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Incidence, viral etiology, and risk factors of wheezing in children under two years of age: findings from a low-income urban community in Dhaka, Bangladesh

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Abstract

Background The burden of early childhood wheezing in Bangladesh remains poorly characterised, despite infants' exposure to viral pathogens and substantial particulate pollution. We conducted a longitudinal birth cohort study to estimate incidence, describe viral detections around episodes, and identify major risk factors of wheezing in children under two years of age.

Method We enrolled 447 newborns between May 2015 and March 2016 and followed them through 2022. In this study, we restricted the analysis to follow-ups conducted during the first two years of life through twice-weekly household surveillance. Physicians confirmed wheezing episodes, and nasopharyngeal wash samples collected during episodes were tested by rRT-PCR for major respiratory viruses, including rhinovirus (RV), respiratory syncytial virus (RSV), human metapneumovirus (hMPV), influenza virus, human parainfluenza virus (HPIV), and adenovirus. Incidence rates were calculated using Poisson-based methods with 95% confidence intervals, and multivariable Cox proportional hazards regression models were used to estimate adjusted hazard ratios (aHRs) to identify risk factors for wheezing.

Results A total of 276 wheezing episodes were identified among 163 children. The incidence of wheezing was 35 episodes/100 child-years (95% CI: 31–40). Respiratory viruses were detected in 74.6% of wheezing episodes, yielding a viral wheezing incidence of 26 episodes/100 child-years (95% CI: 23–30). RV (35%) and RSV (22%) were the most commonly detected pathogens. Male sex (aHR: 1.48, 95% CI: 1.08–2.03), greater daily hours of $PM_{2.5}$ concentrations above 50 µg/m^3 (aHR: 1.05, 95% CI: 1.02–1.10), kerosene stove use (aHR: 3.23, 95% CI: 2.33–4.45), and wheezing episodes after intervals preceded by a prior ARI (aHR: 1.41, 95% CI: 1.09–1.83) were associated with an increased hazard of wheezing among the children.

Conclusion Early childhood wheezing was common, and the majority of these episodes were caused by viral pathogens in this high-density setting. Elevated particulate exposure and kerosene stove use further increased the

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risk. Interventions that reduce household particulate exposure and improve early wheeze management may help lower respiratory morbidity in similar environments.

Keywords Viral wheezing, Rhinovirus, RSV, $PM_{2.5}$, Kerosene stove

Background

'Wheezing' is a continuous, musical, high-pitched sound produced due to narrowed lower airways and is a common manifestation of respiratory illness in infancy and early childhood [1]. In this age group, wheezing arises from a combination of a child's inherent susceptibility, including airway reactivity and age-dependent immune responses [2]. External exposures, such as tobacco smoke or suboptimal breastfeeding, further increase this vulnerability [3, 4]. Viral pathogens are also a major contributing factor to childhood wheezing, as infections commonly spread to the lower airways and trigger acute wheezing episodes in this age group. The viruses most frequently associated with childhood wheezing include respiratory syncytial virus (RSV), rhinovirus (RV), human parainfluenza virus (HPIV), human metapneumovirus (hMPV), and influenza virus [5, 6]. Among these, RSV and RV predominate and account for the majority of wheezing episodes [7–9].

Global data demonstrate that wheezing is widespread in early childhood. The International Study of Wheezing in Infants (EISL), which surveyed more than 30,000 infants across Latin American and European urban settings, reported an overall prevalence of 45% for any wheezing during the first year of life [10, 11]. Across population-based studies, the prevalence of wheezing ranges from 16% to 40%, depending on the study design and diagnostic criteria [12, 13]. Additionally, community-based evidence from low- and middle-income countries (LMICs) also indicates a high burden of wheezing in early childhood. Studies from South Asia and sub-Saharan Africa report frequent wheezing episodes in children, with estimates ranging from 21% to 50% [14–16].

Beyond its high prevalence, early childhood wheezing is associated with substantial morbidity and frequent healthcare use. In the EISL cohort, nearly 60% of infants with recurrent wheeze experienced severe episodes, more than 70% sought emergency care, and approximately 27% were admitted to the hospital [10]. Severe episodes are particularly common when wheezing occurs alongside viral lower respiratory infections caused by RSV or RV [17, 18]. Furthermore, although mortality from isolated wheezing is rare, wheeze accompanying severe viral bronchiolitis has been found to contribute to infant respiratory deaths in LMICs [19]. Wheezing in infancy also leads to long-term consequences in later life [20]. Impaired lung function [21], chronic obstructive pulmonary disease (COPD), and asthma during adulthood [22, 23] are seen to develop in children with recurrent or persistent wheeze.

In Bangladesh, wheezing has been reported among both rural and urban children [24, 25]. However, existing evidence is limited as most studies involved children up to five years of age, relied on clinic-based samples, or used cross-sectional designs. Thus, available risk factor data, including poor nutritional status, history of pneumonia, exposure to respiratory viruses, parental history of asthma, ascariasis, atopic conditions, and poverty [25–28], are not specific to the early life period. Children in urban slum settings may face additional vulnerabilities, including low socio-economic conditions, suboptimal housing, dietary inadequacy, and high levels of household air pollution [24, 29]. We therefore conducted a longitudinal birth cohort study in a low-income urban community in Dhaka to estimate the incidence of wheezing, characterise its viral etiologies, and identify associated risk factors among children under two years of age.

Method

Study site

We conducted this study in Mirpur, a low-income urban area in the northwestern part of the capital city of Dhaka, Bangladesh. The field activities were conducted in the informal settlement in Sect. 11 of the area, commonly referred to as the "Mirpur Slum", which housed approximately 50,000 residents. During the study period, the slum was characterised by high population density, narrow, interconnected roads, and limited access to municipal services (Fig. 1).

