

Epidemiology of Respiratory Virus Infections Among Infants and Young Children Admitted to Hospital in Oman

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The aim of this prospective study was to determine the epidemiology of respiratory viruses responsible for seasonal epidemics of influenza-like illness in infants and young children in Oman. All children ≤ 5 years of age consecutively admitted to Sultan Qaboos University Hospital in Oman over a 1-year period between December 2007 and December 2008 with acute respiratory infections were included. A multiplex polymerase chain reaction (PCR) for viral detection was performed on nasopharyngeal aspirates. Analyses were conducted using univariate statistical methods. Of the 259 infants and young children, at least one respiratory virus was detected in 130 samples (50%). The most prevalent viruses were respiratory syncytial virus (RSV; 43%; $n = 56$), adenovirus (15%; $n = 20$), and parainfluenza virus (PIV) (11%; $n = 14$). Dual or multiple viral infections were found in 23 cases (18%). The three most prominent symptoms of the cohort were fever (78%; $n = 201$), tachypnoea (77%; $n = 200$), and runny nose (61%; $n = 158$). The majority had bronchiolitis (39%; $n = 101$) while 37% ($n = 96$) had pneumonia. RSV was more likely to affect those that were young (4 months vs. 7.5 months; $P = 0.002$) and had tachypnoea (93% vs. 69%; $P = 0.004$), lower respiratory tract infections (91% vs. 80%; $P = 0.039$), and bronchiolitis (57% vs. 38%; $P = 0.024$). The study indicated that respiratory viruses are highly prevalent in children ≤ 5 years presenting with acute respiratory infections in Oman, of which RSV is the most prominent. **J. Med. Virol.** 84:1323–1329, 2012. © 2012 Wiley Periodicals, Inc.

KEY WORDS: respiratory syncytial viruses; adenoviruses; parainfluenza viruses; prevalence; infants

INTRODUCTION

Respiratory tract infections (RTIs) are a major cause of morbidity and mortality in children younger than 5 years old. The World Health Organization ranks respiratory diseases as the second-leading cause of death worldwide for children in this age group [Bryce et al., 2005]. In the pediatric population, respiratory syncytial virus (RSV), parainfluenza viruses (PIVs), and influenza account for a majority of cases of bronchiolitis and pneumonia, although the cause of 15–34% of these illnesses cannot be determined [Meissner and Rennels, 2004]. Since 2001, human metapneumovirus (hMPV) has emerged, as a respiratory pathogen that causes a significant proportion of both upper and lower RTIs in infants and children [Van den Hoogen et al., 2001; Esper et al., 2003].

Many respiratory viruses are the cause of yearly winter epidemics of severe lower respiratory infections in infants and young children. Few population-based estimates of the incidence of these viruses in

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developing countries are available. In addition, clear data are lacking on seasonality, severity, and case-fatality rates of these viruses. The acquisition and spread of respiratory viral infections among individuals has been attributed to several risk factors such as large family size, lateness in the birth order, crowding within the home, low birth weight, malnutrition, vitamin A deficiency, lack of breast feeding, pollution, and youth [Weber et al., 1999]. However, these factors vary considerably among different study populations in different countries. The variations can be due to cultural and socioeconomic factors, geographical or climatic differences, or variations in health care systems. A clear understanding of the local epidemiology of the disease and identifying risk factors is critical for the successful implementation of a prevention and control program.

The objective of the study was to estimate the prevalence of respiratory viruses, and identify the viruses responsible for seasonal epidemics of flu-like illness in children ≤ 5 years of age who presented with acute respiratory infections at the Sultan Qaboos University Hospital (SQUH) in Oman throughout a calendar year. The study is also aimed at identifying risk factors associated with the acquisition of these viruses in Oman.

