DOI: 10.1111/tmi.14003

RESEARCH ARTICLE

Risk factors for the development of severe or very severe respiratory syncytial virus-related lower respiratory tract infection in Indian infants: A cohort study in Melghat, India

Rowena Crow[1] | Ashish Satav[2] | Varsha Potdar[3] | Shilpa Satav[2] | Vibhawari Dani[2] | Eric A. F. Simões[1,4]

[1]Department of Paediatric Infectious Diseases, University of Colorado School of Medicine and Children's Hospital Colorado, Aurora, Colorado, USA

[2]MAHAN Trust Mahatma Gandhi Tribal Hospital, Amravati, India

[3]National Institute of Virology, Indian Council of Medical Research, Pune, India

[4]Centre for Global Health, Department of Epidemiology, Colorado School of Public Health, Aurora, Colorado, USA

Correspondence
Eric A. F. Simões, 12123 E 16th Ave, Aurora, Colorado 80045, USA.
Email: eric.simoes@cuanschutz.edu

Ashish Satav, Mahatma Gandhi Tribal Hospital, Karmgram, Utavali, Tahsil Dharni, Amaravati, Maharashtra, India.
Email: drashish@mahantrust.org

Funding information
Bill and Melinda Gates Foundation, Grant/Award Number: OPP1128468

Abstract

Objectives: Respiratory syncytial virus (RSV) is undoubtedly the single most important cause of severe lower respiratory tract infection (LRTI) globally. While new prevention measures in young infants have become available, their use in developing countries is likely many years away. While risk factors for severe or very severe RSV LRTI in impoverished rural areas likely differ to urban areas, there are very few studies, especially those conducted in India, the major country contributing to the global burden of disease.

Methods: Active surveillance for acute LRTI in enrolled infants and children <2 years of age, was conducted through weekly home visits in 93 villages of Melghat, India, from August 2016 to December 2020. Local hospitals and primary health centres were surveyed for admissions of enrolled subjects. Nasopharyngeal swabs were collected from children with severe, or very severe LRTIs and all who died, with RSV testing using nucleic acid tests at ICMR, National Institute of Virology Pune. Risk factors for both RSV associated and non-RSV associated, severe and very severe LRTI were identified through univariate and multivariate logistic regression.

Results: There were 483 severe or very severe RSV LRTI cases and 2807 non-RSV severe or very severe LRTI infections in a cohort of 13,318 children. Weight for age z-score ≤ -2, the use of kerosene or wood for cooking, obtaining drinking water from a public tap and low gestational age significantly increased the risk of RSV LRTI. A higher wealth score index and water purification were protective. Comparison with non-RSV LRTI showed male sex as an additional risk factor. The analysis highlighted the risk of kerosene use [OR = 17.8 (3.0–104.4) ($p \leq 0.001$)] and [OR = 3.4 (0.8–14.4) ($p \leq 0.05$)] for RSV and non-RSV LRTIs, respectively.

Conclusions: Nutritional status and environmental air quality are predisposing factors for developing an RSV LRI in young children, factors which are amenable to environmental and behavioural interventions.

KEYWORDS
environmental pollution, epidemiology, home visitation, longitudinal study

INTRODUCTION

Respiratory syncytial virus (RSV) is the most common cause of acute lower respiratory tract infection (LRTI) in young children, with an estimate of 33 million cases globally in children younger than 5 years in 2019 [1]. It is estimated that more than 95% of RSV-associated acute lower respiratory infection episodes and more than 97% of RSV-attributable deaths were in low-income and middle-income countries (LMICs) [1]. Current estimations of the burden of RSV

Sustainable Development Goals: Good Health and Well-being.

morbidity and mortality in LMICs are limited by the lack of available surveillance data of RSV in the community and may underestimate it. Recent studies in Argentina, India, Pakistan and Zambia have shown a high and previously unmeasured burden of community RSV mortality among young infants in LMICs [2, 3] highlighting the burden of disease in the community.

The anti RSV-specific humanised monoclonal antibody, palivizumab, is an effective prophylactic measure, but its use is restricted to a small number of infants who are at high risk for severe RSV disease. Newer effective RSV prevention treatments have become available. These include passive immunisation by maternal vaccination during pregnancy [4] and new long half-life prophylactic monoclonal antibodies that can be administered at birth [5]. As these new prophylactic measures become widely available to all infants including healthy term infants in high income countries, affordability and access will likely limit their availability in LMICs, at least for the near future [6, 7]. It is important therefore to identify risk factors for RSV LRIs for young children in LMICs, to identify those with the higher risk of severe disease and to also identify risk factors that are amenable to environmental and behavioural interventions.

While hospital-based studies have identified risk factors on the severity of an RSV infection—including age, prematurity and underlying immune, pulmonary or cardiac disease [8, 9]—these studies focused on the most severe infections while underestimating the substantial burden of disease within the community. There are few epidemiological and environmental community-based studies [4–6] and even fewer studies from LMIC countries studies identifying risk factors for an RSV infection [7, 10]. Previous studies have identified factors such as crowding, day-care, birth in the first half of the RSV season and tobacco smoke exposure that increase the severity of RSV infections [11].

The objective of this study was to identify demographic, socioeconomic, and environmental factors in India associated with developing RSV LRIs in children <2 years of age in a rural community with a high infant mortality rate and poor access to care.

METHODS

Study design

This was a prospective active community and hospital surveillance study conducted in Melghat, India, between 1 September 2016 and 31 December 2020. The methods, described in detail elsewhere [2, 12] are briefly summarised below.

Study population

Melghat is located in central Maharashtra, a forested hilly area with a predominantly rural community. Facility-based medical care for the 93 participating tribal villages is provided mainly by five primary health centres, a charitable trust Hospital (MAHAN) and two government district/subdistrict hospitals.

