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Burden of respiratory syncytial virus in hospitalized infants and young children in Amman, Jordan

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Abstract

Acute respiratory infections (ARI) play a major role in hospitalizations in the Middle East, but the specific viral causes are unknown. We conducted prospective viral surveillance in children <5 y of age admitted with ARI and/or fever at 2 dissimilar hospitals in Amman, Jordan during peak respiratory syncytial virus (RSV) season. We collected prospective clinical and demographic data and obtained nose/throat swabs for testing for RSV by real-time polymerase chain reaction (RT-PCR). We obtained clinical and laboratory data for 728/743 (98%) subjects enrolled. The children's median age was 4.3 months, 58.4% were males, 87% were breastfed, 4% attended day care, 67% were exposed to smokers, 7% were admitted to the intensive care unit, and 0.7% died ($n = 5$). Out of 728 subjects, 467 (64%) tested positive by RT-PCR for RSV. Comparing RSV-positive with RSV-negative subjects, the RSV-positive subjects had lower median age (3.6 vs 6.4 months, $p < 0.001$) and fewer males (55% vs 64%, $p = 0.02$). RSV-positive children had higher rates of oxygen use (72% vs 42%, $p < 0.001$), a longer hospital stay (5 vs 4 days, $p = 0.001$), and higher hospital charges (US \$538 vs US\$431, $p < 0.001$) than RSV-negative children. In young hospitalized Jordanian infants, the medical and financial burden of RSV was found to be high. Effective preventive measures, such as an RSV vaccine, would have a significant beneficial impact.

Introduction

Acute respiratory infection (ARI) is the leading cause of hospitalization and death in children <5 y of age worldwide outside the postnatal period [1]. ARI causes a significant number of

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hospitalizations among children yearly. In one population-based viral surveillance study of children <5 y of age in the USA, 61% of those hospitalized with ARI had evidence of a viral infection and 47% of these were due to influenza, RSV, or parainfluenza viruses [2]. However, the viral aetiologies and their distribution are poorly documented in most developing countries [3–5].

Few viral surveillance studies have been performed in the Middle East, and most have not used highly sensitive molecular techniques such as real-time polymerase chain reaction (RT-PCR) [6–11]. In this study, we studied 2 key issues: (1) the frequency of RSV disease in children <5 y of age hospitalized with respiratory symptoms and/or fever at 2 major hospitals in Amman, Jordan, and (2) the associated risk factors for hospitalization during the peak winter months.

Methods

Study design

We conducted a prospective respiratory surveillance study of hospitalized children with acute respiratory symptoms over a 3-month period during the peak winter season. Study personnel enrolled children Sundays–Thursdays within 48 h of admission. Eligible children were those <5 y of age, admitted with respiratory symptoms with or without fever ($>100.4^{\circ}\text{F}/38.0^{\circ}\text{C}$) or with fever alone, and without neutropenia (defined as an absolute neutrophil count of $<1500/\mu\text{l}$). Newborn infants who had never been discharged from the hospital were excluded. Subjects were enrolled from either the Jordan University Hospital or the government-owned Al Bashir Hospital, the latter serving a less prosperous patient population. The study was conducted with the approval of the institutional review boards of Vanderbilt University and Jordan University and the Jordanian Ministry of Health. Verbal consent was obtained from the parents/guardians of all children prior to enrolment.

Demographic and clinical information

Study personnel completed a questionnaire by interviewing the parents/guardians and then recorded the child's clinical symptoms, medical history, demographic information, social history, exposure history, and influenza vaccination status. Missing data were obtained from the medical records. After a subject's discharge, study personnel reviewed the medical charts for hospital stay duration, hospitalization charges, and living status. Data were entered into a handheld electronic device and synchronized daily with the database.

Laboratory tests

We collected 1 nasal and 1 throat swab from each child with immediate storage in viral transport medium. The specimens were then divided into 5 aliquots. Lysis buffer (Roche Applied Science) was added to 3 aliquots to enhance RNA stability, and all 5 aliquots were stored at -70°C at Jordan University. The specimens were shipped on dry ice to Vanderbilt University for RT-PCR testing.

