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Natural history and epidemiology of respiratory syncytial virus infection in the Middle East: Hospital surveillance for children under age two in Jordan

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ABSTRACT

Respiratory syncytial virus (RSV) is the leading cause of bronchiolitis and viral pneumonia in infants and young children worldwide. In the Middle East and Arab countries, the burden of RSV-associated hospitalizations is not well characterized. We sought to determine the burden and clinical/epidemiological characteristics of RSV hospitalization in young children in Amman, Jordan. We investigated risk factors for severity including vitamin D levels.

Methods: We conducted viral surveillance with clinical and demographic data in children <2 years admitted with respiratory symptoms and/or fever at the Al-Bashir Government Hospital from March16, 2010 to March 31, 2013. Nasal/throat swabs were obtained and placed into lysis buffer, and frozen at −80 °C until testing by real-time RT-PCR for 11 respiratory viruses. Heel stick blood or sera samples for 25-hydroxyvitamin D [25(OH)D] levels were obtained and sent to a central laboratory for mass spectrometry.

Results: Of the 3168 children, >80% testing positive for one virus, with RSV the most common virus detected (44%). The RSV-associated hospitalization rate was highest in children <6 months with an annual range of 21.1–25.9 per 1000, compared to 6.0–8.0 in 6–11-month-olds and 1.6–2.5 in 12–23-month-olds. RSV-positive children compared with RSV-negative were more likely to be previously healthy without underlying medical conditions, less likely to be born prematurely, had a higher frequency of supplemental oxygen use, and had lower median vitamin D levels. Risk factors for oxygen use in RSV-positive children included underlying medical conditions, lack of breastfeeding, younger age, and higher viral load.

Conclusion: RSV is a major cause of illness in hospitalized Jordanian children and is associated with increased severity compared to other respiratory viruses. Children with RSV in the Middle East would benefit from future RSV vaccines and antiviral therapy.

1. Introduction

Respiratory syncytial virus (RSV) is the leading cause of bronchiolitis and viral pneumonia in infants and young children worldwide [1]. A global incidence estimate for RSV-associated acute respiratory infections (ARI) in children <5 years in 2005 suggests 33.8 million new episodes of RSV-associated ARI with at least 3.4 million episodes necessitating hospital admission [2]. An estimated 66,000–190,000 children died from RSV-associated ARI, and 99% of these deaths occurred in developing countries, though the Middle East was not considered due to paucity of published data [2].

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Specifically, very few population-based viral surveillance studies, including determining burden of RSV disease, have been performed in the Middle East, and few of these have used highly sensitive molecular techniques such as real-time reverse-transcriptase polymerase chain reaction [3–13]. Also, many of these studies had small samples sizes and the duration of the study period was usually for only one respiratory season. Thus, the true prevalence and burden of RSV disease in the Middle East remains unknown.

Recognizing that the viral etiology of ARI among Middle Eastern children in Arab countries was poorly characterized, in 2007 we had conducted a pilot viral surveillance study in children <5 years admitted with respiratory symptoms and/or fever at two hospitals in Amman, Jordan over a three-month winter period [14–16]. Of the 728 subjects enrolled, >80% tested positive for a virus by RT-PCR, with 64% testing positive for RSV. Compared to RSV-negative subjects, the RSV-positive subjects had lower median age, higher rates of oxygen use, longer hospital stay, and higher hospital charges. These pilot data suggested that in young hospitalized Jordanian children, the medical and financial burden of RSV was high. To more definitively address the burden of RSV disease in the present study, we conducted a three-year viral surveillance in Amman, Jordan and limited the age group to children <2 years, the age group representing >90% of the cases in our 2007 pilot study.

2. Methods

2.1. Study design

We conducted a prospective, year-round viral surveillance study enrolling children <2 years with respiratory symptoms and/or fever within 48 h of hospital admission at Al-Bashir Hospital, the major government-run referral center in Amman, Jordan. Children were enrolled five days a week (Sunday through Thursday) if they presented with a history of fever and/or respiratory symptoms and one of the following admission diagnoses: ARI, apnea, asthma exacerbation, bronchiolitis, bronchopneumonia, croup, cystic fibrosis exacerbation, febrile seizure, fever without localizing signs, respiratory distress, pneumonia, pneumonitis, pertussis, pertussis-like cough, rule out sepsis, upper respiratory infection (URI), or other. Children were excluded only if they had chemotherapy-associated neutropenia and/or were newborns who had never been discharged.

Written informed consent was obtained from parents or guardians before enrollment into the study. The institutional review boards at the University of Jordan, the Jordanian Ministry of Health, and Vanderbilt University approved the study.

2.2. Study location

Al-Bashir Hospital is one of three major government-run referral medical centers that serve the population of Amman, which is estimated to be >2 million. With its 185 pediatric beds (120 pediatric and 65 neonatal intensive care unit), the Ministry of Health estimates that during the study period, the Al-Bashir Hospital provided care for at least 50–60% of children in Amman (author SF, personal communication). Al-Bashir provides care to government employees and their dependents, underprivileged families in Amman, and patients who are referred from other health care centers in Jordan [17]. It is located in the low-income and densely populated Al-Ashrafieh area of eastern Amman, which includes the nearby Al Wihdat Palestinian refugee camp. Patients with financial constraints are also admitted to this hospital since Jordan adopted a policy of providing no-cost medical care to children <6 years at government-run institutions regardless of insurance status. During the 3-year study period, there were 17,557 hospitalizations admitted to the pediatric wards, 11,230 (64%) among children <2 years.