Study settings

In 2015, the International Centre for Diarrheal Disease Research, Bangladesh (icddr,b) initiated a birth cohort study to assess the respiratory-virus-associated infections among young children in the study area. The study team identified pregnant women in the third trimester and newborns in the first week of life residing in the area. Enrollment began in May 2015, and the study was an open cohort that continued to enrol eligible children until March 2016. All enrolled children were prospectively followed until 2022 to address multiple study objectives. However, active respiratory surveillance with systematic virological testing was conducted only during the first two years of life. For the present analysis, follow-up was therefore restricted to respiratory illnesses occurring within this two-year period to estimate the incidence, viral etiology, and risk factors of wheezing in

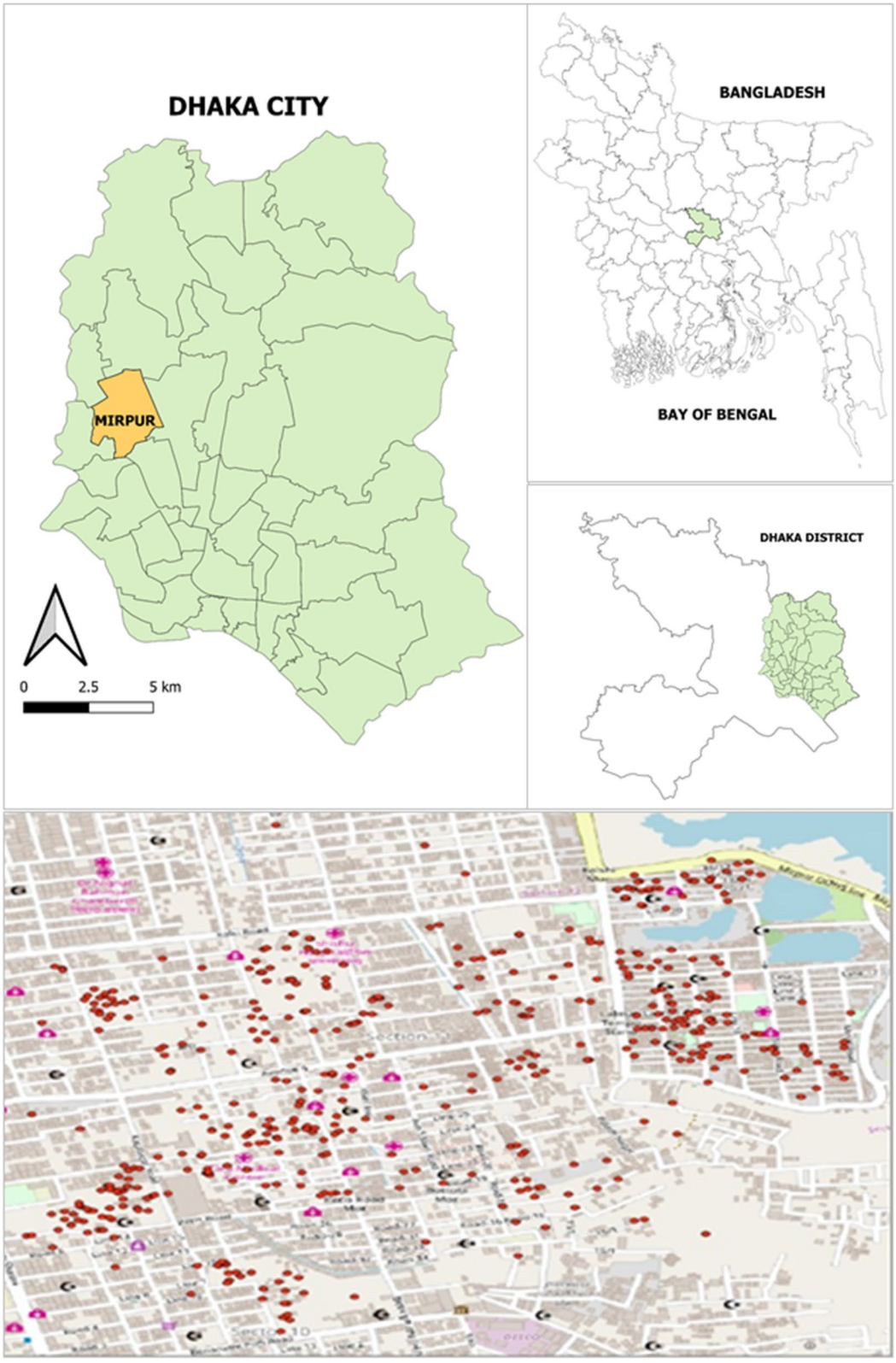

Fig. 1 Household distribution of children enrolled in the birth cohort from a low-income urban community of Dhaka, Bangladesh (May 2015-March 2018)

early childhood. As the last child was enrolled in March 2016, two-year follow-up for this analysis was completed by March 2018. Because the primary objective was to estimate incidence rates, the effective study size is reflected in the total accumulated child-time and the number of observed wheezing episodes, rather than in a separate a priori power calculation specific to wheezing incidence.

Enrollment criteria

Enrollment of children in this birth cohort was based on predefined criteria. Newborns aged 0–7 days without visible congenital anomalies were eligible if their families reported stable residence in the area (no planned relocation during the study period) and only if the parents provided written informed consent. The study team also obtained consent from the parents of all enrolled children to install a portable indoor particulate matter (PM) monitoring device. The field team collected data from the machine monthly to assess the household's indoor air quality.

Children were not included in the study if parents were unwilling to provide consent to allow nasal wash sample collection from the child, had any plan to involve the child in another interventional clinical study during this study period, didn't permit the field team for twice-weekly follow-up visits or allowed to install the PM monitor in their household, the infant had a history of seizures or any other apparent neurological disorders, or had a sibling or a twin enrolled in the same study.

