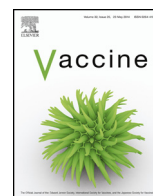




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# Natural history and epidemiology of respiratory syncytial virus infection in the Middle East: Hospital surveillance for children under age two in Jordan

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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 March 16, 2010 to March 31, 2013. Nasal/throat swabs were obtained and placed into lysis buffer, and frozen at  $-80^{\circ}\text{C}$  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.

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## 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].

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