2.3. Data and specimen collection

Trained research staff obtained nasal and throat swabs from all enrolled children. If permission was granted, staff also obtained blood by a heel stick or venipuncture. Demographic characteristics and medical and social histories were obtained using standardized questionnaires; parents were queried in Arabic and the information was later translated and transcribed into English. The medical charts were abstracted after discharge; demographic, epidemiologic, and clinical data were collected systematically. Vital signs at admission were recorded by clinicians. Oxygen saturations were collected as ranges:95–100%, 90–94%, 85–89%, and <85%. Flaring or retractions were categorized as none, mild (flaring only), moderate (retractions), or severe (accessory muscle use). Wheezing on physical exam was categorized as none, end-expiratory, full expiratory or inspiratory, full expiratory and inspiratory, or not specified. Cyanosis was recorded as none, circumoral on crying only, circumoral at rest, generalized cyanosis at rest, or not specified. Documentation of microbiological data was obtained and viral identification laboratory results were recorded. Intensive care unit (ICU) stays included children who were either admitted directly to the ICU or were transferred in during the admission. Smoke exposure included both cigarette and/or nargalia (hookah pipe) exposure. Underlying conditions were collected and were categorized as the following: diabetes, heart disease, down's syndrome, kidney disease, sickle cell, cystic fibrosis, cancer, genetic/metabolic, cerebral palsy, neurological, mental retardation/developmental delay, seizure disorder, chronic diarrhea(e.g. >2 weeks), gastroesophageal reflux disease, immunodeficiency, asthma/reactive airway disease, and liver disease. We entered data into a standardized, secured REDCap™ (Research Electronic Data Capture, Vanderbilt University, Nashville, TN, USA) database system [18]. Data quality checks were performed on at least 10% of the charts and all case report forms were verified after entry.

2.4. Classification

To better understand the role of RSV in pediatric lower respiratory tract infection (LRTI), we identified a sub-cohort of children. The LRTI cohort consisted of children with an admission diagnosis of asthma, bronchiolitis, bronchopneumonia, pneumonia, respiratory distress, or wheezing; or clinical signs of retractions or accessory muscle use; or wheezing on examination.

2.5. Laboratory testing

Nasal and throat swabs were collected and combined in transport medium (M4RT®, Remel, USA), aliquoted into MagMAX™Lysis/Binding Solution Concentrate (Life Technologies, USA), snap frozen, and stored at −80 °C. Original and lysis buffer aliquots were shipped on dry ice and were tested by RT-PCR for eleven respiratory viruses (RSV, human metapneumovirus (HMPV), human rhinovirus (HRV), influenza (flu) A and B, C, and parainfluenza (PIV) virus 1, 2, and 3, adenovirus (adeno), and Middle East respiratory syndrome coronavirus (MERS-CoV) [19–25,15,26,27].

2.6. Vitamin D testing

Blood was placed directly onto filter paper and air dried for ≥30 min before storage at room temperature and kept in a dry state until shipment to ZRT Laboratory (Beaverton, OR, USA) for vitamin D assay per protocol [28].

2.7. Statistical analysis

Descriptive statistics were presented as frequency (percentage) or median and interquartile range (IQR) where appropriate. Categorical variables were compared using Pearson Chi-square test. Continuous variables were compared using Mann-Whitney U test. For ≥3 groups comparison of continuous variables, Kruskal–Wallis test was used. We fit a multivariable logistic model to analyze the risk of oxygen use, ICU stay, mechanical ventilation, and length of stay as indicators for severity. The risk factors assessed included breastfeeding, vitamin D level, age at enrollment, gestational age, birth weight, gender, past medical history, smoke exposure, daycare, the four most common admission diagnoses (pneumonia, bronchopneumonia, bronchiolitis, and suspected sepsis) and RSV count, except for ICU stay, daycare was removed from the model because there were not subjects who were admitted to the ICU who attended daycare. All analyses were performed using statistical software R version 3.1.2 (http://www.R-project.org/).

Al-Bashir Hospital admissions data were used to estimate the population prevalence of each RSV. These data were filtered to exclude admissions of individuals not residing in Amman. We used a Bayesian hierarchical model to derive estimates for each of the three years of the study [29]. Estimates of the under 2-year-old Jordanian population were obtained from the World Bank online database, and the proportion of the population residing in Amman (35%) was taken from the2012 national census [30]. These values were used in a binomial model to estimate the population of children <2 years of age in Amman in 2010–2012. The market share for Al-Bashir hospital was modeled as a random variable, and given a uniform prior distribution between 50 and 60% of the market share. Finally, to account for the enrollment effort, the probability of enrollment was set to 71.4% (5 of 7 days) and used in a binomial model for the number enrolled in the study. Prevalence was given diffuse beta(1,5) priors for all models. An RSV model was fitted using Markov chain Monte Carlo [31] methods as implemented in the PyMC 2.3 software package [32]. Models were run for 100,000 iterations, with the first 90,000 iterations conservatively discarded as burn-in. Models were checked for convergence using the Gelman-Rubin diagnostic [29] and for goodness of fit using posterior predictive checks[33].

