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***Human metapneumovirus* in Hospitalized Children in Amman, Jordan**

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Abstract

Human metapneumovirus (HMPV) has recently been identified as an important cause of acute respiratory infections (ARI) in children worldwide. However, there is little systematic data on its frequency and importance as a cause of ARI in the Middle East. We conducted a viral surveillance study in children <5 years of age admitted with respiratory symptoms and/or fever at two major tertiary care hospitals in Amman, Jordan from 1/18-3/29/07. Nose and throat swabs were collected and tested for HMPV and other respiratory viruses by real-time RT-PCR. A total of 743 subjects were enrolled. Forty-four (6%) subjects were positive for HMPV, 467 (64%) were positive for RSV and 13 (1.3%) had co-infection with both HMPV and RSV. The frequency of HMPV in January, February, and March was 4.1%, 3.0%, and 11.9% respectively. Clinical features associated with HMPV infection were similar to those of other respiratory viruses, except children with HMPV were more likely to present with fever than children not infected with HMPV. Children with HMPV and RSV co-infection were administered supplemental oxygen and were admitted to the ICU more frequently than children infected with HMPV alone or RSV alone, though these differences did not reach statistical significance. We conclude that HMPV is an important cause of acute respiratory infections in children in Amman, Jordan. Longer surveillance studies are needed to better understand the seasonal epidemiology of HMPV and to assess if co-infection with HMPV and RSV leads to more severe illness.

Keywords

HMPV; MPV; bronchiolitis; middle east

INTRODUCTION

Respiratory viruses are identified in over half of the children hospitalized with severe acute respiratory infections (ARI) in developed countries [Iwane et al., 2004]. However, the role of respiratory viruses in severe ARI in developing countries remains largely unknown. While *Respiratory syncytial virus* (RSV), *influenza virus* and *parainfluenza viruses* are considered to be the most common respiratory viruses, the roles of other less known viruses such as *Human metapneumovirus* (HMPV), and that of viral-viral co-infections are increasingly being explored [Weber et al., 1998].

HMPV has recently been identified as an important cause of ARI worldwide. There is little systematic data on the frequency, risk factors and clinical features of HMPV in the Middle East, particularly in Jordan [Al-Sonboli et al., 2005; Kaplan et al., 2006, 2008]. Using real-time reverse transcriptase-polymerase chain reaction (RT-PCR), we sought to determine the burden and clinical features of HMPV and other respiratory viruses in hospitalized children in Amman, Jordan.

METHODS

We conducted a prospective respiratory surveillance study of children hospitalized with acute respiratory symptoms over a 3-month winter period, corresponding to the annual peak in respiratory infections in Amman, Jordan. Children in our study were recruited from two major hospitals in Amman, the Jordan University Hospital and the Government Al Bashir Hospital. Study personnel enrolled children Sundays–Thursdays within 48 hr of admission. Eligible children were less than 5 years old and admitted with respiratory symptoms (cough, difficulty breathing, or wheezing) or one or more of the following admission diagnoses: acute respiratory illness (ARI), apnea, asthma exacerbation, bronchiolitis, croup, cystic fibrosis exacerbation, febrile neonate, febrile seizure, influenza, fever without localizing signs, respiratory distress, otitis media, pharyngitis, pneumonia/pneumonitis, or rule out sepsis. Children were excluded if they had neutropenia or were newborns that were never discharged from the hospital. Institutional Review Boards from the Vanderbilt University Medical Center, Jordan University Medical Center and the Jordan Ministry of Health approved the study. Verbal consent was obtained by parents/guardians of all the subjects prior to enrollment. Study staff completed a questionnaire by interviewing the parents/guardians and recorded the child's clinical symptoms, medical history, demographic information, social history, and exposure history. Any missing data were obtained from the medical record. After the subject's discharge, study staff performed a chart review to obtain hospital stay duration, hospitalization charges, and living status. Data were entered into a handheld device and synchronized daily.