Patient and public involvement

Previous survey-based analysis in Melghat performed in 2002–2003 indicated a very high mortality in children <5 years. It also revealed that the existing health care systems, and government interventions did not cater to the community's needs and socio-cultural practices, resulting in low health-care seeking behaviour.

Community participation and patient and public involvement (PPI) was critical to understand the causes for the high under five and infant mortality. Gramsabha/community meetings were held in 2015–2016 with >60% of adults in the villages in attendance, where it was established that addressing the high infant and under 2 years mortality rate was a priority for the community. Hence, we focused on this as a primary outcome measure. The experience, preferences and health needs of community members were incorporated into the study design with study procedures respecting their culture, traditional practices, language and socioeconomic conditions and in close association with the traditional health system (i.e., birth attendants, community leaders, and traditional faith healers). A final study design and methodology was explained to the community by the principal investigator and study team and informed written consent was obtained from community members.

Patient recruitment

Before study start up, clearances were obtained from the Indian Council of Medical Research, Government of Maharashtra, National Institute of Virology Pune, COMIRB of University of Colorado, and MAHAN Institutional Review Board. An initial baseline population census of all households in the study population of 93 villages was conducted, collecting demographic and socioeconomic factors. This census identified all infants and children 0 to 24 months for recruitment into the initial cohort.

The study implemented trained, socially sensitive, female village health workers (VHWs) to recruit study participants from the community where they lived. Informed written consent was obtained from parents of all children <2 years old who participated in the trial, prior to any study related interventions. Initial recruitment occurred in September 2016 and was followed by the ongoing recruitment of all live-born neonates identified through community pregnancy monitoring [11] up until December 2020.

This enrolment strategy, with an initial baseline cohort and ongoing recruitment of all newborns throughout the study period ensured a consistent and representative distribution of enrolled children aged 0 to 24 months throughout the study period. Subjects were followed longitudinally until they reached 24 months of age, migrated permanently out of the study villages, the parents withdrew consent, the subject died or until the end of the study period.

Risk factor survey

At enrolment, a detailed parental questionnaire was administered capturing the child's birth and medical history, household demographics, socioeconomic data and household environmental factors. Data collection included housing characteristics (e.g., cooking fuel, type of walls, sanitation) and household ownership of durable assets (e.g., car, refrigerator, television).

Active surveillance for development of LRI

Trained VHWs were assigned to each village to monitor all enrolled subjects providing active surveillance of LRTIs in the community. The VHWs performed weekly home visits to assess for acute LRTI in subjects and if present, categorised the severity. Identified LRTI cases were assessed by a supervisor with another home visit [2, 13]. Trained counsellors assigned at the local hospitals and community health centres identified and assessed all enrolled subjects seeking medical care for an acute LRTI.

All VHW's, their supervisors and counsellors were trained, using a modified World Health Organisation (WHO) methodology, in the recognition of WHO defined Pneumonia and the WHO classifications of non-severe, severe and very severe categories of pneumonia [14]. A nasopharyngeal swab was obtained in cases of severe LRTI in both the community and in all hospitalised children with an LRTI, since hospitalisation was considered to be a severe form of LRTI in the community.

VHWs were trained to record all respiratory symptoms, using the 2005 WHO classification to identify severe pneumonia. In our analysis, we defined severe pneumonia as the presence of cough or difficulty in breathing and tachypnoea (≥50 breaths per minute for children aged 2–11 months and ≥ 40 breaths per minute for children aged 12–59 months) plus lower chest indrawing, and very severe LRTI defined as the presence one or more of the observable danger signs: an inability to drink; convulsions; unconsciousness; cyanosis.

Since children may be seen successively by healthcare workers with data longitudinally collected, all assessments within 15 days of the initial assessment were grouped together as an episode of illness, using the worst categories of respiratory rate, chest drawing and danger signs to classify the illness.

Nasopharyngeal swab collection and sample processing

Flocked nasopharyngeal (NP) swabs were collected and transported in PrimStore MTM, (Longhorn Vaccines & Diagnostics, Bethesda, MD) to MAHAN hospital where they were stored at 4–8°C. Batches were transported to ICMR-National Institute of Virology Pune and tested for RSV and other respiratory viruses by real time PCR using standardised protocols [15, 16].

Anthropometry

Anthropometry data was collected on study subjects on a regular basis during home visits.

Data entry

Data entry operators entered data into an access database with data quality checks performed by the data manager. Any incomplete data forms were sent back to the field for correction. The Indian PI (AS) sent data to UCD for analysis and monthly reviews.

Statistical methods

Data were double-entered into a Microsoft Access database. Statistical analysis was performed using Stata statistical software, version 14.2. Differences in demographics were tested for significance using chi square and *t*-tests. Univariate logistic regression analyses were performed to find predictors for the first documented RSV LRI. Only univariate predictors with $p < 0.20$ significance level were considered for inclusion in the logistic multivariate models. For groups of colinear variables, only those with the strongest univariate association were included. A stepwise method was used, starting with the variable with the highest test statistic. The results are reported as adjusted odds ratios (aOR) with 95% confidence intervals (95% CI).

A wealth index score was derived from the household's durable assets and housing characteristics, as described elsewhere [12]. It is a composite measure of a household's socioeconomic status, giving a wealth index score which can be used to determine the subject's wealth quintile (poorest/poor/medium/wealthy/wealthiest) compared to the general rural Indian population.

A mean weight-for age z-score was calculated for each child to provide an overall measure of nutritional status from 0 to 24 months of age that is adjusted for age and sex. Anthropometry data collected during a respiratory illness was disregarded, to ignore acute changes in a child's weight during an illness.

