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Bronchiolitis outbreak caused by respiratory syncytial virus in southwest Bangladesh, 2010*

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SUMMARY

Background—During July 2010, newspapers reported a respiratory disease outbreak in southwestern Bangladesh resulting in the admission of children to a secondary care hospital. We investigated this outbreak to determine the etiology and explore possible risk factors.

Methods—The hospital's physician diagnosed children aged <2 years with cough, tachypnea or dyspnea, and expiratory wheeze as having acute bronchiolitis. We reviewed the hospital records and listed case patients admitted between 26 June and 26 July 2010. We surveyed the case patients and collected nasal and throat swabs to test for respiratory viruses.

Results—We identified 101 admitted acute bronchiolitis case patients. Fifty-nine (58%) of these were admitted between 16 and 20 July. Among the 29 case patients surveyed, the median age was 4 months and 65% were males. We identified respiratory syncytial virus (RSV) in 91% (21/23) of the samples, 43% of which had a dual viral infection. Most case patients (90%) were treated with broad-spectrum antibiotics. There were no reported deaths.

Conclusions—The sudden increase in admitted acute bronchiolitis case patients, their median age, and identification of RSV in the majority of samples suggest an outbreak of RSV bronchiolitis. Research to identify strategies to prevent respiratory infections including RSV in low-income settings should be prioritized. Factors that perpetuate antibiotic use in managing this viral syndrome should also be explored.

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Ethical approval: Ethical approval was not required for this investigation. This investigation was conducted in response to an outbreak and was approved by the Government of the People's Republic of Bangladesh, but because this was an emergency response the activity was not reviewed by an independent human subjects committee. However, verbal informed consent was sought from parents of all participants.

Conflict of interest: The authors do not have any commercial or other association that might pose a conflict of interest.

Keywords

Bronchiolitis; Outbreak; Respiratory syncytial virus; RSV; Bangladesh

1. Introduction

Respiratory syncytial virus (RSV) is recognized globally as the leading cause of acute bronchiolitis both in epidemics and sporadic cases.¹⁻³ Although disease burden data from low-income countries are limited, extrapolation using data from high-income countries suggests an estimated annual global RSV burden of approximately 64 million cases with 160 000 annual deaths.⁴⁻⁶ It is estimated that 2–3% of all children aged <1 year require hospitalization during seasonal RSV epidemics.^{3,6}

Acute bronchiolitis is a potentially life-threatening lower respiratory tract infection in infants that results from inflammatory obstruction of the small airways.^{1,3} Although bronchiolitis is common and most infants recover, the lack of a standard case definition,⁷ little knowledge about what makes infants particularly vulnerable to RSV, and no recommended specific therapy, all make bronchiolitis prevention and management difficult for clinicians, researchers, and public health professionals.³ Adding to the clinical perplexity, the data on disease burden, epidemiology, seasonality, risk factors, and clinical profiles of bronchiolitis are limited in the majority of resource-limited settings, including Bangladesh.

The Institute of Epidemiology, Disease Control and Research (IEDCR), the Government of Bangladesh's institute responsible for outbreak investigations and disease surveillance, contracts a media agency to scan reports from 10 national newspapers and six popular local television channels on a daily basis and forward reports of potential outbreaks to IEDCR authorities. Several newspapers first reported an outbreak of a pneumonia-like illness that affected “hundreds of children” <2 years of age who were seeking admission to a government secondary care hospital in Meherpur District in southwestern Bangladesh during July 17–18, 2010. Within the disease surveillance team, these media reports raised the possibility of the emergence of a new respiratory pathogen of public health importance, and so a collaborative team from IEDCR and the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B) investigated this outbreak during July 2010. This paper summarizes the results of the outbreak investigation, which aimed to determine the etiology of illness, explore possible exposures, and describe the clinical profiles of case patients to recommend possible control and prevention measures.