Data collection

Baseline data collection

At enrollment, the trained study team collected anthropometric measurements (age, height, weight), demographic information, socioeconomic status data (parental education, family income, household characteristics, etc.), and indoor air quality-related information (cigarette smoking, source of indoor smoking, cooking fuel, etc.) as baseline data for each participant.

Follow-up data collection

To follow up on enrolled children, field staff visited each household every 3 days. During routine follow-up visits, parents were interviewed using a standardised symptom checklist to assess whether the children had experienced any respiratory symptoms in the past 72 h. The assessed symptoms included sudden or subjective fever, cough, sore throat, difficulty breathing, rapid, laboured, or noisy breathing, chest indrawing when calm, nasal discharge, ear pain, reluctance or inability to drink, convulsions, lethargy, decreased activity, and repeated vomiting [30]. If the field staff identified any of the above-mentioned respiratory symptoms during the follow-up visit, the child was referred to the study clinic for clinical assessment. In addition, parents of enrolled children were encouraged to bring their children to the study clinic (located in the study area) if they experienced any of the acute respiratory infection (ARI) symptoms listed above.

Clinical assessment and data collection from the study clinic

In the study clinic, study physicians used a structured questionnaire to obtain a history of the illness episode, the duration of symptoms at onset, and symptom severity. The physician at the study clinic performed a clinical examination to assess subjective or measured fever (temperature ≥ 38 °C) and any respiratory symptoms, such as cough, nasal discharge, or breathing difficulty. Acute respiratory infection (ARI) was defined as the presence of cough and/or runny nose, as assessed by study physicians during clinic visits. Pneumonia was diagnosed in children with cough accompanied by tachypnea or difficulty breathing, consistent with WHO criteria. Wheezing in them was identified on lung auscultation as a long, high-pitched whistling sound on expiration, including the following respiratory signs: crepitus, ronchi, and wheezes [31]. Study physicians recorded wheezing presence or absence in each child who visited the study clinic with respiratory illness. Initial treatment was administered to the child in the study clinic. In case of severe disease, the physicians could refer the child to designated public or private hospitals if required. The study clinic provided clinical care, diagnostics, and, if required, referral to the study hospital at no cost.

Respiratory sample collection and testing

For each new episode of respiratory illness, study physicians collected a nasopharyngeal wash sample from the children. Study physicians used a 10 mL syringe prefilled with 5 mL of sterile normal saline and inserted it into the nasopharynx via a butterfly catheter, maintaining aseptic procedures throughout. Specimens were collected with the child in a 30° semi-Fowler position and the head slightly flexed forward. A catheter was inserted 2–3 cm into the nasal passage, saline was instilled, and suction was applied during withdrawal [30].

Collected samples were then transferred into viral transport medium containing Dulbecco's Modified Eagle Medium (DMEM) and kept at 4 °C at the field site. Samples were transported to the virology laboratory at icddr,b within eight hours of collection and subsequently stored at − 70 °C until analysis. Respiratory viral pathogens, including influenza viruses, RSV, adenovirus, HPIV, RV, and hMPV, were detected using real-time reverse transcription polymerase chain reaction (rRT-PCR) assays with primers and probes supplied by the U.S. Center for Disease Control and Prevention (CDC), Atlanta [32].

However, RV detection was incorporated into the respiratory virus panel in May 2016.

Indoor air particulate matter (PM) data collection

For each enrolled household, a portable, low-cost indoor particulate matter (PM) monitoring device manufactured by the Berkeley Air Monitoring Group (University of California, Berkeley, California) was installed [33] to collect repeated 24-h measurements. The device was mounted on the wall nearly 2 feet above the child's sleeping area. The device recorded 1-min-averaged PM2.5 concentrations by sampling the preceding 60-s interval, in accordance with the manufacturer's operating protocol. Daily $PM_{2.5}$ data were included in the analysis only if the 24-h monitoring session gave at least 1,300 min of valid readings. A field team visited households monthly to retrieve data and ensure proper device functioning. $PM_{2.5}$ measurements were obtained from all enrolled households.

Major explanatory variables

The selection of explanatory variables was guided by prior work on early-life respiratory illness and wheezing [33–39]. We grouped the variables into three domains: child-level, household/socioeconomic, and environmental. Child-level variables included sex, birth weight (low or normal), weight-for-height z-score category (severely wasted, moderately wasted, normal, or overweight) at birth, feeding status at birth (exclusive breastfeeding or other), and season of birth. Anthropometric measurements were collected only at baseline enrollment, and weight-for-height z-scores were calculated using WHO growth standards. As repeated anthropometric measurements were not obtained during follow-up, baseline z-score categories were used in the analysis.

Socioeconomic status (SES) was measured using a principal component analysis (PCA) based on household asset ownership (television, bicycle, fan), housing materials (floor, roof, walls), and access to utilities (electricity, gas). The first principal component was used to create a continuous SES score, which was divided into tertiles (Low, Middle, High). As a sensitivity check, we repeated the PCA after adding household income, expenditure, and rent. The resulting SES groups showed poor agreement with the asset-only classification (Kappa = −0.18), suggesting that reported income did not consistently align with material wealth. We therefore retained the asset-based SES index as the primary measure. Other household factors included maternal education (no formal education vs any formal education) and number of siblings (0–2 or ≥ 3).

Environmental exposures included the type of cooking fuel used (natural gas, electric stove, wood, kerosene), stove location (inside or outside the house), exposure to passive smoke, and particulate matter levels. Particulate matter was characterised using the time-weighted average concentration and the daily hours with PM above 50 μg/m^3, each estimated with 95% CIs. We used 50 μg/m^3 as the threshold because it captures exposure levels that markedly exceed the WHO 24-h guideline (15 μg/m^3) and lie within the high-exposure range commonly observed in South Asian household air-quality studies [40, 41]. Finally, we also included family history of asthma [42] and the season of the wheeze episode as potential explanatory factors [43, 44].