RESULTS

The initial recruitment enrolled 3611 children under two of years age, and a further 9707 newborns were enrolled over the next 4 years. Among these 13,318 subjects, there were 3290 severe or very severe index LRTI cases of which 483 (14.6%) were RSV-associated, with 198/483 (41%)

TABLE 1 Demographics of study population.

	Severe/very severe LRTI RSV-associated	Severe/very severe LRTI—not RSV	Controls	Total cohort
	N **= 483**	***N*** **= 2807**	***N*** **= 10,028**	***N*** **= 13,318**
	n **(%)**	***n*** **(%)**	***n*** **(%)**	***n*** **(%)**
Male	262 (54.2%)	1513 (53.9%)	5008 (49.9%)	6783 (50.9%)
Birth wt (g)	2650.9 (SD = 468.0)	2644.8 (SD = 458.0)	2660.0 (SD = 445.9)	2656.4 (SD = 448.5)
Weight				
Weight-for-age Z-score	−2.1 (SD = 1.1)	−2.0 (SD = 1.2)	−1.8 (SD = 1.2)	−1.9 (SD = 1.2)
Weight-for-age Z-score < −2	208 (43.1%)	1015 (36.2%)	2457 (24.5%)	3680 (27.6%)
Home birth	172 (35.6%)	874 (31.1%)	3271 (24.6%)	4317 (32.4%)
Child caretaker				
Parents	472 (97.7%)	2706 (96.4%)	9410 (93.8%)	12,588 (94.5%)
Grandparents	10 (0.1%)	56 (2.0%)	288 (2.9%)	354 (2.7%)
Other/Not known	1 (0.0%)	45 (1.6%)	330 (3.3%)	376 (2.8%)
Parents				
Mothers age (years)	23.6 (SD = 3.3)	23.5 (SD = 3.3)	23.8 (SD = 3.5)	23.8 (SD = 3.4)
Mothers education				
No education	51 (10.6%)	263 (9.4%)	858 (8.6%)	1172 (8.8%)
Some primary education	181 (37.5%)	999 (35.6%)	3273 (32.6%)	4453 (33.4%)
More than primary education	248 (51.3%)	1517 (54.0%)	5817 (58.0%)	7582 (56.9%)
Mothers employment status				
Employed	174 (36.0%)	973 (34.7%)	3927 (39.2%)	5074 (38.1%)
Not employed	298 (61.7%)	1771 (63.1%)	5929 (59.1%)	7998 (60.1%)
Other/unknown	11 (2.3%)	63 (2.2%)	172 (1.7%)	246 (1.8%)
Mothers employment type				
Unskilled labour	112 (64.4%)	625 (64.2%)	2484 (63.3%)	3221 (63.5%)
Farmer	58 (33.3%)	313 (32.2%)	1342 (34.2%)	1713 (33.8%)
Other	4 (2.3%)	34 (3.5%)	1436 (36.6%)	132 (2.6%)
Fathers age (years)	26.7 (SD = 4.0)	26.8 (SD = 3.9)	26.9 (SD = 4.0)	26.8 (SD = 3.9)
Fathers education				
No education	30 (6.2%)	123 (4.4%)	448 (4.5%)	601 (4.5%)
Some primary education	136 (28.2%)	807 (28.7%)	2489 (24.8%)	3432 (25.8%)
More than primary education	315 (65.2%)	1863 (66.4%)	7041 (70.2%)	9219 (69.2%)
Fathers employment status				
Employed	456 (94.4%)	2683 (95.6%)	9576 (95.5%)	12,715 (95.5%)
Not employed	19 (3.9%)	101 (3.6%)	346 (3.5%)	466 (3.5%)
Other/Unknown	8 (1.7%)	23 (0.8%)	106 (1.1%)	137 (1.0%)
Fathers employment type				
Unskilled labour	292 (64.0%)	1579 (58.9%)	5517 (57.6%)	7388 (58.1%)
Farmer	150 (32.9%)	1005 (37.5%)	3683 (38.5%)	4838 (38.0%)
Other	163 (35.7%)	1099 (41.0%)	353 (3.7%)	476 (3.7%)
Household details				
Other children <5 years				
No other children	0 (0.0%)	49 (1.7%)	127 (1.3%)	176 (1.3%)
1 other child	205 (42.4%)	1262 (45.0%)	4438 (44.3%)	5905 (44.3%)
2 others	194 (40.2%)	1066 (38.0%)	3998 (39.9%)	5258 (39.5%)
>2 other	84 (17.4%)	403 (14.4%)	1193 (11.9%)	1680 (12.6%)

TABLE 1 (Continued)

	Severe/very severe LRTI RSV-associated	Severe/very severe LRTI—not RSV	Controls	Total cohort
	$N = 483$	$N = 2807$	$N = 10{,}028$	$N = 13{,}318$
	n (%)	n (%)	n (%)	n (%)
Other children 5–14 years				
No other children	340 (70.4%)	2023 (72.1%)	6974 (69.5%)	9337 (70.1%)
1 other child	85 (17.6%)	449 (16.0%)	1636 (16.3%)	2170 (16.3%)
2 others	43 (8.9%)	199 (7.1%)	739 (7.4%)	981 (7.4%)
>2 other	15 (3.1%)	109 (3.9%)	407 (4.1%)	531 (4.0%)
National wealth quintile				
Poorest	206 (42.7%)	1053 (37.5%)	3488 (34.8%)	4747 (35.6%)
Poor	160 (33.1%)	945 (33.7%)	3268 (32.6%)	4373 (32.8%)
Medium	89 (18.4%)	565 (20.1%)	2053 (20.5%)	2707 (20.3%)
Wealthy	22 (4.6%)	193 (6.9%)	846 (8.4%)	1061 (8.0%)
Wealthiest	6 (1.2%)	51 (1.8%)	373 (3.7%)	430 (3.2%)
Wealth Score Index	−1.8 (SD = 1.4)	−1.6 (SD = 1.5)	−1.4 (SD = 1.7)	−1.5 (SD = 1.6)