Nasal and throat swabs were collected from all the enrolled subjects within 48 hr of admission. The swabs were combined and transported in the veal infusion broth to the Jordan University Microbiology Research Laboratory. The specimens were divided in to multiple aliquots and lysis buffer was added to enhance RNA stability. These aliquots were stored in -70°C freezers, until they were shipped to Vanderbilt University on dry ice. The specimens were then stored at -80°C until processing.

At Vanderbilt, RNA was extracted from frozen aliquots using automated methods (MagNapore LC, Roche Applied Science). Real-time RT-PCR assays were performed using primers and probes for HMPV [Maertz-dorf et al., 2004], RSV [Mentel et al., 2003], influenza A and B [Kandun et al., 2006; Mehlmann et al., 2007] *human rhinovirus* (HRV), and *human enterovirus* (HEV) [Lu et al., 2008]. Each specimen was also tested by real-time RT-PCR for the house keeping gene, human β -actin (Applied Biosystems). Specimens

without detectable β -actin on two separate analyses were considered inadequate and excluded. Real-time RT-PCR was performed with the Smart Cycler II (Cepheid) using Quantitect Probe RT-PCR chemistry (Qiagen). Batched assays of 32 patient specimens were assessed using virus positive RNA, non-template controls, and β -actin as an extraction control.

Statistical Analysis

Subjects were compared by HMPV status or the presence of other viruses. Characteristics of children were evaluated with the use of chi-square test for categorical covariates and non-parametric Mann–Whitney test for continuous variables. For categorical variables with small expected values in any cell, the Fisher's exact test was used. The summary statistics of median and inter-quartile range (IQR) were reported for continuous covariates. Frequency and percentage were reported for categorical covariates. A two-sided *P*-value of less than 0.05 was considered to indicate statistical significance. All statistical analyses were performed with use of R 2.4.1 (www.r-project.org).

RESULTS

Study Population

Of the 803 eligible children, 743 (92.5%) subjects were enrolled. Both clinical and laboratory data were available for 728 (98%) subjects. A total of 44 (6%) subjects were enrolled from Jordan University and the remaining from the Government Al Bashir Hospital. The median age of study subjects was 4.3 months (IQR 1.8–9.7 months), and 58% were males. Average number of children in the household was 3.3. One hundred sixty-eight children (23%) had a known underlying medical condition, 27/728 (3.7%) attended day care, 488/728 (67%) subjects were exposed to smokers, 48/713 (6.7%) were less than 36-week gestational age.

Detection of HMPV and Other Respiratory Viruses

At least one respiratory virus was identified in 638/728 (88%) subjects. Forty four out of 728 (6%) of the subjects tested positive for HMPV. Other viruses tested included RSV (467/728, 64%), *rhinovirus* (240/728, 33%), *enterovirus* (26/728, 3.6%) *influenza A* (1/728, 0.001%), and *influenza B* (5/728, 1%). Of the 44 subjects positive for HMPV, 18 were positive only for HMPV, 8 were co-infected with RSV alone, 12 were co-infected with *rhinovirus* alone, 1 with *human enterovirus*, and 5 were co-infected with both RSV and *rhinovirus*.

Demographic information comparing HMPV positive and negative subjects is presented in Table I. HMPV positive subjects were older in comparison to HMPV negative subjects, median age 7.5 months (IQR 3.5–13.5 months) versus 4.2 months (IQR 1.6–9.5 months, *P*=0.003). Among the HMPV positive subjects, differences in frequency by enrollment month were observed, with rates of 4.1%, 3.0%, and 11.9% in January, February, and March respectively.

Clinical Features

The clinical features and hospital course of HMPV positive patients as compared to HMPV negative subjects are presented in Table I. Common presenting symptoms of HMPV infected children included cough (100%), trouble breathing (89%), wheezing (89%), fever (77%), nasal congestion (70%), and poor appetite (70%). Children with HMPV were more likely to present with fever (77%) than children not infected with HMPV (53%) (*P*=0.002). Of the 44 HMPV positive children, 4 had underlying heart disease, 2 had a known genetic defect, 2 had an underlying immune deficiency, 3 had asthma, and 3 were born prematurely

(<36 weeks gestation). Children with HMPV were more likely to have immune deficiency than HMPV negative subjects (5% vs. 0%, $P = 0.01$). No children with HMPV died in this cohort.

