Comparison of Human Metapneumovirus, Respiratory Syncytial Virus and Rhinovirus Respiratory Tract Infections in Young Children Admitted to Hospital

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Respiratory Syncytial Virus (RSV), Human metapneumovirus (HMPV), and Rhinoviruses (RV) are frequent causes of respiratory tract infections in young children. We compared laboratory and clinical findings in children with comparable age distribution and hospitalized due to RSV, HMPV or RV infections. Viral pathogens were detected by a quantitative real time PCR from nasopharyngeal aspirates. No significant differences in the admission diagnosis, laboratory parameters, patient demographics and treatment measures between the three viral causes of respiratory illness were found. No correlation between viral load and disease severity was observed however, there was a significantly lower concentration of the nasopharyngeal interleukin 8 (IL-8) in children with RV compared to HMPV and RSV, indicating a milder proinflammatory reaction. Moreover, RV-infected children had significantly lower body temperature, higher leucocyte counts in peripheral blood, and a tendency to have a shorter stay in hospital than children with either HMPV or RSV infection. Taken together, clinical presentation of the infections with RSV, HMPV, and RV is similar among children of the same age group and not clearly distinguishable by standard clinical or laboratory findings. Therefore, virus specific testing should be included regularly for routine diagnosis of children with respiratory tract infections.

INTRODUCTION

Respiratory syncytial virus (RSV) and Human metapneumovirus (HMPV) are important causes of upper and lower respiratory tract infections and hospitalization in young children worldwide. Additionally, recent studies suggest that rhinoviruses also play a major role as a cause of respiratory tract infections leading to hospitalization within this group, however these studies varied in their study populations, severity of cases, age, and comorbidities [Kellner et al., 1989; Juven et al., 2000; Kusel et al., 2006; Miller et al., 2007; Bonzel et al., 2008; Franz et al., 2010; Iwane et al., 2011]. Clinical signs and symptoms of HMPV infection overlap with those of RSV and rhinovirus infections and reliable clinical distinction is not possible. Some reports have tried to correlate laboratory parameters such as specimen viral load with disease severity [Bosis et al., 2008; Martin et al., 2008; Houben et al., 2010].

The Human Metapneumovirus (HMPV) is related to RSV. Both are members of the Paramyxoviridae family and share several epidemiologic and clinical characteristics, HMPV, however affect children of a slightly older age than RSV [Cuevas et al., 2003; Martin et al., 2008; Gaunt et al., 2009]. A previous study found [Franz et al., 2010] that the median age of children with rhinovirus infections was 1.4 years in contrast to children with RSV infections (median

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0.5 years). This finding has been confirmed by others [Korpip et al., 2004]. Since the clinical manifestation and the disease severity depend substantially on the age, a direct comparison of the clinical course of HMPV, RSV, and RV infection is made more difficult by the different average age at presentation.

In the present study three groups of children with comparable age distribution hospitalized with RSV, HMPV or RV infections were compared to minimize this age bias.

**PATIENTS AND METHODS**

During a 2-year period from November 2006 to October 2008 nasopharyngeal aspirates of children aged 0–16 years hospitalized for a respiratory tract infection at the University Children's Hospital Düsseldorf were investigated. Nasopharyngeal aspirates (NPA) were collected on the day of admission. Out of this collective three groups each encompassing 30 individuals with either HMPV, RSV or RV infection were defined. There were only minor differences in the age distribution as measured by both, the mean age and the range. This was done because in children in the second year of life HMPV, RSV, and RV are frequently found in contrast to very young children who are mostly infected and hospitalized by RSV. These older children are thought to be beyond the period of maternal immunity. Each patient was included only once and no patient was included if more than one viral pathogen was detected.