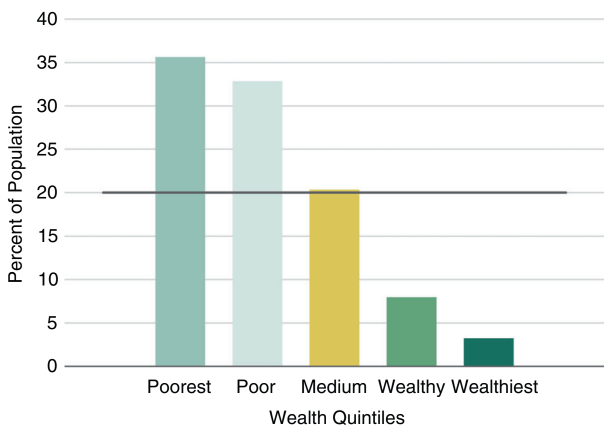

FIGURE 1 The wealth quintile distribution of the study population.

hospitalised. The first index episode of an RSV-associated LRI occurred at a mean age of 9.4 months (range: 0–24), with an overall incidence of 3.6% and 16 RSV+ deaths.

Table 1 shows the demographics of the total cohort and three comparison groups: the 483 RSV-positive severe or very severe LRTI subjects, the 2807 subjects with RSV-negative severe or very severe LRTI and 10,028 control subjects.

Control subjects were defined as children who did not have a severe or very severe LRTI. Overall, 6783 (50.9%) boys were enrolled in the study. Parental characteristics, such as age, education and employment were similar for the three groups. The socioeconomic status of the study population compared to the rural population in India is represented as a wealth quintile distribution, shown in Figure 1. The study population showed more subjects in the lower wealth quintiles with 35.6% in the 'poorest' category and 32.8% in the 'poor' category compared to the 25% expected for each wealth quintile, if the population was representative of the general rural population.

The total cohort had a median weight-for-age z-score of −1.9 (SD = 1.2) with 3680 (27.6%) subjects having a z-core ≤−2 (2 SD below the reference median). The detailed household socioeconomic and environmental characteristics for each group is shown Table S1. For the total cohort, housing consisted of buildings constructed with mud/cow dung/stone (35.9%) or thatch (33.5%) rather than cement/bricks (28.4%). The housing had flooring that is predominantly mud/cow dung (91.6%) with tin roofing (65.4%). Only 24.8% had their own household water tap and few dwellings had a home toilet (14.2%). The most common source of drinking water was from a public tap (39.9%). The majority of households (81.1%) used a water purification method for drinking water, with chlorination the most common method (59.3%). For cooking, 92.3% of households used firewood. Other fuel sources were gas (4.7%), cow dung (0.6%) and kerosene (0.1%).

Table 2 shows the univariate risk factor analysis for RSV-associated severe or very severe LRTI with the associated odds ratios (ORs).

Significant risk factors include low gestational age at birth, having a weight-for-age z score <−2, the mother or father with primary education or less and the father employed in unskilled labour. Home environment risk factors include the use of wood or kerosene as a cooking fuel, obtaining drinking water from a public tap and having no household toilet facility. The use of a purification method for drinking water was protective.

A multivariate analysis gave adjusted odds ratios (aOR) showing weight-for-age z-score ≤−2, the use of kerosene or wood for cooking, obtaining drinking water from a public tap and low gestational age at birth significantly increased the risk of an RSV LRTI (Table 3).

TABLE 2 Univariate risk factors for severe/very severe RSV LRTI and non RSV LRTI.

	RSV LRTI infections		LRTI infections (RSV excluded)	
Characteristic	**Odds ratio (95% CI)**	***p***	**Odds ratio (95% CI)**	***p***
Male	1.2 (1.0–1.4)	NS	1.2 (1.1–1.3)	≤0.001
Birth weight (g)	1.0 (1.0–1.0)	NS	1.0 (1.0–1.0)	NS
Gestational age at birth (weeks)	0.9 (0.9–1.0)	≤0.001	0.9 (0.9–1.0)	≤0.001
Preterm	1.2 (0.7–2.0)	NS	1.1 (0.9–1.5)	NS
Home birth	1.1 (0.9–1.4)	NS	0.9 (0.9–1.0)	NS
Mothers age	1.0 (1.0–1.0)	NS	1.0 (1.0–1.0)	≤0.001
Mother—primary education or less	1.3 (1.1–1.6)	≤0.01	1.2 (1.1–1.3)	≤0.001
Mother—unskilled labour	0.9 (0.7–1.1)	NS	0.9 (0.8–1.0)	≤0.01
Mother—not employed	1.1 (0.9–1.4)	NS	1.2 (1.1–1.3)	≤0.001
Fathers age	1.0 (1.0–1.0)	NS	1.0 (1.0–1.0)	≤0.001
Father—primary education or less	1.3 (1.0–1.5)	≤0.05	1.2 (1.1–1.3)	≤0.001
Father—unskilled labour	1.2 (1.0–1.5)	≤0.06	1.0 (1.0–1.1)	NS
Other children 0 to 5 years	1.1 (0.9–1.4)	NS	1.0 (0.9–1.0)	NS
Wealth index score—rural	0.9 (0.8–0.9)	≤0.001	0.9 (0.9–1.0)	≤0.001
Weight z score < −2	2.3 (1.9–2.8)	≤0.001	1.7 (1.6–1.9)	≤0.001
Kerosene as cooking fuel	6.9 (1.4–34.4)	≤0.05	2.2 (0.6–7.9)	NS
Wood as cooking fuel	3.2 (1.9–5.5)	≤0.001	2.0 (1.6–2.4)	≤0.001
No handwashing after toilet	2.9 (1.4–6.2)	≤0.01	1.1 (0.7–1.9)	NS
Water source from public tap	1.4 (1.2–1.7)	≤0.001	1.1 (1.0–1.2)	≤0.01
Water source from own tap	0.9 (0.7–1.1)	NS	0.8 (0.8–0.9)	≤0.001
Public water source	1.3 (1.0–1.5)	≤0.05	1.2 (1.1–1.3)	≤0.001
Water source from public well	0.7 (0.5–1.0)	≤0.05	0.9 (0.7–1.0)	≤0.05
Water source from public pump	1.0 (0.8–1.3)	NS	1.2 (1.1–1.4)	≤0.001
Purification of drinking water used	0.7 (0.5–0.9)	≤0.001	0.8 (0.8–0.9)	≤0.01
No home toilet facility	1.7 (1.2–2.3)	≤0.001	1.2 (1.0–1.3)	≤0.05

