Human Metapneumovirus

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Name of Virus: Human metapneumovirus

12.1 Brief Introduction

Human metapneumovirus (hMPV), a frequent cause of acute respiratory illness in young children, was first isolated in 2001. Retrospective serological tests have shown that the virus has been present since at least 1958. Its slow growth and trypsin dependency in culture contributed to its late identification (van den Hoogen et al. 2001). hMPV is most closely related to the avian pneumovirus, a cause of tracheobronchitis in turkeys and other birds and the only other member of the genus metapneumovirus (van den Hoogen et al. 2001).

hMPV is a cause of bronchiolitis and pneumonia, particularly in young children, with a similar clinical picture as respiratory syncytial virus (RSV) infection, its most closely related human pathogen. Infections in adults are most common in the elderly and immunocompromised (van den Hoogen 2007).

Synonyms: hMPV

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12.2 Classification

Family – *Paramyxoviridae*
Genus – *Metapneumovirus*

12.3 Epidemiology

First isolated in the Netherlands, hMPV has since been described in many countries and appears to have a worldwide distribution (van den Hoogen et al. 2001; Peret et al. 2002; Stockton et al. 2002; Boivin et al. 2002, 2004; Peiris et al. 2003; Williams et al. 2004; García-García et al. 2006). Infection with hMPV peaks in the late winter and spring in temperate climates (Williams et al. 2004; García-García et al. 2006) and in the late spring and summer in subtropical regions (Peiris et al. 2003). Infection with hMPV is most common in children younger than 2 years of age, and serological evidence of infection is present in most children by the age of 5. Reinfection in older children and adults typically results in milder disease (van den Hoogen et al. 2001; van den Hoogen et al. 2004b). By comparison to similar respiratory viruses, transmission is assumed to be through respiratory secretions and fomites (Crowe 2004). The virus has been shown to survive for a prolonged period in nonporous surfaces such as plastic and metal, making such surfaces a potential source for infection (Tollefson et al. 2010). Nosocomial transmission and outbreaks have been reported (Boivin et al. 2007; Cheng et al. 2007; Degail et al. 2012).

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12.4 Ultrastructure

Negative-contrast electron microscopy of supernatants of infected cells in culture has shown ultrastructural similarities between hMPV and other paramyxoviruses. The viral particles are pleomorphic and may be spherical or filamentous. Spherical particles range from 150 to 600 nm in diameter, with 13–17 nm envelope projections corresponding to surface glycoproteins. The nucleocapsids average 17 nm in diameter (van den Hoogen et al. 2001; Peret et al. 2002). The ultrastructural characteristics of the virus in tissue have not been described.

12.5 Immunology

hMPV is an enveloped, negative-sense, single-stranded RNA virus. Phylogenetic analyses have shown two hMPV lineages, A and B, and at least four sublineages, A1, A2, B1, and B2 (van den Hoogen et al. 2001, 2002; Boivin et al. 2004; Peret et al. 2002). There is conflicting data as to whether the hMPV lineages represent distinct serotypes (van den Hoogen et al. 2004a; Skiadopoulos et al. 2004). Both lineages appear to be globally distributed and circulate randomly during any given season (Boivin et al. 2004). hMPV has three surface glycoproteins: the fusion (F) protein, the attachment (G) protein, and small hydrophobic (SH) proteins of unknown function. hMPV infection begins with attachment of the virus to respiratory epithelial cells. Attachment to the host cell appears to be mediated by nonspecific binding of the G protein to glycosaminoglycans on the cell surface (Thammawat et al. 2008) and by specific binding of the F protein to integrin receptors on the host cell (Cseke et al. 2009). This role of the F protein in cell attachment appears to be unique to hMPV among the paramyxoviruses.

Fusion of the virus to the host cell membrane, mediated by the F protein, results in release of the nucleocapsid into the cell cytoplasm. As with other viruses, transcription of viral proteins and replication ensue, with assembly of virions. Viral surface glycoproteins are incorporated into the host cell membrane and become part of the enveloped virus with the release of viruses from the host cell by budding (Feuillet et al. 2012).

