

# New Respiratory Viruses of Humans

*Albert D. M. E. Osterhaus, DVM, PhD*

**Abstract:** Acute respiratory viruses are a major cause of morbidity and mortality in humans worldwide and most acute respiratory infections are caused by viruses. Many of these viruses cause the highest burden of disease in specific risk groups such as young infants, the elderly, and immune-compromised individuals. Although the most important respiratory viruses of humans have been identified in the last century, in the past decade about a dozen “new” viruses have been discovered that may cause a high burden of acute respiratory disease in humans. Not only viruses were discovered that must have been with humans for many decades or centuries, such as human metapneumovirus and 2 different human coronaviruses, but also viruses that are truly new for humans and have emerged as a result of recent interspecies transmissions from other mammalian or avian reservoirs. The latter include highly pathogenic avian influenza viruses, severe acute respiratory syndrome (SARS) coronavirus, and Nipah virus. The discovery, etiologic role, and burden of disease caused by these infections are described.

**Key Words:** avian influenza, SARS, coronavirus, henipaviruses, metapneumovirus, bocavirus

(*Pediatr Infect Dis J* 2008;27: 000–000)

Acute respiratory infections in humans are in most cases caused by viruses, and the burden of disease caused by these infections and their complications is considerable. Many of these infections may have particularly high morbidity and mortality in certain risk groups such as young infants, the elderly, and immune-compromised individuals. Newly discovered human respiratory viruses can be divided in 2 categories. The first category results from recent interspecies transmission events from other mammalian or avian reservoirs and these infections have recently caused severe disease in individual patients, or even outbreaks of major public health concern. The other category consists of truly human viruses that have probably been with us for many decades if not centuries and have only recently been discovered as a result of increased attention for discovery activities with state of the art technologies. Especially the threat posed to human health worldwide by the first category raises the question of

what we may expect in the future from such truly emerging viruses. Should we prepare for pandemic outbreaks caused by these virus infections and if so how well can we be prepared, not knowing what the next pandemic virus will be. For the second category of viruses we would like to know what their individual global prevalence, variability, and associated disease burden is, to decide whether intervention strategies such as diagnostic and surveillance activities, preventive vaccination strategies, and treatment options should be developed. In addition it may be expected that also in this category new discoveries will be made, because we have not yet fully closed the gap of undiagnosed acute respiratory infections in humans.

## Truly New Respiratory Viruses in Humans Associated With Serious Disease

*Avian Influenza Viruses.* There are 3 forms of human influenza caused by viruses of the influenza A virus type: seasonal, avian, and pandemic influenza. The symptoms and signs of these 3 forms are largely the same, although they differ in severity. In the lay press these 3 different but related disease entities are often mixed up, creating confusion among the general public.

In the past century there have been 3 major influenza pandemics, the “Spanish Flu” that started in 1918 (H1N1 virus), the “Asian Flu” of 1957 (H2N2 virus), and the “Hong Kong Flu” of 1968 (H3N2 virus), which caused the deaths of more than 40 million, about 2 million, and about 2 million people worldwide, respectively. All these pandemics resulted from the introduction of a reassorted or mutated influenza A virus from an avian reservoir into the human population. After the respective pandemics, all these viruses continued to circulate as continuously “drifting” seasonal influenza viruses in subsequent years.<sup>1</sup> In the past decade zoonotic transmissions of avian influenza viruses have been recorded with unprecedented and increasing frequency (Table 1). The first isolation of a highly pathogenic avian influenza (HPAI) virus of the H5N1 subtype was from the lungs of a young boy who died in Hong Kong in 1997.<sup>2,3</sup> The virus was virtually identical to the virus that caused outbreaks of HPAI among poultry in the region at that time. After 5 of the 17 individuals who had become hospitalized with the same infection in Hong Kong had died, it was decided to cull all the poultry at the live bird markets in Hong Kong at that time. This interrupted the further spread of this virus to humans in the area.<sup>4</sup>

In 2003 during a major HPAI outbreak among poultry in The Netherlands, caused by a virus of the H7N7 subtype that led to the culling of more than 30 million poultry, 89 poultry workers and their family members were clinically infected, despite all the precautionary measures that were taken. One veterinarian involved in the sampling of infected poultry died of this infection.<sup>5,6</sup>

From the Department of Virology, Erasmus MC, University Medical Center, Rotterdam, The Netherlands.