TABLE 3 Multivariate risk factors for RSV LRTI and non RSV LRTI.

	RSV LRTI infections		LRTI infections (RSV excluded)	
	$n = 483$		$n = 2807$	
Characteristic	**Odds ratio (95% CI)**	***p***	**Odds ratio (95% CI)**	***p***
Male	1.1 (1.0–1.4)	NS	1.2 (1.1–1.3)	≤0.001
Weight z-score < −2	2.2 (1.8–2.6)	≤0.001	1.7 (1.5–1.8)	≤0.001
Wealth score rural	0.9 (0.9–1.0)	NS	1.0 (1.0–1.0)	NS
Cooking fuel—kerosene	17.8 (3.0–104.4)	≤0.001	3.4 (0.8–14.4)	NS
Cooking fuel—wood	2.2 (1.2–4.1)	≤0.01	1.6 (1.3–1.9)	≤0.001
Drinking water purified	0.8 (0.6–1.0)	≤0.05	0.9 (0.8–1.0)	≤0.05
Drinking water from public tab	1.3 (1.1–1.6)	≤0.01	1.1 (1.0–1.2)	NS
Gestational age at birth (weeks)	0.9 (0.9–1.0)	≤0.05	1.0 (0.9–1.0)	≤0.001
Mother—primary education or less	1.1 (0.9–1.4)	NS	1.1 (1.0–1.2)	≤0.05
Father—unskilled labour	1.1 (0.9–1.4)	NS	1.0 (0.9–1.1)	NS

Comparison with non-RSV LRTI showed male sex as an additional risk factor and did not find higher wealth index score to be significant. The analysis highlighted, the risk of kerosene use [aOR = 17.8 (3.0–104.4), ($p \leq 0.001$)] for RSV LRTIs.

DISCUSSION

This study, conducted in a poor rural community, enrolled over 13,000 newborns, infants, and children, and followed them with active surveillance for the first 2 years of life. We identified the use of either kerosene or wood for cooking in the child's household, as a risk factor for RSV LRTI.

Infant and child acute respiratory illness has been associated with biomass burning for cooking, in developing countries [17, 18], but the association with RSV LRTI has not been well studied. The effect of kerosene fuel and its association with RSV LRTI is also not well defined, but kerosene is often assumed to be "cleaner burning" than biomass fuels, such as wood and dung, and regarded as a "step up the energy ladder" and provide less indoor air pollution in comparison to wood burning. However, the magnitude of emissions and level of indoor air pollution exposure from kerosene combustion can vary greatly, depending on the stove design, operation, and fuel grade [19]. Unfortunately, it was beyond the scope of this study to collect this level of detail and obtain levels of indoor air pollution.

Generally, household air pollution has been previously recognised as a risk factor for LRTIs and associated with the substantial burden of disease in LMICs [17]. But there is sparse data on the effect of household air pollution on RSV LRTIs and in particular in LMICs, where the factors affecting indoor air quality will differ substantially from an industrialised country. Studies that can quantify the exposure to emissions from both wood and kerosene fuel, providing a dose-based effect on LRTIs in young children are important to guide interventions that reduce risk. A community-based study in Guatemala [20], performed active surveillance for pneumonia in children <18 months while collecting regular blood carbon monoxide levels as a measure of exposure to emissions from wood fuel. They found that providing a chimney stove reduced carbon monoxide exposure by 50% leading to a significant reduction in severe pneumonia, but not for RSV LRTI.

Further support on the connection between air quality and RSV LRTIs comes from studies on outdoor air pollution. A study based in the USA found some evidence of increased risk of bronchiolitis attributable to chronic traffic-derived particulate matter exposure particularly for infants born just before or during peak RSV season [21]. Wrotek et al. [22] concluded that air pollutants play a significant role in RSV hospitalizations in Polish children in their multivariate analysis.

It is theorised that ambient air pollution, induces host susceptibility to a respiratory viral infection [21, 23]. Air pollution may induce proinflammatory mediators and altered immune function that, increase lung susceptibility to virally induced bronchiolitis [24, 25]. The combustion of both wood and kerosene for cooking has been shown to increase levels of carbon monoxide and fine particulate matter in the air [26]. The combustion of kerosene indoors can also expose occupants to air contaminants, including particulate matter (PM), carbon monoxide, polycyclic aromatic hydrocarbons and volatile organic compounds, even during normal operation [23]. The fine PM2.5 (particulate matter with an aerodynamic diameter ≤10 and 2.5 μm) emitted from kerosene combustion enables inhaled particles to be deposited in the deep lung [22]. As infants and young children breathe faster than adults, they can inhale more pollutants in proportion to their body weight than adults at a time when their immune systems and organs are still developing.