2. Methods

2.1. Outbreak verification, case detection, and descriptive investigation

To collect preliminary information and verify the occurrence of the outbreak that was reported in the newspapers, the outbreak investigation team contacted the Civil Surgeon of Meherpur District and the Upazila Health and Family Planning Officers of Gangni and Mujibnagar subdistricts (upazilas). From 24 to 26 July 2010, the team visited Meherpur General Hospital and collected information on patient demographics (age, gender, and address), dates of admission and discharge, and the diagnoses from the hospital's registry. In

order to simplify case management of childhood illnesses including acute respiratory infections (ARI) and diarrheal diseases at the primary health care settings, the Government of Bangladesh introduced the Integrated Management of Childhood Illnesses (IMCI) strategy nationwide in 2002. According to this IMCI guideline, any child aged <5 years presenting with cough and fast breathing and/or difficult breathing for less than 30 days and with any general danger sign (unable to drink or breast feed, vomits everything, convulsions, lethargy, grunting, fever of 37.5 °C or above or feels hot, low body temperature of less than 35.5 °C or feels cold, movement only when stimulated, no movement at all, unconsciousness), or chest indrawing or stridor in a calm child, was categorized as a case of ARI.⁸ We assumed that the hospital physicians used this IMCI case definition during admissions to classify patients presenting with respiratory symptoms under the broad category of ARI. Following admission, the single pediatrician at the hospital re-assessed all admitted ARI patients and diagnosed children aged <2 years who initially developed coryza and/or low-grade fever followed by cough, fast breathing (tachypnea) or shortness of breath (dyspnea), and expiratory wheeze^{8,9} as acute bronchiolitis. From the hospital's registry, we listed all children aged <5 years who were admitted with ARI between 26 June and 26 July 2010. We also listed the patients diagnosed as cases of acute bronchiolitis between 26 June and 26 July 2010 and sought hospital records to note their clinical prognosis. We chose the 30-day time period to permit comparison of the monthly admission rates for acute bronchiolitis with previous months. We requested the Civil Surgeon to review the hospital records and then report to IEDCR the total number of patients discharged with a diagnosis of acute bronchiolitis who were classified using the same criteria by the pediatrician in the Meherpur General Hospital from January to December 2010.

To describe the outbreak in terms of persons, the team surveyed the case patients who were still in the hospital during the period of the investigation. We selected the mother as the primary survey respondent to provide information regarding her child's health. If the mother was unavailable, we interviewed other family members. We explored clinical histories of these case patients, including exposure to possible risk factors, using a pretested, structured questionnaire that was jointly developed by IEDCR and ICDDR,B for investigating respiratory disease outbreaks. Physicians on the outbreak investigation team physically examined the hospitalized case patients looking for symptoms and signs of illness severity including central (bluish tongue) and peripheral cyanosis (bluish limbs).¹⁰⁻¹² The team recorded both the clinical features they observed and those reported in the patient information sheet by the attending physician during admission. We reviewed the patient treatment records to gather information regarding clinical management.

To determine if the acute bronchiolitis case patients surveyed in the hospital were similar to or different from those already discharged prior to the investigation and to identify possible clusters, we segregated the 101 cases in the line-list (identified from the hospital's registry) based on the villages where they lived. The team defined a cluster of bronchiolitis if at least three admitted bronchiolitis cases came from the same village and lived within 15 min walking distance from each other according to the local community health worker. The team visited village communities with suspected clusters to survey and physically examine selected acute bronchiolitis cases who had been discharged from the hospital after June 26 until the beginning of the investigation. The team collected information on demographic and

clinical profiles and exposures of these bronchiolitis cases from their mothers (or family members if the mother was not available) using the same questionnaire that was used for the hospital survey. Team members also visited the three government-run primary care hospitals of the district to seek additional cases of acute bronchiolitis in admitted children aged <2 years.

