The Clinical Presentation and Outcomes of Children Infected with Newly Identified Respiratory Tract Viruses

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Lower respiratory infection (LRI) is a leading cause of morbidity and mortality in children worldwide [1]. Upper respiratory infection (URI) is associated with significant societal costs for children in terms of lost school days and accounts for numerous health care visits, including unnecessary antibiotic prescriptions. Viral URI also commonly is associated with acute otitis media (AOM) in children, which is the most frequent diagnosis leading to antibiotic prescriptions for young children. Classic epidemiologic studies using culture and serologic methods have determined many of the etiologic agents of these common infections, such as respiratory syncytial virus (RSV), parainfluenza viruses (PIV), influenza virus, coronaviruses, and rhinoviruses [2,3]. These studies have been unable to identify a specific virus, however, in greater than 50% of such infections using traditional methods of viral culture, serology, and newer rapid antigen assays. In recent years, several novel respiratory viruses associated with acute respiratory tract illness (ARI) in humans have been identified. Some of these viruses, including human metapneumovirus (hMPV), human coronavirus–Netherlands (HCoV-NL), and human coronavirus–Hong Kong (HCoV-HK), likely have been circulating undetected for decades at least and are better described as emerging, rather than entirely new. Other viruses, including the severe acute respiratory syndrome–coronavirus (SARS-CoV), avian-derived influenza A strains, and Hendra and Nipah viruses, seem to be of more recent zoonotic origin, however, and truly are new pathogens. The distinction has important public health implications because of the effects of pre-existing immunity in the populace as a whole.

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Human metapneumovirus

Discovery

Researchers in the Netherlands reported the finding of a novel para-myxovirus associated with respiratory tract disease in 2001 [4]. The Dutch group collected numerous unidentified virus isolates, mostly from children, over a 20-year period that grew poorly in cell culture. Electron micrograph and biochemical studies of the virus showed that it was pleomorphic with a lipid envelope, consistent with a paramyxovirus. Elegant reverse transcription polymerase chain reaction (RT-PCR) experiments yielded a genomic sequence from the virus that identified it as a member of the Paramyxoviridae family, which contains many classic childhood viruses, including mumps, measles, PIV, and RSV. The gene order of the new virus was related most closely to avian pneumovirus, the sole previous member of the metapneumovirus genus. Avian pneumovirus was discovered in 1979 and is an important agricultural pathogen, causing major economic losses owing to severe respiratory disease in commercial poultry flocks. The new human metapneumovirus was unable to infect chickens and turkeys, however, and this combined with sequence comparison showed that it was a distinct human pathogen. The Dutch group also conducted serologic testing on archived human serum samples from the 1950s and found that 100% of subjects older than age 5 years were seropositive for hMPV, suggesting a high rate of infection early in life and showing that hMPV had been circulating for at least 50 years.

Diversity

hMPV has a negative-sense, single-stranded RNA genome similar to other paramyxoviruses, with a lipid envelope containing membrane proteins. Partial gene sequences for many hMPV strains worldwide are now available, and phylogenetic analysis of these sequences define two major genetic subgroups of hMPV, A and B, each with two minor subgroups. These are described presently as genogroups; it has not been shown in humans that they are antigenically distinct. In one large prospective study, primary infection during infancy was associated with LRI and subsequent infections with URI, showing that reinfection with hMPV occurs [5]. It is unclear whether this is due to infections with different subgroups that do not induce cross-protective immunity or, more likely, as is the case with RSV, to partial immunity induced by primary infection that protects the lower but not the upper respiratory tract against subsequent infection. There are no data in humans to show that infection with a virus from one subgroup protects against reinfection with a virus from a different subgroup. Animal studies suggest, however, that there is cross-protective immunity in hamsters and primates between hMPV subgroups that protects the lungs against reinfection [6,7]. These studies have important implications for the

development of candidate vaccines and prophylactic antibodies against hMPV similar to palivizumab, a monoclonal antibody licensed for immunoprophylaxis against RSV for premature infants at high risk for severe disease.

Epidemiology of human metapneumovirus in children

Initial epidemiologic studies of hMPV were primarily retrospective RT-PCR analyses of diagnostic virology laboratory specimens that were previously negative for other viruses [8–10]. The percentage of hMPV detection varied from 6% to 15%, with hospitalization most prominent in infants and elderly patients. A prospective study of 587 Hong Kong children (≤18 years old) hospitalized for LRI over a 13-month period detected hMPV in 6% of the children compared with 8% for RSV and 8% for influenza virus [11]. Canadian investigators detected hMPV in 12 of 208 (6%) children younger than 3 years old hospitalized for ARI [12]. A prospective study of more than 2000 previously healthy outpatient infants and children in Tennessee found that 12% of all LRI in that cohort was attributable to hMPV [5]. In that 25-year longitudinal study, there was substantial variation in the annual prevalence of hMPV, ranging from none to 31% of otherwise negative samples in a given year. hMPV is rarely detected in nasal washes from asymptomatic patients [5,10].

Studies conducted over multiple seasons show that the annual prevalence of hMPV varies from year to year, suggesting periodic epidemics, and that strains from different subgroups frequently circulate simultaneously in the same season. In temperate zones, the seasonal peak of hMPV infections occurs in late winter and spring months, slightly later than the peak of RSV infections but overlapping substantially with the RSV season.