Statistical analysis

Descriptive statistics were used to summarise the characteristics of the enrolled children in the cohort. Baseline characteristics were described using means and standard deviations or medians and interquartile ranges for continuous variables, depending on their distribution. We further reported categorical variables using counts and percentages. Characteristics of children who experienced any wheezing episode were presented as row percentages. Child-time at risk was calculated from the date of enrolment until censoring, defined as the two-year visit, the last follow-up contact, or loss to follow-up.

We estimated the incidence rate of wheezing by dividing the number of new wheezing episodes by the total accumulated child-time under observation. Incidence was expressed per 100 child-years, and 95% confidence intervals were derived using Poisson distributions. Children could experience more than one wheezing episode, and episodes were considered distinct if separated by at least seven consecutive days without respiratory symptoms. Respiratory illness episodes (including ARI, pneumonia, and wheezing) were considered distinct if separated by at least seven consecutive symptom-free days. Accordingly, "prior ARI" was defined as a documented ARI episode occurring before a wheezing episode and separated by ≥ 7 consecutive symptom-free days. An illness that evolved from ARI symptoms and progressed to wheezing within the same symptomatic episode was not classified as a prior ARI. To estimate virus-specific wheezing incidence, only episodes with laboratory confirmation of the corresponding virus were included. The denominator for each virus reflected only the period during which that virus was included in the testing panel. Because RV testing was introduced in May 2016, RV-specific incidence analyses were restricted to the period from May 2016 onward. The numerator included only laboratory-confirmed RV-associated wheezing episodes detected after the implementation of RV testing, and the denominator comprised child-time under observation from May 2016 onward. Child-time prior to RV panel introduction did not contribute to RV-specific incidence estimates. The analytic period for RV (May 2016–March 2018) spanned nearly two full

seasonal cycles. Age-specific incidence was calculated based on the child's age at the start of each wheezing episode and grouped into 0– < 6 months, 6– < 12 months, and 12–24 months. When more than one virus was detected in the same specimen, the episode was counted once and classified as "multiple viruses" to avoid inflating incidence estimates for individual viruses.

We used Cox proportional-hazards regression models with the Andersen-Gill approach to account for recurrent wheezing episodes, with time since birth (i.e., child's age) specified as the underlying time scale. At first, univariate models were utilised to examine the crude associations between explanatory variables and the outcome (wheezing episode). Results from these models were presented as unadjusted hazard ratios (uHR) with 95% confidence intervals (CIs). Robust standard errors were used to address within-child correlation across episodes. Variables with $p < 0.20$ in univariate analysis were then evaluated in separate multivariable Cox models, where each was adjusted for the a priori confounders identified through our Directed Acyclic Graph (DAG) (Supplemental Fig. 1). Based on the DAG, the type of fuel used and location of the stove was adjusted for socioeconomic status; particulate matter concentration was adjusted for type of fuel used, stove location, season of the wheeze episode and exposure to passive smoke; and respiratory tract infection history before the first wheezing episode was adjusted for type of fuel used, stove location, exposure to passive smoke, number of siblings, particulate matter concentration, food at birth, season of birth and season of wheeze. Results from the multivariable models were reported as adjusted hazard ratios (aHR) with 95% confidence intervals. As a sensitivity analysis, we assessed the robustness of associations for sparse exposure categories by re-estimating models after excluding influential observations. To explore whether associations differed when restricting to virus-positive wheezing episodes, we fitted a separate multivariable Cox model for virus-positive episodes. Adjusted hazard ratios from this model were descriptively compared with those from the primary model (all wheezing episodes). Statistical significance was defined using a two-tailed alpha level of 0.05. All analyses were conducted in STATA version 15.0 (Copyright 1985–2017 StataCorp LLC, StataCorp, 4905 Lakeway Drive, College Station, Texas 77845 USA).

Ethical consideration

Written informed consent was obtained from each child's parent or caregiver before enrolment into the study. The study received ethical clearance from the Institutional Review Board of the icddr,b, with the CDC Institutional Review Board deferring to icddr,b's review and approval.

Results

Baseline characteristics of the enrolled children

Our study enrolled 447 children between May 2015 and March 2016 and followed them for the first two years of their lives. Children were followed for a median of 23 months (IQR: 20–24), contributing 773 child-years of observation. Across the follow-up period, children contributed 96.9 child-years of observation while aged < 6 months, 178.2 child-years while aged 6–12 months, and 497.7 child-years while aged 12–24 months. At enrollment, they were a median of 6 days old (IQR: 4–116) and had a birthweight of 2740 g (IQR: 2490–3020). Among the children, 46% were male, 56% came from nuclear families, and 58% of children were exposed to tobacco smoke (Table 1). Most households relied on natural gas (61.5%) or electric stoves (34.0%), while only a small proportion used wood (2.7%) or kerosene stoves (1.8%). Valid $PM_{2.5}$ measurements were available for 223 of 447 households (49.9%). Among households with valid data, children were exposed to PM levels exceeding 50 $\mu g/m^3$ for an average of 2.2 h per day (95% CI: 1.9–2.6).