MATERIALS AND METHODS

Patients and Samples

Data from this prospective study were collected from infants and children ≤ 5 years of age who were consecutively seen at SQUH over a period of one year (December 2007 to December 2008). They were admitted to SQUH with respiratory symptoms and were diagnosed as having RTIs. Bronchiolitis was defined as a constellation of clinical symptoms and signs including a viral upper respiratory prodrome followed by increased respiratory effort and wheezing in children less than 2 years of age [American Academy of Pediatrics, 2006]. Pneumonia was defined as the presence of fever, acute respiratory symptoms, or both, plus evidence of parenchymal infiltrates on chest radiography [McIntosh, 2002]. The exclusion criteria for this study were known immunosuppressive conditions, including human immunodeficiency virus (HIV); cancer or chemotherapy; hematological malignancies and autoimmune disorders; chronic use of high dose systemic corticosteroids (>30 mg/day for more than 2 weeks in the preceding 4 weeks); and children with symptoms of a respiratory infection starting 7 days after hospitalization. Written consent was obtained from their parents. A detailed epidemiological questionnaire, which included information on demographics, clinical presentation, medical history, and risk factors for respiratory illnesses, was completed by the treating physician. Furthermore, research and ethics approval was sought and granted by the College of Medicine and Health Sciences Research and Ethics Committee at Sultan Qaboos University, Muscat, Oman.

Samples were collected using disposable mucus extractors (Vygon, Ecoen, France), and transported to the laboratory according to the manufacturer's instructions. Samples were then divided into two aliquots: one vial was tested for common respiratory viruses including RSV; influenza types A and B; PIV types 1, 2, or 3; and adenoviruses using an immunofluorescence detection kit (OXOID, IMAGENTM, Thermo Fisher Scientific, Inc., Waltham, MA) (unpublished results), while the second vial was stored at -70°C for further processing by a multiplex polymerase chain reaction (PCR).

Extraction of Viral Nucleic Acid (DNA/RNA)

Viral nucleic acid (DNA/RNA) was extracted simultaneously from 200 μl of patient nasopharyngeal aspirates and cells were separated to increase the amount of extracted nucleic acid using a QIAamp MinElute Virus Spin Kit (Qiagen, Hilden, Germany), employing an automated nucleic acid extraction using a QIAcube instrument (Qiagen).

Reverse Transcription

With the exception of human adenovirus and human bocavirus (hBoV), the respiratory viruses detected in this study are RNA viruses; hence the conversion of RNA into cDNA is essential in order to be amplified using conventional PCR methods. RNA viruses were subjected to RevertAidTM. A First Strand cDNA Synthesis Kit (Fermentas, Thermo Fisher Scientific, Inc., Waltham, MA) was selected using a RevertAidTM M-MuLV (molony-murine leukemia virus) enzyme for the reverse transcription process (Fermentas, Thermo Fisher Scientific Inc.).

Detection of 12 Respiratory Viruses by Multiplex RT-PCR

Seeplex RV12 Kits (Seegene, Inc., Seoul, Korea) were used to detect RSV A and B; influenza flu A and B; PIV types 1, 2, and 3; human adenovirus; hMPV; coronaviruses OC43/HKU1, and coronavirus 229E/NL63 in a single reaction. Detection of hBoV was performed separately using the extracted nucleic acid for the detection of bocavirus with primers made on the basis of previously published sequence Data [Allander et al., 2005]. Primers were supplied by Alpha DNA, Montreal, QC, Canada. Samples with uncertain results in both multiplex RT-PCR and singleplex PCR for hBoV detection were repeated from the extraction step using the backup samples stored at -70°C , but the nucleic acid was extracted manually (Qiagen).

Statistical Analysis

Descriptive statistics were used to describe the data. For categorical variables, frequencies and percentages were reported. Differences between groups were analyzed using Pearson's chi-squared tests (or Fisher's exact tests for cells <5). For continuous

variables, median, and interquartile ranges (IQR) were presented. Differences between groups were analyzed using Kruskal–Wallis tests. An a priori was set at 0.05. Statistical analyses were performed using version 11.1 of Stata (StataCorp, College Station, TX).

RESULTS

A total of 259 nasopharyngeal aspirate samples were collected from infants and children aged ≤ 5 years who were seen at the hospital over a period of one year (December 2007 to December 2008). The study population consisted of 259 young children ≤ 5 years of age, hospitalized with suspected acute respiratory infection. At least one respiratory virus was detected in 130 samples (50%). Of the positive samples, 43% ($n = 56$) were RSV, 15% ($n = 20$) were adenovirus, and 11% ($n = 14$) were PIV. All other viruses detected in the descending order including influenza, rhinovirus, hMPV, bocavirus, and their combinations are listed in Table I. Dual or multiple infections were found in 23 cases (18%). For the purpose of this study, the cohort was divided into three groups, namely RSV group (22%; $n = 56$), other viruses (29%; $n = 74$), and those with negative samples (49%; $n = 129$).