Studies of children hospitalized for ARI in diverse regions have found rates of hMPV associated with 6% to 40% of ARI in a given season [12–27]. The average prevalence in most pediatric populations with ARI studied is approximately 5% to 10% overall, although it may be much higher during the peak months of hMPV circulation. With few exceptions, hMPV ranks after RSV in most studies and has prevalence comparable to that of influenza virus and PIV.

Hospitalization of children for hMPV infection occurs primarily in the first year of life, although many studies reported that the peak age of hospitalization for hMPV is 6 to 12 months of age [10–12,14–16,21–26], significantly later than the 2-month peak age of hospitalization for RSV. Whether this age range reflects a difference in the decline of maternal antibodies, later acquisition of hMPV infection, or developmental airway physiology is not known. Boys are at greater risk for LRI with hMPV infection than girls, similar to RSV.

hMPV may be more severe in patients with underlying medical conditions. Many hMPV studies are of hospitalized patients and subject

to selection bias. Nonetheless, 30% to 85% of children hospitalized with hMPV have chronic conditions, such as asthma, chronic lung disease secondary to prematurity, congenital heart disease, or cancer. Although most studies were not prospective, the rate of chronic disease was generally higher in hMPV-infected children than in RSV-infected children [10, 12,16,17,22–25]. A multicenter prospective study examined 641 children younger than 5 years old hospitalized for ARI or fever and found that 54% of children hospitalized with hMPV had underlying conditions versus 29% of RSV-infected patients ($P < .05$) [25].

Clinical presentation

hMPV is associated with a variety of respiratory symptoms and diagnoses. Children with hMPV infection typically present with URI symptoms, such as rhinorrhea, cough, and fever. The duration of symptoms before seeking medical attention is usually less than 1 week, and limited data suggest that children may shed virus for 1 to 2 weeks [5,10,19]. Symptoms such as conjunctivitis, vomiting, diarrhea, and rash are reported occasionally, but are not prominent in most studies. Only one study detected hMPV by RT-PCR in patients' serum [14], suggesting that similar to RSV, hMPV infection is limited to the respiratory tract. The clinical LRI syndromes associated with hMPV are bronchiolitis, croup, pneumonia, and asthma exacerbation. In the Tennessee study of previously healthy outpatients, the hMPV-infected children were diagnosed with bronchiolitis (59%), croup (18%), asthma (14%), and pneumonia (8%) [5]. In that prospective study, however, hMPV was less likely to be associated with croup than PIV and less likely to be associated with pneumonia than influenza virus. A similar spectrum of diagnoses is seen in most studies of hMPV-associated LRI, and signs and symptoms of hMPV infection overlap sufficiently with the signs and symptoms of other common respiratory viruses that reliable distinction cannot be made clinically.

In a study of more than 2400 distinct episodes of URI in previously healthy outpatient children, hMPV was associated with URI at rates similar to RSV, PIV, and influenza virus (John V. Williams, MD, et al, unpublished data). Of the children, 54% also were diagnosed with AOM, suggesting that hMPV is associated with a substantial proportion of AOM in otherwise healthy children. AOM is the most common reason for antibiotic prescription to children, and URI and AOM have significant economic impacts owing to time lost from school and work. hMPV likely has substantial medical and economic effects nationally. The only published study to examine the socioeconomic impact of hMPV directly was an Italian study of 42 hMPV-infected children seen in the emergency department in which questionnaires were administered to subjects' parents [26]. In 12% of subjects' households, other family members had similar illnesses. Parents reported a median of 4 lost working days (range 2–10), and older children

reported median 4 lost school days (range 3–15). These findings were similar for children infected with RSV or influenza virus in the same study population.

Human metapneumovirus in high-risk pediatric populations

Several investigators have examined a potential relationship between hMPV infection and asthma. A prospective Australian study of outpatient children with asthma did not find an association between hMPV and asthma exacerbations [28], whereas a large prospective study of 2000 outpatient children found a highly significant association between hMPV and the diagnosis of acute asthma exacerbation [5]. A Finnish study found elevated interleukin-8 in nasal secretions from hMPV-infected infants [29], whereas another study from Argentina found decreased interleukin-8 and other cytokines in nasal washes of hMPV-infected infants compared with infants infected with RSV [30]. All such studies are complicated by the difficulty of assigning the diagnosis of asthma during infancy, when acute wheezing associated with viral infections is common.

hMPV is capable of causing severe and even fatal infections in immunocompromised hosts. There are two reports of fatal infection attributed to hMPV in cancer patients, a 33-year-old woman with leukemia who was 7 days status post hematopoietic stem cell transplant and a 17-month-old girl with relapsed leukemia [31,32]. The 17-month-old patient had had another unexplained LRI 1 year previously during chemotherapy for leukemia. Postmortem RT-PCR on respiratory samples from both illnesses detected hMPV in both, but from two distinct strains. Studies the author's group is conducting in adult and pediatric patients with cancer, including hematopoietic stem cell transplant recipients, suggest that hMPV is a relatively common cause of acute respiratory infection in these patients, with significant morbidity and mortality (John V. Williams, MD, et al, unpublished data). Further long-term prospective studies are needed to characterize fully the extent and severity of disease secondary to hMPV in immunocompromised children.