RNA was extracted from frozen aliquots using automated methods (MagNAPure LC, Roche Applied Science). Real-time reverse transcriptase PCR (real-time RT-PCR) assays were performed using primers and probes for RSV [12] and 5 other pathogens to investigate co-infections: influenza A and B [13,14], human rhinovirus (HRV) and human enterovirus (HEV) [15], and human metapneumovirus (hMPV) [16]. Each specimen was also tested by real-time RT-PCR for human β -actin (Applied Biosystems). Specimens without detectable β -actin on 2 separate analyses were considered inadequate and excluded. Real-time RT-PCR was performed with the Smart Cycler II (Cepheid) using Quantitect Probe RT-PCR chemistry (Qiagen). Batched assays of 32 patient specimens were assessed using virus-positive RNA, non-template controls, and β -actin as an extraction control.

Statistical analysis

Characteristics of children with and without RSV were compared, assessing the strength of associations and their statistical significance with the Chi-square test for categorical covariates. The non-parametric Mann–Whitney test was used for continuous variables. For categorical variables with small expected values in any cell, Fisher's exact test was used. The summary statistics of median and interquartile range (IQR) were reported for continuous covariates. Frequency and percentage were reported for categorical covariates. Logistic regressions with flexible spline curves for continuous covariates were used to study the risk factors in RSV-positive children. A 2-sided p -value of less than 0.05 was considered to indicate statistical significance. All statistical analyses were performed using R 2.4.1 (www.r-project.org).

Results

Study population

Of the 803 eligible subjects with respiratory symptoms and/or fever from 18 January to 29 March 2007, 743 (92.5%) of the subjects were enrolled. Clinical and laboratory data were available for 728/743 (98%) subjects. Only 44 (6%) of the subjects were enrolled from Jordan University. The median age of the subjects was 4.3 months, 425 (58.4%) were male, 27 (4%) attended day care, 488 (67%) were exposed to smokers, 168 (23%) had an underlying medical condition, 52 (7%) were admitted to the intensive care unit, and 5 (0.7%) died (Table I).

Virus data

At least 1 of 6 viruses (RSV, influenza A and B, HRV, HEV, and hMPV) were detected in 638/728 (88%) of the subjects, and 467/728 (64%) were positive by RT-PCR for RSV. The median age of the RSV-positive subjects was 3.6 months, and 83.4% of the infants were <1 y of age. The majority of RSV infections occurred in January and February, with 78% of individuals testing positive for RSV during those months compared to 34% in March ($p < 0.01$).

Demographic data

Demographic characteristics of the infants demonstrated significant differences between RSV-positive and RSV-negative children (Table I). RSV-positive children were younger (median 3.6 vs 6.4 months, $p < 0.001$), breastfed for fewer months (2 vs 4 months, $p < 0.001$), and had a smaller portion of males compared to those children who tested negative for RSV (55% vs 64%, $p = 0.002$) (Table I).

Clinical manifestations

RSV-positive children were significantly more likely to present with cough, poor appetite, trouble breathing, post-tussive emesis, and wheezing/noisy breathing than those children who tested negative for RSV (Table II). RSV-positive children had a higher percentage of oxygen use (72% vs 42%, $p < 0.001$), had a longer hospital stay (5 vs 4 days, $p = 0.001$), and their hospital charges were higher (380 JD (US\$538) vs 304 JD (US\$431), $p < 0.001$) than RSV-negative children. There was no significant difference in underlying medical conditions between RSV-positive and RSV-negative children, except that more children with heart disease were RSV-negative ($p = 0.002$, Table I). After adjusting for all factors, the odds ratio (OR) for the following factors remained significant between RSV-positive and RSV-negative subjects: age (for IQR of 1.8 vs 9.7 months, OR 3.03, 95% confidence interval (CI) 1.89–4.76), number of days in the hospital (IQR of 2 vs 0 days, OR 5.1, 95% CI 3.3–8.0), post-tussive vomiting (OR 1.62, 95% CI 1.13–2.33), poor appetite (OR 1.58, 95% CI 1.08–2.29), and female/male ratio (OR 1.49, 95% CI 1.03–2.16).