12.6 Clinical Features

The clinical features of hMPV in children are similar to those of respiratory syncytial virus. Children may present with an upper respiratory tract infection, evidence of bronchiolitis, including fever, rhinorrhea, cough, and diffuse wheezes and rales, or pneumonia, with dyspnea and localized infiltrates by chest x-ray. Systemic symptoms such as anorexia, vomiting, diarrhea, and myalgias may also be present (Williams et al. 2004, 2006, 2010). Symptoms may be severe, particularly in very young children, and require hospitalization and, in some instances, mechanical ventilation (van den Hoogen et al. 2001; García-García et al. 2006). hMPV is responsible for 4–6 % of hospitalizations for acute respiratory infections in young children (García-García et al. 2006; Williams et al. 2010; Boivin et al. 2003).

In otherwise healthy adults, hMPV is an uncommon cause of acute respiratory tract infection and influenza-like illness (Louie et al. 2005; Stockton et al. 2002). More severe diseases, including bronchitis, bronchospasm, and pneumonia, requiring hospitalization and mechanical ventilation are more likely with immunosuppression, underlying disorders, and advanced age (Boivin et al. 2002; Shahda et al. 2011). hMPV has also been identified in sputum and nasal lavages of a small number of patients with acute exacerbation of chronic obstructive pulmonary disease (Rohde et al. 2005).

12.7 Pathologic Changes

The pathological changes of hMPV infection have not been well described, with only a small number of cases reported in the literature. Vargas et al. (2004) described the findings in

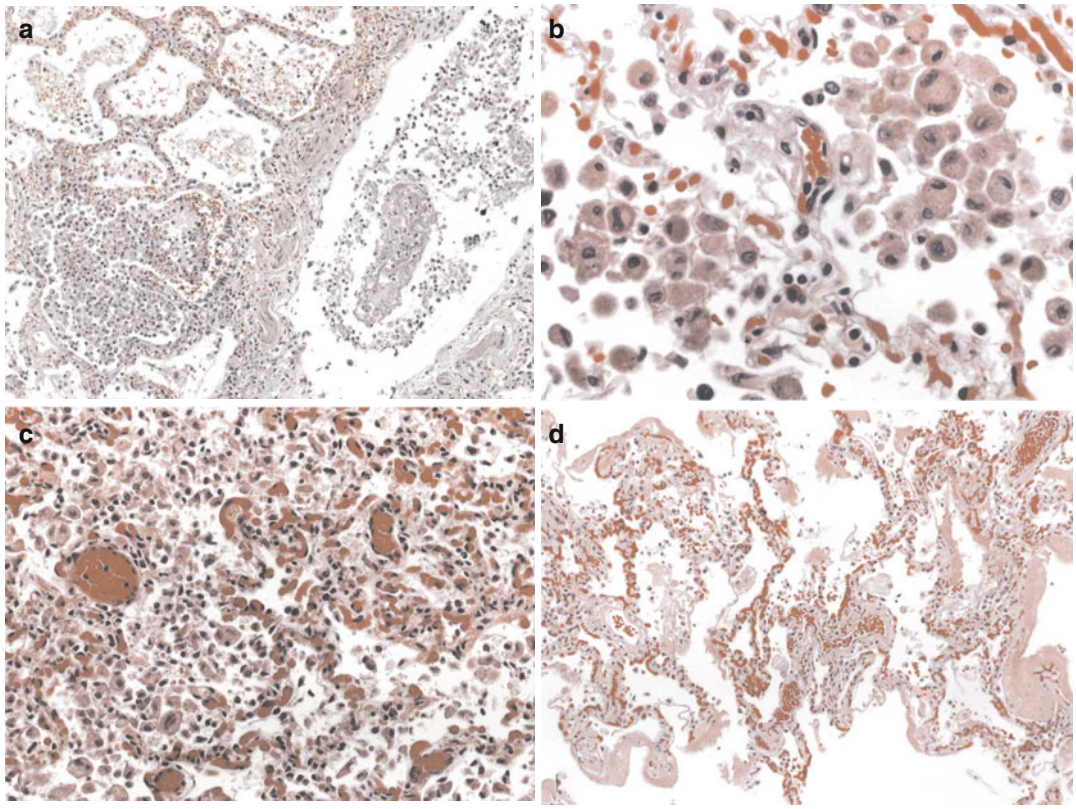

Fig. 12.1 (**a**) hMPV infection. Note severe bronchiolitis with ulcerated bronchiolar epithelium. (**b**) Higher power showing accumulation of intra-alveolar macrophages. (**c**) Note pulmonary congestion and mild interstitial lymphocytic inflammation. (**d**) Note prominent formation of hyaline membrane (Courtesy of Dr. S.R. Zaki, Centers for Disease Control and Prevention, Atlanta, GA; from Dail and Hammar's Pulmonary Pathology, 3rd ed, Ch 11 Viral Infections of the Lung, by Tomashefski, with kind permission of Springer Science + Business Media)