Supported by BSIK project 03012 (VIRGO).

Address for correspondence: Albert D. M. E. Osterhaus, DVM, PhD, Department of Virology, Erasmus MC, University Medical Center, PO Box 2040, 3000 CA Rotterdam, The Netherlands. E-mail: a.osterhaus@erasmusmc.nl.

Copyright © 2008 by Lippincott Williams & Wilkins

ISSN: 0891-3668/08/2705-0001

DOI: 10.1097/INF.0b013e3181684d7c

**TABLE 1.** Influenza A Virus: Recent Zoonotic Transmissions

Subtype	Country	Year	Cases	Deaths
H7N7	United Kingdom	1996	1	0
H5N1	Hong Kong	1997	18	6
H9N2	SE Asia	1999	>2	0
H5N1	Hong Kong	2003	2	1
H7N7	Netherlands	2003	89	1
H7N2	United States	2003	1	0
H7N3	Canada	2004	2	0
H5N1	SE Asia/M. East/Europe/ W. Africa	2003–2007	>330	>210

Since 2003, more than 330 people have become hospitalized with an HPAI H5N1 infection and more than 210 of them have died while the virus spread from Southeast Asia to the Middle East, Europe, and West Africa.<sup>7</sup> Most, if not all, of these people were infected by direct or indirect contacts with infected poultry or their products. The geographical spread of the virus has probably been caused by infected wild birds or their products through migration or trade or smuggling activities.

The genetic and phenotypic changes of the H5N1 virus as well as its unprecedented spread over the different continents in the past decade, illustrate the pandemic threat that is posed by this avian influenza virus subtype. However, it cannot be excluded that an avian influenza virus of another subtype (eg, H2, H7, or H9) will eventually cause the first pandemic of the 21st century.

**SARS CoronaVirus (SARS-CoV).** When a new transmissible respiratory disease entity with a high case fatality rate was identified in the Peoples Republic of China at the end of 2002, it was first thought that it was caused by an avian influenza virus. The disease rapidly spread to different Asian, European, and North American countries. Initial attempts to identify the causative agent by the World Health Organization (WHO) led SARS etiology group yielded a paramyxovirus that upon further characterization proved to be human metapneumovirus (hMPV), a virus that was identified 2 years previously (see below). A not previously recognized coronavirus was subsequently found in virtually all patients with SARS.<sup>7–10</sup> Through the unprecedented and exemplary collaboration between the different participants of the group, the virus was sequenced within 10 days.<sup>7,11</sup> Because more than 1 virus and some other infectious agents had been identified in SARS patients, it was decided to prove the unique etiological role of one of the viruses identified, by fulfilling the Koch postulates for either the hMPV or the SARS-CoV.<sup>7,12,13</sup> Intratracheal inoculation of cynomolgus macaques with SARS-CoV and not with hMPV resulted in the development of SARS in these animals. This was largely concluded on basis of the pathologic lesions found, the associated presence of virus and viral antigen, and the development of SARS-CoV specific serum antibodies. Collectively, the data allowed WHO, in a press conference held 1 month after the WHO etiology group had decided to start its intensive collaboration, to state that the SARS-CoV was the primary cause of SARS. This then rapidly led to the development of diagnostic and

surveillance tools, which made it possible to control the ongoing epidemic soon thereafter by implementing epidemiological measures. Soon the epidemic was brought under control. After the identification of SARS-CoV, its origin has been the subject of much speculation.<sup>14</sup> Initially it was shown that animal handlers and several carnivore species at live animal markets were or had been infected with SARS-CoV or closely related viruses. More recently it was shown that several fruit bat species carry a plethora of genetically distinct coronaviruses, some of which are closely related to SARS-CoV. This led to the speculation that the original reservoir of SARS-CoV should rather be sought in bats than in carnivores.<sup>15</sup>