Co-Infections

Comparison of the 8 children co-infected with RSV alone with the remaining 18 HMPV only positive children and 341 RSV only positive children (without any co-infection) is presented in Table II. Children with HMPV/RSV co-infection were breast-fed for a shorter period as compared to children infected with HMPV alone (1.5 vs. 5 months, $P = 0.01$). Children with HMPV alone were older than those infected with RSV alone (9.2 months, IQR 5.9–14.1 vs. 3.8 months, IQR 1.5–8.7, $P < 0.05$). Children with HMPV and RSV co-infection had a longer and more expensive hospital stay than those with HMPV only. Children with HMPV and RSV co-infection were administered supplemental oxygen and were admitted to the ICU more frequently than children infected with HMPV alone or RSV alone, though these differences did not reach statistical significance.

DISCUSSION

This study shows moderate frequency of HMPV (6%) in children hospitalized with ARI or fever at two major hospitals in Amman. There are only a few other studies reported on frequency of HMPV in hospitalized children in the Middle East, and their reports showed percentages ranging from 2.5% at King Jordan and Queen Rania Hospitals in Amman, Jordan [Kaplan et al., 2008], to 13% at Soroka University Medical Center in Israel [Wolf et al., 2006]. Our study, the largest such cohort to date, shows HMPV frequency in similar range confirming that HMPV is associated with severe ARI in Amman, Jordan.

We found that the HMPV-infected children were older than the RSV-infected children, a finding which is comparable to other studies of HMPV epidemiology [Jartti et al., 2002; Boivin et al., 2003; Peiris et al., 2003; van den Hoogen et al., 2003; Dollner et al., 2004; Esper et al., 2004; Mullins et al., 2004; Prins and Wolthers, 2004; Bosis et al., 2005]. The reason for this difference is not clear. Possible mechanisms include disproportionate infection of younger children by RSV, differing kinetics of maternally acquired antibodies against HMPV or RSV, or a component of immunopathogenesis that increases with host immunologic maturity.

This study demonstrated that children with HMPV and RSV co-infections tend to have more severe disease as compared to children infected with HMPV alone or RSV alone. Children with HMPV and RSV co-infection had a longer and more expensive hospital stay compared to HMPV infection only. Co-infected children were more likely to require supplemental oxygen and ICU admission than children infected with HMPV alone or RSV alone. These differences may have failed to reach statistical significance due to the small number of co-infected subjects. The hypothesis that HMPV and RSV co-infections cause more severe disease has been explored in a few other studies but with conflicting results, mainly because of different study designs and inadequate power [Greensill et al., 2003; Semple et al., 2005; van Woensel et al., 2006; McNamara et al., 2007]. More studies are required to address the issue of possible increased severity of disease with RSV and HMPV co-infection, since these viruses often co-circulate.

This study has its limitations. Surveillance was conducted during 3 months, which were selected based on the peak winter season in Jordan. Therefore, HMPV cases outside the winter season were not captured. In fact, the proportion of HMPV positive cases progressively increased during the study months, and the peak frequency of 11.9% was detected in March. It is therefore likely that the HMPV season in Jordan extends beyond

winter, into the spring season. HMPV typically peaks in spring later than RSV in temperate regions [Williams et al., 2004, 2006]. We did not look for bacterial pathogens in the etiology of the respiratory illness; thus, we cannot assess the role of viral and bacterial coinfections in our study. The government hospital cares for subjects from lower socioeconomic backgrounds compared to the University hospital, but socioeconomic differences in HMPV infection have not been demonstrated [Mullins et al., 2004; van den Hoogen et al., 2004; Williams et al., 2006]. This study also did not test concurrent healthy controls to determine the prevalence of asymptomatic HMPV infection. However, detection of HMPV is uncommon in asymptomatic children [van den Hoogen et al., 2001, 2004; Osterhaus and Fouchier, 2003; Williams et al., 2004].