All specimens were submitted to the Institute of Virology of the University Hospital Düsseldorf and evaluated for RSV (subtype A and B), RV (species A, B, and C), influenza types A and B, parainfluenza types 1, 2, and 3, enterovirus, adenovirus, human metapneumovirus, coronaviruses 229E, OC43, and NL63 and human bocavirus using a quantitative real-time RT-PCR as described elsewhere [Bonzel et al., 2008]. Quantitation for HMPV, RSV, and Rhinovirus-genomes was performed using known concentrations of plasmids containing the target regions of the viruses. A standard graph of the C_\text{T} values obtained from serial dilutions of the standard was constructed by the software, the C_\text{T} values of the unknown samples were plotted on the standard curves and the number of genomes was calculated. Quantitation of Interleukin-8 (IL-8) was performed using a purified anti-cytokine capture antibody (Cat. No. 554716, BD Biosciences, Heidelberg, Germany), a biotinylated anti-cytokine detection antibody (Cat. No. 554718, BD Biosciences, Heidelberg, Germany), and recombinant human IL-8 (Cat. No. 554609, BD Biosciences, Heidelberg, Germany) as a standard in concentrations from 4.0 pg/ml to 500 pg/ml. Standard curves were calculated using the Magellan™ software (Tecan, Crailsheim, Germany). The capture antibody was bound to 96-well microtiter plates at a concentration of 2 μg/ml binding solution. Cell-free supernatants of nasopharyngeal aspirates were diluted 1:10 and 1:20 in blocking buffer (PBS-Tween) and tested in duplicate. Samples with IL-8 concentration above the highest standard were retested at higher dilutions.

Clinical data collected from patient's medical files included gender, prematurity, the presence of chronic underlying diseases, clinical diagnosis, duration of hospitalization, need for oxygen treatment, antibiotic use, chest radiography findings, presence of fever, white cell count, C-reactive protein, and IL-8 concentration in NPA. Leucocytosis was defined as values above 15,000/μl and a significantly raised C-reactive protein (CRP) when raised above 5 mg/dl (normal value <5 mg/dl). Pneumonia was defined using WHO criteria in those patients who underwent chest radiography. Severe respiratory tract infections (sRTI) was defined as the presence of pneumonia, acute viral wheeze (obstructive bronchitis), and bronchiolitis. Bronchitis, upper respiratory tract infection, and two cases of other respiratory tract infections (one patient with underlying chronic lung disease and one with otitis media) were grouped as mild respiratory tract infections (mRTI). Values are expressed as percentages for discrete variables, or as mean and standard deviation for continuous variables, except age and days of hospitalization, which are described by their median.

The data were analyzed using SigmaStat 3.5 and GraphPad Prism 5.01. Categorical data were studied using Fisher's exact test or Pearson's chi-square test, depending on the sample size. Quantitative data were analyzed by the non-parametric Mann-Whitney U test for two groups and by the one way ANOVA test for more than two groups. The 95% confidence interval (95% CI) for proportions was calculated using the modified Wald method. A two sided P-value <0.05 was considered statistically significant. Sample collection and diagnostic procedures were conducted for the purpose of the guidelines of good clinical practice. The study was approved by the Institutional Review Board of the University Hospital Düsseldorf.

**Results**

Demographic characteristics and medical history are shown in Table I. As described above the three groups of patients were of similar age with a median value of 551 (45–2386) days for HMPV, 525 (110–2250) days for RSV, and 522 (44–2779) days for Rhinovirus. All other characteristics were not significantly different.

The clinical diagnoses, presentations and findings are shown in Table II. Pneumonia, acute viral wheeze, and bronchiolitis (severe respiratory tract infections, sRTI) was highest in RSV-patients (23/30, 77%) but did not differ significantly between the three groups. Viral load in nasopharyngeal aspirates showed no statistically significant correlation to the
disease severity in any group. The median HMPV viral load was \(1.6 \times 10^6\) in the mRTI group (range \(1.2 \times 10^6–2.5 \times 10^8\)) and \(9.9 \times 10^7\) in the sRTI group (range \(5.0 \times 10^6–1.7 \times 10^7\)) \(P = 0.08\). The median RSV viral load was \(7.2 \times 10^7\) in the mRTI group (range \(2.6 \times 10^6–1.7 \times 10^8\)) and \(2.0 \times 10^7\) in the sRTI group (range \(2.3 \times 10^6–5.4 \times 10^8\)) \(P = 0.84\), and the median RV viral load was \(1.1 \times 10^6\) in the mRTI group (range \(5.1 \times 10^5–3.1 \times 10^8\)) and \(8.8 \times 10^5\) in the sRTI group (range \(5.6 \times 10^5–2.8 \times 10^8\)) \(P = 0.45\). Initiated treatment such as oxygen requirement, frequency of chest X-rays, initiation of antibiotic treatment showed no significant difference between the three groups, although a non significantly higher oxygen require-