Clinical presentation and laboratory-confirmed respiratory viral pathogens in children with wheezing

In our cohort, a total of 276 wheezing episodes were identified among 163 children. Two-thirds of the children (63%) experienced a single wheezing episode, while 23% had two episodes and 9% had three episodes. Only a small proportion experienced four (3%) or five (2%) episodes during follow-up. Among the children, 110 (68%) had their first wheezing episode in the first year of life. The median age at the onset of the first wheezing episode in our cohort of children was 4 months (IQR: 3 months – 5 months). Wheezing was observed in approximately 40% of male children of the cohort (Table 1). Among 163 children who experienced wheezing during follow-up, 162 (99%) received at least one antibiotic prescription at the time of diagnosis. Bronchodilators were prescribed less frequently. Only nine children received oral bronchodilators, and 15 received inhaled bronchodilators. Among children with wheezing episodes, 84 (51.5%) had a prior ARI-only episode, 5 (3.1%) had a prior pneumonia-only episode, and 35 (21.5%) had both ARI and pneumonia. The remaining 39 (23.9%) children had no prior respiratory illness visit recorded during follow-up, and for these children, the wheezing episode represented their first respiratory presentation to the study clinic. These prior diagnosis classifications were done based on the follow-up visits before the onset of wheezing. None of the wheezing episodes was referred for or resulted in hospitalisation during follow-up.

At least one viral pathogen was detected in 206 of the 276 (74.6%) wheezing episodes. Overall, 138 children

Table 1 Baseline characteristics of enrolled children (*N* = 447) and of those who developed wheezing in a low-income urban community of Dhaka, Bangladesh (May 2015-March 2018)

Socio-demographic characteristics	Baseline, n (col%)	Children with wheezing, n (row%)
All sample	447 (100)	163 (36.5)
Child Characteristics		
Sex		
Male	206 (46)	82 (39.8)
Female	241 (54)	81 (33.6)
Birth weight		
Median birth weight in grams (IQR)	2740 (2490–3020)	2740 (2520–3090)
Low birth weight	117 (26)	39 (33.3)
Normal birth weight	330 (74)	124 (37.6)
Weight for height z score		
Severely wasted	29 (6.5)	10 (34.5)
Moderately wasted	63 (14.1)	22 (34.9)
Normal	341 (76.3)	127 (37.2)
Overweight	14 (3.1)	4 (28.6)
Food at birth		
Exclusive breastfeeding	394 (88.1)	144 (36.5)
Others	53 (11.9)	19 (35.8)
Season of birth[†]		
Spring	74 (16.6)	46 (62.2)
Winter	120 (26.8)	25 (20.8)
Monsoon	169 (37.8)	62 (36.7)
Autumn	84 (18.8)	30 (35.7)
Household and Socioeconomic Characteristics		
Socioeconomic status (SES)[‡]		
Low SES	147 (32.9)	55 (37.4)
Middle SES	157 (35.1)	54 (34.4)
High SES	143 (32.0)	54 (37.8)
Maternal education		
No formal education	97 (21.7)	38 (39.2)
Formal education	350 (78.3)	125 (35.7)
No. of siblings		
0–2	240 (53.7)	86 (35.8)
≥ 3	207 (46.3)	77 (37.2)
Environmental Exposures		
Type of fuel used		
Natural gas	275 (61.5)	95 (34.5)
Electric stove	152 (34.0)	55 (36.2)
Wood	12 (2.7)	6 (50.0)
Kerosene oil stove	8 (1.8)	7 (87.5)
Location of stove		
Inside house	283 (63.3)	102 (36.1)
Outside house	164 (36.7)	55 (33.5)
Exposure to passive smoke		
Yes	258 (57.7)	53 (20.5)
Particulate matter concentration		
Time-weighted average in $\mu g/m^3$ (95% CI)	250 (222–279)	384 (203–567)
Daily hours > 50 $\mu g/m^3$ (95% CI)	2.2 (1.9–2.6)	2.1 (2.0–2.4)
Family History		
Family history of asthma		
Yes	57 (12.8)	25 (43.9)

[†]Season of birth: Winter = December, January, February; Spring = March, April, May; Monsoon = June, July, August; Autumn = September, October, November

[‡]SES: Derived from PCA of assets, housing, and utilities, categorised into tertiles of the first component score

Table 2 Virus-specific distribution and incidence of wheezing episodes among children under two years of age, in a low-income urban community, Dhaka, Bangladesh (May 2015-March 2018)

Respiratory viruses	Viral wheezing episodes, n (%)	Median age in months at first episode (IQR)	Incidence of wheezing/100-child year (95% CI)			
			Overall	< 6 months	6—< 12 months	12—24 months
All	206 (100)	4 (2–5)	26 (23–30)	78 (63–98)	37 (29–47)	12 (10–16)
Rhinoviruses (RV)	73 (35)	3 (2–5)	9 (8–12)	19 (12–29)	11 (7–17)	7 (5–10)
Respiratory syncytial virus (RSV)	44 (22)	4 (2–5)	6 (4–8)	15 (9–26)	11 (7–17)	2 (1–4)
Human parainfluenza viruses (HPIV)	28 (14)	3.5 (2.5–4.5)	4 (3–5)	14 (9–24)	7 (4–13)	1 (0.08–2)
Human metapneumovirus (HMPV)	14 (7)	4 (2–5)	2 (1–3)	7 (3–15)	3 (1–7)	1 (0.2–2)
Influenza viruses	15 (7)	3 (1–5)	2 (1–3)	10 (6–19)	0 (0–0)	1 (0.3–2)
Adenoviruses	7 (3)	4 (3–5)	1 (0.4–2)	1 (0.1–7)	1 (0.3–5)	1 (0.3–2)
Multiple viruses	25 (12)	5 (3–6)	3 (2–5)	12 (7–22)	5 (2–9)	1 (0.4–2)

Fig. 2 Symptom distribution by virus among children under two years of age with viral wheezing in a low-income urban community of Dhaka, Bangladesh (May 2015-March 2018)

experienced at least one virologically confirmed wheezing episode in our study. RV was the most commonly detected pathogen (35%), followed by RSV (22%) and HPIV (14%) (Table 2). Multiple viruses were identified in 25 episodes, most frequently RV with adenovirus ($n = 7$), RV with HPIV ($n = 7$), and RV with RSV ($n = 4$). Furthermore, among virologically confirmed wheezing episodes, 92 (44.7%) were associated with ARI, and 46 (22.3%) with pneumonia at the time of the wheezing episode.

