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ORIGINAL RESEARCH

Identifying agents triggering bronchiolitis in the State of Qatar

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Background: Bronchiolitis is considered as the most frequent lower respiratory tract infection in infants and young children. This disorder is marked by acute inflammation, edema, damage of epithelial cells lining small airways, and augmentation of mucus production.
Objective: The goal of the study was to identify agents triggering bronchiolitis in the State of Qatar.
Materials and methods: A cross-sectional retrospective study was performed at Hamad Medical Corporation, the only tertiary and academic medical center in the State of Qatar. The study included infants and young children aged 0–24 months who were admitted to our pediatric ward with diagnosis of acute bronchiolitis (2010–2012)
Results: Eight hundred thirty-five infants and young children met the study inclusion criteria with mean age at diagnosis of 3.61±3.56 months. Respiratory virus real-time polymerase chain reaction was performed on 769 (92.0%) of the participants. Respiratory syncytial virus (RSV) was positive in 352 (45.7%) children admitted with clinical bronchiolitis. In addition, no viruses were identified in 142 (18.4%) of those admitted, and respiratory viruses other RSV were found in 275 (35.7%) of the children. Our investigations and observations show that there has been a steady and periodic seasonal variation in the RSV rate over the study period. A seasonal trend for the RSV (detected by respiratory virus real-time polymerase chain reaction) rate was evident, showing annual peaks in the months of October, November, December, and January, with a significant test for seasonality (test statistics [*T*]=3.15, *P*=0.009).
Conclusion: In countries with desert hot weather, bronchiolitis might affect children throughout the year. Our results suggest that the combination of date regarding uninterrupted RSV seasonality can provide guidance for health care planning and application of RSV prevention scheme, such as extending the palivizumab immunoglobulin series.
Keywords: bronchiolitis, desert, syncytial, virus, Qatar

Introduction

Bronchiolitis is considered as the most frequent lower respiratory tract infection in infants and young children. This disorder is marked by acute inflammation, edema, and damage of epithelial cells lining small airways, and augmentation of mucus production.[1]

Young patients usually present with cough and rhinitis, with the possibility of advancing to wheezing, tachypnea, rales, increased use of accessory muscles, and/or nasal flaring. The most commonly detected virus in bronchiolitis is the respiratory syncytial virus (RSV), with the peak incidence of infection taking place in the period of December till March.[2]

Nearly all children get an RSV infection by the time they are 2 years old, but only 1–2% of infants younger than 6 months of age may require hospitalization.[3] Due to

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the high prevalence, RSV infections inflict considerably economic hardship on families and health care systems.[4,5]

In the Middle East, RSV bronchiolitis is a very common disease,[6–8] constituting almost 60% of all children hospitalization in the State of Qatar.[6]

Regardless of risk factors, all infants and young children have the chance of acquiring serious illness by RSV. A large study conducted by Hall et al[9] showed that most RSV-infected young patients who had been hospitalized for RSV bronchiolitis had been healthy with no risk factors.

Some respiratory viruses have a predictable seasonality, which varies regionally. For example, in the USA and other parts of the world with similar climates, RSV affects children during fall, winter, and spring.[3] Previous studies have shown that RSV infection in the tropics is more common in the rainy season.[10–12] The reason for such seasonality is not well known yet, but atmospheric factors such as high humidity and temperature may assist virus survival in small particle droplets or aerosols, and on infected surfaces. Other factors that might affect seasonality are crowdedness such as initiation of school term.[12]

The State of Qatar is situated in the Asian continent with absolute location of 25.3000° N and 51.5333° E. It is a peninsula bordering, terrestrially, Saudi Arabia. The maritime boundaries include Bahrain, United Arab Emirates, and Iran.[13]

Qatar has a hot desert climate. The temperature typically varies from 14°C to 41°C. The warm season starts around May 10 and ends approximately September 26 with an average daily high temperature above 37°C. The cold season commences in early December and ends in early March with an average daily high temperature below 25°C. The chance of precipitation is 1% during the warm season and almost 15% during the cold season. In terms of humidity, it usually ranges from 18% to 94%.[14]

The aim of our study was to identify agents triggering bronchiolitis in the State of Qatar, and to describe the seasonality of viral bronchiolitis in hospitalized infants and young children in the State of Qatar.

