. Pediatrics **2004**; 113:1758–64.
18. Vicente D, Montes M, Cilla G, Perez-Yarza EG, Perez-Trallero E. Hospitalization for respiratory syncytial virus in the paediatric population in Spain. Epidemiol Infect **2003**; 131:867–72.
19. Bennett S, Woods T, Liyanage WM, Smith DL. A simplified general method for cluster-sample surveys of health in developing countries. World Health Stat Q **1991**; 44:98–106.
20. Nokes DJ, Okiro EA, Ngama M, et al. Respiratory syncytial virus infection and disease in infants and young children observed from birth in Kilifi District, Kenya. Clin Infect Dis **2008**; 46:50–7.
21. Li Y, Reeves RM, Wang X, et al. Global patterns in monthly activity of influenza virus, respiratory syncytial virus, parainfluenza virus, and metapneumovirus: a systematic analysis. Lancet Glob Health **2019**; 7:e1031–45.
22. Staadegaard L, Caini S, Wangchuk S, et al. Defining the seasonality of respiratory syncytial virus around the world: national and subnational surveillance data from 12 countries. Influenza Other Respir Viruses **2021**; 15:732–41.
23. American Academy of Pediatrics Committee on Infectious Diseases, American Academy of Pediatrics Bronchiolitis

Guidelines Committee. Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. Pediatrics **2014**; 134:415–20.
24. European Medicines Agency. Synagis: summary of the European public assessment report. http://www.ema.europa.eu/en/medicines/human/EPAR/synagis#product-information-section. Accessed 23 September 2021.
25. Ginsburg AS, Srikantiah P. Respiratory syncytial virus: promising progress against a leading cause of pneumonia. Lancet Glob Health **2021**; 9:e1644–5.
26. Griffin MP, Yuan Y, Takas T, et al. Single-dose nirsevimab for prevention of RSV in preterm infants. N Engl J Med **2020**; 383:415–25.
27. Drysdale SB, Barr RS, Rollier CS, Green CA, Pollard AJ, Sande CJ. Priorities for developing respiratory syncytial virus vaccines in different target populations. Sci Transl Med **2020**; 12:eaax2466.
28. Giersing BK, Karron RA, Vekemans J, Kaslow DC, Moorthy VS. Meeting report: WHO consultation on respiratory syncytial virus (RSV) vaccine development. Geneva: 25–26 April 2016. Vaccine **2019**; 37:7355–62.
29. PATH. RSV vaccine and mAb snapshot. http://www.path.org/resources/rsv-vaccine-and-mab-snapshot/. Accessed 23 September 2021.
30. Calvo C, García-García ML, Pozo F, et al. Respiratory syncytial virus coinfections with rhinovirus and human bocavirus in hospitalized children. Medicine **2015**; 94:e1788.
31. da Silva ER, Pitrez MCP, Arruda E, et al. Severe lower respiratory tract infection in infants and toddlers from a non-affluent population: viral etiology and co-detection as risk factors. BMC Infect Dis **2013**; 13:41.
32. Mazur NI, Bont L, Cohen AL, et al. Severity of respiratory syncytial virus lower respiratory tract infection with viral coinfection in HIV-uninfected children. Clin Infect Dis **2017**; 64:443–50.
33. Li Y, Pillai P, Miyake F, Nair H. The role of viral co-infections in the severity of acute respiratory infections among children infected with respiratory syncytial virus (RSV): a systematic review and meta-analysis. J Glob Health **2020**; 10:010426.
34. Tempia S, Walaza S, Bhiman JN, et al. Decline of influenza and respiratory syncytial virus detection in facility-based surveillance during the COVID-19 pandemic, South Africa. January to October 2020. Euro Surveill **2021**; 26: 2001600.
35. van Summeren J, Meijer A, Aspelund G, et al. Low levels of respiratory syncytial virus activity in Europe during the 2020/21 season: what can we expect in the coming summer and autumn/winter? Euro Surveill **2021**; 26:2100639.
36. Baker RE, Park SW, Yang W, Vecchi GA, Metcalf CJE, Grenfell BT. The impact of COVID-19 nonpharmaceutical interventions on the future dynamics of endemic infections. Proc Natl Acad Sci USA **2020**; 117:30547–53.
37. Ujiie M, Tsuzuki S, Nakamoto T, Iwamoto N. Resurgence of respiratory syncytial virus infections during COVID-19 pandemic, Tokyo, Japan. Emerg Infect Dis **2021**; 27: 2969–70.
38. von Hammerstein AL, Aebi C, Barbey F, et al. Interseasonal RSV infections in Switzerland—rapid establishment of a clinician-led national reporting system (RSV EpiCH). Swiss Med Wkly **2021**; 151:w30057.
39. Limb M. RSV: The year the respiratory infection "took its gloves off". BMJ **2021**; 374:n2078.
40. Eden JS, Sikazwe C, Xie R, et al. Off-season RSV epidemics in Australia after easing of COVID-19 restrictions. Nat Commun **2022**; 13:2884.
41. Agha R, Avner JR. Delayed seasonal RSV surge observed during the COVID-19 pandemic. Pediatrics **2021**; 148: e2021052089.
42. Centers for Disease Control and Prevention, Health Alert Network. Increased interseasonal respiratory syncytial virus (RSV) activity in parts of the Southern United States. http://emergency.cdc.gov/han/2021/han00443.asp. Accessed 23 September 2021.
43. Romanello M, McGushin A, Di Napoli C, et al. The 2021 report of the lancet countdown on health and climate change: code red for a healthy future. Lancet **2021**; 398:1619–62.
44. Betran AP, Ye J, Moller AB, Souza JP, Zhang J. Trends and projections of caesarean section rates: global and regional estimates. BMJ Glob Health **2021**; 6:e005671.