3. Results

3.1. Study population

From March 16, 2010 to March 31, 2013, 3793 patients were eligible, of whom 3175 (83.7%) were enrolled. Seven patients (0.2%) were excluded: three were ≥2 years and four had the admission diagnosis of meningitis. Thus, 3168 subjects (83.5% of eligible subjects) were included in the final cohort.

3.2. Clinical and demographic characteristics of entire surveillance cohort

The median age was 3.5 months (range 0.07–23.96 months), with 12% of the children <1 month, 47.6% 2–5 months, 22.8% 6–11 months (total 82.4% <1 year) and 17.6% 12–23 months. Sixty percent were male. Nearly 90% of the children had Jordanian parents, 7% Palestinian, and 3% other. By medical chart reviews or parent histories, 11.8% of the children were noted to have an underlying medical condition and 14% of the children had a history of prematurity (<37 weeks). Prior to hospitalization, 41% received an antibiotic and nearly the entire cohort (92%) were administered an antibiotic during their hospital stay. Almost 93% of the children had one of five admission diagnoses: bronchopneumonia (32%), suspected sepsis (29%), bronchiolitis (17%), pneumonia (12%), and pertussis-like cough (7%). We had vitamin D levels for 2688 (85%) children; the median vitamin D level was 16.5 ng/mL.

3.3. Viral detection

All 3168 children had a nasopharyngeal swab obtained. A virus was detected in 81% of the children. The most common virus detected was RSV (44%), followed by HRV (39%), adeno (15%), HMPV (9%), PIV 1, 2, and 3 (6%), and Flu A, B and C(4%). MERS-CoV was not detected. Fig. 1 includes the frequency and distribution of RSV over a three-year period, with peaks in January and February. Of the 1397 RSV-positive children, 669 (48%) had at least one other virus detected and Fig. 2 illustrates the combination of these co-infections.

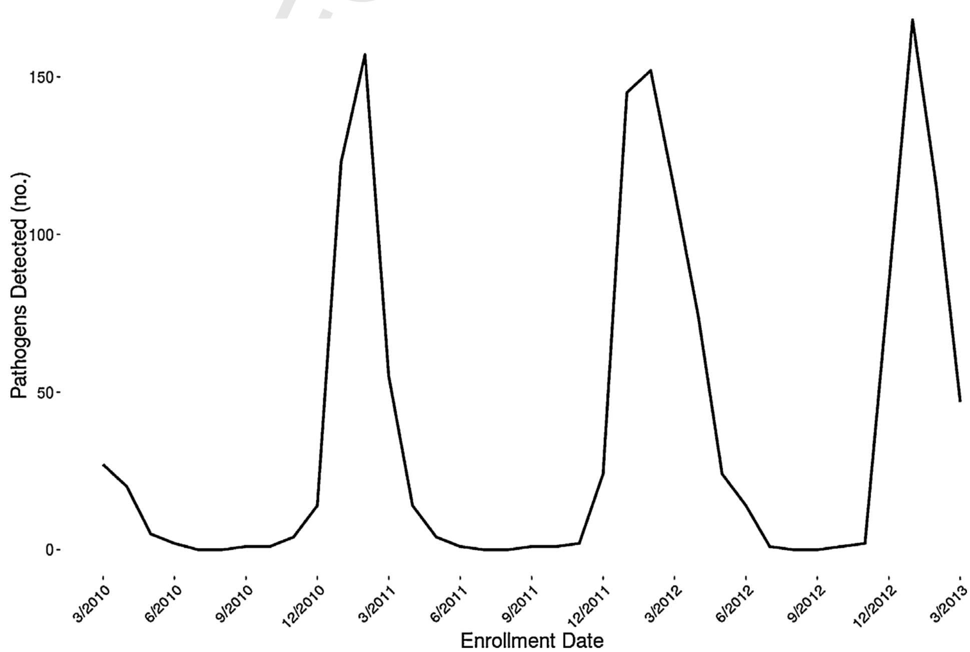

Fig. 1. The frequency of RSV-positive hospitalized children over the three-year study period (March 16, 2010 through March 31, 2013).