The most commonly reported symptoms in children with wheezing (163) were cough (100%) and runny nose (95%). However, symptom frequencies varied across respiratory viruses among children who wheezed in this study (Fig. 2). Fever was reported in 75% of viral wheezing episodes and was particularly common with RSV (81%) and adenovirus (100%). A runny nose was almost universal across all pathogens. Chest indrawing was frequently observed in RV (44%) and RSV (29%) episodes. Decreased activity, inability to drink, and vomiting occurred less commonly but also showed variation across viral etiologies.

Incidence of viral wheezing episodes

The overall incidence of wheezing among the children was 35 episodes/100 child-years (95% CI: 31–40). Furthermore, the overall incidence of viral wheezing was 26 episodes/100 child-years (95% CI: 23–30). The incidence of viral wheezing was highest in children < 6 months of age, at 78 episodes/100 child-years (95% CI: 63–98). It then declined to 37 episodes/100 child-years (95% CI: 29–47) at 6– < 12 months and 12 episodes/100 child-years (95% CI: 10–16) in children 12–24 months.

RV accounted for the largest share of viral wheezing episodes, with an overall incidence of 9 episodes/100

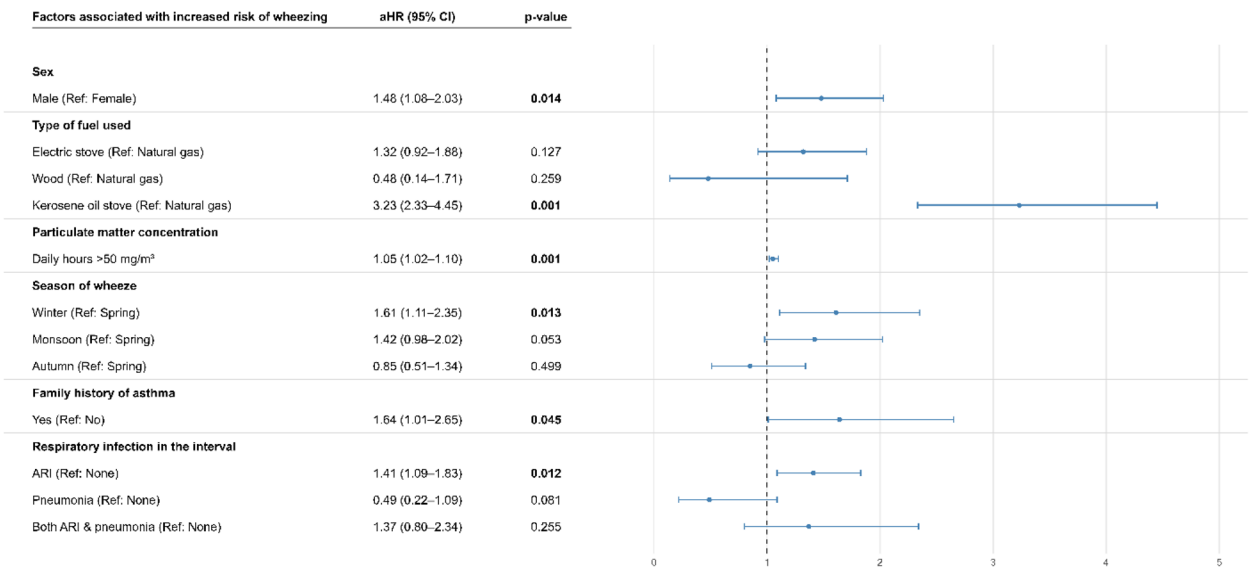

Fig. 3 Hazards of early life wheezing among children under two years of age in a low-income urban community of Dhaka, Bangladesh (May 2015-March 2018)

child-years. The highest rates of RV incidence were observed in children < 6 months of age, with 19 episodes/100 child-years. This was followed by RSV, which showed an overall incidence of 6 episodes/100 child-years, peaking among infants < 6 months (15/100 child-years). HPIV contributed to an overall rate of 4 episodes/100 child-years in this cohort of children. In contrast, HMPV and influenza viruses contributed relatively few episodes across all age groups. Wheezing episodes involving multiple viruses were uncommon, occurring at an average of 3/100 child-years, though rates were highest among the youngest infants (Table 2).

Risk factors of early life wheezing among children under two years of age

Our multivariable models showed that male children had a 1.48-fold higher risk of wheezing than their female counterparts (aHR: 1.48; 95% CI: 1.08–2.03; $p = 0.014$). Children living in households that used kerosene oil stoves also experienced a substantially elevated hazard of wheezing, with more than a three-fold increase compared with those using natural gas (aHR: 3.23; 95% CI: 2.33–4.45; $p < 0.001$) (Fig. 3). In a sensitivity analysis excluding an influential observation in the kerosene-exposed group, the association remained elevated but attenuated (aHR: 2.45; 95% CI: 2.12–3.98).

Exposure to particulate matter significantly contributed to the development of wheezing among the children in this cohort. For every additional hour per day that $PM_{2.5}$ concentrations exceeded 50 μg/m^3, the hazard of wheezing increased by 5% (aHR: 1.05; 95% CI: 1.02–1.10; $p < 0.001$) in this cohort of children (Supplemental Table 1). Furthermore, children with a family history of asthma had 64% higher risk of developing wheezing than those without such a history (aHR: 1.64; 95% CI: 1.01–2.65; $p = 0.045$). Finally, prior respiratory illness also significantly increased the likelihood of wheezing. Wheezing episodes that were preceded by ARI had roughly 1.5 times the hazard of occurring compared with episodes with no documented respiratory illnesses (aHR: 1.41; 95% CI: 1.09–1.83; $p = 0.012$).