The availability of the macaque model also allowed the testing of broadly reactive antiviral compounds that were shown to be effective in controlling SARS-CoV replication in vitro. Thus it was shown that pegylated interferon (IFN)- $\alpha$  could be used both for preventive and postexposure treatment.<sup>16</sup> Subsequently other intervention strategies were preclinically tested in different animal models, such as the use of antiviral antibodies and vaccination, leading to an armamentarium of strategies to combat this newly emerged disease entity, if it would re-emerge.

**Henipaviruses.** Two related zoonotic paramyxoviruses, Hendra virus and Nipah virus, have recently been described (for review, see Ref. 17). Hendra virus was reported in horses and subsequently in humans in Australia in 1994.<sup>18</sup> Nipah virus was reported in pigs and subsequently in humans in Malaysia 4 years later.<sup>19,20</sup> Human disease associated with Henipah virus infections is characterized by severe respiratory disease, often with fatal outcome. Since 2001, human cases of Nipah virus infection have also been reported in Bangladesh with fruit bats being the most likely source of the infection.<sup>21</sup> Fruit bat species have been identified as the natural hosts of both agents.

## Recently Discovered Human Respiratory Viruses

**Human Metapneumovirus (hMPV).** hMPV was identified as the first non-avian member of the recently defined genus Metapneumovirus of the *Pneumovirinae* subfamily, in young children in The Netherlands in 2001.<sup>22</sup> The causative role of hMPV for respiratory disease was shown by fulfilling the Koch postulates in a macaque infection experiment. The virus proved to be ubiquitous and all children over 5 years of age were shown to have been infected at least once. Reinfections occur quite frequently. The virus must have been in the human population for at least 50 years, and probably much longer. Two serotypes of hMPV were identified, each of which represents 2 lineages (A1, A2, B1, and B2, respectively), which are also reflected by the genetic diversity of the virus.<sup>23</sup> Each of the lineages seems to circulate largely independently and no significant differences in associated disease patterns have been observed. Disease symptoms and signs in young children largely parallel those of respiratory syncytial virus (RSV) in this age group, although the overall age of children with hMPV infection tends to be slightly higher and the clinical manifestations slightly less severe. In several studies, the burden of respiratory disease in young children caused by hMPV proved to be second to that caused by RSV

infection. About 10% of children hospitalized with acute respiratory tract infections suffer from hMPV infection.<sup>24</sup> In addition, hMPV infections were shown to be a major cause of severe and sometimes even fatal respiratory infections in immune-compromised patients. Finally the virus was shown to be a major pathogen of the elderly and up to 5% of common colds in the community are caused by hMPV.<sup>25</sup> Like RSV infections, also hMPV infections predominantly occur in the winter months. The burden of hMPV-associated disease justifies the development of adequate intervention strategies, such as the use of rapid diagnostic methods, specific antibody, and other antiviral compounds and preventive vaccines.

**Human Coronaviruses.** When SARS-CoV was discovered, another human coronavirus isolated from infants in The Netherlands with serious respiratory symptoms, was characterized independently by 2 Dutch groups: HCoV-NL.<sup>26,27</sup> The virus was both genetically and antigenically clearly distinct from the 2 previously identified human coronaviruses HCoV-OC43 and HCoV-229E. The latter are both associated with relatively mild respiratory disease or common cold. HCoV-NL also proved to be ubiquitous and was mainly found in young children with respiratory disease of different severities, ranging from mild upper respiratory tract to severe lower respiratory tract infections. HCoV-NL also proved to cause severe infections in the elderly and immunocompromised individuals. Interestingly, in contrast to hMPV infections, HCoV-NL infections were often found in combination with other respiratory virus infections and in patients with underlying disease.