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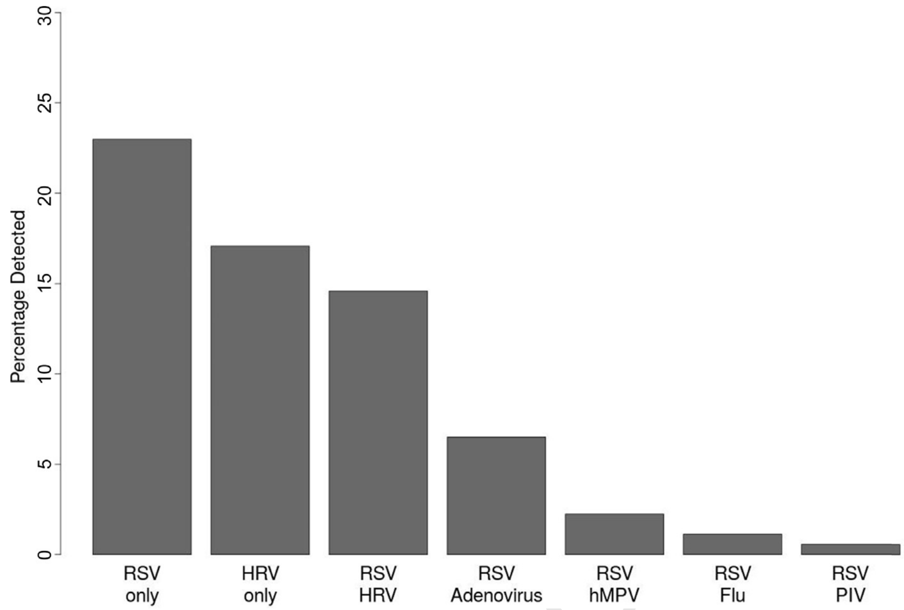

Fig. 2. The percent of RSV-positive only and RSV-positive with co-detection.

Table 1
Estimated Rates of RSV Hospitalizations with 95% credible intervals by year and by age groups per 1000 persons.

	<6 months	6–11 months	12–23 months
Year 1 (03/16/2010–3/31/2011)	21.1 (17.9, 24.4)	6.8 (5.4, 8.4)	1.6 (1.1, 2.1)
Year 2 (04/01/2011–3/31/2012)	23.5 (19.8, 26.8)	6.0 (4.7, 7.5)	2.3 (1.7, 2.9)
Year 3 (04/01/2013–3/31/2013)	25.9 (22.0, 29.4)	8.0 (6.5, 9.9)	2.5 (1.9, 3.2)

3.4. RSV hospitalization rates

Using Jordanian census data and restricting our cohort to children who resided in Amman, we were able to estimate RSV hospitalization rates for each study year (Table 1). Of the 3168 children, 3048 (96.2%) resided in Amman. The RSV rates were substantially higher in children <6 months (21.1–25.9 per 1000) compared to the older age groups: 6–8 per 1000 in 6–11-month-olds and 1.6–2.5 per 1000 in children ages 12–23 months.

3.5. Clinical and demographic characteristics comparing RSV-positive to RSV-negative children

A comparison of RSV-positive children compared to RSV-negative is shown in Table 2. RSV-positive children were more likely to have been previously healthy, with no significant underlying medical condition, and were less likely to be born prematurely (Table 2). RSV-positive subjects were also more likely to have the diagnoses of bronchiolitis, bronchopneumonia, pneumonia, and pertussis-like cough compared to RSV-negative children (Table 2). When comparing presenting symptoms as reported by parents, RSV-positive children were more likely to present with cough and shortness of breath and less likely to present with fever, decreased activity, diarrhea, or vomiting (Table 2).

The RSV-positive children were more likely to have a physician document wheezing, cyanosis, and abnormal flaring and retractions on exam and an abnormal chest radiograph (Table 2). These children had a comparatively higher frequency of supplemental oxygen use, were more likely to have <90% oxygen saturation at admission (9% vs. 6% for RSV-negative children, $p < 0.01$), and were less likely to have oxygen saturation >95% (36% vs. 42%, $p < 0.01$). The RSV-positive children also had lower median vitamin D levels (Table 2). The mortality rate was lower in the RSV-positive children, (0.5% vs. 1%, $p = 0.015$). In order to understand if co-infection with another virus was associated with increased severity, we compared RSV-only children with RSV co-infected children. RSV-only children had slightly higher percentage of cough reported prior to admission 96% vs. 93% ($p < 0.01$), were more likely to report a runny nose/congestion (3% vs. 1%, $p = 0.01$), and had comparable severity of disease.

3.6. Clinical characteristics of children with lower respiratory tract infection

In order to characterize the features of RSV-associated LRTI, we analyzed the subset of children who presented with LRTI. Of the 3168 children, 2263 (71.4%) met criteria for LRTI. Of these, 1210 (53.5%) had RSV, 785 (34.7%) had another virus detected, and 268 (11.8%) had no virus detected (Table 3). Children with RSV were more likely to be younger, have a history of breastfeeding, have the diagnoses of bronchiolitis or pertussis-like cough, present with cough or shortness of breath, and have cyanosis on exam compared to other virus-positive and virus-negative children (Table 3). In addition, they were more likely to require oxygen and had lower median vitamin D levels (Table 3). Children who had virus-negative LRTI were more likely to have an underlying medical condition, be admitted to the ICU, and die compared to the other groups (Table 3).

3.7. Risk factors for illness severity: Oxygen use, ICU stay, mechanical ventilation, and length of stay

To assess for severity of illness indicators, we compared the following outcomes in RSV-positive children: oxygen requirement, any ICU stay, mechanical ventilation, and length of stay (Tables 4 and 5) in a univariate and/or multivariable analyses. Lack of breastfeeding, lower age, and higher viral load (indicated by lower Ct values) were associated with oxygen use, while the diagnoses of bronchiolitis, suspected sepsis, and bronchopneumonia

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Table 2
Clinical and demographic comparisons of RSV-positive and RSV-negative children.