**TABLE I. Comparison of Demographic Characteristics and Medical History in Children With HMPV, RSV and Rhinovirus Infection**

| Characteristic                                      | HMPV (n = 29) | RSV (n = 30) | Rhinovirus (n = 30) | \(p\) |
|----------------------------------------------------|---------------|--------------|---------------------|------|
| Median age (days)                                  | 551 (66) a    | 524,6        | 521,8               | 0.664|
| Gender (male)                                      | 19 (66) a     | 16 (53)      | 15 (50)             | 0.451|
| History of prematurity                             | 3 (10)        | 4 (13)       | 6 (20)              | 0.599|
| History of heart disease                           | 3 (10)        | 4 (13)       | 3 (10)              | 0.904|
| History of pulmonary diseases                      | 0             | 1 (3)        | 1 (3)               | 0.610|
| History of neurological diseases                    | 1 (3)         | 1 (3)        | 0                   | 0.594|
| History of chromosome disorder                     | 1 (3)         | 1 (3)        | 0                   | 0.594|
| History of innate metabolic diseases               | 1 (3)         | 0            | 2 (7)               | 0.359|

*a number, in parentheses percent.

**DISCUSSION**

HMPV and RSV generally circulate in the community during the winter seasons along with the influenza viruses and some other respiratory viruses [van den Hoogen et al., 2003; van den Hoogen et al., 2004; Mejias et al., 2004; Williams et al., 2004; Williams, 2005; Williams et al., 2005]. In contrast rhinovirus infections is found during the whole year with peaks in spring and autumn [Monte, 2002a, 2002b].

In young children the clinical picture of most respiratory infections tends to be more severe, but a straightforward correlation between clinical presentation and

**TABLE II. Comparison of Clinical Diagnosis, Presentation and Findings in Children With HMPV, RSV, and Rhinovirus Infection**

| Characteristic                  | HMPV          | RSV           | Rhinovirus    | \(p\)     |
|---------------------------------|---------------|---------------|---------------|-----------|
| Severe RTI                      | 13/27 (48)    | 23/30 (77)    | 16/25 (64)    | 0.053     |
| Pneumonia                       | 8/27 (30)     | 14/30 (47)    | 8/25 (32)     | 0.435     |
| Obstructive bronchitis          | 5/27 (19)     | 8/30 (27)     | 9/25 (36)     | 0.364     |
| Bronchiolitis                   | 1/27 (4)      | 2/30 (7)      | 0/25 (0)      | 0.423     |
| Milder RTI                      |               |               |               |           |
| Bronchitis                      | 9/27 (33)     | 5/30 (17)     | 5/25 (20)     | 0.298     |
| URTI                            | 2/27 (7)      | 1/30 (3)      | 3/25 (12)     | 0.470     |
| Other                           | 2/27 (7)      | 0/30 (0)      | 0.25 (0)      | 0.123     |
| Temperature (°C) (Mean, 95% CFI) | 38.7 (38.2–39.2) | 38.7 (38.3–39.1) | 37.8 (37.3–38.2) | 0.066 |
| Leukocytes (sd/μl) (Mean, 95% CFI) | 10.7 (9.0–12.4) | 12.2 (10.8–13.7) | 14.1 (11.8–16.3) | 0.035 |
| CRP > 0.5 mg/dl                 | 13/22 (59%)   | 19/29 (66%)   | 17/23 (74%)   | 0.574     |
| IL-8 (4.6 μg/ml; Mean, 95 CFI)  | 25.1 (11.53–38.7) | 12.02 (7.57–16.47) | 6.33 (0.02–12.65) | <0.05 b |
| Oxygen requirement              | 6/22 (27%)    | 13/29 (44%)   | 6/23 (26%)    | 0.271     |
| Length of stay (median)         | 3             | 3             | 3             | 0.387     |
| Antibiotic treatment            | 11/22 (50%)   | 14/28 (50%)   | 13/23 (56%)   | 0.873     |

*a1 \times underlying chronic lung disease and 1 \times otitis media.