Coinfections with human metapneumovirus and other viruses

All epidemiologic studies of hMPV that have tested for other viruses have found coinfection rates of 5% to 17%, usually with RSV, and most have not noted more severe disease in these coinfected patients. A few studies of hospitalized patients have noted much higher coinfection rates of 30% to 60% [15,29,33–35], some of these authors suggesting that hMPV infections may be more severe if another virus is present. One British group addressed this question by using a nested RT-PCR assay to test bronchoalveolar lavage fluid from 30 intubated infants with RSV infection and detected hMPV in 21 of 30 (70%) [36]. The authors subsequently used the same nested assay to test respiratory specimens from children admitted to the

pediatric intensive care unit (ICU) and the general wards. hMPV and RSV coinfection was detected in 18 of 25 (72%) pediatric ICU patients and 15 of 171 (9%) general ward patients [37]. The authors concluded that dual infection with RSV and hMPV was associated with severe bronchiolitis. A Connecticut study of 46 inpatients with either mild or severe RSV disease found no coinfections with hMPV, however [38]. Whether these conflicting findings are due to methodologic differences or geographic variability in circulating virus strains is unknown. Further prospective studies are needed to clarify the nature of disease associated with coinfections.

Coronaviruses

Human coronaviruses were discovered in the 1960s by researchers studying the etiology of URI in children and young adults [39]. Three major serologic groups of coronaviruses have been described. Two prototypic human viruses, each belonging to a different serologic group, originally were detected in patients who presented with URI. The group I strain, 229E, and group II strain, OC43, were the only extensively studied human coronaviruses until the identification of SARS-CoV in 2003. Coronaviruses are difficult to cultivate in tissue cell culture, so most epidemiologic studies have been based on serologic methods and likely have underestimated the extent of disease associated with human coronavirus. Early, large epidemiologic studies in the United States noted that human coronaviruses 229E and OC43 caused numerous respiratory infections with an incidence that peaked in late winter or early spring. In addition, the predominant type of coronavirus infection changed every 2 to 3 years, with the two identified human coronaviruses causing about 15% of URI, but ranging from 1% to 35% depending on the specific year [39]. The human coronaviruses originally were thought to cause only URI until the discovery of patients with pneumonia during outbreaks of human coronavirus [40]. Numerous studies now have described the role of human coronaviruses OC43 and 229E in LRI in young children [41–47].

Severe acute respiratory syndrome–coronavirus

In fall 2002, a mysterious new respiratory illness appeared in the Guangdong province of China. The illness was associated with hypoxia and rapid respiratory failure and was designated as SARS, although there were other systemic manifestations of disease. Although a subset of SARS cases also had hMPV and other viruses detected, a novel coronavirus (SARS-CoV) was determined to be the primary etiology of SARS [48–50]. Between November 2002 and July 2003, the SARS-CoV infected more than 8000 people and caused almost 800 deaths in 32 countries. Serologic evidence of previous infection in healthy humans was not detected, suggesting that SARS-CoV had emerged recently in the human population. A coronavirus

with more than 99% nucleotide homology to SARS-CoV was isolated from Himalayan palm civets and raccoon dogs found in live animal markets in Guangdong, suggesting these as possible animal reservoirs [51].

The primary manifestation of SARS-CoV infection in adults is febrile LRI, with diffuse lung involvement and profound hypoxia. Other organs are affected, however, and diarrhea, lymphopenia, and hepatic abnormalities have been described. Overall mortality in adults is 10% to 17% [52]. The disease seems to have a much milder course and more favorable outcome in children, however. The first reported series of 10 children with SARS noted no deaths [53]. All children had fever and lymphopenia, and 9 of 10 had abnormal chest radiographs. All received corticosteroids and defervesced within 48 hours. Only 1 older child required mechanical ventilation.

Another institution in Hong Kong reported on 21 patients with a mean age of 11 years (range 10 months–17 years) [54]. All of the children presented with fever, and most had cough. Younger children were more likely to present with rhinorrhea and cough, whereas children older than 12 years were more likely to complain of malaise, myalgias, chills, and rigors. Although 57% of children had lymphopenia at presentation, 90% of children developed lymphopenia during the illness. Older children had generally more severe disease compared with younger children. Children older than 12 years were more likely to have higher fever for longer duration, develop thrombocytopenia, require steroid therapy, and have chest radiograph progression. Many children in both age groups had mild chemical hepatitis that resolved. All children developed radiographic abnormalities during the course of the illness, most commonly unilateral focal opacity, with occasional multifocal or bilateral opacities. Of the children, 86% had progression of the radiographic findings during the illness, but all had resolved by 2 weeks. Only 2 patients required supplemental oxygen, and none required mechanical ventilation.

A subsequent study reported 44 children with serologically confirmed SARS, including many from the two previous reports [55]. Half were male; the mean age was 12 years (range 50 days–18 years). All children presented with fever, and 64% presented with cough. Nausea and vomiting also were common. Younger children were more likely to have rhinorrhea, whereas older children were more likely to experience malaise, headache, and myalgia. None of the children had wheezing on physical examination, and few had crepitations. Three quarters of the children had lymphopenia at presentation, and 86% developed lymphopenia during their illness. Other hematologic abnormalities present during the course of infection included neutrophilia in 52%, thrombocytopenia in 27%, and anemia in 5%. Half of all patients had transient elevations of alanine aminotransferase and lactate dehydrogenase, and 39% had prolonged activated partial thromboplastin time, although none of the children had clinical jaundice or bleeding. Nine patients developed hypoxia; five of these were cared for in the ICU, and three were mechanically ventilated. Forty-two children were treated with ribavirin,

and 37 were treated with steroids. Although there was no control group, a close temporal association was observed between steroid administration and clinical and radiologic improvement. None of the children died. There were 10 deaths among the adult family members of this pediatric cohort, emphasizing the difference in mortality between children and adults.