Materials and methods

The retrospective and cross-sectional study was performed at Hamad Medical Corporation (HMC), the only tertiary and academic medical center in the State of Qatar. The study included infants and young children aged 0–24 months who were admitted to the pediatric ward with diagnosis of acute bronchiolitis during the period of January 2010 till December 2012. The identification of the patient population was obtained from an advanced search in the HMC medical records database. The search comprised diagnosis of bronchiolitis (primary diagnosis) in patients 24 months of age and under. The diagnosis of bronchiolitis was based on the definition suggested by the American Academy of Pediatrics, subcommittee on diagnosis and management of bronchiolitis.[1] Our young patients met the criteria of bronchiolitis as documented in the patients' files. We excluded children who did not have virology testing from their nasopharyngeal secretions, and those whose primary diagnosis was a disease other than bronchiolitis.

Approval for the study was obtained from the HMC Ethics Committee (Ref # 13139/13). The committee waived the need to obtain informed consent for retrospective studies, and so only deidentified information was collected.

The following details were collected: gestational age, gender, respiratory virus real-time polymerase chain reaction (RVRT-PCR) conducted on nasopharyngeal secretions, and hospital length of stay (LOS). The laboratory in our institution performs an identification panel for every requested nasopharyngeal secretion sample for the following organisms: pandemic influenza A H1N1, influenza virus A and B, parainfluenza virus types 1–4, coronavirus, novel coronavirus, rhinovirus, bocavirus, enterovirus, parechovirus, human metapneumovirus, and adenovirus.

For the aim of data analysis, we divided the patient population into three groups: group A, which comprised children hospitalized with clinical bronchiolitis and RVRT-PCR was positive for RSV; group B comprised children hospitalized with clinical bronchiolitis caused by an unidentified agent where RVRT-PCR was negative; and group C contained children hospitalized with clinical bronchiolitis due to a respiratory virus other than RSV such as rhinovirus, human metapneumovirus, parainfluenza 1–3, coronavirus, adenovirus, bocavirus, etc.

Statistical analysis

We used descriptive statistics to summarize demographic data, frequency of each virus, and all other clinical characteristics of the included patients. Quantitative and qualitative data values were expressed as frequency along with percentage and mean ± SD or median and range as appropriate. The primary outcome was to estimate the types of respiratory viruses triggering bronchiolitis. In addition, we examined the trend in RSV over the different months. Test for seasonality was evaluated by fitting the

data to a series of Box–Jenkins regression-autoregressive integrated moving average models. These models are stochastic models in that describe a univariate time series as a function of its past values. To test the null hypothesis that no seasonality was present, the likelihood ratio statistic was used. The autoregressive integrated moving average model procedure estimates the equivalent of the least-square parameter estimates of a regression model when the data are time series and the error term is an autoregressive process. Pictorial presentations of the key results were made using appropriate statistical graphs. All statistical analyses were done using statistical packages SPSS 22.0 (SPSS Inc. Chicago, IL, USA).

Results

Eight hundred thirty-five infants and young children met the study criteria. RVRT-PCR was performed on 769 (92%) of the participants. RVRT-PCR was not performed on 66 patients due to parental refusal or because the laboratory in our hospital does not run this specific test during the nights or weekends.

RSV was positive in 352 (45.7%) children admitted with clinical bronchiolitis. In addition, no viruses were identified in 142 (18.4%), while respiratory viruses other than RSV were found in 275 (35.7%) of children. Among the respiratory viruses other than RSV, rhinovirus constituted one third of the total followed by adenovirus (14%), parainfluenza virus type 4 (14%), bocavirus (10%), coronavirus (7%), H1N1 (3.4%), parainfluenza virus type 1 (3.4%), parainfluenza virus type 2 (3.4%), and parainfluenza virus type 3 (3.4%).