2.2. Laboratory investigations

The investigation team collected nasal and throat swabs from all bronchiolitis case patients surveyed in the hospital and from those discharged case patients who were still symptomatic during the cluster investigation. Following collection, both samples obtained from the same patient were immediately placed in a single vial with viral transport medium containing DMEM (Dullbecco's modified Eagle's medium), 2.5% BSA (bovine serum albumin) fraction V, 1% glutamine, 2% HEPES (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid), 1% penicillin–streptomycin, and Fungizone (250 mg/ml). The specimens were stored at 4–8 °C until transported within 72 h to IEDCR. The specimens were aliquoted in a biosafety level 2 safety cabinet and were stored in freezers at or below –70 °C until testing. At the Virology Laboratory of IEDCR, we performed RNA extraction and detected subtypes of influenza A and influenza B using a real-time reverse transcriptase polymerase chain reaction (rRT-PCR).¹³ Both RNA and DNA extraction were performed in a separate aliquot sent to the Virology Laboratory of ICDDR,B for molecular identification of other common respiratory viruses and bacteria. A real-time PCR respiratory pathogen panel assay developed by the Centers for Disease Control and Prevention (CDC), Atlanta, Georgia, USA, was used to detect respiratory pathogens including RSV, human parainfluenza virus 1, 2, and 3 (HPIV1, HPIV2, and HPIV3), human metapneumovirus (HMPV), adenovirus, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, *Streptococcus pneumoniae*, *Legionella pneumophila*, and *Legionella longbeachae*.

2.3. Ethical considerations

We sought verbal informed consent from a parent of all participants. We suggested simple preventive measures including hand washing, and social distancing measures including cancellation of sports events to protect the wider community of the cluster villages. We also advised that parents avoid taking their ill child to public gatherings including mosques, weddings, and schools. This investigation was conducted in response to an outbreak and was approved by the Government of the People's Republic of Bangladesh, but because this was an emergency response the activity was not reviewed by an independent human subjects committee.

3. Results

3.1. Spatial distribution, demographic, and clinical profiles of case patients

Acute bronchiolitis cases were admitted to Meherpur General Hospital throughout the year. However, monthly acute bronchiolitis admissions increased between June and October, with the highest number of admissions occurring during July 2010 (Figure 1). We identified 101 children who were hospitalized and diagnosed with acute bronchiolitis between 26 June and 26 July 2010. Compared to the previous month, acute bronchiolitis admissions increased by

more than 60% during the month of July 2010 (Figure 1), with more than half of these cases (59/101) admitted between 16 and 20 July 2010 (Figure 2). Of the 258 children hospitalized with acute respiratory infections (ARIs) during this month, 101 (39%) had a discharge diagnosis of acute bronchiolitis. All except nine cases lived in different communities within the three subdistricts of Meherpur (Figure 3). Fifty-six percent (57/101) of the cases lived in the urban subdistrict, while the rest lived in the two other rural subdistricts (Mujibnagar and Gangni). We surveyed 20 case patients admitted to Meherpur General Hospital and nine from the two villages where we had identified clusters. The mean age of the 29 case patients was 5.4 months (median 4 months); 65% (19/29) were males and the average monthly household income was US\$ 53 (range US\$ 22–124).

The main clinical symptoms included cough, fast breathing, shortness of breath, and feeding difficulty. About a quarter (7/29) reported a family history of atopy (defined as having asthma, eczema, or allergic rhinitis in the parents, or siblings or grandparents); 17% (5/29) of case patients had been affected at least once before with a similar illness that required hospitalization and 35% (10/29) were born prematurely. Thirty-one percent of respondents also reported that either another sibling or an extended family member had developed similar symptoms (cough/fast breathing/respiratory difficulty with a preceding mild fever/runny nose) within 1 week following the onset of illness in the child affected with bronchiolitis. All case patients were treated with supplemental oxygen, oral or inhalational bronchodilators, and nasal decongestants. Among the chest radiographs from nine case patients, the hospital's pediatrician found patchy opacities or radiological evidence of bacterial pneumonia in only one case patient. Ninety percent (26/29) of the case patients received at least one broad-spectrum injectable antibiotic. There were no reported deaths from bronchiolitis or its complications among the 29 case patients (Table 1). As the hospital's registry did not record patient outcome, we tried to assess the illness outcome of the remaining 72 cases by reviewing patient information sheets including copies of discharge and/or death certificates. We found that 75% (54/72) of the cases were discharged alive and 8% (6/72) were discharged against medical advice, a decision that families in low-income countries often make because of their inability to afford continued hospitalization, poor response to treatment, or dissatisfaction with the hospital environment.¹⁴ We could not retrieve the information sheets of 12 patients and the hospital records were insufficient to evaluate their outcomes.