b HMPV/RSV versus Rhino.
the causing respiratory pathogen is absent. Therefore, in the present study hospitalized children with RSV, HMPV, or RV infections and comparable age distribution were compared to minimize the effects of age on the clinical manifestation. It was found that rhinovirus infections could not be differentiated clearly by clinical signs and laboratory parameters on admission from HMPV and RSV infections. The frequency of severe respiratory tract infection was similar between the three groups however some differences could be found regarding the course of illness. Several recent studies compared the clinical signs and the severity mainly between HMPV and RSV with conflicting results. Most studies have found no clear difference [Mullins et al., 2004; Wolf et al., 2006], however some reports describe more severe infections in patients with HMPV or RSV [von Linstow et al., 2004; Wilkesmann et al., 2006]. This could be due to different study populations and an age-related frequency of severe manifestations. The third group of the present study, the rhinovirus-infected children showed clinical courses with significantly lower body temperature and a non-significant shorter length of stay in hospital. This slightly milder course could be predicted neither by regarding the standard laboratory parameters at admission nor by the more sophisticated determination of the viral loads in the nasopharyngeal aspirates. The finding of higher leucocyte counts in RV-infected patients as compared to HMPV- and RSV-infections is in agreement with previous studies [Franz et al., 2010] and might be due to an immune suppressive effect of the latter.

Determination of the viral load in respiratory tract infections has been investigated in the past by several groups [Bosis et al., 2008; Martin et al., 2008; Franz et al., 2010; Houben et al., 2010]. In a recent study, a difference in the viral load of most viruses between the date of admission and a second sample several days later and between mono- and mixed infections could be found. In this study, a correlation between viral load and the severity of lower respiratory tract infection was not found in contrast to other reports [Bosis et al., 2008; Martin et al., 2008; Houben et al., 2010].

The most significant difference in laboratory parameters was seen with nasopharyngeal IL-8 concentrations, which was significantly lower in patients with rhinovirus infections. IL-8 also known as neutrophil chemotactic factor, is a member of the CXC chemokine family and induces chemotaxis in neutrophils and other granulocytes, causing them to migrate towards the site of infection and initiate phagocytosis [Bargiolini and Clark-Lewis, 1992; Bargiolini et al., 1994; Bargiolini et al., 1995]. IL-8 is often associated with localized inflammation and has been described as a proinflammatory mediator [Vlahopoulos et al., 1999]. There are conflicting results in the literature concerning the correlation of cytokine concentrations in the respiratory specimens and the underlying virus. The role of acute phase cytokines (IL1β, IL-6, TNFα) in the nasopharynx during upper respiratory infections with influenza virus, adenovirus, enterovirus, and rhinovirus in children were also investigated by others [Patel et al., 2009]. They found significantly higher IL-6 concentration during adeno virus and influenza virus infections as compared to rhinoviruses and generally in children with systemic febrile response during upper respiratory infection.

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In contrast, others compared RSV lower respiratory tract infections with rhinovirus lower respiratory tract infection and determined a variety of cytokines and chemokines and could only find a significant difference for IL-15 but not for IL-6 or IL-8 [Garcia et al., 2012]. However, the latter study enrolled less than 20 children in each study group younger than 2 years. The former studies are in agreement with the data presented here showing lower concentrations of the proinflammatory cytokine IL-8 in children with rhinovirus infections as compared to HMPV- and RSV-infections and a tendency to lower body temperature. The lower concentrations of the chemotactic factor IL-8 in the nasopharyngeal aspirates contrasts to the higher leucocyte counts in the blood of the rhinovirus infected children underlining that local and systemic immune responses might show different patterns. Increased or prolonged inflammatory responses have been discussed as a reason for a higher disease burden [Turner et al., 1998; Gern et al., 2000; Gern et al., 2002]. Nevertheless, it remains to be elucidated if a shorter hospital stay in children with rhinovirus infections indeed correlates with lower concentrations of IL-8 in the nasopharynx.

There were several limitations to the present study. For some patients the documentation of clinical parameters was not complete and a higher number of patients would be necessary to reach higher levels of significance of parameters as length of stay and leucocyte counts. This is supported by a former prospective study [Franz et al., 2010] where significant differences between these two parameters could be found. Finally, a control group of healthy children was not enrolled, unfortunately a common fault in many studies of pediatric patients. Taken together the present data lead to the conclusion that a reliable identification of a HMPV, RSV, or RV infection can only be made by a molecular techniques such as qualitative real time PCR. In contrast quantitation of virus was, in this context, not useful for the assessment of the severity or duration of the disease. Where HMPV- and RSV-infections were quite similar in their clinical course, rhinovirus infections seem to have a tendency to faster recuperation in young children.

REFERENCES

Baggiolini M, Clark-Lewis I. 1992. Interleukin-8, a chemotactic and inflammatory cytokine. FEBS Lett 307:97–101.