Deaths

The status at discharge was known for 700/728 (96%) of the subjects. Five children died, 3 of whom were RSV-positive only; of the 2 other children, 1 had RSV/HRV and 1 had HRV only. All 3 deceased children infected with RSV alone had presented with apnoea as their primary diagnosis. One was a 1.8-month-old former 33-week gestational age female with a birth weight of 1.6 kg, a current weight of 2.15 kg, and requirement for oxygen upon admission. This child had a secondary diagnosis of pneumonia and died on day 16 of admission. Another death occurred on day 2 of admission in a 2.1-month-old female term infant with a birth weight of 2.8 kg, a current weight of 4.2 kg, and history of cerebral palsy; she required mechanical ventilation. The third who died with RSV only was a 9-month-old female term infant with a birth weight of 4.1 kg and a current weight of 8.4 kg and a 15-day history of illness prior to admission; she died on day 5 of admission. The RSV/HRV-positive fatality was a 1.4-month-old male term infant with a birth weight 2.4 kg and a current weight of 3.5 kg and heart disease (undetermined); he required oxygen on admission, dying on day 11 of admission. The fifth deceased child with HRV only was an 18-month-old male with a birth weight of 3.25 kg, a current weight of 4.4 kg, and a history of mental retardation and developmental delay; the admitting diagnosis was ARI and pneumonia and he died the same day.

Children infected with RSV alone

Of 467 RSV-positive children, 341 (73%) tested positive for RSV only and negative for HRV, influenza A and B, HEV, and hMPV by PCR. The 341 RSV-positive only subjects were more likely to have wheezing/noisy breathing, trouble breathing, post-tussive emesis, poor appetite, nasal congestion, and cough in comparison to RSV-negative subjects. RSV-positive only subjects also had a greater number of days of symptoms prior to hospitalization (4 vs 3 days, $p = 0.01$) than RSV-negative subjects. In addition, RSV-positive only subjects were more likely to require oxygen use than RSV-negative subjects (74% vs 42%, $p < 0.001$).

Co-infections

Of the 467 RSV-positive infants, 126 (27%) tested positive for another virus: 110 with RSV/HRV, 8 with RSV/hMPV, 5 with RSV/HRV/hMPV, 2 with RSV/influenza B, and 1 with RSV/HEV. Compared to RSV-positive only infection, children who were co-infected with RSV and another virus were more likely to have been exposed to smoking (74% vs 62%, $p = 0.022$) and less likely to report nasal congestion (52% vs 74%, $p < 0.001$) or sore throat (30% vs 42%, $p = 0.025$). Co-infected children also had longer hospital stays (5 vs 4 days, $p = 0.021$) and higher hospital charges (380 JD (US\$538) vs 304 JD (US\$431), $p = 0.012$). There was no significant difference in oxygen use (67% vs 74%, $p = 0.12$) or age (2.99 months vs 3.81 months, $p = 0.21$) between co-infected children and those infected with RSV alone.

Discussion

This prospective respiratory viral surveillance study conducted in 2 disparate hospitals in Jordan during the peak winter season documented a serious burden of viral ARI. This study represents one of the largest series of young hospitalized children in the Middle East. The use of sensitive molecular diagnostic testing enabled the detection of at least 1 virus in 88% of the children, with RSV being the most common. RSV is the most common virus identified in hospitalized children with ARI in other studies in the Middle East and worldwide [8–10,17–20]. Fully 89.4% of the hospitalized Jordanian infants in this study were <1 y of age and 1 of 4 children had an underlying medical condition. The median age of 3.6 months in our cohort is consistent with other studies worldwide documenting RSV hospitalization in young infants [8,21,22]. In the USA, 66% of the children hospitalized with RSV at 3 major hospitals were young, previously healthy children [23]. We believe it is essential to characterize viral aetiologies and high-risk individuals in developing countries to identify candidates for future

prevention measures. Unfortunately, this was done late for pneumococcus and Haemophilus influenzae, resulting in delays in vaccine deployment in developing nations with tremendous need [24–27].