Respiratory viruses should be the focus of additional efforts to decrease pneumonia-associated morbidity and mortality in developing countries. Defining the burden of these viruses using reliable and sensitive diagnostic tests is an important step to accomplish this goal. Remarkably, we identified a respiratory virus in 88% of samples collected during the study. This was possible with the use of real-time RT-PCR, which is the most sensitive assay for viral diagnosis. It is possible that the role of respiratory viruses in the global ARI burden has been underestimated because of the less sensitive antigen and viral culture-based diagnostic assays used previously. This study shows that HMPV is an important pathogen in causing severe infections in hospitalized children in Amman, Jordan. A longer surveillance period is needed to accurately determine the frequency and peak of HMPV season in this region.

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TABLE I

Comparison of HMPV Positive and HMPV Negative Patients

	HMPV positive (n = 44)	HMPV negative (n = 684) ^a	P-Value
Baseline characteristics			
Age in months (median, IQR)	7.5 (3.5–13.5)	4.2 (1.7–9.5)	0.003
Male	52%	59%	0.40
Birth weight (kg) (median, IQR)	3.0 (2.7–3.2)	3.05 (2.7–3.5)	0.18
Months of breast feeding (median, IQR)	3.5 (1.8–6.0)	2 (1.0–7.0)	0.32
Daycare attendance	7%	4%	0.26
Smokers in the house	75%	67%	0.25
Number of household members (median, IQR)	5 (4.0–7.0)	6 (4.0–7.0)	0.84
Clinical features			
Fever	77%	53%	0.002
Cough	100%	95%	0.25
Wheezing/noisy breathing	89%	87%	0.71
Earache	23%	19%	0.47
Nasal congestion	70%	67%	0.6
Poor appetite	70%	73%	0.70
Sore throat	47%	38%	0.26
Post-tussive emesis	50%	51%	0.87
Hospital course			
Oxygen use	50%	62%	0.11
ICU admission	11%	7%	
Need for mechanical ventilation	2%	3%	1
Died during hospitalization	0%	1%	1
Days hospitalized (median, IQR)	4 (3.0–6.3)	4 (3.0–6.0)	0.88
Total charges (USD) (median, IQR)	304 (228–456), \$430 (US)	304 (228–456), \$430 (US)	0.85

^a“HMPV negative” includes children with HRV, RSV, influenza, or no virus detected.

TABLE II

HMPV and RSV Co-Infections Compared to HMPV Only and RSV Only Infections

	HMPV positive (no co-infection) (n = 18)	HMPV/RSV co-infection (no other co-infection) (n = 8)	RSV positive (no co-infection) (n = 341)
Baseline characteristics			
Age in months (median, IQR)	9.2 (5.9–14.1)	4.3 (1.6–13.0)	3.8 (1.5–8.7) ^b
Male	44%	50%	56%
Birth weight (kg) (median, IQR)	3.0 (2.7–3.5)	3.0 (2.5–3.0)	3.0 (2.6–3.5)
Months of breastfeeding (median, IQR)	5 (3–9) ^a	1.5 (0–2.2)	2 (1–6) ^b
Daycare attendance	6%	12%	3%
Smokers in the house	72%	75%	62%
Number of household members (median, IQR)	4.5 (4–6.5)	5.5 (4.7–6.2)	6 (4–7)
Clinical features			
Fever	83%	75%	53%
Cough	100%	100%	99%
Wheezing/noisy breathing	89%	88%	89%
Earache	35%	12%	18%
Nasal congestion	78%	38%	74%*
Poor appetite	67%	88%	77%
Sore throat	67%	43%	42%
Post-tussive emesis	50%	62%	57%
Hospital course			
Oxygen use	44%	88%	74%
ICU admission	6%	25%	7%
Need for mechanical ventilation	6%	0%	4%
Died during hospitalization	0%	0%	1%
Days hospitalized (median, IQR)	4 (3–5.7) ^a	8.5 (4–9.7)	4 (3–6.2)
Total charges (JD) (median, IQR)	304 (228–399) ^a (\$430 US)	608 (304–798) (\$860)	304 (228–456) (\$430)

^aStatistically significant difference ($P < 0.05$) when compared to the HMPV/RSV co-infected group.^bStatistically significant difference ($P < 0.05$) when compared to the HMPV only group.