bronchoalveolar lavage in children infected with hMPV as consisting of red, round, 3–4 μm inclusions in the cytoplasm of epithelial cells, macrophages, and multinucleated giant cells, as well as nonspecific degenerative changes of the respiratory epithelial cells and abundant neutrophils and macrophages. The presence of cytoplasmic inclusions has not been confirmed in other reports. However, cytoplasmic inclusions are characteristic of other paramyxoviruses, such as parainfluenza, measles, and respiratory syncytial virus. Hence, their presence in hMPV infection would not be surprising.

Degenerative changes of the respiratory epithelium have also been reported in experimental hMPV infections in primates in which mild, multifocal erosive lesions in the conducting airways and increased numbers of macrophages in the bronchioles and alveoli are the salient findings. By immunohistochemistry the virus is localized to the bronchial epithelial cells (Kuiken et al. 2004). Similar findings can occur in humans (Fig. 12.1a). Lung biopsy findings in hMPV infection include acute and organizing diffuse alveolar damage (DAD) and organizing pneumonia, with localization of the virus in bronchial epithelial cells and pneumocytes by immunohistochemistry and in situ hybridization (Sumino et al. 2005; Boivin et al. 2007). Chronic airway inflammation may also be seen (Vargas et al. 2004). A more complete picture of pulmonary hMPV infection awaits further study (Fig. 12.1b–d).

12.8 Diagnosis

Human metapneumovirus grows slowly in a limited number of conventional cell cultures, such as tertiary monkey kidney cells (tMKC), rhesus monkey kidney cells (LLC-MK2), and African green monkey (Vero) cells. Growth in these cell lines is trypsin dependent. Variable cytopathic effects including rounding of cells and cell destruction with or without the formation of syncytia have been reported (van den Hoogen et al. 2001; Peret et al. 2002; Boivin et al. 2002; Deffrasnes et al. 2005; Tollefson et al. 2010). HMPV's slow and unreliable growth and nonspecific cytopathic effects make routine cultures suboptimal for routine diagnosis of infection.

Reverse transcription polymerase chain reaction (RT-PCR) of nasopharyngeal aspirates or swabs is the most reliable method to establish the diagnosis of hMPV infection. Up to 2/3 of specimens positive for hMPV by RT-PCR may be negative by culture (Ebihara et al. 2004). Multiplex platforms that allow for the simultaneous detection of several respiratory viruses have the advantage of providing specific results with a rapid turnaround time and are commercially available (Freymuth et al. 2006; Mahony et al. 2007). Other methods for diagnosis include enzyme immunoassays (Fuenzalida et al. 2010) and direct and indirect immunofluorescence (Ebihara et al. 2005; Vinh et al. 2008; Landry et al. 2005, 2008; Jun et al. 2008).

12.9 Differential Diagnosis

The clinical signs and symptoms of hMPV infection are nonspecific and overlap with those of other acute respiratory tract infections. Respiratory syncytial virus is more common than hMPV and is also seen in young children, with a mean age which is slightly younger than hMPV. Infections by other viruses, including adenovirus, coronavirus, and rhinovirus, may present similarly. Influenza must be considered in the differential diagnosis in both children and adults. The cytoplasmic inclusions in epithelial cells, macrophages, and multinucleated giant cells described in one study of bronchoalveolar lavage must be differentiated from those caused by other viruses, such as parainfluenza virus, measles, and RSV (Vargas et al. 2004).

12.10 Prevention

No specific preventive methods are known for hMPV. Respiratory infection control measures to restrict exposure, as well as frequent use of alcohol hand rubs and hand hygiene, have been successful in containing or preventing outbreaks in hospitalized patients (Degail et al. 2012; Cheng et al. 2007).