Kerosene is used minimally in this study population (0.1%) but is an important finding as it still has widespread use in many developing countries, replacing the use of biomass fuels, especially in urban populations where electricity and liquefied pressured gas (LPG) can be expensive or unavailable [27]. A similar surveillance study in Indonesia, where kerosene is the predominant fuel used for cooking, also found kerosene a significant risk factor for RSV LRTIs (aOR = 2.16) along with other factors that affected indoor air quality, such window ventilation [13].

Analyses of anthropometry data collected throughout the study showed the population to be significantly underweight with a median weight-for-age z-score (WFA) of −1.9 and with 28% scoring ≤−2 z-scores; an indicator of being undernourished. Low body weight showed to be a significant factor in both univariate and multivariate analyses for both RSV associated LRTI and non-RSV LRTI (aOR = 2.2 [1.8–2.6], $p \le 0.001$) and (aOR = 1.7 [1.5–1.8], $p \le 0.001$), respectively, suggesting low body weight has more impact on the risk of RSV LRTI than LRTI due to other causes. This finding is supported by a study in the Philippines [28] but contrasts with studies finding RSV children are relatively better nourished than other pneumonias [29–31]. Our finding may reflect the overall poor nutritional status of this study population and the lack of large-scale community-based studies in similar populations.

A somewhat unexpected finding was the association between drinking water source and the decreased risk when a water purification method was used for drinking water. As the RSV pathogen and most other respiratory infections are not contracted through water, these measures are likely proxies for the sanitation level in the household. Obtaining drinking water from a public tap likely correlates with a lack of an at-home water supply and leading to increased difficulty in maintaining basic sanitation at the home. Lack of home water service has been previously associated with higher RSV LRTI hospitalisation rates in children <5 years, in a study in rural Alaska [32], when comparing hospitalisation rates in regions with low and higher proportion of home water service to regions.

Other measures of sanitation; handwashing after using the toilet and having no at-home toilet facility reached statistical significance in the univariate analyses for RSV LRTI but not in the multivariate analyses, adding to our hypothesis that sanitation at home is an important factor. This is supported by a systematic review and meta-analysis, concluding that interventions promoting handwashing with soap can reduce acute respiratory illness in LMICs, and could help to prevent the large burden of respiratory disease [33]. Our finding that collecting water from a public tap is a risk factor may also be due to social behaviour, as in this community women will often congregate at the public tap, bringing their young children which would increase their exposure to respiratory pathogens.

The relatively high mean age of the first episode of severe RSV LRTI has been has been reported [12]. Most hospital-based studies show a younger age for severe disease, but active surveillance in the community, captures the entire burden of disease. A community-based study from Indonesia [13] and older community-based studies [34–36] showed a similar distribution of disease. Interestingly, we did not find low birth weight to be correlated with increased risk of RSV LRTI, but rather poor infant growth. A large cohort study in Philippines found that poor infant growth increases the risk for severe RSV infection hospitalisation [27].

Risk factors for RSV LRTI identified in other studies [37, 38] did not reach statistical significance in our analyses. This includes male sex and other young children in the household. It appears that in this population the identified environmental risk factors play a larger role in increasing the risk of developing an RSV LRTI.

The comparison of RSV LTRI cases with non-RSV LRTI shows which risk factors appear to be specific to RSV. However, non-RSV LRTI cases will, by definition, be due to multiple pathogens, both viral and bacterial and therefore be a less homogeneous group as this should be considered in interpretation of results.

Limitations to our study include the possibility of multicollinearity due to the type of cooking fuel used in households being related to their poverty index score, as kerosene users are likely to reside in lower socioeconomic neighbourhoods than LPG/electricity users [27]. Both measures can be seen as proxies for socioeconomic status. Also, while the study collected simple measures of indoor exposure to air pollution and found wood and kerosene fuel to be contributing factors to the risk of RSV LRTI, it is not able to directly quantify the level of emissions contributing to indoor air pollution or the level of outdoor pollution. The nutritional status of children in the different cohorts were compared as mean WFA z-scores representing nutritional status from 0 to 24 months which may fail to reflect the nutritional status of the RSV LRTI children just before infection.

CONCLUSIONS

This study shows that nutritional status and environmental air quality are predisposing factors for developing an RSV LRI, factors that are amenable to environmental and behavioural interventions.

ACKNOWLEDGEMENTS

Funding: This work was supported in whole or in part by the Bill & Melinda Gates Foundation OPP1128468. Under the grant conditions of the foundation, a Creative Commons Attribution 4.0 Generic License has already been assigned to the Author Accepted Manuscript version that might arise from this submission. Caring Friends and Bajaj Holdings and Investment Department. We would like to thank Niteen Wairagkar, Padmini Srikantiah and Prachi Vora from the Bill and Melinda Gates foundation for their input and guidance at every stage of this study; Members of the steering committee Prof. Shabir A. Madhi, Dean: Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa, Dr. Sanjay Mehendale, Director Research, PD Hinduja Hospital and Medical Centre, Pune India, Former Additional Director General, Indian Council of Medical Research New Delhi India; Prof. Sanjay Zodpey, Vice President—Academics, Public Health Foundation of India, New Delhi, Director—Indian Institute of Public Health, Delhi and Dr. Subhash R. Salunke Senior Advisor, PHFI and Officiating Director, IIPH-Bhubaneswar and former Director General Health Services of Maharashtra State. We would like to thank the MAHAN trust foundation, Dr. Kavita Satav, staff and data entry team, all the study team the supervisors, counsellors and village health workers who worked tirelessly through the study. Dr. Shinde who was the paediatrician that took care of our study subjects at the MAHAN hospital and was one of the readers of the verbal autopsies. We acknowledge with gratitude the assistance of the Hon. District Collector and Additional District Medical Officer Dr. Bobade, the paediatricians at the subdistrict hospital, the 93 village Panchayat Heads and Council Members, Dr. Shubhada Khirwadakr, Dr. Abhijit Bharadwaj, Dr. Deoghare, and Dr. Patil who taught all our supervisors and counsellors as well as the local traditional healers and auxiliary nurse midwives in grief counselling and provided grief counselling; and all the traditional midwives and auxiliary midwives who assisted with sample collection and grief counselling. We acknowledge Dr. Elisabeth Root, Ohio State University, who set up the Geographic Information System at the site. Finally and most importantly, we acknowledge with gratitude all of the families and their young children that participated in the study who graciously let us into their homes and allowed us to follow their babies throughout the study and especially those families with babies that died, to whom we could offer no solace, except to know that their participation will help other babies in the future from dying of preventable causes.

