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NEW, EMERGING, AND REEMERGING RESPIRATORY VIRUSES

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19.1 INTRODUCTION

19.1.1 History

Infectious diseases have been a major cause of mortality in human history. However, in the last century, this picture has changed remarkably with the introduction of hygienic and sanitary as well as veterinary control measures and new medical intervention strategies, like vaccination and the use of antibiotics and antivirals. Vaccination even resulted in the complete eradication of smallpox, a virus disease that has claimed the lives of millions of humans over the centuries. Recently vaccination has also contributed to the final eradication of rinderpest that has likewise devastated cattle populations (Morens et al., 2011; Roeder, 2011). It is reasonable to expect that the eradication of other human infectious diseases like polio and measles will follow in the decades to come (Aylward and Tangermann, 2011; Centers for Disease Control and Prevention, 2012; Moss and Griffin, 2012). In the 1970s of the last century, these developments prompted influential policymakers and scientists to speculate that infectious diseases would become a minor health issue in the future. However, this assumption proved completely wrong in the decades thereafter when the world was confronted with an unexpected number of new or reemerging infectious diseases. Most of these were viral diseases derived from the animal world, like pandemic influenza, severe acute respiratory syndrome (SARS), Ebola, Nipah, and dengue (Kuiken et al., 2011; Osterhaus, 2001, 2008; Reperant et al., 2012a, b).

Probably the most striking example is the still ongoing HIV/AIDS pandemic that started by multiple introductions of a simian lentivirus into the human population in the early decades of the twentieth century (Keele et al., 2006). Currently, almost 60 million people have been infected with HIV and approximately one-third of them have died from AIDS (WHO, 2012b). To date we continue to be confronted with new, emerging, and reemerging infectious diseases causing mild to severe illnesses in humans and animals. Emerging and reemerging infections are defined as "infections that have newly appeared in

a susceptible population or have existed previously but are rapidly increasing in incidence and/or geographic range" (Morens et al., 2004). They also include infections of which the incidence in humans threatens to increase in the near future (Lederberg et al., 1992). These two characteristics set them aside from newly discovered pathogens, which may have been circulating for a long time, but may have gone unnoticed. In this chapter we will focus on newly discovered, emerging, and reemerging respiratory viruses causing acute respiratory tract infections (ARTIs). In the population at large, each person experiences on average two to three ARTIs every year. Furthermore, it is the most frequent reason for emergency department visits and hospital admissions of infants (Brodzinski and Ruddy, 2009). The disease burden is estimated at more than 94 million disability-adjusted life years lost globally (WHO, 2011). Since ARTIs may aggravate and lead to pneumonia, their clinical impact is considerable, as pneumonia is one of the leading causes of death among children under the age of five. The World Health Organization (WHO) estimates that 1.4 million children die annually from pneumonia (WHO, 2012c).

19.1.2 Newly discovered human respiratory viruses that recently crossed the species barrier

In the past two decades, several viruses have been described as the cause of human respiratory tract infections for the first time. Among the clinically most significant ones are avian, swine, and pandemic influenza viruses; Hendra and Nipah virus; human metapneumovirus (HMPV); three human coronaviruses (HCoV), including the virus that caused SARS; and human bocavirus (HBoV) (Allander et al., 2005; Fouchier et al., 2005; Fraaij and Osterhaus, 2010; van den Hoogen et al., 2001; Ksiazek et al., 2011).

All these viruses have crossed animal–human species barriers, from either wild or domestic animals, in the recent or more distant past. Some of these have just manifested themselves as zoonotic viruses, while others have subsequently adapted to become real human viruses, spreading efficiently from human to human (Lederberg et al., 1992; Morens et al., 2004). The WHO definition of a zoonosis is any disease or infection that is naturally transmissible from vertebrate animals to humans. Although not called zoonosis, all living organisms can be affected by such an event of interspecies transmission (Osterhaus, 2001; WHO, 2013). A complex interplay of predisposing factors governs the occurrence of emerging infectious diseases. These include behavioral changes such as air travel, close contact with animals, and progressive deforestation—exposing humans to pathogens never encountered on a large scale before. In addition environmental changes will affect ecological factors contributing to the spread of viruses in new susceptible populations (Harvell et al., 1999; Kuiken et al., 2003a,b; Osterhaus, 2001).