12.11 Treatment and Outcome

Treatment of hMPV infection is largely supportive. Severe infections may require oxygen therapy or mechanical ventilation in young children and adults with other comorbidities as well as the elderly. Acute respiratory distress syndrome (ARDS) and death have been reported (Boivin et al. 2007; Schlapbach et al. 2011). Rare reports of successful outcomes in immunosuppressed patients with hMPV pneumonia treated with ribavirin and immunoglobulin have been published (Bonney et al. 2009).

12.12 Vaccine

No vaccine is yet available for human metapneumovirus. Animal studies have demonstrated that immunization with inactivated hMPV results in an aberrant immune response with more severe disease upon subsequent hMPV infection (Hamelin et al. 2007), analogous to the experience with children immunized with formalin inactivated RSV (Kim et al. 1969; Kapikian et al. 1969). Therefore, live inactivated hMPV virus vaccines are unlikely candidates for future development.

Other approaches being explored take advantage of the highly conserved and immunogenic F surface protein which has been reported, in some

animal studies, to give rise to neutralizing and protective antibodies against both (A and B) lineages (Skiadopoulos et al. 2004, 2006). These include the use of chimeric, live attenuated vaccines, such as bovine/human chimeric parainfluenza virus type 3 expressing hMPV F protein (Tang et al. 2005) or hMPV/avian MPV C chimera (Pham et al. 2005). Recombinant hMPV vaccines lacking the G and/or SH genes or the M gene (Biacchesi et al. 2004, 2005; Buchholz et al. 2005) or component proteins such as soluble hMPV F protein (Herfst and Fouchier 2008; Cseke et al. 2007) have shown promising results in animal studies. These and other vaccination strategies await further studies and trials in human subjects.

12.13 Clinicopathologic Capsule

hMPV causes acute respiratory infections, ranging from mild upper respiratory infections to severe bronchiolitis and pneumonia. Severe infections are more common in children younger than 2 years of age, the elderly, and the immunosuppressed. Diagnosis depends on identification of the virus in nasopharyngeal swabs or aspirates most commonly by RT-PCR or antigen detection methods. The pulmonary pathological changes of hMPV infection have not been extensively described but include acute and organizing diffuse alveolar damage. Treatment of hMPV is supportive and there are no specific preventive measures.

References

Biacchesi S, Skiadopoulos MH, Yan L et al (2004) Recombinant human metapneumovirus lacking the small hydrophobic SH and/or attachment G glycoprotein: deletion of G yields a promising vaccine candidate. J Virol 78:12877–12887

Biacchesi S, Pham QN, Skiadopoulos MH et al (2005) Infection of nonhuman primates with recombinant human metapneumovirus lacking the SH, G or M2-2 protein categorizes each as a nonessential accessory protein and identifies vaccine candidates. J Virol 79:12608–12613

Boivin G, Abed Y, Pelletier G et al (2002) Virological features and clinical manifestations associated with human metapneumovirus: a new paramyxovirus responsible for acute respiratory- tract infections in all age groups. J Infect Dis 186:1330–1334

Boivin G, De Serres G, Côté S et al (2003) Human metapneumovirus infections in hospitalized children. Emerg Infect Dis 9:634–640

Boivin G, Mackay I, Sloots TP et al (2004) Global genetic diversity of human metapneumovirus fusion gene. Emerg Infect Dis 10:1154–1157

Boivin G, De Serres G, Hamelin ME et al (2007) An outbreak of severe respiratory tract infection due to human metapneumovirus in a long-term care facility. Clin Infect Dis 44:1152–1158

Bonney D, Razali H, Turner A et al (2009) Successful treatment of human metapneumovirus pneumonia using combination therapy with intravenous ribavirin and immune globulin. Br J Haematol 145:667–669

Buchholz UJ, Biacchesi S, Pham QN et al (2005) Deletion of M2 gene open reading frames 1 and 2 of human metapneumovirus: effects on RNA synthesis, attenuation and immunogenicity. J Virol 79:6588–6597

Cheng VC, Wu VC, Cheung CH et al (2007) Outbreak of human metapneumovirus infection in psychiatric inpatients: implications for directly observed use of alcohol hand rub in prevention of nosocomial outbreaks. J Hosp Infect 67:336–343

Crowe JE (2004) Human metapneumovirus as a major cause of human respiratory tract disease. J Pediatr Infect Dis 23:S215–S221