One study examined 47 serologically confirmed pediatric SARS cases 6 months after their acute illness [56]. Mild residual changes were seen on high-resolution chest CT in 34%. Younger children who had not required oxygen during acute illness were more likely to have normal studies. Four children had mild residual abnormalities measured by pulmonary function testing, but none of the children had residual clinical symptoms.

Maternal-fetal transmission of SARS-CoV has not been documented, although only one study addressed this important pediatric issue [57]. Five infants born to mothers with SARS were tested extensively by RT-PCR and viral culture on multiple body fluids, routine laboratory tests and chest radiographs, and serologic testing. No evidence for SARS-CoV infection was found in any of the infants. Two infants had gastrointestinal complications that may have been related to prematurity.

SARS-CoV infections in children seem to be relatively mild compared with adults. Two patterns of illness are seen. Younger children present with more prominent rhinorrhea, cough, and often diarrhea, whereas older children present with malaise, myalgias, chills, and rigors similar to adult disease. Fever, lymphopenia, and radiographic abnormalities are prominent at all ages. In contrast to other common respiratory viruses, male sex did not seem to be a risk factor for more severe disease because boys and girls were equally represented among hospitalized patients. Although older children are more likely to have hypoxia and a prolonged course, virtually all children recover completely without significant long-term sequelae.

Human coronavirus–Netherlands

Since the discovery of SARS-CoV, two groups in the Netherlands almost simultaneously published the discovery of another human coronavirus tentatively named *HCoV-NL*. HCoV-NL originally was cultured from respiratory specimens collected from infants with bronchiolitis [58]. Subsequently, Van der Hoek et al [58] tested respiratory specimens of hospitalized patients and outpatients collected from December 2002 to August 2003 and detected seven HCoV-NL-positive specimens in patients with ARI. Overall, 7 of 614 samples (1%) tested positive, but 7% of samples collected during January contained HCoV-NL RNA. Five of the seven samples were from infants, with a mean age of 8 months (range 4–11 months), three with URI and two with LRI. HCoV-NL was detected in specimens only from December through February. Sequencing of the isolates showed that HCoV-NL is a group I coronavirus most closely related to 229E. Another group in the Netherlands, which had discovered the virus

independently, detected HCoV-NL in 4 of 139 (3%) respiratory samples [59]. The patients were three infants age 3 to 4 months and a 10-year-old child. All had presented with rhinorrhea, fever, and cough, and three had underlying conditions.

Canadian researchers tested specimens previously negative for other viruses collected from patients with ARI from several provinces and detected HCoV-NL in 19 of 525 (4%) [60]. Of these, 8 were in children younger than 5 years old, in whom the rate was higher (8 of 110, 7%). HCoV-NL was detected from January through March, but in only 1 of 2 study years. This is similar to OC43 and 229E, which are known to cause epidemics in 2- to 3-year cycles. The HCoV-NL-infected children were 85% male and presented with URI and LRI illnesses, including bronchiolitis.

Investigators in the United States screened 1265 specimens from children younger than 5 years old collected over 1 year, who previously had been negative for other viruses, and detected HCoV-NL by RT-PCR in 79 of 1265 (6%) [61]. Nine of 76 (12%) were coinfected with another virus, most with RSV. HCoV-NL was detected predominantly in the months of January and February; 67 patients had HCoV-NL detected as a sole agent. Eleven of these patients had been hospitalized since birth in the neonatal ICU and potentially had nosocomial infections. The mean age of the HCoV-NL-infected children was 6.5 months (range 1 day–5 years). Sixty-three percent were younger than 1 year old, 34% were younger than 3 months old, and 62% were male. The most common presenting signs and symptoms in non–neonatal ICU patients were cough in 77%, rhinorrhea in 68%, fever and tachypnea in 54%, and adventitious lung findings in 43%. One third of these children had hypoxia, wheezing, or retractions. Twenty of 31 had abnormal chest radiographs, mostly with peribronchial cuffing. Information on clinical diagnoses, duration of hospitalization, treatment, and outcome was not provided. The clinical description of these children, winter occurrence, and chest radiograph findings suggest, however, an illness consistent with typical viral bronchiolitis caused by RSV or hMPV. Further prospective studies are needed to clarify the clinical presentation and course of illness with HCoV-NL. A major limitation of all of these studies is that no control groups were included to examine asymptomatic carriage and strengthen the case for a causal relationship between HCoV-NL and ARI.

Avian influenza virus

Influenza has been well described as an important respiratory pathogen in young children, with the greatest morbidity and rates of hospitalization in young infants [62,63]. The major hemagglutinin types associated with disease in humans are H1 and H3, and these are the most important protective antigens. Severe pandemics of influenza occur as a result of major antigenic changes in the hemagglutinin (antigenic shift) caused by reassortment of one or more of the genomic segments, introducing novel

strains into circulation. The lack of preexisting immunity in most or all of the population allows pandemics to occur, and disease may be more severe because of the lack of even partially protective immunity. Avian influenza viruses carry novel hemagglutinins, such as H5, H7, and H9, but generally do not replicate efficiently in humans. Reassortment with human strains can allow a recombinant virus to emerge, however, that is highly pathogenic and infectious for human hosts. This reassortment between human and avian strains is though to occur primarily in pigs, which are susceptible to infection by both strains. Numerous outbreaks of such novel avian influenza viruses have been reported in recent years. Almost all have been linked epidemiologically to close contact with poultry, chiefly chickens or ducks, and human-to-human transmission has been documented rarely.