3.2. Laboratory findings

Among the 29 acute bronchiolitis patients surveyed, we collected samples from 23 cases (including samples from all the 20 hospitalized cases and from three symptomatic discharged cases). Out of the 23 samples tested for different respiratory pathogens, 21 had detectable RNA for RSV, one had influenza A (H1N1), and one had influenza B. More than one virus was identified in 43% (9/21) of the RSV-positive cases. These co-infections included RSV with influenza A/H1N1 ($n = 6$), with influenza B ($n = 1$), and with adenovirus ($n = 2$) (Table 2). We did not detect any nucleic acids for bacterial pathogens in the specimens.

4. Discussion

The sharp rise in the number of infant hospitalizations with a diagnosis of acute bronchiolitis heralded the occurrence of an outbreak in southwestern Bangladesh. We identified RSV in 91% of the samples tested from children hospitalized with acute bronchiolitis, which is comparable with findings from previous seasonal epidemics in other countries.^{15–19} The median age of the affected children was 4 months, consistent with RSV bronchiolitis data from previous hospital-based studies.^{19,20} Seventeen percent of the case patients in our investigation had been hospitalized at least once before with similar symptoms within 1 year. Although RSV can re-infect, often with the same serotype, these prior admissions may also have been from other respiratory viruses including adenovirus, human metapneumovirus, and parainfluenza virus circulating earlier in the year.

Nine out of the 21 respiratory specimens with detectable RNA from RSV also had detectable RNA from at least one other viral respiratory pathogen. This result supports previous studies, which have found a strong association between dual viral infections and severe bronchiolitis requiring hospitalization.²¹ In many communities the RSV epidemic period overlaps with human metapneumovirus (HMPV) seasonal epidemics, and co-infection with RSV and HMPV has been commonly reported in previous investigations.^{22–24} However, our investigation found co-infections of RSV with H1N1, adenovirus, and influenza B virus. A previous study from Bangladesh that detected HMPV circulation during January through the end of June also detected co-infection of HMPV with influenza A virus but not RSV.²² This investigation carried out at the end of July was apparently conducted during a time when HMPV was not circulating.

Acute bronchiolitis, most likely caused by RSV, was responsible for more than a third of ARI admissions to Meherpur General Hospital during July 2010. This finding is comparable to previous studies conducted in low-income countries that have identified RSV in 15–40% of hospital admissions for pneumonia or bronchiolitis.^{25,26} We found no deaths among the cases that we investigated. A previous study on children hospitalized with a diagnosis of bronchiolitis in Bangladesh found a mortality rate of 2%.²⁷ As we could not follow up all 101 cases in this investigation, we may have underestimated the mortality among hospitalized cases. It is also possible that the case definition we used did not identify those infants aged <2 months who were at higher risk of mortality from RSV bronchiolitis,¹² as irritability, feeding difficulty, and breathing difficulty are often the only symptoms in this age group.²⁸ Indeed, since in approximately a third of these investigated outbreak case patients other siblings or older family members also developed similar symptoms within 1 week, this suggests that the total community burden of RSV was greater than only those children hospitalized. Since we surveyed only 29 out of 101 cases over a few days and because various respiratory pathogens other than RSV could lead to similar symptoms, it is possible that the findings of the survey cases may be different from all outbreak-associated cases. However, the epidemiological and the laboratory findings of the nine cases surveyed in the cluster investigation to trace back discharged cases were comparable to the findings of the 20 cases surveyed in the hospital, suggesting that the 29 surveyed patients were representative of the larger affected population.

Despite evidence from developed nations suggesting a very low risk of secondary bacterial infection following RSV bronchiolitis²⁹ and Bangladesh's national bronchiolitis guidelines restricting antibiotic use only to severe cases with laboratory and/or radiological evidence of bacterial pneumonia,³⁰ antibiotics were administered to 90% of the case patients. Undue use of antibiotics, variation in clinical care, and poor adherence to national guidelines in the management of acute bronchiolitis have been reported previously.^{12,31} Evidence from controlled trials, including one multicenter randomized controlled trial that was conducted in five tertiary care hospitals of Bangladesh, showed that antibiotics were not effective in the management of bronchiolitis in low-income countries with a high ARI burden.^{32,33} Further research within Bangladesh could determine if this non-compliance to clinical guidelines with regard to avoiding antibiotics in acute bronchiolitis results from structural issues, including a lack of diagnostic facilities, or from attitudinal factors that consider antibiotics an essential therapy for infectious disease management.