Demographic and clinical characteristics are shown in Table II. The overall median age of the children was 7 months, with a range of 0.3–60 months. Of the patients, 59% were males ($n = 154$). There was a significant difference in median age distribution among the three groups ($P = 0.002$). RSV was more likely to affect those who were young (4 months vs. 7.5 months; $P = 0.002$). In fact, RSV infections solely affected those that were ≤ 2 years. Among the cohort, 50 (19%) infants were documented as having been born prematurely, while 86% ($n = 224$) were breastfed.

Forty-two percent ($n = 109$) of the children had a family history of asthma and 20% ($n = 51$) of the children had ≥ 5 siblings. The proportion of those from a household with animals and households in which smokers also live were 20% ($n = 52$) and 17% ($n = 45$), respectively. Ten percent ($n = 26$) of the children had a history of congenital heart disease. Significant differences in the clinical and demographic characteristics should be interpreted with caution due to low study power.

Symptomatic and diagnostic characteristics are listed in Table III. The children and infants' three most prevalent symptoms were fever (78%; $n = 201$), tachypnoea (77%; $n = 200$), and runny nose (61%; $n = 158$). Viral infections (including RSV) were more likely to be associated with wheezing than other types of infections, while tachypnoea was associated more with RSV infections than those infected with other viral respiratory infections (93% vs. 69%; $P = 0.004$). Those with RSV were significantly more likely to have lower rather than upper RTIs (91% vs. 80%; $P = 0.039$). The majority of the children and infants had bronchiolitis (41%; $n = 101$) while 37% ($n = 96$) had pneumonia. RSV infections were more likely to be associated with bronchiolitis than those with other infections (57% vs. 38%; $P = 0.024$). Nineteen percent ($n = 49$) of the cohort presented with the common cold and those with RSV tended not to present with this ailment as compared to those with other viral infections (9% vs. 20%; $P = 0.073$).

The seasonal prevalence of viral respiratory infections was estimated by using admission dates for the affected children and infants. This is found in Figure 1. As can be clearly demonstrated, the infections are more likely to be seen in winter months (October–March) with a decline in infections in the summer months (April–September).

TABLE I. Virus Types and Their Combinations Suspected of the Respiratory Infections ($n = 130$)

Type	Number	Percentage (%)
RSV A/B	46	35.38
Adenovirus	20	15.38
PIV 1/2/3	14	10.77
INF A	11	8.46
h rhinovirus A/B	10	7.69
h MPV	3	2.31
Bocavirus	3	2.31
Combined viruses		
PIV 1/2/3 + INF A	2	1.54
INF A + adenovirus	1	0.77
INF A + bocavirus	1	0.77
PIV-1 + INF A	1	0.77
Adenovirus + h rhinovirus A/B	1	0.77
Adenovirus + bocavirus	1	0.77
Human adenovirus + PIV-1	1	0.77
Human adenovirus + PIV-1 + bocavirus	1	0.77
Human adenovirus + rhinovirus A/B	1	0.77
Human adenovirus + bocavirus	1	0.77
Human coronavirus 229E/NL63 + PIV-2	1	0.77
Human rhinovirus + bocavirus	1	0.77
RSV + others	10	7.69

A total of 129 (49.81%) cases reported negative for viruses. There were, in total, 23 (17.69%) cases that had dual or multiple infections.