Mild respiratory disease in two children caused by reassortment human-avian influenza strains was reported in the Netherlands in 1994 [64]. In 1997, a 3-year-old boy in Hong Kong died as a result of acute respiratory failure and multiorgan system dysfunction secondary to an H5 influenza strain. Genetic analysis of the virus showed that it was an avian strain [65]. In that outbreak, five other children younger than age 18 were infected. A 13-year-old girl died of acute respiratory failure and multiorgan system dysfunction, a 2-year-old boy was hospitalized for 3 days with pneumonia, and three other children experienced uneventful URI. Twelve cases were reported, with more severe disease and a higher fatality rate in the adults [66].

Several sporadic outbreaks of avian influenza have occurred since the 1997 cases. There were two confirmed H5N1 cases and one probable H5N1 case in Hong Kong in February 2003 [67]. A 33-year-old man developed fatal progressive respiratory failure, and his 8-year-old son recovered from respiratory disease after a prolonged hospitalization. Both patients had profound lymphopenia, hypoxia, and consolidation of chest radiographs. The family had a 7-year-old daughter who had died of a febrile pneumonia 1 week before the father's illness, but she had not been tested for influenza. Two cases of H9N2 avian influenza infection of humans occurred in Hong Kong, one a child, with typical influenza symptoms of fever, rhinorrhea, and cough [68]. Both patients fully recovered. From January to March 2003, there were 34 cases of confirmed H5N1 infection in humans in Thailand and Vietnam [69,70]. Of the five laboratory-confirmed cases in Thailand with clinical data provided, four were boys age 6 to 7 years. All had fever, cough, and tachypnea. Lymphopenia and elevated transaminases were common. All patients had abnormalities on chest radiograph consisting of focal consolidation or multifocal opacities, and all required mechanical ventilation. These 4 children all died, and overall mortality in the Thailand outbreak was 8 of 12 (67%). In January 2004, 10 H5N1 cases were reported in Vietnam. Eight patients were 18 years old or younger, with a mean age of 12, and the youngest child was 5. All patients had fever, tachypnea, cough, and hypoxia. Five had diarrhea, and none of the children had myalgia, rash, or conjunctivitis. Prominent laboratory abnormalities included

lymphopenia, thrombocytopenia, and elevated transaminases. All had focal consolidation or extensive infiltrates on chest radiographs, which worsened significantly during the course of illness. All developed respiratory failure requiring mechanical ventilation, and seven of eight children died, despite aggressive supportive care and treatment with oseltamivir, ribavirin, or steroids for acute respiratory distress syndrome.

Subsequently, two other children were identified with probable or confirmed H5N1 infection during the same outbreak [71]. A 9-year-old girl presented with fever, watery diarrhea, hypotension, and depressed level of consciousness. Laboratory studies, including cerebrospinal fluid, were normal. She had rapidly progressive hemodynamic instability and coma and died the next day. Eight days later, her 4-year-old brother developed fever, headache, vomiting, and severe watery diarrhea. His initial diagnostic studies were remarkable only for elevated transaminases. He developed pneumonia and depressed mental status, became comatose, and died of respiratory failure 5 days after admission. During the course of his illness, he developed lymphopenia, thrombocytopenia, and bilateral infiltrates on chest radiograph. Cerebrospinal fluid was remarkable only for elevated protein. He was given the diagnosis of encephalitis, and postmortem testing detected H5N1 influenza by RT-PCR in cerebrospinal fluid, serum, and throat and rectal swabs, and culture of cerebrospinal fluid grew H5N1 influenza virus. No testing was done on his sister, but it is highly likely that she also was infected with H5N1. Neither child presented with respiratory symptoms, and the sister never had respiratory disease. Both had had significant exposure to ducks and chickens.

Avian influenza virus strains have the potential to be highly pathogenic in humans, and disease seems to be at best only slightly less severe in children. Most cases, but not all, have clear exposure to domestic fowl. Human-to-human transmission is rare. Most children present with fever, rhinorrhea, and cough, and lymphopenia, thrombocytopenia, and elevated transaminases are common. Some children can present with gastrointestinal disease alone. There are insufficient data to determine the efficacy of the neuraminidase inhibitors, oseltamivir and zanamivir, or the adamantanes, amantadine and rimantidine. The potential for widespread pandemics exists, and it is likely that more cases will be seen in sporadic outbreaks.

Hendra and Nipah viruses

Novel paramyxoviruses have been identified in Australia and Malaysia associated with acute febrile encephalitis and respiratory tract disease in humans. Hendra virus infected three adults, two of whom died with pneumonitis and multiorgan failure, and numerous horses [72]. No pediatric cases have been reported yet. The closely related Nipah virus was identified during an outbreak in Malaysia during 1998–1999 that included more than 250 patients [73]. Most presented with fever, headache, and vomiting, and

half had a depressed level of consciousness; 14% of the patients had cough, but respiratory or multiorgan system disease was less prominent than neurologic disease. A variety of neurologic symptoms were noted, primarily related to brainstem and spinal cord involvement. One third of the patients died, and 28% of the survivors had neurologic sequelae. Most of the patients were men who were pig farmers, and only a few children were affected, the youngest age 13 years. In Bangladesh in 2001 and 2003, there were outbreaks of a Nipah-like virus involving 13 and 12 patients [74]. Several children, the youngest age 4 years, were infected in each outbreak, and the overall mortality was 67%. Similar to the Malaysian outbreak, the most prominent symptoms were fever, headache, vomiting, and an altered level of consciousness. Respiratory illness was much more common in the Bangladesh cases, however, with 64% having cough and dyspnea. Whether the increased involvement of the respiratory tract was due to differences between virus strains is not known. Epidemiologic investigations identified fruit bats of the *Pteropus* genus as asymptomatic carriers of Hendra and Nipah viruses and possible animal reservoirs. Further outbreaks have not been reported, and these viruses have not yet been detected in other geographic regions. Their apparent virulence for humans warrants further research and surveillance for similar viruses in other populations.