Baggiolini M, Dewald B, Moser B. 1994. Interleukin-8 and related chemotactic cytokines–CXCC and CC chemokines. Adv Immunol 55:97–179.

Baggiolini M, Loetscher P, Moser B. 1995. Interleukin-8 and the chemokine family. Int J Immunopharmacol 17:103–108.

Bonzel L, Tenenbaum T, Schröt H, Schildgen O, Schweitzer-Krantz S, Adams O. 2008. Frequent detection of viral coinfection in children hospitalized with acute respiratory tract infection using a real-time polymerase chain reaction. Pediatr Infect Dis J 27:589–594.

Bosio S, Esposito S, Osterhaus AD, Tremolati E, Beglietti E, Tagliabue C, Corti F, Principi N, Niesters HG. 2009. Association between high nasopharyngeal viral load and disease severity in children with human metapneumovirus infection. J Clin Virol 42:286–290.

Cuevas LE, Nasser AM, Dove W, Gurgel RQ, Greensill J, Hart CA. 2003. Human metapneumovirus and respiratory syncytial virus, Brazil Emerg Infect Dis 9:1626–1628.

Franz A, Adams O, Willems R, Bonzel L, Neuhausen N, Schweizer-Krantz S, Rugegeber JU, Willers R, Henrich B, Schroten H, Tenenbaum T. 2010. Correlation of viral load of respiratory pathogens and co-infections with disease severity in children hospitalized for lower respiratory tract infection. J Clin Virol 48:239–245.

Garcia C, Soriano-Fallas A, Lozano J, Leos N, Gomez AM, Ramilo G, Mejias A. 2012. Decreased innate immune cytokine responses correlate with disease severity in children with respiratory syncytial virus and human rhinovirus bronchiolitis. Pediatr Infect Dis J 31:86–89.

Gaunt E, McWilliam-Leitch EC, Templeton K, Simmonds P. 2009. Incidence, molecular epidemiology and clinical presentations of human metapneumovirus; assessment of its importance as a diagnostic screening target. J Clin Virol 46:318–324.

Gern JE, Martin MS, Ankiam KA, Shen K, Roberg KA, Carlson-Dakes KT, Adler K, Gilbertson-White S, Hamilton R, Shult PA, Kirk CJ, Du Silva DF, Sund SA, Kosorok MR, Lemanske RF Jr. 2002. Relationships among specific viral pathogens, virus-induced interleukin-8, and respiratory symptoms in infancy. Pediatr Allergy Immunol 13:386–393.

Gern JE, Vrtis R, Grindle KA, Swenson C, Busse WW. 2000. Relationship of upper and lower airway cytokines to outcome of experimental rhinovirus infection. Am J Respir Crit Care Med 162:2226–2231.

Houben ML, Coenjaerts FE, Rossen JW, Belderbos ME, Hoffand RW, Kimpen JL, Bont L. 2010. Disease severity and viral load are correlated in infants with primary respiratory syncytial virus infection in the community. J Med Virol 82:1266–1271.

Iwane MK, Prill MM, Lu X, Miller EK, Edwards KM, Hall CB, Griffin MR, Staat MA, Anderson LJ, Williams JV, Weinberg GA, Ali A, Sizlajicy PG, Zhu Y, Erman DD. 2011. Human rhinovirus species associated with hospitalizations for acute respiratory illness in young US children. J Infect Dis 204:1702–1710.

Juven T, Mertsola J, Waris M, Leinonen M, Meurman O, Roivainen M, Eskola J, Saikku P, Russkahan O. 2000. Etiology of community-acquired pneumonia in 254 hospitalized children. Pediatr Infect Dis J 19:293–298.

Kellner G, Popow-Kraupp T, Kundi M, Binder C, Kunz C. 1989. Clinical manifestations of respiratory tract infections due to respiratory syncytial virus and rhinoviruses in hospitalized children. Acta Paediatr Scand 78:390–394.

Korppi M, Kotaniemi-Syrjanen A, Waris M, Vainionpaan R, Reijonen TM. 2004. Rhinovirus-associated wheezing in infancy: comparison with respiratory syncytial virus bronchiolitis. Pediatr Infect Dis J 23:995–999.

Kusel MM, de Klerk NH, Holt PG, Kebadze T, Johnston SL, Sly PD. 2006. Role of respiratory viruses in acute upper and lower respiratory tract illness in the first year of life: a birth cohort study. Pediatr Infect Dis J 25:680–686.