Cseke G, Wright DW, Tollefson SJ et al (2007) Human metapneumovirus fusion protein vaccines that are immunogenic and protective in cotton rats. J Virol 81:698–707

Cseke G, Maginnis MS, Cox RG et al (2009) Integrin αvβ1 promotes infection by human metapneumovirus. Proc Natl Acad Sci U S A 106:1566–1571

Deffrasnes C, Côté S, Boivin G (2005) Analysis of replication kinetics of the human metapneumovirus in different cell lines by real-time PCR. J Clin Microbiol 43:488–490

Degail MA, Hughes GJ, Maule C et al (2012) A human metapneumovirus outbreak at a community hospital in England, July to September 2010. Euro Surveill 17(15) pii=20145

Ebihara T, Endo R, Kikuta H et al (2004) Human metapneumovirus infection in Japanese children. J Clin Microbiol 42:126–132

Ebihara T, Endo R, Ma X et al (2005) Detection of human metapneumovirus antigens in nasopharyngeal secretions by an immunofluorescent-antibody test. J Clin Microbiol 43:1138–1141

Feuillet F, Lina B, Rosa-Calatrava M et al (2012) Ten years of human metapneumovirus research. J Clin Virol 53:97–105

Freymuth F, Vabret A, Cuvillon-Nimal D et al (2006) Comparison of multiplex PCR assays and conventional techniques for the diagnostic of respiratory virus infections in children admitted to hospital with an acute respiratory illness. J Med Virol 78:1498–1504

Fuenzalida L, Fabrega J, Blanco S et al (2010) Usefulness of two new methods for diagnosing metapneumovirus