More boys than girls were admitted with acute bronchiolitis, the male-to-female ratio being 1.6:1 (39.2% girls and 60.8% boys) with mean age at diagnosis being 3.61±3.56 months, ranging from 0.33 to 24 months. The mean gestational age was 37.01±3.37, with less than one fifth of the total participants were born at gestational age fewer than 35 weeks. A seasonal trend for the RSV isolation rate was evident (Figure 1), showing annual peaks in the months of October, November, December, and January, with a significant test for seasonality (test statistics [*T*] =3.15, *P*=0.009). Figure 1 clearly shows that there has been a steady and periodic seasonal variation in the RSV rate over the study period. The series exhibited several peaks; aside from the small range fluctuations, the significant peak appeared to be separated by more than a few months. It shows a seasonal pattern as the peak of RSV cases follows a similar pattern with an interval of few months between the peaks.

The mean duration of hospital stay (Figure 2) was 8±7.9 days (median 6 days, range 1–71 days). The LOS (We were not able to verify the LOS in all patients. The reason is attributed to the fact that some families refused to allow the infant to be discharged from the hospital until he/she was "100%" back to baseline. Another common reason is that the patients might stay in the hospital for other concomitant illnesses) in hospital was found to be significantly higher among children in group C (9.3±9.8) compared to group B (7±6.3) and group

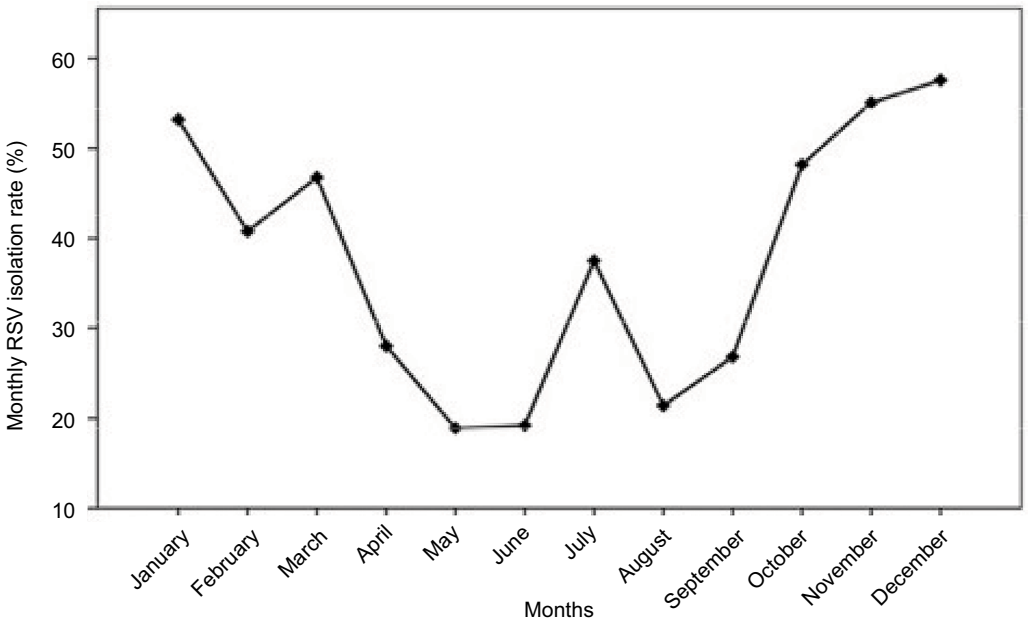


Figure 1 Sequence chart for RSV rate of infection during various months in 769 children admitted with acute clinical bronchiolitis.
Abbreviation: RSV, respiratory syncytial virus.