Soon after the discovery of HCoV-NL, yet another not previously recognized virus was identified in patients with pneumonia in Hong Kong: HCoV-HKU1.<sup>28</sup>

Phylogenetically HCoV-NL is more closely related to HCoV-229E, whereas HCoV-HKU1 is more related to HCoV-OC43. Also this virus has a global circulation, is primarily seen in children, the elderly and patients with underlying disease. The disease caused by HCoV-HKU1 also ranges from upper respiratory disease to severe pneumonia, whereas also an association with gastrointestinal disease has been suggested. More studies are needed before the true disease burden caused by these newly discovered coronaviruses will be fully understood.

**Other Newly Identified Human Respiratory Viruses.** Newly developed systems for large-scale molecular virus screening of clinical samples to systematically search for unrecognized human pathogens have been applied for virus screening of human respiratory tract samples. These efforts have recently resulted in the identification of a new parvovirus: human Bocavirus. This virus has a close genetic relationship with both bovine parvovirus and minute virus of canines.<sup>29</sup> It has recently been identified in not only respiratory secretions, but also in feces and serum. It is associated with lower and most likely also upper respiratory tract infections. Most commonly reported symptoms are cough, rhinorrhea, expiratory wheezing and fever, and the virus is preferentially detected in young children. Similarly, previously unknown polyomaviruses provisionally named KI and WU polyomaviruses were identified in respiratory samples.<sup>30,31</sup>

The evidence for an association between infections with these newly discovered parvo- and polyomaviruses and respiratory tract disease or other disease, such as enteric disease, is currently subject of further investigation.

## CONCLUSIONS

In the past decade human infections with viruses that have spilled over from animal reservoirs such as migratory birds, carnivores, and bats, have caused serious disease in humans. In most of these cases such as HPAI H5N1 influenza or Nipah virus infections the viruses did not or not efficiently spread from human to human. This was different in the case of SARS, which was a disease that did spread efficiently between humans and started to become a pandemic outbreak. Consequently, HPAI H5N1 influenza or Nipah virus infections would acquire pandemic potential if they could spread efficiently between humans.

On the other hand, more interest in the discovery of not previously identified human pathogens and the use of both classic and state of the art molecular screening technology have led to the identification of an increasing number of human respiratory viruses in the past decade. For this category of newly discovered viruses we would like to know what their individual global prevalence, variability, and associated disease burden is, to decide whether intervention strategies such as diagnostic and surveillance activities, preventive vaccination strategies, and treatment options should be developed. Finally it may be expected that also in this category new discoveries will be made, because we have not yet fully closed the gap of undiagnosed acute respiratory infections in humans.

## REFERENCES

- De Jong JC, Rimmelzwaan GF, Fouchier RA, Osterhaus AD. Influenza virus: a master of metamorphosis. *J Infect.* 2000;40:218–228.
- De Jong JC, Claas EC, Osterhaus AD, Webster RG, Lim WL. A pandemic warning? *Nature.* 1997;389:554.
- 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;279:393–396.
- Claas EC, Osterhaus AD. New clues to the emergence of flu pandemics. *Nat Med.* 1998;4:1122–1123.
- Fouchier RA, Schneeberger PM, Rozendaal FW, et al. Avian influenza A virus (H7N7) associated with human conjunctivitis and a fatal case of acute respiratory distress syndrome. *Proc Natl Acad Sci USA.* 2004;101:1356–1361.
- Koopmans M, Wilbrink B, Conyn M, et al. Transmission of H7N7 avian influenza A virus to human beings during a large outbreak in commercial poultry farms in the Netherlands. *Lancet.* 2004;363:587–593.
- World Health Organization. Avian influenza. Available at: [www.who.int/csr/disease/avian\\_influenza/en](http://www.who.int/csr/disease/avian_influenza/en). Accessed 20 December, 2007.
- 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;348:1967–1976.
- Ksiazek TG, Erdman D, Goldsmith CS, et al. A novel coronavirus associated with severe acute respiratory syndrome. *N Engl J Med.* 2003;348:1953–1966.
- Peiris JS, Lai ST, Poon LL, et al. Coronavirus as a possible cause of severe acute respiratory syndrome. *Lancet.* 2003;361:1319–1325.
- Rota PA, Oberste MS, Monroe SS, et al. Characterization of a novel coronavirus associated with severe acute respiratory syndrome. *Science.* 2003;300:1394–1399.
- Fouchier RA, Kuiken T, Schutten M, et al. Aetiology: Koch's postulates fulfilled for SARS virus. *Nature.* 2003;423:240.