Summary

Several emerging or truly novel respiratory tract viruses affecting children have been described in recent years. The most important of these novel viruses in children seems to be hMPV. hMPV is a common cause of URI and LRI in healthy infants and children and those with underlying medical conditions. Clinical disease resulting from hMPV is most similar to that caused by RSV. hMPV may be more severe in children with underlying conditions and has been associated with fatal disease in immunocompromised hosts. Further outbreaks of SARS-CoV have not occurred, but children younger than 12 years old with SARS have a relatively mild course and good prognosis. Older children are more likely to present with severe respiratory disease similar to adults. The coronavirus HCoV-NL seems to be a less common cause of ARI, but its full epidemiology and clinical spectrum of disease have not been defined. The emergence of avian influenza viruses in humans is highly concerning for potential pandemics. Avian influenza viruses have extreme virulence in children, with multiorgan disease and high mortality. Suspicion for the presence of avian influenza relies heavily on epidemiologic risk factors, such as exposure to poultry or travel to endemic regions. Nipah and Hendra viruses have been associated with severe encephalitis and pneumonitis in children and adults, although these viruses have not yet been detected in Europe or the Americas.

References

[1] World Health Organization. Acute respiratory infection in children. Available at: http://www.who.int/fch/depts/cah/resp_infections/en/. Accessed January 10, 2005.

[2] Glezen WP, Loda FA, Clyde WA Jr, et al. Epidemiologic patterns of acute lower respiratory disease of children in a pediatric group practice. J Pediatr 1971;78:397–406.

[3] Henderson FW, Clyde WA Jr, Collier AM, et al. The etiologic and epidemiologic spectrum of bronchiolitis in pediatric practice. J Pediatr 1979;95:183–90.

[4] van den Hoogen BG, DeJong JC, Groen J, et al. A newly discovered human pneumovirus isolated from young children with respiratory tract disease. Nat Med 2001;7:719–24.

[5] Williams JV, Harris PA, Tollefson SJ, et al. Human metapneumovirus and lower respiratory tract disease in otherwise healthy infants and children. N Engl J Med 2004;350:443–50.

[6] MacPhail M, Schickli JH, Tang RS, et al. Identification of small-animal and primate models for evaluation of vaccine candidates for human metapneumovirus (hMPV) and implications for hMPV vaccine design. J Gen Virol 2004;85:1655–63.

[7] Skiadopoulos MH, Biacchesi S, Buchholz UJ, et al. The two major human metapneumovirus genetic lineages are highly related antigenically, and the fusion (F) protein is a major contributor to this antigenic relatedness. J Virol 2004;78:6927–37.

[8] Boivin G, Abed Y, Pelletier G, et al. 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 2002;186:1330–4.

[9] Bastien N, Ward D, Van Caeseele P, et al. Human metapneumovirus infection in the Canadian population. J Clin Microbiol 2003;41:4642–6.

[10] van den Hoogen BG, van Doornum GJ, Fockens JC, et al. Prevalence and clinical symptoms of human metapneumovirus infection in hospitalized patients. J Infect Dis 2003;188:1571–7.

[11] Peiris JS, Tang WH, Chan KH, et al. Children with respiratory disease associated with metapneumovirus in Hong Kong. Emerg Infect Dis 2003;9:628–33.

[12] Boivin G, De Serres G, Cote S, et al. Human metapneumovirus infections in hospitalized children. Emerg Infect Dis 2003;9:634–40.

[13] Freymouth F, Vabret A, Legrand L, et al. Presence of the new human metapneumovirus in French children with bronchiolitis. Pediatr Infect Dis J 2003;22:92–4.

[14] Maggi F, Pifferi M, Vatteroni M, et al. Human metapneumovirus associated with respiratory tract infections in a 3-year study of nasal swabs from infants in Italy. J Clin Microbiol 2003;41:2987–91.

[15] Viazov S, Ratjen F, Scheidhauer R, Fiedler M, Roggendorf M. High prevalence of human metapneumovirus infection in young children and genetic heterogeneity of the viral isolates. J Clin Microbiol 2003;41:3043–5.

[16] Thanasugarn W, Samransamruajkit R, Vanapongtipagorn P, et al. Human metapneumovirus infection in Thai children. Scand J Infect Dis 2003;35:754–6.

[17] IJpma FF, Beekhuis D, Cotton MF, et al. Human metapneumovirus infection in hospital referred South African children. J Med Virol 2004;73:486–93.

[18] Galiano M, Videla C, Puch SS, Martinez A, Echavarria M, Carballal G. Evidence of human metapneumovirus in children in Argentina. J Med Virol 2004;72:299–303.

[19] Ebihara T, Endo R, Kikuta H, et al. Human metapneumovirus infection in Japanese children. J Clin Microbiol 2004;42:126–32.