Total *N* = 3168	RSV-positive *N* = 1397	RSV-negative *N* = 1771	*p*-Value
Age (months) median	3.5 months	3.5 months	0.16
0–1 months	135 (10%)	248 (14%)	<0.01
2–5 months	736 (53%)	772 (44%)	
6–11 months	327 (23%)	394 (22%)	
12–23 months	199 (14%)	357 (20%)	
Sex (male)	834 (60%)	1078 (61%)	0.50
Daycare	27 (2%)	23 (1%)	0.16
Breastfeeding	1200 (86%)	1461 (82%)	0.01
No past medical history	1286 (92%)	1507 (85%)	<0.01
Smoke exposure	1070 (77%)	1355 (77%)	0.96
Antibiotics prior to hospitalization	653 (47%)	633 (36%)	<0.01
Antibiotics during hospitalization[a]	1279 (92%)	1612 (91%)	0.61
Gestational Age Median % < 37 weeks	179 (13%)	271 (15%)	0.046
Birth weight (median, kg)	3.0	3.0	0.58
Admission diagnosis			
Bronchiolitis	374 (27%)	173 (10%)	<0.01
Bronchopneumonia	476 (34%)	544 (31%)	0.045
Pneumonia	225 (16%)	169 (10%)	<0.01
Suspected sepsis	248 (18%)	664 (37%)	<0.01
Pertussis-like cough	129 (9%)	96 (5%)	<0.01
Presenting symptoms			
Fever	649 (46%)	1113 (63%)	<0.01
Cough	1320 (94%)	1046 (59%)	<0.01
Shortness of breath	1039 (74%)	793 (45%)	<0.01
Runny nose/congestion	40 (3%)	37 (2%)	0.16
Decrease appetite	301 (22%)	399 (23%)	0.51
Seizures/convulsions	19 (1%)	106 (6%)	<0.01
Decrease activity	77 (6%)	238 (13%)	<0.01
Diarrhea	69 (5%)	248 (14%)	<0.01
Vomiting	186 (13%)	336 (19%)	<0.01
Key examination findings			
Wheezing	926 (66%)	831 (47%)	<0.01
Cyanosis	362 (26%)	258 (15%)	<0.01
Flaring/retractions	173 (12%)	108 (6%)	<0.01
Abnormal chest X-ray[b]	1122 (82%)	955 (60%)	<0.01
Outcomes			
O2 requirement[c]	566 (41%)	447 (25%)	<0.01
Days on oxygen (25th, 50th, 75th, mean, standard deviation)	1 2 5 (3.76 ± 3.3)	1 2 4 (3.28 ± 3.1)	0.041
Mechanical ventilations[d]	52 (4%)	59 (3%)	.54
ICU stay[e]	126 (9%)	158 (9%)	0.89
Median length of stay (days)[f]	4	4	0.2
Death[d]	7 (0.5%)	24 (1%)	0.015
Vitamin D level (ng/mL)[g]	14.3 ng/mL	18.2 ng/mL	<0.01

[a] 3147.
[b] 2961.
[c] 3137.
[d] 3136.
[e] 3140.
[f] 313.
[g] 2688.

were not associated (Table 4). The diagnoses of pneumonia and suspected sepsis and lower age were more likely to be associated with ICU stay but less likely with the diagnosis of bronchopneumonia (Table 4). Mechanical ventilation was associated with younger age and higher vitamin D level (Table 4). The following were associated with longer length of stay: having an underlying medical condition, lack of breastfeeding, the diagnoses of pneumonia and suspected sepsis, younger age, lower gestational age, and higher viral load (indicated by lower Ct values) in contrast, the diagnoses of bronchiolitis and bronchopneumonia were associated with shorter length of stay (Table 5).

4. Discussion

In our 2010–2013 surveillance window, RSV was a major cause of ARI hospitalizations in Jordanian children <2 years, with consistent annual peaks in January and February. Our study represents one of the largest cohort studies of RSV-infected hospitalized children, including within the Middle East [10–13,34–43]. RSV is well-recognized cause of ARI globally [2], but even comprehensive reports typically fail to include information from the Middle East region due to lack of published data. Therefore, our study fills a knowledge gap of RSV burden in the Arab region.

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Table 3
Clinical and demographic comparisons of lower respiratory tract infection by RSV-positive, other virus-positive, and virus-negative children.