In a country where approximately 70% of the health care expenditure is out-of-pocket for patients, the economic burden associated with the hospital-based management of RSV bronchiolitis, particularly the cost associated with injectable antibiotic therapy, can be catastrophic to the affected household.³⁴ Specific diagnostic tests, such as PCR for the detection of RSV in the hospital, have led to the reduced prescription of antibiotics in the management of bronchiolitis in the USA.³¹ The introduction of affordable rapid diagnostic tests in the hospital setting for the service users, including antigen detection tests with an overall sensitivity of 80–90%,⁷ could decrease the indiscriminate use of antibiotics and also reduce financial loss. However, the practical applicability and cost-effectiveness of introducing advanced diagnostic techniques should be evaluated in the Bangladeshi context.

We identified this outbreak of RSV from newspaper reports. Even though what we identified was not a novel respiratory pathogen, following up on mass media reports of outbreaks might be a valuable strategy to identify events of public health concern. RSV, the leading cause of potentially life-threatening viral respiratory tract infection in infants,^{4,5,35,36} likely contributes significantly to childhood morbidity and mortality in low-income settings.³⁷ Given the paucity of public health interventions to prevent respiratory infections including RSV in low-income settings, further research for identifying preventive strategies including improvement of hand hygiene practices and cough etiquette employed in developed nations^{38,39} should be prioritized.

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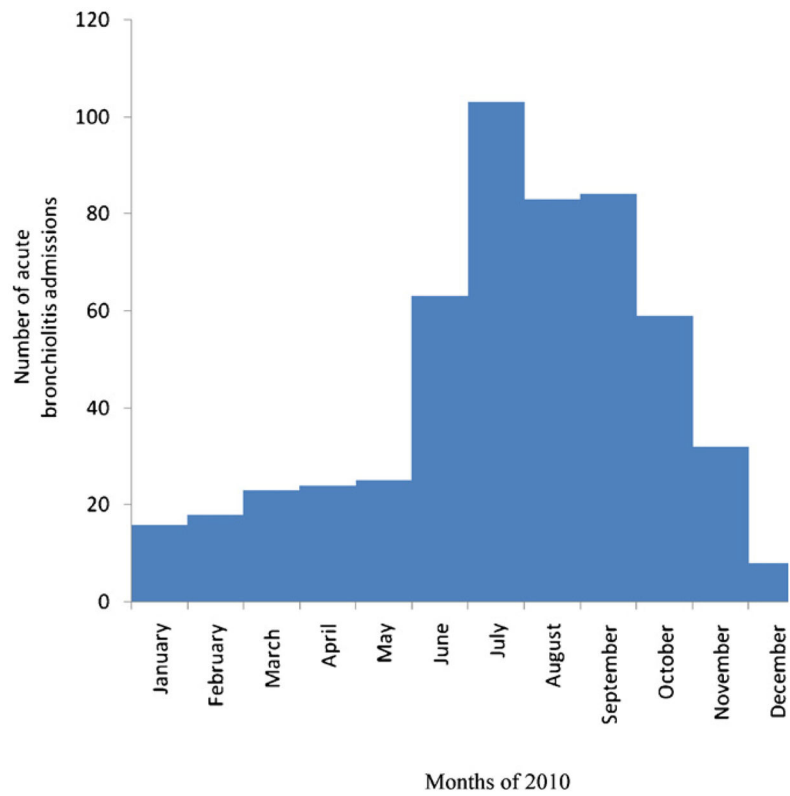


Figure 1. Total monthly acute bronchiolitis admissions in the Meherpur General Hospital, Bangladesh during 2010.