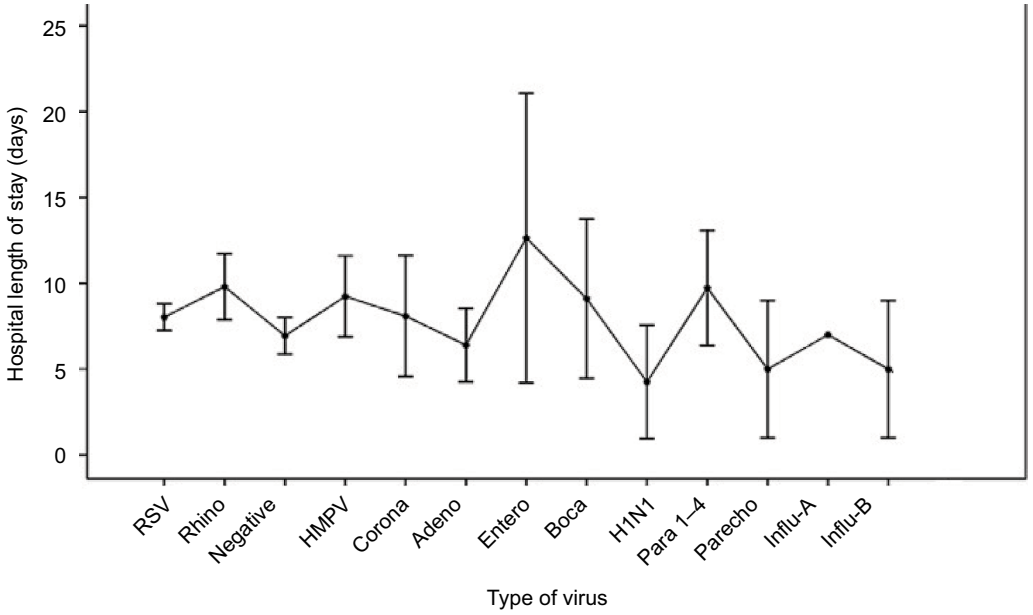


Figure 2 Mean length of stay in hospital (days) per virus among 769 children admitted with clinical acute bronchiolitis.
Abbreviations: Adeno, adenovirus; Boca, bocavirus; Corona, coronavirus; Entero, enterovirus; HMPV, human metapneumovirus; Influ, influenza; Para, parainfluenza; Parecho, parechovirus; Rhino, rhinovirus; RSV, respiratory syncytial virus.

A (8.1±7.2); *P*=0.002. Approximately 532 (64.3%) patients had mean LOS of 7 days or less, 223 (26.9%) had 7–14 days, and 73 (8.8%) had length of stay more than 14 days. Among the participants in group A, the mean duration of hospital stay was 8±7.2 days (median 6 days, range 1–71 days) distributed as 215 (61.8%) patients with a mean LOS of 7 days or less, 106 (30.5%) with 7–14 days, and 27 (7.8%) with length of stay more than 14 days. Mean LOS in hospital was found to be less among boys compared to girls (7.7±7.3 vs 8.5±8.7 days); however, the differences between them did not achieve statistical significance (*P*=0.547)

Discussion

Our study showed that the RSV contributes to almost 50% of all bronchiolitis cases in the State of Qatar. Despite the seasonal peaks, it is obvious that RSV bronchiolitis can infect young children throughout the year. In addition, the mean LOS due to RSV was found to be 8 days, which almost double the days required for young children with H1N1 bronchiolitis to be discharged from our medical institution. This could be perhaps attributed to the use of the H1N1 vaccine on most children as well as medications such oseltamivir for acute infections. In the developed countries, the mean LOS in children hospitalized with bronchiolitis is 6 days. The USA mean average is 4 days, while Germany reports 9 days.[15] Our results are comparable to that of West Europe.

Seasonality of RSV varies according to the geographical location. For instance, in Turkey (Northern Hemisphere), the peak RSV season starts in January and ends in May, coinciding with the cold season.[16] In countries that are in the southern hemisphere, like Argentina, the RSV peak season lies between June and September.[17] In Artic areas, like Alaska, the RSV peak season starts in late December and lasts for ~11 weeks.[18] Yusuf et al[19] conducted a study on the relationship of meteorological conditions to the epidemic RSV activity in the USA. The investigators registered year-round RSV activity in nine major cities that differ significantly in weather and geographic location. The study concluded that in moderate weather, RSV activity peaked during winter, corresponding to lower temperatures. In areas with continuous warm temperatures and high humidity, RSV activity was uninterrupted. In sites where temperatures remained colder throughout the year, RSV activity again was almost continuous.

The CDC reports that throughout the country in the USA, RSV onset occurred the week ending November 19, 2011, and lasted 21 weeks, until the week ending April 7, 2012. The percentage of specimens positive for RSV by antigen detection attained a season high of 26.2% during the week ending January 28, 2012. States that had hot summers such as Arizona and New Mexico did not differ much from the national average RSV season.[20] In warm equatorial areas, RSV infection is uninterrupted throughout the year.[21,22]

There are no studies that describe RSV seasonality in Qatar, but there are few studies in our geographical area that investigated the cyclical divergence of RSV bronchiolitis.