Total Cohort $N = 2263$	RSV-positive LRTI	Virus other-positive LRTI	Virus-negative LRTI	*p*-Value
Age (months) median	4.2	7.1	6.2	<0.01
0–1 months	78 (6%)	30 (4%)	20 (7%)	<0.01
2–5 months	618 (51%)	249 (32%)	92 (34%)	
6–11 months	320 (26%)	279 (36%)	76 (28%)	
12–23 months	194 (16%)	227 (29%)	80 (30%)	
Sex (male)	733 (61%)	484 (62%)	154 (57%)	0.48
Daycare	26 (2%)	12 (2%)	7 (3%)	0.46
Breastfeeding	1031 (85%)	627 (80%)	211 (79%)	0.002
No past medical history	1104 (91%)	629 (80%)	207 (77%)	<0.01
Smoke exposure	929 (77%)	594 (76%)	213 (79%)	0.44
Antibiotics prior to hospitalization	605 (50%)	371 (47%)	128 (48%)	0.46
Antibiotics during hospitalization	1099 (91%)	708 (91%)	236 88%)	0.28
Gestational	148 (12%)	127 (16%)	41 (15%)	0.04
Age				
Median % < 37 weeks				
Birth weight (kg) (25th, 50th, 75th, mean, standard deviation)	2.6 3.0 3.5(3.0 ± 0.6)	2.5 3.0 3.5(2.9 ± 0.7)	2.5 3 3.4(2.9 ± 0.6)	0.02
Admission Diagnosis				
Bronchiolitis	374 (31%)	129 (16%)	44 (16%)	<0.01
Bronchopneumonia	476 (39%)	410 (52%)	134 (50%)	<0.01
Pneumonia	225 (19%)	126 (16%)	43 (16%)	0.28
Suspected sepsis	150 (12%)	65 (8%)	33 (12%)	0.01
Pertussis-like cough	51 (4%)	16 (2%)	8 (3%)	0.03
Presenting symptoms				
Fever	595 (49%)	463 (59%)	142 (53%)	<0.01
Cough	1176 (97%)	685 (87%)	142 (53%)	<0.01
Shortness of breath	964 (80%)	545 (69%)	65% (175)	<0.01
Runny nose/congestion	38 (3%)	17 (2%)	9 (3%)	0.38
Decrease appetite	234 (19%)	95 (12%)	47 (18%)	<0.01
Seizures/convulsions	8 (1%)	19 (2%)	9 (3%)	<0.01
Decrease activity	45 (16%)	22 (12%)	18 (20%)	0.15
Diarrhea	58 (5%)	63 (8%)	17 (6%)	0.01
Vomiting	149 (12%)	97 (12%)	41 (15%)	0.39
Key examination findings				
Cyanosis	339 (28%)	150 (19%)	64 (24%)	<0.01
Outcomes				
O_2 requirement[a]	478 (40%)	248 (32%)	100 (38%)	0.002
Days on oxygen (25th, 50th, 75th, mean, standard deviation)	1 2 5 (3.6 ± 3.3)	1 2 4 (3.3 ± 3.1)	1 2 3 (2.9 ± 3.1)	0.042
Mechanical ventilations[b]	48 (4%)	31 (4%)	15 (6%)	0.46
ICU stay[c]	107 (9%)	63 (8%)	40 (15%)	0.003
Median length of stay in days[c] (25th, 50th, 75th, mean, standard deviation)	2 3 6 (4.1 ± 3.3)	1 3 6 (4.2 ± 4.7)	1 3 6 (4.1 ± 4.3)	0.05
Death[b]	7 (0.6%)	7 (0.9%)	7 (3%)	0.007
Vitamin D level (ng/mL)[d]	15.1	20.3	20.5	<0.01

[a] 2239.
[b] 2238.
[c] 2241.
[d] 1942.

Our estimates of hospitalized RSV incidence are consistent and even slightly higher than other estimates from developed and developing counties in which RT-PCR was used to calculate RSV-associated hospital rates. For instance, our estimated RSV-associated hospitalization rates in children <6 months (range, 21–25 per 1000) were higher than a population-based study of three US hospitals that reported RSV-associated hospitalization rates for children <6 months as averaging 17 per 1000 (range: 12.4–21.7) over a five-year period, in which 20% (564/2892) of the subjects were RSV-positive [44]. In a large population-based study of ARI in Egypt, of the 4993 children <5 years of age in which a specimen was collected, 518 (11%) of the children were positive by RSV by RT-PCR, with the highest portion in the 1–11 months group (45%). They estimated RSV-associated hospitalized rates in children 1–11 months as 17.45 per 1000 [42]. Of note, they excluded children <1 month of age, which most likely underestimated the burden of RSV. Other studies that estimated population-based RSV-associated hospital rates used less sensitive methods of RSV detection or only included children with children with severe ARI [45–48], making comparisons challenging. Our study highlights the importance of active surveillance over longer study periods and the advantage of sensitive molecular RSV detection techniques to accurately estimate the true burden of RSV hospitalizations.

Not only are the hospitalization rates of RSV-positive children higher compared to RSV-negative, but the clinical characteristics are different and the severity of illness seems to be greater in these children [14,44,49,50]. Prematurity and underlying medical conditions (e.g., heart or lung disease) are well-recognized risk factors for severe RSV [51]. However, the majority of our RSV-positive children were less likely to have been born prematurely or have an underlying medical condition compared to RSV-negative, consistent with other studies [34,44]. In our cohort, RSV-positive children were more likely to be admitted with evidence of lower respiratory involvement (e.g., higher frequency of pneumonia, bronchiolitis and bronchopneumonia diagnoses and physical findings such as wheezing and retractions), present with hypoxemia and cyanosis, and require supplemental oxygen compared to RSV-negative children. Taken together, these results suggest that RSV is more likely to cause severe infection compared to other viruses.