A changing local climate as the result of global warming may destroy but also create new habitats for animals. For instance, rodents seeking new ground after flooding are more likely to come in close contact with humans. This encounter may give rise to rodent-borne infections, like in 1993, the rodent-borne Sin Nombre virus (SNV) that was detected in the United States of America (Duchin et al., 1994). It causes hantavirus pulmonary syndrome, which until today continues to be a health problem in the USA (Carver et al., 2010; Klempa, 2009; Macneil et al., 2011). Virus spread appeared to follow El Niño events, creating a good environment for the reproduction of the deer mouse, which harbors SNV, and increased human–mouse interaction (Carver et al., 2010; Klempa, 2009). An additional example of this phenomenon is the change in habitats of mosquitoes that may function as vectors for several viral pathogens. This was illustrated in Italy in 2007 where the combination of lack of adequate garbage disposal and warm temperatures led to an

TABLE 19.1 Virus characteristics

Virus	Influenza viruses	HMPV	HCoV	HBoV	KI and WU polyomaviruses	NiV and HeV
Order	Unassigned	Mononegavirales	Nidovirales	Unassigned	Unassigned	Mononegavirales
Family	Orthomyxoviridae	Paramyxoviridae	Coronaviridae	Parvoviridae	Polyomaviridae	Paramyxoviridae
Subfamily		Pneumovirinae	Coronavirinae	Parvovirinae		Pneumovirinae
Genus	*Influenzavirus A, Influenzavirus B, Influenzavirus C, Thogotovirus Isavirus*	*Metapneumovirus*	*Alpha- Beta- Delta- Gammacoronavirus*	*Bocavirus*	*Polyomavirus*	*Henipavirus*
Species	Influenza A virus Influenza B virus Influenza C virus Dhori virus Thogoto virus	HMPV	Group 1 (HCoV- 229E, HCoV-NL63) Group 2 (SARS-CoV, HCoV-OC43) Group 3	Human bocavirus Bovine parvovirus Canine minute virus	Human polyomavirus	Hendra virus Nipah virus
Subtypes	Influenza A virus: H1N1, H3N2, H5N1, H7N3, H7N7, H9N2	A1, A2, B1, B2	—	HBoV type 1–4	KIPyV, WUPyV	—
Genome	− ssRNA eight segments	− ssRNA non-segmented	+ ssRNA non-segmented	− ssDNA	circular dsDNA	− ssRNA non-segmented
Baltimore group[a]	V	V	IV	II	I	V

Source: *Field's Virology* Fifth edition 2007, www.ictvonline.org, viralzone.expasy.org.

−, negative sense; +, positive sense; ss, single stranded; ds, double stranded; RNA, ribonucleic acid; DNA, deoxyribonucleic acid.

Note: We depicted the viruses according to their taxonomy. On the left side we sorted order, family, subfamily, genus, species, and subtypes.

[a]The Baltimore group is a classification system according to viral genome replication.

unprecedented spread of the newly introduced mosquito *Aedes albopictus* harboring *Chikungunya* virus (Carrieri et al., 2011).

In the following sections, we will further highlight emerging and reemerging human respiratory viruses in relation to climate change that (may) have a great impact on public health. Their characteristics have been summarized in Table 19.1.

19.2 INFLUENZA VIRUSES

Influenza viruses belong to the *Orthomyxoviridae* family, which encompasses five genera: *Influenzavirus A*, *Influenzavirus B*, *Influenzavirus C*, *Thogotovirus* (a tick-borne virus of mammals), and *Isavirus* (infectious salmon anemia virus). Influenza A viruses are further divided into subtypes, characterized by their surface glycoproteins, hemagglutinin ((HA), $n=17$ (Tong et al., 2012)), and neuraminidase ((NA), $n=9$) (see Figure 19.1). Influenza A viruses are able to infect a wide array of birds and mammals, including humans. Influenza B virus infections are generally considered to be restricted to the human host, although recently, infections in seals were also demonstrated (Osterhaus et al., 2000). Influenza C viruses seem to have a somewhat broader host range, with the virus being isolated from humans, pigs, and dogs (Wright et al., 2007). *Thogotovirus* and *Isavirus* are of limited or no consequences for the human population (Fraaij and Osterhaus, 2010).