infections in children. Clin Microbiol Infect 16: 1663–1668
García-García ML, Calvo C, Pérez-Breña P et al (2006) Prevalence and clinical characteristics of human metapneumovirus infections in hospitalized infants in Spain. Pediatr Pulmonol 41:863–871
Hamelin ME, Couture C, Sackett MK et al (2007) Enhanced lung disease and Th2 response follows human metapneumovirus infection in mice immunized with the inactivated virus. J Gen Virol 88: 3391–3400
Herfst S, Fouchier RAM (2008) Vaccination approaches to combat human metapneumovirus lower respiratory tract infections. J Clin Virol 41:49–52
Jun KR, Woo YD, Sung H et al (2008) Detection of human metapneumovirus by direct antigen test and shell vial cultures using immunofluorescent antibody staining. J Virol Methods 152:109–111
Kapikian AZ, Mitchell RH, Chanock RM et al (1969) An epidemiologic study of altered clinical reactivity to respiratory syncytial (RS) virus infection in children previously vaccinated with an inactivated RS virus vaccine. Am J Epidemiol 89:405–421
Kim HW, Canchola JG, Brandt CD et al (1969) Respiratory syncytial virus disease in infants despite prior administration of antigenic inactivated vaccine. Am J Epidemiol 89:422–434
Kuiken T, van den Hoogen BG, van Riel DAJ et al (2004) Experimental human metapneumovirus infection of cynomolgus macaques (*Macaca fascicularis*) results in virus replication in ciliated epithelial cells and pneumocytes with associated lesions throughout the respiratory tract. Am J Pathol 164:1893–1900
Landry ML, Ferguson D, Cohen S et al (2005) Detection of human metapneumovirus in clinical samples by immunofluorescence staining of shell vial centrifugation cultures prepared from the three different cell lines. J Clin Microbiol 43:1950–1952
Landry ML, Cohen S, Ferguson D (2008) Prospective study of human metapneumovirus detection in clinical samples by use of light diagnostics direct immunofluorescence reagent and real-time PCR. J Clin Microbiol 46:1098–1100
Louie JK, Hacker JK, Gonzales R et al (2005) Characterization of viral agents causing acute respiratory infection in a San Francisco University Medical Center clinic during the influenza season. Clin Infect Dis 41:822–828
Mahony J, Chong S, Merante F et al (2007) Development of a respiratory panel test for detection of twenty human respiratory viruses by use of multiplex PCR and a fluid microbead based assay. J Clin Microbiol 45:2965–2970
Peiris JSM, Tang WH, Chan KH et al (2003) Children with respiratory disease associated with metapneumovirus in Hong Kong. Emerg Infect Dis 9:628–633
Peret TCT, Boivin G, Li Y et al (2002) Characterization of human metapneumovirus isolated from patients in North America. J Infect Dis 185:1660–1663
Pham QN, Biacchesi S, Skiadopoulos MH et al (2005) Chimeric recombinant human metapneumovirus with the nucleoprotein or phosphoprotein open reading frame replaced by that of avian metapneumovirus exhibit improved growth in vitro and attenuation in vivo. J Virol 79:15114–15122
Rohde G, Borg I, Arinir U et al (2005) Relevance of human metapneumovirus in exacerbations of COPD. Respir Res 6:150
Schlapbach LJ, Agyeman P, Hutter D et al (2011) Human metapneumovirus infection as an emerging pathogen causing acute respiratory distress syndrome. J Infect Dis 203:294–295
Shahda S, Carlos WG, Kiel PJ et al (2011) The human metapneumovirus: a case series and review of the literature. Transpl Infect Dis 13:324–328
Skiadopoulos MH, Biacchesi S, Buchholz UJ et al (2004) The two major human metapneumovirus genetic lineages are highly related antigenic, and the fusion (F) protein is a major contributor to this antigenic relatedness. J Virol 78:6927–6937
Skiadopoulos MH, Biacchesi S, Buchholz UJ et al (2006) Individual contributions of the human metapneumovirus F, G, and SH surface glycoproteins to the induction of neutralizing antibodies and protective immunity. Virology 345:492–501
Stockton J, Stephenson I, Fleming D et al (2002) Human metapneumovirus as a cause of community-acquired respiratory illness. Emerg Infect Dis 8: 897–901
Sumino KC, Agapov E, Pierce RA et al (2005) Detection of severe human metapneumovirus infection by real-time polymerase chain reaction and histopathological assessment. J Infect Dis 192:1052–1060
Tang RS, Mahmood K, MacPhail M et al (2005) A host-range restricted parainfluenza virus type 3 (PIV3) expressing the human metapneumovirus (hMPV) fusion protein elicits protective immunity in African green monkeys. Vaccine 23:1657–1667
Thammawat S, Sadlon TA, Hallsworth PG et al (2008) Role of cellular glycosaminoglycans and charged regions of viral G protein in human metapneumovirus infection. J Virol 82:11767–11774
Tollefson SJ, Cox RG, Williams JV (2010) Studies of culture conditions and environmental stability of human metapneumovirus. Virus Res 151:54–59
van den Hoogen BG (2007) Respiratory tract infection due to human metapneumovirus among elderly patients. Clin Infect Dis 44:1159–1160
van den Hoogen BG, de Jong JC, Groen J et al (2001) A newly discovered human pneumovirus isolated from young children with respiratory tract disease. Nat Med 7:719–724
van den Hoogen BG, Bestebroer TM, Osterhaus ADME et al (2002) Analysis of the genomic sequence of a human metapneumovirus. Virology 295:119–132
van den Hoogen BG, Herfst S, Sprong L et al (2004a) Antigenic and genetic variability of human metapneumoviruses. Emerg Infect Dis 10:658–666

van den Hoogen BG, Osterhaus DME, Fouchier RAM (2004b) Clinical impact and diagnosis of human metapneumovirus infection. Pediatr Infect Dis 23:S25–S32

Vargas SO, Kozakewich HPW, Perez-Atayde AR et al (2004) Pathology of human metapneumovirus infection: insights into the pathogenesis of a newly identified respiratory virus. Pediatr Dev Pathol 7:478–486

Vinh DC, Newby D, Charest H et al (2008) Evaluation of a commercial direct fluorescent-antibody assay for human metapneumovirus in respiratory specimens. J Clin Microbiol 46:1840–1841

Williams JV, Harris PA, Tollefson SJ et al (2004) Human metapneumovirus and lower respiratory tract disease in otherwise healthy infants and children. N Engl J Med 350:443–450

Williams JV, Wang CK, Yang CF et al (2006) The role of human metapneumovirus in upper respiratory tract infections in children: a 20 year experience. J Infect Dis 193:387–395

Williams JV, Edwards KM, Weinberg GA et al (2010) Population- based incidence of human metapneumovirus infection among hospitalized children. J Infect Dis 201:1890–1898