Table 4
Univariate and multivariable analysis of factors associated with oxygen use, ICU stay, and mechanical ventilation in RSV-positive children.

Oxygen Use							
Univariate analysis					Multivariable analysis		
	N	Oxygen *N* = 566 (%)	No oxygen *N* = 816 (%)	*p*-Value	Adjusted OR (95% CI)	*p*-Value	95% CI
Gender, male	1397	321 (57%)	501 (61%)	0.08	1.21	0.15	0.94–1.56
Underlying medical condition	1397	44 (8%)	63 (8%)	0.97	**1.54**	**0.09**	**0.93–2.53**
Daycare	1397	13 (2%)	14 (2%)	0.44	1.52	0.38	0.60–3.86
Breastfeeding	1397	482 (85%)	708 (87%)	0.40	**0.60**	**0.01**	**0.40–0.89**
Smoke exposure	1397	428 (76%)	631 (77%)	0.46	1.14	0.39	0.85–1.53
Vitamin D level (ng/mL) (25th, 50th, 75th, mean, standard deviation)	1193	2.9 10.7 23.6 (14.1 ± 12.4)	4.6 15.8 26 (16.6 ± 12.5)	<0.01	0.89	0.67	0.69–1.15
Gestational age (weeks) (25th, 50th, 75th, mean, standard deviation)	1397	38 4040 (38.5± 2.3)	38 40 40 (38.8± 2.2)	0.02	0.90	0.30	0.71–1.14
Median age, months [IQR]	1397	2.3	4.8	<0.01	**0.26**	**<0.01**	**0.18–0.40**
RSV ct count	1396	24.9	26.4	<0.01	**0.72**	**<0.01**	**0.59–0.87**
Birth Weight	1396	3	3	0.77	**1.12**	**0.37**	**0.88–1.42**
Pneumonia	1397	128 (23%)	96 (12%)	<0.01	**1.46**	**0.16**	**0.98–2.18**
Bronchopneumonia	1397	126 (22%)	342 (42%)	<0.01	**0.65**	**0.14**	**0.43–0.98**
Bronchiolitis	1397	151 (27%)	221 (27%)	0.87	**0.64**	**0.13**	**0.43–0.98**
Sepsis	1397	128 (23%)	120 (15%)	<0.01	**0.57**	**0.01**	**0.37–0.86**
ICU Stay							
Gender, male	1397	67 (53%)	754 (60%)	0.13	1.31	0.22	0.85–2.01
Underlying medical condition	1397	12 (10%)	94(7%)	0.41	**1.45**	**0.43**	**0.58–3.59**
Daycare	1397	0 (0%)	27 (2%)	0.10	NA	NA	NA
Breastfeeding	1397	102 (81%)	1087 (87%)	0.08	**0.55**	**0.08**	**0.28–1.07**
Smoke exposure	1397	93 (74%)	965 (77%)	0.44	1.01	0.98	0.61–1.67
Vitamin D level (ng/mL)	1193	9.7	14.5	0.13	0.85	0.73	0.53–1.36
Gestational age (weeks)	1397	39	40	<0.01	0.76	0.06	0.50–1.15
Median age (months) [IQR]	1397	1.5	3.7	<0.01	**0.35**	**0.02**	**0.17–0.74**
RSV ct count	1396	25.6	25.6	0.28	**1.06**	**0.09**	**0.76–1.48**
Birth Weight	1396	3	3	0.08	**0.88**	**0.55**	**0.59–1.33**
Pneumonia	1397	45 (36%)	179 (14%)	<0.01	**1.89**	**0.02**	**1.11–3.20**
Bronchopneumonia	1397	12 (10%)	456 (36%)	<0.01	**0.38**	**0.03**	**0.16–0.90**
Bronchiolitis	1397	22 (17%)	350 (28%)	0.01	**0.70**	**0.31**	**0.36–1.38**
Sepsis	1397	59 (47%)	189 (15%)	0.01	**1.81**	**0.4**	**1.02–3.21**
Mechanical ventilation (MV)							
Gender, male	1397	29 (56%)	792 (60%)	0.58	1.09	0.78	0.61–1.95
Underlying medical condition	1397	4 (8%)	102 (8%)	1	**0.85**	**0.80**	0.24–3.04
Daycare	1397	2 (4%)	25 (2%)	0.32	3.09	0.15	0.66–14.52
Breastfeeding	1397	45 (87%)	1144 (86%)	0.92	**1.54**	**0.37**	**0.59–4.00**
Smoke exposure	1397	41 (79%)	1017 (77%)	0.7	0.72	0.37	0.35–1.49
Vitamin D level (ng/mL)	1193	20.5	13.9	0.19	1.94	0.06	1.06–3.57
Gestational age (weeks)	1397	40	40	0.58	0.87	0.21	0.50–1.50
Median age, months [IQR]	1397	2.5	3.6	0.02	**0.29**	**0.03**	0.11–0.77
RSV ct count	1396	26.8	25.6	0.53	**1.25**	**0.39**	0.77–2.05
Birth Weight	1396	3.05	3	0.76	**1.52**	**0.14**	0.87–2.67
Pneumonia	1397	14 (27%)	210 (16%)	0.03	**1.83**	**0.16**	0.78–4.28
Bronchopneumonia	1397	13 (25%)	455 (34%)	0.17	**1.04**	**0.94**	0.38–2.81
Bronchiolitis	1397	14 (27%)	358 (27%)	1	**0.96**	**0.92**	0.39–2.35
Sepsis	1397	11 (21%)	237 (18%)	0.54	**0.65**	**0.34**	**0.27–1.57**