TABLE II. Demographic Characteristics Stratified by Virus Status (n = 259)

Characteristic	RSV, 56 (22%)	Others, 74 (29%)	Negative, 129 (49%)	P-value
Age groups (%)				
<6 months	57%	38%	41%	0.064
6–12 months	27%	26%	24%	0.916
12–24 months	16%	27%	20%	0.291
24–60 months	0	9%	15%	0.003
Median (IQR), months	4 (1–9)	7.5 (4–15)	7 (2.3–15)	0.002
Gender (%)				
Male	66%	61%	56%	0.410
Female	34%	39%	44%	
Birth weight				
Median (IQR), kg	2.9 (2.5–3.3)	2.8 (2.4–3.1)	2.9 (2.4–3.3)	0.137
<2.5 kg (%)	20%	32%	29%	0.313
Others (%)				
Breastfed	85%	96%	85%	0.081
≥5 Siblings	26%	27%	14%	0.058
Asthma	51%	43%	40%	0.396
Animal	15%	26%	21%	0.360
Smoke	13%	26%	16%	0.132
CHD	5%	12%	11%	0.400
IDA	7%	5%	6%	0.890

IQR, interquartile range; Asthma, family history of Asthma; Animal, lives in a household that has animals; Smoke, lives in a household that someone smokes; CHD, congenital heart disease; IDA, Iron deficiency anemia. Analyses were performed using Pearson's chi-squared tests, Fisher's exact test, or Kruskal–Wallis tests, wherever appropriate.

DISCUSSION

The current study was to estimate the prevalence of respiratory viruses in Omani children aged 5 years and under who had been admitted to SQUH with acute flu-like illness and their epidemiological characteristics. In the present study, respiratory viruses were detected in 50% of children hospitalized with symptoms and signs of acute RTIs. The leading cause of hospitalization was RSV A and B followed by adenovirus and PIV. Globally in 2005, an estimated 66,000–199,999 children younger than 5 years of age died from acute lower RTIs caused by RSV, with most of these deaths occurring in developing countries [Naira et al., 2010]. The burden of RSV in developing countries has been substantial and varies from one country to another, probably due to socioeconomic factors and health care patterns. This study

demonstrates that RSV causes significant morbidity in Omani children ≤5 years of age with higher rates of infection than those reported from countries within the region, including Saudi Arabia, Kuwait, and Egypt [Al-Hajjar et al., 1998; Khadadah et al., 2010; Fattouh et al., 2011]. The higher detection rate can be attributed to the use of more sensitive molecular-based diagnostic assays in the current study. In a recent study by Ali et al. [2010], the prevalence of RSV infection detected by real-time RT-PCR was 64%.

Influenza is common in young children. Prospective studies from the USA of laboratory-proven influenza have shown that in a single influenza season, up to 12% of all children aged <5 years seek medical care, and about one child in 1,000 is admitted to hospital [Steinhoff, 2011]. Published estimates of viral prevalence among children range from 6% to 16% for influenza [Poeling et al., 2006]. This has been similar to

TABLE III. Symptomatic and Diagnostic Characteristics Stratified by Virus Status (n = 259)

Characteristic	RSV, 56 (22%)	Others, 74 (29%)	Negative, 129 (49%)	P-value
Symptoms (%)				
Runny nose	66%	57%	61%	0.557
Cough	9%	15%	10%	0.497
Sore throat	20%	20%	11%	0.125
Ear ache	7%	7%	6%	0.948
Fever	79%	82%	74%	0.411
Wheezing	50%	49%	29%	0.005
Tachypnoea	93%	69%	75%	0.004
Chest indrawing	52%	49%	43%	0.495
Diagnosis				
LRTI (vs. URTI)	91%	80%	75%	0.039
Common cold	9%	20%	23%	0.073
Bronchiolitis	57%	38%	36%	0.024
Pneumonia	34%	41%	36%	0.726

LRTI, lower respiratory tract infection; URTI, upper respiratory tract infection. Analyses were performed using Pearson's chi-squared tests or Fisher's exact test, wherever appropriate.