DATA AVAILABILITY STATEMENT

Data are available upon reasonable request. Aggregate data that underlie the results reported in this article, after de-identification (text, tables, figures and appendices) will be shared. As per guidelines of Government of India (GOI), individual participant data will not be available. Data will be made available from 9 months up until 36 months following article publication. Data will be shared with investigators whose proposed use of the data has been approved by an independent review committee, the GOI and ethical review by the ICMR and Government of Maharashtra (India), Tribal Section clearance, identified for this purpose. Proposals may be submitted up to 35 months following article publication. After 36 months the data will be available with investigator support.

ORCID

Ashish Satav https://orcid.org/0000-0002-2694-1082
Vibhawari Dani https://orcid.org/0000-0002-2265-1352

REFERENCES

1. Li Y, Wang X, Blau DM, Caballero MT, Feikin DR, Gill CJ, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in children younger than 5 years in 2019: a systematic analysis. Lancet. 2022; 399(10340):2047–64.
2. Simões EAF, Dani V, Potdar V, Crow R, Satav S, Chadha MS, et al. Mortality from respiratory syncytial virus in children under 2 years of age: a prospective community cohort study in rural Maharashtra, India. Clin Infect Dis. 2021;73(Suppl_3):S193–202.
3. Srikantiah P, Vora P, Klugman KP. Assessing the full burden of respiratory syncytial virus in young infants in low- and middle-income countries: the importance of community mortality studies. Clin Infect Dis. 2021;73(Suppl_3):S177–9.
4. Simões EAF, Center KJ, Tita ATN, Swanson KA, Radley D, Houghton J, et al. Prefusion F protein-based respiratory syncytial virus immunization in pregnancy. N Engl J Med. 2022;386(17):1615–26.
5. Simões EAF, Madhi SA, Muller WJ, Atanasova V, Bosheva M, Cabañas F, et al. Efficacy of nirsevimab against respiratory syncytial virus lower respiratory tract infections in preterm and term infants, and pharmacokinetic extrapolation to infants with congenital heart disease and chronic lung disease: a pooled analysis of randomised controlled trials. Lancet Child Adolesc Health. 2023;7(3):180–9.
6. Li Y, Johnson EK, Shi T, Campbell H, Chaves SS, Commaille-Chapus C, et al. National burden estimates of hospitalisations for acute lower respiratory infections due to respiratory syncytial virus in young children in 2019 among 58 countries: a modelling study. Lancet Respir Med. 2021;9(2):175–85.
7. Carbonell-Estrany X, Rodgers-Gray BS, Paes B. Challenges in the prevention or treatment of RSV with emerging new agents in children from low- and middle-income countries. Expert Rev Anti Infect Ther. 2021;19(4):419–41.
8. Hall CB, Weinberg GA, Iwane MK, Blumkin AK, Edwards KM, Staat MA, et al. The burden of respiratory syncytial virus infection in young children. N Engl J Med. 2009;360(6):588–98.
9. DeVincenzo JP. Factors predicting childhood respiratory syncytial virus severity: what they indicate about pathogenesis. Pediatr Infect Dis J. 2005;24(11):S177–83.
10. Weber MW, Milligan P, Sanneh M, Awemoyi A, Dakour R, Schneider G, et al. An epidemiological study of RSV infection in The Gambia. Bull World Health Organ. 2002;80(7):562–8.
11. Simoes EA. Environmental and demographic risk factors for respiratory syncytial virus lower respiratory tract disease. J Pediatr. 2003; 143(5):118–26.
12. Satav A, Crow R, Potdar V, Dani V, Satav S, Chadha M, et al. The burden of respiratory syncytial virus in children under 2 years of age in a rural Community in Maharashtra, India. Clin Infect Dis. 2021;73(Suppl_3):S238–47.
13. Crow R, Mutyara K, Agustian D, Kartasasmita CB, Simões EAF. Risk factors for respiratory syncytial virus lower respiratory tract infections: Evidence from an Indonesian Cohort. Viruses. 2021;13(2):331.
14. WHO. In: Organisation WH, editor. Handbook: IMCI integrated management of childhood illness. Geneva, Switzerland: World Health Organisation; 2005.
15. Koul PA, Mir H, Saha S, Chadha MS, Potdar V, Widdowson MA, et al. Respiratory viruses in returning Hajj & Umrah pilgrims with acute respiratory illness in 2014-2015. Indian J Med Res. 2018;148(3):329–33.
16. CDC. CDC protocol of realtime RTPCR for influenza A(H1N1). 2009. Available at: https://www.who.int/csr/resources/publications/swineflu/CDCRealtimeRTPCR_SwineH1Assay-2009_20090430.pdf?ua=1
17. Lee KK, Bing R, Kiang J, Bashir S, Spath N, Stelzle D, et al. Adverse health effects associated with household air pollution: a systematic review, meta-analysis, and burden estimation study. Lancet Glob Health. 2020;8(11):e1427–34.
18. Arku RE, Brauer M, Duong M, Wei L, Hu B, Ah Tse L, et al. Adverse health impacts of cooking with kerosene: a multi-country analysis within the prospective urban and rural epidemiology study. Environ Res. 2020;188:109851.