13. Kuiken T, Fouchier RA, Schutten M, et al. Newly discovered coronavirus as the primary cause of severe acute respiratory syndrome. *Lancet*. 2003;362:263–270.
14. Guan Y, Zheng BJ, He YQ, et al. Isolation and characterization of viruses related to the SARS coronavirus from animals in southern China. *Science*. 2003;302:276–278.
15. Li W, Shi Z, Yu M, et al. Bats are natural reservoirs of SARS-like coronaviruses. *Science*. 2005;310:676–679.
16. Haagmans BL, Kuiken T, Martina BE, et al. Pegylated interferon-alpha protects type 1 pneumocytes against SARS coronavirus infection in macaques. *Nat Med*. 2004;10:290–293.
17. Field H, Young P, Yob JM, Mills J, Hall L, Mackenzie J. The natural history of Hendra and Nipah viruses. *Microbes Infect*. 2001;3:307–314.
18. Murray K, Selleck P, Hooper P, et al. A morbillivirus that caused fatal disease in horses and humans. *Science*. 1995;268:94–97.
19. Chua KB, Goh KJ, Wong KT, et al. Fatal encephalitis due to Nipah virus among pig-farmers in Malaysia. *Lancet*. 1999;354:1257–1259.
20. Goh KJ, Tan CT, Chew NK, et al. Clinical features of Nipah virus encephalitis among pig farmers in Malaysia. *N Engl J Med*. 2000;342:1229–1235.
21. Hsu VP, Hossain MJ, Parashar UD, et al. Nipah virus encephalitis reemergence, Bangladesh. *Emerg Infect Dis*. 2004;10:2082–2087.
22. van den Hoogen BG, De Jong JC, Groen J, et al. A newly discovered human pneumovirus isolated from young children with respiratory tract disease. *Nat Med*. 2001;7:719–724.
23. van den Hoogen BG, Herfst S, Sprong L, et al. Antigenic and genetic variability of human metapneumoviruses. *Emerg Infect Dis*. 2004;10:658–666.
24. 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;188:1571–1577.
25. Osterhaus A, Fouchier R. Human metapneumovirus in the community. *Lancet*. 2003;361:890–891.
26. Fouchier RA, Hartwig NG, Bestebroer TM, et al. A previously undescribed coronavirus associated with respiratory disease in humans. *Proc Natl Acad Sci USA*. 2004;101:6212–6216.
27. van der Hoek L, Pyrc K, Jebbink MF, et al. Identification of a new human coronavirus. *Nat Med*. 2004;10:368–373.
28. Woo PC, Lau SK, Chu CM, et al. Characterization and complete genome sequence of a novel coronavirus, coronavirus HKU1, from patients with pneumonia. *J Virol*. 2005;79:884–895.
29. Allander T, Tammi MT, Eriksson M, Bjerkner A, Tiveljung-Lindell A, Andersson B. Cloning of a human parvovirus by molecular screening of respiratory tract samples. *Proc Natl Acad Sci USA*. 2005;102:12891–12896.
30. Allander T, Andreasson K, Gupta S, et al. Identification of a third human polyomavirus. *J Virol*. 2007;81:4130–4136.
31. Gaynor AM, Nissen MD, Whiley DM, et al. Identification of a novel polyomavirus from patients with acute respiratory tract infections. *PLoS Pathog*. 2007;3:e64.