[20] Cuevas LE, Nasser AM, Dove W, Gurgel RQ, Greensill J, Hart CA. Human metapneumovirus and respiratory syncytial virus, Brazil. Emerg Infect Dis 2003;9:1626–8.

[21] Zhu RN, Qian Y, Deng J, et al. Human metapneumovirus may associate with acute respiratory infections in hospitalized pediatric patients in Beijing, China. Zhonghua Er Ke Za Zhi 2003;41:441–4.

[22] Esper F, Martinello RA, Boucher D, et al. A 1-year experience with human metapneumovirus in children aged <5 years. J Infect Dis 2004;189:1388–96.

[23] Dollner H, Risnes K, Radtke A, Nordbo SA. An outbreak of human metapneumovirus infection in Norwegian children. Pediatr Infect Dis J 2004;23:436–40.

[24] McAdam AJ, Hasenbein ME, Feldman HA, et al. Human metapneumovirus in children tested at a tertiary-care hospital. J Infect Dis 2004;190:20–6.

[25] Mullins JA, Erdman DD, Weinberg GA, et al. Human metapneumovirus infection among children hospitalized with acute respiratory illness. Emerg Infect Dis 2004;10: 700–5.

[26] Bosis S, Esposito S, Niesters HG, Crovari P, Osterhaus AD, Principi N. Impact of human metapneumovirus in childhood: comparison with respiratory syncytial virus and influenza viruses. J Med Virol 2005;75:101–4.

[27] Bach N, Cuvillon D, Brouard J, et al. Acute respiratory tract infections due to a human metapneumovirus in children: descriptive study and comparison with respiratory syncytial virus infections. Arch Pediatr 2004;11:212–5.

[28] Rawlinson WD, Waliuzzaman Z, Carter IW, Belessis YC, Gilbert KM, Morton JR. Asthma exacerbations in children associated with rhinovirus but not human metapneumovirus infection. J Infect Dis 2003;187:1314–8.

[29] Jartti T, van den Hoogen B, Garofalo RP, Osterhaus AD, Ruuskanen O. Metapneumovirus and acute wheezing in children. Lancet 2002;360:1393–4.

[30] Laham FR, Israele V, Casellas JM, et al. Differential production of inflammatory cytokines in primary infection with human metapneumovirus and with other common respiratory viruses of infancy. J Infect Dis 2004;189:2047–56.

[31] Cane PA, van den Hoogen BG, Chakrabarti S, Fegan CD, Osterhaus AD. Human metapneumovirus in a haematopoietic stem cell transplant recipient with fatal lower respiratory tract disease. Bone Marrow Transplant 2003;31:309–10.

[32] Pelletier G, Dery P, Abed Y, Boivin G. Respiratory tract reinfections by the new human metapneumovirus in an immunocompromised child. Emerg Infect Dis 2002;8:976–8.

[33] Madhi SA, Ludewick H, Abed Y, Klugman KP, Boivin G. Human metapneumovirus-associated lower respiratory tract infections among hospitalized human immunodeficiency virus type 1 (HIV-1)-infected and HIV-1-uninfected African infants. Clin Infect Dis 2003;37: 1705–10.

[34] Garcia Garcia ML, Calvo Rey C, Martin del Valle F, et al. Respiratory infections due to metapneumovirus in hospitalized infants. An Pediatr (Barc) 2004;61:213–8.

[35] Konig B, Konig W, Arnold R, Werchau H, Ihorst G, Forster J. Prospective study of human metapneumovirus infection in children less than 3 years of age. J Clin Microbiol 2004;42: 4632–5.

[36] Greensill J, McNamara PS, Dove W, Flanagan B, Smyth RL, Hart CA. Human metapneumovirus in severe respiratory syncytial virus bronchiolitis. Emerg Infect Dis 2003;9:372–5.

[37] Semple MG, Cowell A, Dove W, et al. Dual infection of infants by human metapneumovirus and human respiratory syncytial virus is strongly associated with severe bronchiolitis. J Infect Dis 2005;191:382–6.

[38] Lazar I, Weibel C, Dziura J, Ferguson D, Landry ML, Kahn JS. Human metapneumovirus and severity of respiratory syncytial virus disease. Emerg Infect Dis 2004;10:1318–20.

[39] Monto AS. Medical reviews: coronaviruses. Yale J Biol Med 1974;47:234–51.

[40] McIntosh K, Chao RK, Krause HE, Wasil R, Mocega HE, Mufson MA. Coronavirus infection in acute lower respiratory tract disease of infants. J Infect Dis 1974;130:502–7.

[41] Kaye HS, Marsh HB, Dowdle WR. Seroepidemiologic survey of coronavirus (strain OC 43) related infections in a children's population. Am J Epidemiol 1971;94:43–9.

[42] Isaacs D, Flowers D, Clarke JR, Valman HB, MacNaughton MR. Epidemiology of coronavirus respiratory infections. Arch Dis Child 1983;58:500–3.

[43] Sizun J, Soupre D, Legrand MC, et al. Neonatal nosocomial respiratory infection with coronavirus: a prospective study in a neonatal intensive care unit. Acta Paediatr 1995;84: 617–20.

[44] Sizun J, Soupre D, Legrand MC, Giroux JD, Rubio S, Chastel C, et al. [Pathogen role of coronavirus in pediatric intensive care: retrospective analysis of 19 positive samples with indirect immunofluorescence]. Arch Pediatr 1994;1:477–80.