19. Bruce N, Pope D, Rehfuess E, Balakrishnan K, Adair-Rohani H, Dora C. WHO indoor air quality guidelines on household fuel combustion: strategy implications of new evidence on interventions and exposure-risk functions. Atmos Environ. 2015;106:451–7.
20. Smith KR, McCracken JP, Weber MW, Hubbard A, Jenny A, Thompson LM, et al. Effect of reduction in household air pollution on childhood pneumonia in Guatemala (RESPIRE): a randomised controlled trial. Lancet. 2011;378(9804):1717–26.
21. Karr CJ, Rudra CB, Miller KA, Gould TR, Larson T, Sathyanarayana S, et al. Infant exposure to fine particulate matter and traffic and risk of hospitalization for RSV bronchiolitis in a region with lower ambient air pollution. Environ Res. 2009;109(3):321–7.
22. Wrotek A, Badyda A, Czechowski PO, Owczarek T, Dąbrowiecki P, Jackowska T. Air pollutants' concentrations are associated with increased number of RSV hospitalizations in polish children. J Clin Med. 2021;10(15):3224.
23. Karr C, Lumley T, Shepherd K, Davis R, Larson T, Ritz B, et al. A case–crossover study of wintertime ambient air pollution and infant bronchiolitis. Environ Health Perspect. 2006;114(2):277–81.
24. Harrod KS, Jaramillo RJ, Rosenberger CL, Wang S-Z, Berger JA, McDonald JD, et al. Increased susceptibility to RSV infection by exposure to inhaled diesel engine emissions. Am J Respir Cell Mol Biol. 2003;28(4):451–63.
25. Lambert AL, Mangum JB, DeLorme MP, Everitt JI. Ultrafine carbon black particles enhance respiratory syncytial virus-induced airway reactivity, pulmonary inflammation, and chemokine expression. Toxicol Sci. 2003;72(2):339–46.
26. Ranathunga N, Perera P, Nandasena S, Sathiakumar N, Kasturiratne A, Wickremasinghe R. Effect of household air pollution due to solid fuel combustion on childhood respiratory diseases in a semi urban population in Sri Lanka. BMC Pediatr. 2019;19(1):306.
27. Smith KR, Apte MG, Yuqing M, Wongsekiarttirat W, Kulkarni A. Air pollution and the energy ladder in Asian cities. Energy. 1994;19(5): 587–600.
28. Paynter S, Ware RS, Lucero MG, Tallo V, Nohynek H, Weinstein P, et al. Malnutrition: a risk factor for severe respiratory syncytial virus infection and hospitalization. Pediatr Infect Dis J. 2014;33(3):267–71.
29. Adegbola RA, Falade AG, Sam BE, Aidoo M, Baldeh I, Hazlett D, et al. The etiology of pneumonia in malnourished and well-nourished Gambian children. Pediatr Infect Dis J. 1994;13(11):975–82.
30. Djelantik IGG, Gessner BD, Soewignjo S, Steinhoff M, Sutanto A, Widjaya A, et al. Incidence and clinical features of hospitalization because of respiratory syncytial virus lower respiratory illness among children less than two years of age in a rural Asian setting. Pediatr Infect Dis J. 2003;22(2):150–6.
31. Loscertales MP, Roca A, Ventura PJ, Abacassamo F, Santos FD, Sitaube M, et al. Epidemiology and clinical presentation of respiratory syncytial virus infection in a rural area of southern Mozambique. Pediatr Infect Dis J. 2002;21(2):148–55.
32. Hennessy TW, Ritter T, Holman RC, Bruden DL, Yorita KL, Bulkow L, et al. The relationship between in-home water service and the risk of respiratory tract, skin, and gastrointestinal tract infections among rural Alaska natives. Am J Public Health. 2008;98(11):2072–8.
33. Ross I, Bick S, Ayieko P, Dreibelbis R, Wolf J, Freeman MC, et al. Effectiveness of handwashing with soap for preventing acute respiratory infections in low-income and middle-income countries: a systematic review and meta-analysis. Lancet. 2023;7:218–24.
34. Glezen WP, Loda FA, Clyde WA Jr, Senior RJ, Sheaffer CI, Conley WG, et al. Epidemiologic patterns of acute lower respiratory disease of children in a pediatric group practice. J Pediatr. 1971;78(3):397–406.
35. Murphy TF, Henderson FW, Clyde WA Jr, Collier AM, Denny FW. Pneumonia: an eleven-year study in a pediatric practice. Am J Epidemiol. 1981;113(1):12–21.
36. Henderson FW, Clyde WA Jr, Collier AM, Denny FW, Senior RJ, Sheaffer CI, et al. The etiologic and epidemiologic spectrum of bronchiolitis in pediatric practice. J Pediatr. 1979;95(2):183–90.
37. Okiro EA, Ngama M, Bett A, Cane PA, Medley GF, James Nokes D. Factors associated with increased risk of progression to respiratory

syncytial virus-associated pneumonia in young Kenyan children. Trop Med Int Health. 2008;13(7):914–26.

38. Shi T, Balsells E, Wastnedge E, Singleton R, Rasmussen ZA, Zar HJ, et al. Risk factors for respiratory syncytial virus associated with acute lower respiratory infection in children under five years: systematic review and meta-analysis. J Glob Health. 2015;5(2):020416.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Crow R, Satav A, Potdar V, Satav S, Dani V, Simões EAF. Risk factors for the development of severe or very severe respiratory syncytial virus-related lower respiratory tract infection in Indian infants: A cohort study in Melghat, India. Trop Med Int Health. 2024. https://doi.org/10.1111/tmi.14003