In our analyses restricted to virus-positive wheeze episodes, male sex (aHR: 1.43, 95% CI: 1.02–2.00; $p = 0.039$), higher daily hours with $PM_{2.5} > 50$ μg/m^3 (aHR: 1.02, 95% CI: 1.01–1.08, $p < 0.001$), and kerosene stove use (aHR: 4.30; 95% CI: 3.06–6.06; p-value < 0.001) were associated with increased incidence of virus-positive wheeze (Supplemental Fig. 2).

Discussion

In this prospective cohort of 447 children from a densely populated urban slum in Dhaka, Bangladesh, wheezing was notably common in early life. One-third of the cohort experienced at least one episode by age two, and two-thirds did so before their first birthday. This is in line with evidence from a meta-analysis, which showed that the global pooled prevalence of "ever-wheeze" in children under two was 36% (95% CI: 35.17%–36.96%) [13]. The incidence of wheezing in children under two was 35 per 100 child-years in our study. A majority of these episodes had a detectable respiratory virus in the collected samples. The highest incidence of virus-associated wheezing was observed in children < 6 months in our study. In addition, elevated household $PM_{2.5}$ exposure and use of a kerosene stove were associated with increased risk of wheezing in our cohort. Overall, our findings

demonstrate a substantial burden of wheezing and highlight the contributions of both viral and environmental exposures among children under two living in high-density, low-resource settings.

Respiratory viruses were identified in three-quarters of all wheezing episodes in our cohort, underscoring the role of viral infections in early-life wheezing. This is consistent with observations from other settings, where viral pathogens have been found to be responsible for most wheezing illnesses in infancy and early childhood [45–47]. Nevertheless, 99% of the children in our cohort who were diagnosed with wheezing were treated with antibiotics at the time of diagnosis. In contrast, bronchodilators were prescribed less frequently (oral: 9 children; inhaled: 15 children). In many low-resource settings where routine viral diagnostics are unavailable, and differentiation between viral wheeze and bacterial lower respiratory infection is clinically challenging, empirical antibiotic prescribing remains common [48, 49]. This pattern exposes children to antibiotics in situations where they offer limited clinical benefit, thereby contributing to the growing threat of antimicrobial resistance [50]. Improving access to diagnostic support, implementing standardised wheeze management pathways, and strengthening antimicrobial stewardship at the primary-care level are therefore critical to better align treatment decisions with underlying etiology and reduce unnecessary antibiotic exposure among children.

RV was detected in 35% of wheezing episodes and was the most frequently observed pathogen in our study. Similar findings have been reported in studies of LRTIs in children under two, in which RV consistently emerged as a dominant trigger of wheezing in early life [51–53]. However, RV's interpretation is complicated by its detection in asymptomatic children, prolonged shedding, frequent co-detections, and weak correlation between viral load and symptoms [54, 55]. These features limit the ability of routine PCR-based surveillance to distinguish the background circulation of RV from episode-specific involvement. Future studies that integrate viral kinetics with host-response markers could help resolve this gap and more clearly delineate RV's role in early-life wheezing.

RSV-associated wheezing episodes among infants younger than six months in our study had the highest incidence (15 episodes per 100 child-years), underscoring that the period of greatest vulnerability occurs very early in life. Previous community-based birth cohort studies from South Asia and other LMIC settings similarly reported high incidence of RSV-associated wheezing during the first six months of life [56, 57]. Although absolute incidence estimates vary across studies due to differences in case definitions and surveillance intensity, findings consistently indicate that RSV burden peaks in the first six months of life. Recent developments in maternal RSV vaccines and long-acting monoclonal antibodies for infants offer new possibilities to protect children during this high-risk period [58, 59]. It is thus essential to assess how these interventions can be incorporated into Bangladesh's existing maternal and newborn care services. Their potential inclusion in the EPI schedule should also be examined to better understand how they may reduce RSV-associated wheezing in similar settings.

Our analysis showed that children living in households that relied on kerosene stoves had more than threefold higher hazard of wheezing (aHR: 3.23; 95% CI: 2.33–4.45) than those using natural gas. This aligns with evidence obtained from other LMICs, such as India, Nepal, and Sri Lanka, which showed increased cough and wheeze among children exposed to kerosene for cooking or lighting [60, 61]. Emissions from kerosene combustion, such as fine particles, soot, and irritant gases, are known to irritate the airway lining and trigger inflammation in young children [62]. This, in turn, can provoke wheezing, especially in infants and toddlers with narrower, more reactive airways. However, kerosene use was uncommon in our cohort, with only eight households (1.8% of the cohort) reportedly using it as fuel, and these households were concentrated in poorer, more crowded dwellings with limited ventilation. Although estimates derived from sparse exposure categories should be interpreted cautiously, sensitivity analysis excluding an influential observation within the exposed group in our study showed that the association remained elevated, although attenuated. These findings suggest that the observed relationship was not solely driven by a single high-contributing household, although some influence of sparse exposure cannot be excluded. Nevertheless, given the known respiratory risks associated with kerosene and the availability of cleaner alternatives, our findings support ongoing efforts to transition households in similar urban settings to safer energy options.