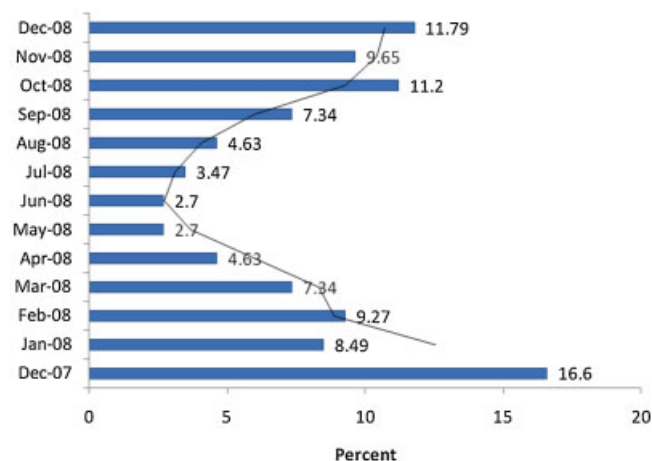


Fig. 1. Seasonal variation of viral infections from December 2007 to December 2008 ($n = 259$). [Color figure can be seen in the online version of this article, available at <http://wileyonlinelibrary.com/journal/jmv>]

our rate of influenza infection (8.4%). As in many different studies, clinical presentation alone could not reliably predicate the causative virus.

Eighteen percent of the cohort in the current study had multiple or dual infections with a predominance of RSV as compared to the other co-viruses. Previous studies have reported similar frequencies of co-infection [Aberle et al., 2005]. Multiple viral infections have been linked in some reports to higher fever, longer hospital stays, more frequent use of antibiotics and increased risk of admission to the ICU [Semple et al., 2005]. However, there is no consensus on the effect of co-infection on disease severity. The effect may depend upon which viruses co-infect [Martin et al., 2011]. The clinical severity of co-infection was not explored in the current study.

Several respiratory viruses were detected in the current study. These include hMPV and hBoV. The clinical impact of these viruses remains unclear. hMPV certainly has a clinical impact [Van den Hoogen et al., 2001; Esper et al., 2003; Broor et al., 2008], and there is evidence to suggest that hBoV is pathogenic [Calvo et al., 2008]. Future studies are required to establish further their impact as respiratory viruses in the Omani population.

The current study showed that RSV infection occurs solely in children 2 years of age and under with 57% of infections in infants younger than 6 months. Age correlates with the size of the child, particularly airway size; transmission dynamics, and immune experience, all of which contribute to an increased severity of infection [Tregoning and Schwarze, 2010]. The predominance of RSV infection in infants has been clearly documented in several other studies where RSV lower RTIs were common among infants less than 6 months of age [Rossi et al., 2007; Hall et al., 2009; Houben et al., 2010]. In these studies premature infants with birth weights less than 2.5 kg, and infants with chronic lung disease due to prematurity constitute high-risk groups with rates of RSV

hospitalization that are approximately five times the hospitalization rate of full term, healthy infants [Meissner, 2003; Weisman, 2003]. The correlation of low birth weight and prematurity to RSV infection rates was not seen in the current study, probably due to small sample size.

Numerous other risk factors that have been linked to RSV infections were also studied, such as gender, socioeconomic status, exposure to smoking or animals, and breastfeeding, and co-morbidities including asthma, chronic heart disease history, and iron deficiency anemia. While several previous studies showed some association with one or more of these risk factors, this study did not reveal any significant correlation, with the exception of household crowding that was reflected by the number of siblings per house (marginal association; $P = 0.058$). This was in line with several other studies, which found that an increase within a home of the number of children between the ages of 3 months and 5 years was the most important risk factor for hospitalization among children with RSV infections [Wang et al., 1995; Okiro et al., 2008].

Respiratory viruses have common symptoms. Therefore, differentiating between them based on clinical presentation has been nearly impossible. Most respiratory virus infections in early childhood are confined to the upper respiratory tract, leading to symptoms of the common cold, with coryza, cough, and hoarseness. However, about one-third of infants with respiratory viral infections develop lower respiratory tract symptoms such as tachypnea, wheezing, severe cough, breathlessness, and respiratory distress [Pavia, 2011]. These symptoms may be accompanied by clinical signs.