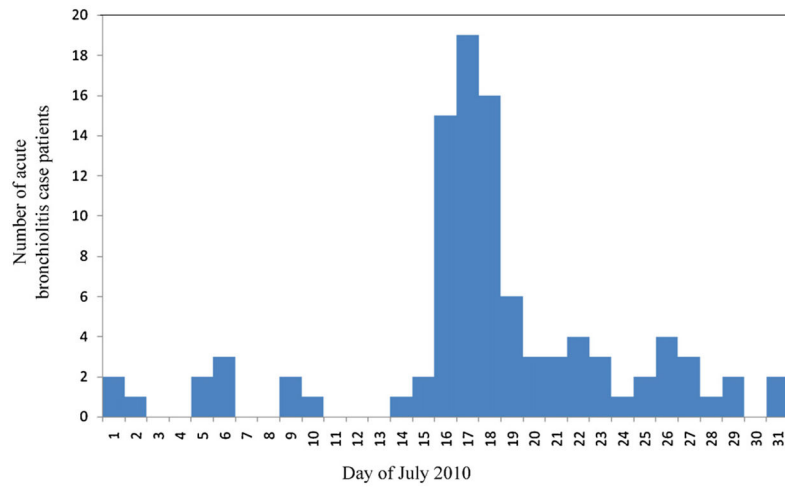


Figure 2. Daily acute bronchiolitis admissions in the Meherpur General Hospital, Bangladesh during July 2010.



Figure 3. Map showing the approximate location of the general (district) hospital and the three RSV outbreak affected upazilas of Meherpur District.

Table 1

Possible exposures, clinical presentation, management, and clinical outcome of case patients admitted with acute bronchiolitis in Meherpur General Hospital, July 24–26, 2010

	Total number (%) (N = 29)
<i>Risk factors^a</i>	
Passive smoking	8 (28)
Positive family history of atopy (asthma/allergic rhinitis/eczema)	7 (24)
Prematurity (reported by mothers as delivery before 9 completed months)	10 (35)
Twin/multiple birth	0 (0)
Exposure to multiple children (as in a health care setting/older siblings within the household)	6 (21)
Recommended feeding practices (exclusive breast feeding for <6 months/softened family foods in addition to breast milk for >6 months)	9 (31)
Past history of similar illness	5 (17)
Past history of similar illness requiring hospitalization	5 (17)
Close contact with any sick person 15 days prior to illness	9 (31)
Close contact with a sick family member 15 days prior to illness	4 (14)
Close contact with any extended family member ill with respiratory illness 15 days prior to illness	5 (17)
Any household member affected with similar illness	5 (17)
Any extended family member affected with similar illness	4 (14)
<i>Clinical presentation</i>	
History of fever	16 (55)
Cough	26 (90)
Fast breathing (tachypnea)	26 (90)
Nasal congestion/coryza	13 (45)
Runny nose/clear rhinorrhea	21 (72)
Shortness of breath (dyspnea)	25 (86)
Feeding difficulty	17 (59)
Chest wall retraction (intercostals and/or subcostal recession)	11 (38)
Cyanosis	2 (7)
Loose motion	5 (17)
<i>Clinical management</i>	
Oxygen therapy	23 (100)
Bronchodilators	23 (100)
Antibiotics	26 (90)
Nasal decongestants	23 (100)
Corticosteroids	5 (22)
Antiviral	0 (0)
<i>Clinical outcomes or complications</i>	
Sepsis	0 (0)
Death	0 (0)
Recovery within 5 days	10 (36)
Still sick after 5 days of illness	11 (39)

^aCategories are not mutually exclusive.

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Table 2

Summary of respiratory viruses detected in nasal and throat swabs collected from acute bronchiolitis cases admitted in the Meherpur General Hospital, July 2010

Virus types	Total number of samples with detectable RNA for respiratory viruses (% of total samples) (N = 23)
RSV	21 (91)
RSV alone	12 (52)
RSV and influenza A (H1N1)pdm09	6 (26)
RSV and adenovirus	2 (9)
RSV and influenza B	1 (4)
Influenza A (H1N1)pdm09 only	1 (4)
Influenza B only	1 (4)
Human parainfluenza virus	0
Human metapneumovirus	0

RSV, respiratory syncytial virus.