In moderate climate zones, influenza A and B virus infections are the cause of the annually recurring seasonal influenza outbreaks. Such seasonality has not been reported for influenza C viruses, which generally cause mild upper respiratory tract infections in young children (Moriuchi et al., 1991). In addition, influenza A viruses can also cause worldwide outbreaks, or pandemics of influenza as recently happened with the 2009 "swine flu" or "Mexican flu." Pandemics can occur after the introduction of novel influenza A viruses, antigenically distinct from their seasonal counter parts, into the global population. Obviously the population at large will largely lack immune-mediated protection, which allows widespread infection. An antigenically new influenza A subtype virus can emerge in the human population through an event called "antigenic shift." This can be the result of

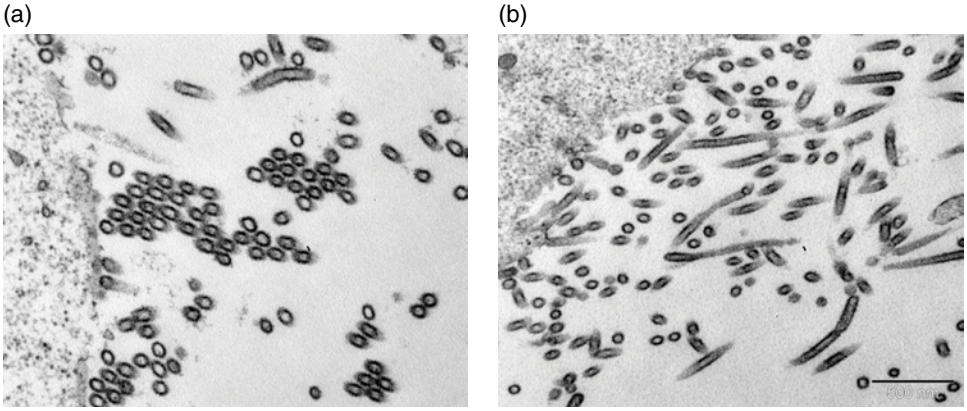

Figure 19.1. **H5N1**. Electron microscopy of viruses budding from human 293T cells. (**a**) Shows viral aggregates released in clusters of spherical particles of virus 1, while (**b**) shows single virus 2 particles being released from the infected cell as both spherical and filamentous virions (Sorrell et al., 2011). Picture courtesy: Ton de Jong.

either of two mechanisms that can also happen simultaneously. The first is the reshuffling or reassortment among the eight RNA genome segments of different influenza A viruses that may simultaneously infect a cell of an avian or mammalian host. This may result in the introduction of a reassortant virus with completely new surface glycoproteins. The second mechanism by which a new influenza A virus subtype can be introduced into the human population is by gradual adaptation of an avian influenza virus upon zoonotic transmission, through sequential mutation (Fraaij and Osterhaus, 2010). The most dramatic influenza pandemic known today started in 1918 and was called "the Spanish flu," causing over 50 million deaths in a relatively short period of time (Johnson and Mueller, 2002). The 1918 virus originated in birds (Taubenberger et al., 2005). Whether it had directly crossed the species barrier to humans, or an intermediate host like the pig was involved before it started to circulate among humans, remains unclear (Gibbs and Gibbs, 2006). Still as such the "Spanish flu" is an ominous well-documented example in recent history on how a zoonosis can eventually develop into a major human health catastrophe.