Described risk factors associated with RSV hospitalization or severe illness include being of male sex, young age, birth in the first half of the RSV season, day care attendance, lack of breastfeeding, chronic medical conditions, smoke exposure, and household crowding or siblings [23,28–32]. In comparison to RSV-negative children, RSV-positive children in our study were more likely to be younger, require oxygen, and have a longer hospital stay. Even after excluding subjects with co-infection, RSV-positive children in comparison to RSV-negative children were more likely to require oxygen. Conversely, RSV-positive subjects who were co-infected with other viruses, mainly HRV, were less likely to require oxygen, less likely to present with nasal congestion and sore throat, more likely to be exposed to smokers, but had a longer hospital stay. In addition, of the 5 children who died, 4 were RSV-positive. These findings suggest that RSV may be more severe than other viral illnesses we identified and that the morbidity and mortality of RSV disease may be under-recognized in Jordan and the Middle East.

We found no differences between RSV-negative and RSV-positive children for environmental exposures such as cigarette smoking, day care, or household size. Overall, two-thirds of children were exposed to tobacco smoke, and this exposure was significantly higher in children co-infected with RSV and another virus compared to those infected with RSV alone. In a survey conducted by the Jordanian Ministry of Health in 2002, of the 8791 respondents, 30% were classified as current smokers (51% of the male respondents and 8% of the female respondents) [33]. This exposure may predispose children to more severe ARI and hospitalization [34,35]. A recent study demonstrated cigarette condensate co-stimulation significantly increased RSV-induced interleukin-8 and monocyte chemoattractant protein-1 secretion compared to either stimulus alone [36]. Cigarette smoke may contribute to an exuberant immune response to RSV by stimulating overlapping signal transduction pathways. The high rate of smoking exposure in our study may partially explain the extreme burden of RSV hospitalization in this cohort. Public health efforts directed toward smoking cessation could also help to ameliorate the burden of RSV disease in Jordanian children.

Not only was RSV associated with more severe disease, but also the hospital charges for RSV-positive children were 25% higher than RSV-negative children. An estimated 51,000–82,000 hospitalizations annually in the USA are due to RSV with an average estimated cost of US \$27,101 per hospitalization [23,37]. Jordan's gross national income per capita is US\$6714 and their total expenditure on healthcare per capita is US\$611, compared to US\$44,070 and US \$4820 for the USA, respectively [38]. Therefore, 1 RSV hospitalization consumes a substantial proportion of the entire annual allocation of healthcare resources per child in Jordan. Healthcare is free for all children <6 y of age in Jordan, and thus these costs directly impact the national resources. Prevention of ARI hospitalizations due to RSV would be an economic boon.

Currently, no approved RSV vaccines or effective therapies exist, and treatment recommendations emphasize supportive care. RSV humanized monoclonal antibody prophylaxis is available, but is mostly used in higher income countries due to high costs [39]. Even if Jordan routinely used RSV prophylaxis as recommended in the USA, the vast majority of the infants hospitalized in our study with RSV would not have met the current recommendations for its use. Thus, alternative prevention strategies such as an RSV vaccine are desperately needed.

Our study had several limitations. We did not test for all known respiratory viruses and thus it is possible that co-infection with other respiratory viruses not tested may have played a role.

Nonetheless, we detected a virus in 88% of the children. Since this was not a population-based study, we have been able to report frequency of viral infections but not incidence rates. We did not collect bacterial culture data, so we cannot confirm whether these children had invasive bacterial infections. The risk of secondary bacterial infection appears to be low following RSV infection in the USA [40], but little is known in relation to this in the developing world. A Gambian study documented that 9/255 (3.5%) of RSV-positive children had concomitant bacterial infections [41]. The actual incidence of invasive bacterial disease is difficult to obtain because many children in Jordan are pre-treated with antibiotics. Antibiotics were administered to 72% of RSV-positive patients in another hospital in Amman, Jordan [42]. Since we did not collect data on antibiotic use, we were unable to assess inappropriate use of antibiotics. We only studied a period of 3 months, while a longer surveillance period might have better reflected the full respiratory viral season. In addition, the majority of the subjects were enrolled from the government hospital, which may represent a different socio-economic population in Jordan.