In our analysis, elevated household $PM_{2.5}$ exposure was associated with a higher hazard of wheezing among the children. For every additional hour per day that $PM_{2.5}$ concentrations exceeded 50 $\mu g/m^3$, the hazard of wheeze increased by 5% (aHR: 1.05; 95% CI: 1.02–1.10). This aligns with prior evidence that shows both short-term elevations and sustained particulate exposure increase susceptibility to wheezing, bronchiolitis, and recurrent lower respiratory infections [63, 64]. Notably, although approximately 95% of households in our cohort used clean cooking fuels (natural gas or electric stove), indoor $PM_{2.5}$ concentrations remained high. A study from a comparable Dhaka slum community reported the same pattern, with elevated $PM_{2.5}$ levels in homes using natural gas or electric stoves [65]. This reflects the broader reality that in dense urban settlements, smoke infiltration

from neighbouring dwellings, high ambient pollution, and poor ventilation often outweigh the benefits of using clean fuels. In crowded, poorly ventilated urban settlements like the one in our study, these exposures tend to accumulate. Such exposures compromise airway defences through oxidative stress and impaired mucosal immunity, heightening children's vulnerability to viral triggers [66]. Thus, to effectively reduce indoor air pollution in these environments, interventions targeting both household emissions and the community-level particulate burden are required to minimise exposure and the risk of early childhood respiratory illness.

ARI in the interval preceding a wheezing episode increased the hazard by 1.41-fold compared to those without any respiratory illness (aHR: 1.41; 95% CI: 1.09–1.83). Similar patterns have been reported in previous studies, where viral and non-viral ARI frequently precede wheezing episodes in infancy and early childhood [67–69]. Such infections induce short-term airway inflammation and heightened bronchial responsiveness, lowering the threshold for wheeze during subsequent respiratory illnesses. Children with repeated early-life infections may therefore represent a more reactive subgroup who warrant closer observation during periods of illness.

Our study has several limitations that warrant caution in interpretation. First, the cohort was drawn from a single low-income urban community in Dhaka. This limits the generalizability of our findings to rural areas or regions with different socio-environmental exposures. Second, although wheezing episodes were identified through frequent biweekly surveillance, some illnesses may have been missed when families were temporarily unavailable for assessment or unable to bring symptomatic children to the study clinic. Third, wheezing was clinically identified without objective measures of airway obstruction. This may have led to misclassification of milder episodes. Fourth, we tested only for viral pathogens in our study and were unable to test for bacterial pathogens. As a result, we were unable to evaluate the potential contribution of bacterial infections to wheezing episodes or to contextualise antibiotic prescribing practices. Future studies incorporating broader microbiologic diagnostics and clinical biomarkers would help better inform antibiotic stewardship in similar settings. Fifth, kerosene stove use was uncommon in this cohort, and although sensitivity analysis suggested that the association with wheezing was not driven by a single influential observation, some influence of sparse exposure on the effect estimate cannot be excluded. In addition, we did not assess potential interaction between air pollution and viral infection due to limited sample size and reduced availability of valid $PM_{2.5}$ measurements, and therefore could not evaluate possible synergistic effects on wheezing risk. Next, we did not apply standardised severity grading or WHO pneumonia severity classifications to wheezing episodes. Although individual clinical signs and symptoms were recorded, we were therefore unable to formally stratify episodes by clinical severity or evaluate severity-specific outcomes. Finally, we lacked asymptomatic comparison groups in our study, which further prevented us from distinguishing background viral circulation from pathogen-specific wheezing. Despite these limitations, our study provides valuable community-level evidence on the viral etiology, incidence patterns, and key risk factors of wheezing from a densely populated urban settlement.

Conclusion

Our study demonstrates a substantial burden of wheezing in children under two years of age in a low-income urban community in Dhaka. RV and RSV were frequently detected around wheezing episodes, with the highest detection in infants < 6 months of age. This suggests that viral circulation plays a predominant role in the early onset of wheezing in this population. Elevated household $PM_{2.5}$ levels and the use of kerosene stoves were associated with wheezing among our children, reinforcing the role of indoor particulate pollution in early respiratory morbidity in high-density settings. These findings highlight the need for strategies that reduce household particulate exposure and support timely recognition of respiratory symptoms in young children. Strengthening community-level surveillance and diagnostic capacity may further improve the detection of respiratory viral illnesses in early childhood. Additionally, incorporating RSV and influenza immunisation measures for pregnant women and young infants into national programmes could help prevent early-life respiratory disease and reduce the burden of wheezing in similar low-resource environments.

Supplementary Information

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Supplementary Material 1.

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Authors' contributions

HRS **:** Software, formal analysis, investigations, data curation, validation, visualization, writing – original draft; ASP: Validation, visualization, software, writing – review and editing; MAAJB: Methodology, validation, visualization, formal analysis, software, writing – review and editing; MAAR: Writing – review and editing, data curation; MR: Investigations, funding acquisition, supervision, writing – review and editing; RH: Methodology, funding acquisition, supervision, writing – review and editing; WP: Methodology, funding

acquisition, supervision, writing – review and editing; FC: Methodology, funding acquisition, supervision, project administration, writing – review and editing; MZH: Conceptualization, investigation, funding acquisition, writing – review and editing, methodology, supervision, project administration. All authors read and approved the final version of the manuscript.

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Data availability
The authors assume responsibility for the data presented in this manuscript. The datasets used and/or analysed in this study are available from the corresponding author upon request.

Declarations

Ethics approval and consent to participate
The Institutional Review Board (IRB) of icddr,b approved the study protocol. The Institutional Review Board at the US CDC relied on icddr.b's approval. Parents/caregivers of the enrolled children provided written informed consent to participate. All procedures performed in this study involving human participants were in accordance with the 1964 Declaration of Helsinki and its subsequent amendments.
Written informed consent was obtained from all participants. The study team provided comprehensive oral and written explanations in the local language (Bangla) regarding the research aims, objectives, potential risks and benefits, confidentiality, voluntary participation, the right to withdraw at any time, conflicts of interest, and compensation. Parents were reminded that their participation was entirely voluntary and that all information would remain confidential before they were asked to sign the consent form.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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