In Saudi Arabia, the RSV peak activity is reported to be in late fall and the beginning of the winter season where the humidity is less than 48% and temperature ranges from 14°C to 21°C.[19,23]

Another study by Uduman et al,[24] from Al Ain, United Arab Emirates, investigated 252 children younger than 3 years admitted to the hospital with moderate-to-severe respiratory disorders during the winter seasons of 1993–1994 and 1994–1995. The clinical arrangement of RSV illness included bronchiolitis in 58.3% of cases. The study demonstrated that the RSV incidence was maximum during the cooler months (temperature 10°C–20°C) when the relative humidity was 50%–60%, even though it was also noticed in substantial numbers during the hotter summer months.

Al-Toum et al,[7] from Amman, Jordan, studied children younger than 2 years hospitalized with respiratory illness in the pediatric ward, from the period of September 2002 to March 2004. A total of 200 nasopharyngeal aspirates was acquired and RSV was demonstrated in 12.5% of patients using direct immunofluorescence technique. Most of the infections were linked with bronchiolitis. RSV showed an obvious seasonal cycle. The epidemic started in December and vanished in March with a peak of incidence during February 2003 and January 2004.

Halasa et al,[25] also from Jordan, surveyed 3,168 children with respiratory symptoms and/or fever at the Al-Bashir Government Hospital, of whom more than 80% tested positive for RSV. The study that took place between the period of 2010 and 2013 showed that RSV infections and hospitalizations peaked in January and February.

Thamer and Ban,[26] from Tikrit, Iraq, investigated the epidemiology of acute respiratory tract infections among children under 5 years old attending Tikrit General Teaching Hospital from the first of November 2004 to the end of April 2005. The sample that included 2,450 children showed that December was the month with the highest frequency of RSV infection (31%), followed by January (20%), November (19%), February (15%), March (9%), and April (6%).

Dede et al[27] studied RSV infections in the arid desert regions of Central Australia. The investigation included 173 children younger than 24 months admitted to Alice Springs Hospital with RSV infection over a period of 5 years (2000–2004). The authors concluded that RSV-related infections peaked in the winter season, but illnesses occurred throughout the year.

Humid wet conditions might stimulate contact transmission of RSV, by augmenting the quantity of virus that is deposited on surfaces and by boosting virus survival in droplets on surfaces. Our results go along with this proposition, keeping in mind that climate change might just be one of the many factors that can have an impact of the prevalence and seasonality of RSV infection.[28] The month of July is one of the most humid months in the State of Qatar, and the surge in RSV infection during the said period can also be explained by the above proposition.

At the end of the last century, determent of RSV disease with the introduction of polyclonal immunoglobulin,[29] and eventually palivizumab, the humanized monoclonal antibody,[30] aimed against the RSV F protein, were historical evolution, both in terms of the advantages of diminishing stern disease in high risk young children as well as developing the field of RSV.

The vast documented analyses of palivizumab display the promising safety and benefit of an RSV fusion protein vaccine during pregnancy,[31–34] and hence this has the potential of being used as maternal immunization.

Our study had the strength of being conducted in the only tertiary and academic medical center in the country; so we are convinced that the majority of children with RSV bronchiolitis requiring hospital admission would have been admitted to HMC. Moreover, we used PCR-based detection techniques to identify respiratory viruses, and therefore our results hold an accurate estimate of the RSV epidemiology in our country. However, our study has some limitations. For instance, our study design methodology might not be perfect. Usually, there is a selection bias when conducting a retrospective study, which bears the consequences of over- or underestimating the true incidence of the disease. Furthermore, not all children with respiratory symptoms had nasopharyngeal samples sent for virology PCR. Finally, our study was conducted on sick children admitted to the pediatric wards. Therefore, we could have missed a proportion of cases that are usually handled as outpatient, and the virology profile could represent the sick kids, but not what is happening in the community.

Conclusion

In countries with hot desert weather, bronchiolitis affects infants and children throughout the year. Our results suggest that the combination of uninterrupted RSV seasonality and the prolonged hospital LOS in children can provide factual guidance for health care planning and application of RSV prevention schemes, such as extending the palivizumab immunoglobulin series.

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Disclosure

The authors report no conflicts of interest in this work.

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