Martin ET, Kuypers J, Heugel J, Englund JA. 2008. Clinical disease and viral load in children infected with respiratory syncytial virus or human metapneumovirus. Diagn Microbiol Infect Dis 62:382–388.

Mejias A, Chavez-Bueno S, Ramilo O. 2004. Human metapneumovirus: a not so new virus. Pediatr Infect Dis J 23:1–7.

Miller EK, Lu X, Erman DD, Pehelung KA, Zhu Y, Griffin MR, Hartert TV, Anderson LJ, Weinberg GA, Hall CB, Iwane MK, Edwards KM. 2007. Rhinovirus-associated wheezing in infancy: comparison with respiratory syncytial virus bronchiolitis. Pediatr Infect Dis J 26:995–999.

Monto AS. 2002a. Epidemiology of viral respiratory infections. Am J Med 112:45–125.

Monto AS. 2002b. The seasonality of rhinovirus infections and its implications for clinical recognition. Clin Ther 24:1987–1997.

Mullins JA, Erman DD, Weinberg GA, Edwards K, Hall CB, Walker PJ, Iwane MA, Anderson LJ. 2004. Human metapneumovirus infection among children hospitalized with acute respiratory illness. Emerg Infect Dis 10:700–705.

Patel JA, Nair S, Reavi K, Grady J, Chonmaitree T. 2009. Nasopharyngeal acute phase cytokines in viral upper respiratory infection: impact on acute otitis media in children. Pediatr Infect Dis J 28:1002–1007.

J. Med. Virol. DOI 10.1002/jmv
Turner RB, Weingand KW, Yeh CH, Leedy DW. 1998. Association between interleukin-8 concentration in nasal secretions and severity of symptoms of experimental rhinovirus colds. Clin Infect Dis 26:840–846.

van den Hoogen BG, Osterhaus DM, Fouchier RA. 2004. Clinical impact and diagnosis of human metapneumovirus infection. Pediatr Infect Dis J 23:S25–S32.

van den Hoogen BG, van Doornum GJ, Fockens JC, Cornelissen JJ, Beyer WE, de GR, Osterhaus AD, Fouchier RA. 2003. Prevalence and clinical symptoms of human metapneumovirus infection in hospitalized patients. J Infect Dis 188:1571–1577.

Vlahopoulos S, Boldogh I, Casola A, Brasier AR. 1999. Nuclear factor-kappaB-dependent induction of interleukin-8 gene expression by tumor necrosis factor alpha: evidence for an antioxidant sensitive activating pathway distinct from nuclear translocation. Blood 94:1878–1889.

von Linstow ML, Larsen HH, Eugen-Olsen J, Koch A, Nordmann WT, Meyer AM, Westh H, Lundgren B, Melbye M, Hogh B. 2004. Human metapneumovirus and respiratory syncytial virus in hospitalized danish children with acute respiratory tract infection. Scand J Infect Dis 36:578–584.

Wilkesmann A, Schildgen O, Eis-Hubinger AM, Geikowski T, Glatzel T, Lentze MJ, Bode U, Simon A. 2006. Human metapneumovirus infections cause similar symptoms and clinical severity as respiratory syncytial virus infections. Eur J Pediatr 165:467–475.

Williams JV. 2005. Human Metapneumovirus: An Important Cause of Respiratory Disease in Children and Adults. Curr Infect Dis Rep 7:204–210.

Williams JV, Harris PA, Tollefson SJ, Halburnt-Rush LL, Pingsterhaus JM, Edwards KM, Wright PF, Crowe JE Jr. 2004. Human metapneumovirus and lower respiratory tract disease in otherwise healthy infants and children. N Engl J Med 350:443–450.

Williams JV, Tollefson SJ, Heymann PW, Carper HT, Patrie J, Crowe JE. 2005. Human metapneumovirus infection in children hospitalized for wheezing. J Allergy Clin Immunol 115: 1311–1312.

Wolf DG, Greenberg D, Kalkstein D, Shemer-Avni Y, Givon-Lavi N, Saleh N, Goldberg MD, Dagan R. 2006. Comparison of human metapneumovirus, respiratory syncytial virus and influenza A virus lower respiratory tract infections in hospitalized young children. Pediatr Infect Dis J 25:320–324.