[45] Macnaughton MR, Flowers D, Isaacs D. Diagnosis of human coronavirus infections in children using enzyme-linked immunosorbent assay. J Med Virol 1983;11:319–25.

[46] Sizun J, Soupre D, Giroux JD, et al. Nasal colonization with coronavirus and apnea of the premature newborn. Acta Paediatr 1993;82:238.

[47] Gagneur A, Sizun J, Vallet S, Legr MC, Picard B, Talbot PJ. Coronavirus-related nosocomial viral respiratory infections in a neonatal and paediatric intensive care unit: a prospective study. J Hosp Infect 2002;51:59–64.

[48] Peiris JS, Lai ST, Poon LL, Guan Y, Yam LY, Lim W. Coronavirus as a possible cause of severe acute respiratory syndrome. Lancet 2003;361:1319–25.

[49] Ksiazek TG, Erdman D, Goldsmith CS, et al. A novel coronavirus associated with severe acute respiratory syndrome. N Engl J Med 2003;348:1953–66.

[50] Drosten C, Gunther S, Preiser W, et al. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. N Engl J Med 2003;348:1967–76.

[51] Guan Y, Zheng BJ, He YQ, et al. Isolation and characterization of viruses related to SARS coronavirus from animals in southern China. Science 2003;302:276–8.

[52] World Health Organization. Summary of probable SARS cases with onset of illness from 1 November 2002 to 31 July 2003. Available at: http://www.who.int/csr/sars/country/table2004_04_21/en/. Accessed February 28, 2005.

[53] Hon KL, Leung CW, Cheng WT, et al. Clinical presentations and outcome of severe acute respiratory syndrome in children. Lancet 2003;361:1701–3.

[54] Chiu WK, Cheung PC, Ng KL, et al. Severe acute respiratory syndrome in children: experience in a regional hospital in Hong Kong. Pediatr Crit Care Med 2003;4:279–83.

[55] Leung CW, Kwan YW, Ko PW, et al. Severe acute respiratory syndrome among children. Pediatrics 2004;113:e535–43.

[56] Li AM, Chan CH, Chan DF. Long-term sequelae of SARS in children. Paediatr Respir Rev 2004;5:296–9.

[57] Shek CC, Ng PC, Fung GP, et al. Infants born to mothers with severe acute respiratory syndrome. Pediatrics 2003;112:e254.

[58] van der Hoek L, Pyrc K, Jebbink MF, et al. Identification of a new human coronavirus. Nat Med 2004;10:368–73.

[59] Fouchier RA, Hartwig NG, Bestebroer TM, et al. A previously undescribed coronavirus associated with respiratory disease in humans. Proc Natl Acad Sci U S A 2004;101:6212–6.

[60] Bastien N, Anderson K, Hart L, et al. Human coronavirus NL63 infection in Canada. J Infect Dis 2005;191:503–6.

[61] Esper F, Weibel C, Ferguson D, Landry ML, Kahn JS. Evidence of a novel human coronavirus that is associated with respiratory tract disease in infants and young children. J Infect Dis 2005;191:492–8.

[62] Neuzil KM, Mellen BG, Wright PF, Mitchel EF Jr, Griffin MR. The effect of influenza on hospitalizations, outpatient visits, and courses of antibiotics in children. N Engl J Med 2000; 342:225–31.

[63] Neuzil KM, Zhu Y, Griffin MR, et al. Burden of interpandemic influenza in children younger than 5 years: a 25-year prospective study. J Infect Dis 2002;185:147–52.

[64] Claas EC, Kawaoka Y, de Jong JC, Masurel N, Webster RG. Infection of children with avian-human reassortant influenza virus from pigs in Europe. Virology 1994;204:453–7.

[65] Subbarao K, Klimov A, Katz J, et al. Characterization of an avian influenza A (H5N1) virus isolated from a child with a fatal respiratory illness. Science 1998;279:393–6.

[66] Yuen KY, Chan PK, Peiris M, et al. Clinical features and rapid viral diagnosis of human disease associated with avian influenza A H5N1 virus. Lancet 1998;351:467–71.

[67] Peiris JSM, Yu WC, Leung CW, et al. Re-emergence of fatal human influenza A subtype H5N1 disease. Lancet 2004;363:617–9.

[68] Peiris M, Leung CW, Chan KH, et al. Human infection with influenza H9N2. Lancet 1999; 354:916–7.

[69] Centers for Disease Control and Prevention (CDC). Cases of influenza A (H5N1)—Thailand, 2004. MMWR Morb Mortal Wkly Rep 2004;53:100–3.

[70] Tran TH, Nguyen TL, Nguyen TD, et al. Avian influenza A (H5N1) in 10 patients in Vietnam. N Engl J Med 2004;350:1179–88.

[71] de Jong MD, Bach VC, Phan TQ, et al. Fatal avian influenza A (H5N1) in a child presenting with diarrhea followed by coma. N Engl J Med 2005;352:686–91.

[72] Murray K, Selleck P, Hooper P, et al. A morbillivirus that caused fatal disease in horses and humans: infection of humans and horses by a newly described morbillivirus. Science 1995; 268:94–7.

[73] Goh KJ, Tan CT, Chew NK, et al. Clinical features of Nipah virus encephalitis among pig farmers in Malaysia. N Engl J Med 2000;342:1229–35.

[74] Hsu VP, Hossain MJ, Parashar UD, et al. Nipah virus encephalitis reemergence, Bangladesh. Emerg Infect Dis 2004;10:2082–7.