Previously described risk factors associated with RSV hospitalization or severe illness include male sex, young age, birth in the first half of the RSV season, day care attendance, lack of breast feeding, chronic medical conditions, smoke exposure, and household crowding or siblings [44,52–58]. Using oxygen use as on of the indicators for severity, our results are consistent with other reports finding a significant higher odds ratios for oxygen use in RSV-positive children with higher RSV viral load [59,60], lack of breast feeding [61], and younger age [44]. When also evaluating for ICU stay, mechanical ventilation, and length of stay, underlying medical conditions [51] and the admission diagnoses of pneumonia and suspected sepsis were other risk factors identified. Environmental tobacco smoke exposure is a known risk factor for serious RSV disease [62]. However, nearly 3/4 of our children were exposed to smoke; this high exposure for the cohort may explain why smoke exposure was not identified as an independent risk factor. Low vitamin D levels and clinical rickets have been associated with pneumonia and severe ARI [63–66]. Low vitamin D levels were associated with supplemental oxygen use in our univariate model; however, in the multivariable model it was no longer significant. Therefore, further investigation and public health interventions to reduce modifiable risk factors such as vitamin D supplementation, smoking cessation programs, and encouraging breastfeeding are needed in our population.

Prevention of RSV disease in young children may ultimately be possible with active immunization or maternal immunization, although no licensed RSV vaccine is currently available [67,68]. The only preventive measure for RSV disease is palivizumab, an RSV monoclonal antibody, which reduces the risk of hospitalization caused by RSV in high-risk children [69]. Use of palivizumab is low in low and middle income countries due to the high cost of the drug. The vast majority of children hospitalized with RSV in our study were full term and previously healthy. Therefore, even if palivizumab were available widely in Jordan, only a few children would have been eligible and thus it would have little impact on overall RSV hospitalization rates. Other strategies to reduce RSV-associated hospitalization are needed, such as infant or maternal

Table 5
Multivariable analysis of Factors Associated with Length of Stay in RSV-Positive Children.

	Adjusted OR (95% CI)	*p*-Value	95% CI
Gender, male	1.01	0.95	0.82–1.24
Underlying medical condition	**1.63**	**0.02**	1.1.0–2.42
Daycare	1.57	0.24	0.73–3.34
Breastfeeding	**0.66**	**0.01**	0.48–0.91
Smoke exposure	0.99	0.94	0.78–1.25
Vitamin D level (ng/mL)	0.97	0.64	0.78–1.19
Gestational age (weeks)	0.92	0.04	0.76–1.11
Median age, months [IQR]	**0.39**	**<0.01**	0.28–0.55
RSV ct count	**0.68**	**<0.01**	0.58–0.80
Birth Weight	**0.87**	**0.16**	0.71–1.05
Pneumonia	**1.77**	**<0.01**	1.27–2.46
Bronchopneumonia	**0.71**	**0.04**	0.51–0.99
Bronchiolitis	**0.57**	**<0.01**	0.41–0.79
Sepsis	**2.08**	**<0.01**	1.47–2.85

vaccination with future vaccines or antiviral therapies specific for RSV.

Our study is one of the largest prospective cohorts of Middle East children hospitalized for ARI. Moreover, each subject had molecular viral testing performed for 11 viruses and systematic data collection. However, our study does have some limitations. The administration of oxygen and other treatments was at the clinicians' discretion and we only collected oxygen saturations at admission, so data may not reflect truly serious disease. Nevertheless, RSV children were more likely to have lower saturation at admission compared to RSV-negative children, suggesting that RSV is associated with increased morbidity. We did not collect current steroid use, except for inhaled steroids, prior or during admission, which may have an effect on viral load and/or fever presentation. Chest radiograph findings were reported by clinicians and were not confirmed by independent radiologists. Children who were classified as virus-negative may have had other viral infections that we did not measure. Bacterial cultures were recorded when ordered by clinicians, but their reliability was uncertain because many infants received antibiotics before admission (over 40%) and the microbiology laboratory is not open for 24 h, delaying the processing of many specimens and therefore, we are not able to comment reliably about viral-bacterial co-infections. However, a recent prospective US study found that the majority of LRTI in hospitalized young children were caused by viral pathogens rather than bacteria (45). Since our RSV samples are not genotyped, we are unable to comment on differences in severity between RSV A and RSV B.

In conclusion, our three years of rigorous hospital surveillance confirm that RSV is a major cause of illness in young hospitalized Jordanian children. RSV is associated with increased severity compared to other respiratory viruses. Children in the Middle East would benefit from an RSV vaccine if one were available. In the meantime, public health policies directed at encouraging breastfeeding could be immediate interventions. RSV-specific chemotherapies are also needed. Future research on judicious use of antibiotics and the role of viral-bacterial co-detection are needed.

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