Our study revealed a substantial burden of RSV hospitalizations in young Jordanian children, with both a serious financial and medical impact. Future prospective surveillance over an extended period in this region is needed to accurately identify the epidemiology and burden of influenza and other viruses. Such information could be used to influence vaccine policy for influenza vaccine now and for future RSV vaccines when they become available. Clinical epidemiological studies can highlight the relative global importance of different respiratory viruses for children in varying parts of the world, avoiding delays in vaccine deployment based on debates of vaccine relevance in a 'data-free zone'.

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Table I

Demographic statistics by RSV-positive and RSV-negative status.

	RSV-positive (<i>N</i> = 467)% (<i>n</i>) or median (IQR)	RSV-negative (<i>N</i> = 261)% (<i>n</i>) or median (IQR)	<i>p</i> -Value
Birth weight (kg)	3.0 (2.6–3.5)	3.1 (2.8–3.5)	0.40
Male	55% (258)	64% (167)	0.02
Median age (months)	3.58 (1.52–8.32)	6.44 (2.56–12.35)	<0.001
Length of breastfeeding (months)	87% (408)	87% (228)	1.0
Months breastfeeding	2.0 (1.0–6.0)	4.0 (1.0–9.0)	<0.001
Jordan University	7% (31)	5% (13)	0.37
Day care	3% (15)	5% (12)	0.34
Smokers in the house	66% (306)	70% (182)	0.25
Homeowner	58% (270)	60% (157)	0.54
Number of household members	5 (4–7)	6 (4–7)	0.90
ICU	7% (33)	7% (19)	0.9
Heart disease	5% (22)	11% (28)	0.002
Premature (<36 weeks)	10% (44)	8% (21)	0.5
Kidney/liver/gastrointestinal reflux disease	2% (8)	2% (4)	0.852
Bronchopulmonary dysplasia/chronic lung disease/CF/ asthma	4% (20)	7% (19)	0.085
Seizure/CP/MRDD/other neurological disorder	4% (18)	3% (7)	0.407
Sickle cell disease/immune deficiency	0.21% (1)	1.53% (4)	0.058 ^a
Genetic disorder/other chronic	4% (20)	3% (7)	0.273

RSV, respiratory syncytial virus; IQR, interquartile range; ICU, intensive care unit; CF, cystic fibrosis; CP, cerebral palsy; MRDD, mental retardation development delay.

^aFisher's exact test.

Table II

Clinical presentation by RSV-positive and RSV-negative status.

	No. with completed data	RSV-positive (<i>N</i> = 467)% (<i>n</i>) or median (IQR)	RSV-negative (<i>N</i> = 261)% (<i>n</i>) or median (IQR)	<i>p</i> -Value
Cough	728	98% (458)	92% (239)	<0.001
Earache	688	17% (75)	23% (56)	0.08
Fever	728	53% (248)	57% (149)	0.30
Nasal congestion	727	68% (317)	65% (169)	0.43
Poor appetite	728	76% (354)	68% (177)	0.02
Trouble breathing	725	90% (420)	84% (218)	0.01
Sore throat	591	39% (149)	38% (80)	0.86
Post-tussive emesis	727	57% (264)	41% (108)	<0.001
Wheezing/noisy breathing	727	89% (416)	82% (215)	0.01
Mechanical ventilation	728	4% (17)	2% (6)	0.38
Oxygen	728	72% (336)	42% (110)	<0.001
Number of days on oxygen	727	1 (0–2)	0 (0–1)	<0.001
Died	700	0.86% (4)	0.4% (1)	0.66
Symptom duration, days (median)	728	4 (3–6)	3 (2–5)	0.01
Temperature (°C)	727	37.5 (37–38.3)	37.2 (37–38.5)	0.36

RSV, respiratory syncytial virus; IQR, interquartile range.