The three most prominent symptoms in the current study of young children and infants were fever (78%), tachypnoea (77%), and runny nose (61%). Tachypnoea and wheezing were more predominant in infants and children with RSV infections, which probably can be attributed to the severity of the infection caused by RSV viruses. Ninety percent of infants with RSV infection were admitted with a diagnosis of lower RTIs while 50% had bronchiolitis. Bronchiolitis is the most common lower respiratory tract illness in children <24 months of age and the most frequent cause of hospitalization in infants under 6 months of age [Wagner, 2009]. Recent studies have indicated that hospitalization rates for bronchiolitis have significantly increased in the last several years mainly due to RSV infections [García et al., 2010]. In a study from the Saudi Arabia, 80% of children <6 months of age hospitalized with bronchiolitis had RSV infection. This was followed by adenovirus, which was isolated in an additional 20% of cases [Al-Shehri et al., 2005].

The epidemiology of respiratory virus infection varies tremendously among geographical regions. In temperate climates, the prevalence of these viruses is well documented as a cause of yearly winter epidemics of acute lower RTIs [Weber et al., 1998]. While

data from developing countries are sparse, this study clearly shows evidence of viral infection throughout the year with the highest rates of infection in winter months from October to February, with a peak in December reaching 16.6% and 11.7% in 2007 and 2008, respectively. This is attributed to the fact that December is the coldest month in Oman. Viral prevalence did not differ in the dry and rainy seasons, as the weather in Oman is mostly dry. In a study from Qatar, a country with a similar climate to Oman, respiratory viruses, particularly RSV epidemics, occurred yearly during the winter months with peak hospitalizations occurring between November and February [Wahab et al., 2001]. The seasonality of RSV infection has been well documented. In temperate climates, RSV activity peaks in the winter months but may occur throughout the year in equatorial areas [Stensballe et al., 2003; Center for Disease Control (CDC), 2010]. In tropical and subtropical areas, RSV infection increases mostly in wet seasons [Mathisen et al., 2009].

The present study has shown that RSV is the leading virus detected in Omani infants and young children hospitalized with respiratory symptoms. Palivizumab, a monoclonal antibody, has been highly indicated for RSV prevention in high-risk infants, including those with chronic lung disease, those with congenital heart disease, and those born prematurely [Bocchini et al., 2009; Empey and Peebles, 2010]. In the current study, only 20% of hospitalized infants and young children with RSV infection were premature. Several studies have shown that the majority of infants hospitalized with severe RSV disease are term infants with no underlying risk factors, and therefore are not considered candidates for palivizumab therapy. Clinical trials on several other novel treatments are ongoing.

Prevention remains the most important measure for reducing the morbidity and mortality associated with respiratory viruses, and their significant burden on the health care system. The obvious choice for the prevention of serious RSV infections would be the development of a vaccine. However, vaccines that have been developed against RSV are either inactivated or live-attenuated. Those that are inactivated produce high levels of serum antibody causing more severe infections than the wild virus. Those that are live-attenuated are too reactive or overly attenuated [Nair et al., 2011]. Thus the best preventive measures currently available are infection control measures and immunoprophylaxis with a monoclonal antibody for high-risk groups. Of the infection control measures employed, hand washing is the most important and the least expensive [Isaacs et al., 1991]. Other possible infection control procedures include isolation or cohorting of infected infants and improving nurse to patient ratios.

This study is not without limitations. The fact that subjects were not randomized could have introduced bias. However, the bias was minimized as the study

attempted to include all patients seen at SQUH over the 1-year study period. This study is also largely underpowered in some respects due to the small sample size, which may not be powerful enough to detect clinically meaningful corollary effects. The fact that other important causes of RTIs among children, such as *Streptococcus pneumoniae* and *Streptococcus pyogenes* were not excluded, could have affected the study results.

CONCLUSION

In Oman, most respiratory viruses circulate throughout the year with peaks in winter months, causing substantial social and economic impacts. RSV is the predominant cause of pediatric viral RTIs. For most of these viruses, treatment remains exclusively supportive. Thus, prevention remains the cornerstone of disease management. Currently, immunoprophylaxis for RSV infections is available. Guidelines published by the American Association of Pediatrics [American Academy of Pediatrics, 2009] have been adopted widely in developed countries to protect high-risk groups, but their implementation in this region has been hindered due to the high cost of the RSV monoclonal antibody and lack of epidemiological studies. The results of this study have important policy implications in the region. Nevertheless, there is an urgent need for the development of novel prevention and treatment strategies including vaccines and effective pharmacotherapy. The implementation of these strategies should remain a high priority.

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