19.2.1 Transmission of avian influenza to humans

Until 1997, infections of humans with avian influenza viruses were sporadic reported and thought to be of minimal public health risk. However, this all changed in 1997 when highly pathogenic avian influenza (HPAI) A (H5N1) virus was first encountered in Hong Kong (Claas et al., 1998a, b; de Jong et al., 1997; Osterhaus et al., 2002). It was first described upon fatal disease in a 3-year-old boy, and subsequently 17 other patients were identified, of these 5 also died. This high mortality rate was at that time atypical, but, as we know now, not uncharacteristic for human infections with HPAI A (H5N1) (Fraaij and Osterhaus, 2010). The human infections coincided with an epizootic caused by the same virus infection in domestic poultry in the same geographical area (Claas et al., 1998a; de Jong et al., 1997). The Hong Kong authorities responded by having 1.6 million birds culled at the live bird marketplaces in order to eradicate the epizootic from the birds and prevent further zoonotic infections. Although this did stop the initial outbreak, it did not prevent the virus from returning, albeit in different genetic constellations. From 1997 on multiple infections with HPAI A (H5N1) in animals and humans, derived from wild birds, have been reported in an increasing number of countries. Up to now more than 600 human hospitalized cases have been registered, of which more than 350 were fatal in 15 countries (WHO, 2012a). One should however be cautious to interpret these mortality figures. A recent meta-analysis on sero-evidence for H5N1 infections concluded that the virus could also cause mild or subclinical infections in humans that are not currently accounted for. Thus the true fatality rate may be lower than 50%, although it remains high in hospitalized cases (Wang et al., 2012).

HPAI A (H5N1) virus is most commonly transmitted to humans through contact with infected birds (Aditama et al., 2012). Human-to-human infections happen only very rarely and apparently inefficiently and in a non-sustained way. The increasing number of avian-to-human infections does give rise to the fear that this virus may mutate or reassort with mammalian influenza viruses. This fear is augmented by data from animal experiments showing that only a limited number of mutation are required for airborne transmission to occur (Chu et al., 2012; Fouchier, 2012; Fouchier et al., 2012; Herfst et al., 2012a, b).

Apart from influenza A (H5N1) virus, four other avian subtypes have also been shown to be pathogenic to humans: H5N1, H7N3, H7N7, and H9N2 (Fraaij and Osterhaus, 2010). In this respect, of note is an outbreak of HPAI A virus (H7N7) in domestic poultry in the Netherlands. Eventually the same virus was also detected in 86 humans who were involved in the mass culling of about 30 million chickens. Three additional cases were found in

family members of infected poultry workers indicating human-to-human transmission. Most patients developed self-limiting conjunctivitis; however, several patients developed more severe respiratory disease, including one veterinarian who died because of acute respiratory distress syndrome (ARDS) (Fouchier et al., 2004; Koopmans et al., 2004).

19.2.2 Clinical manifestations

Influenza virus infection causes influenza or the "flu." According to the WHO, seasonal influenza symptoms are characterized by a combination of the following clinical manifestations: sudden onset of high fever, (dry) cough, sore throat, nasal congestion, muscle and joint pain, fatigue, severe malaise, and headaches (WHO, 2009d). Most of the clinical cases are mild and self-limiting. However, complications leading to more severe disease do occur. Especially feared, mostly associated with H5N1 and pandemic (p)H1N1, but also to a lesser extent with seasonal influenza, is influenza-related ARDS. This distinct clinical manifestation is classically associated with multiorgan failure and disseminated intravascular coagulation (Fraaij and Osterhaus, 2010). Another potential fatal complication is secondary bacterial pneumonia. Influenza virus infection can also cause disease outside the respiratory tract including rhabdomyolysis, pericarditis, and meningoencephalitis (Fraaij and Heikkinen, 2011).

19.2.3 Diagnosis

Diagnosis on the basis of clinical signs and symptoms can be made by an experienced physician—when influenza is in the community—with about 60–80% sensitivity and specificity, depending on experience and adherence to the predefined criteria (Monto et al., 2000).Therefore, clinical diagnosis should be followed by laboratory confirmation, if indeed a definitive diagnosis is required. Current laboratory diagnosis of influenza virus infections may be based on any of the following methods: reverse transcriptase polymerase chain reaction (RT-PCR) (conventional PCR, real-time RT-PCR, and multiplex PCR), direct and indirect specimen immunofluorescence, rapid diagnostic tests (including antigen-detecting (EIA) and neuraminidase detection assay), viral culture, and serological testing (HA inhibition, enzyme-linked immunosorbent assay (ELISA), complement fixation, and neutralization), each with their own characteristic advantages and disadvantages (Fraaij and Osterhaus, 2012).

19.2.4 Treatment, prognosis, and prevention

Specific antiviral medication for the treatment of influenza is available. Medication includes neuraminidase inhibitors (oseltamivir, zanamivir, and in certain countries also peramivir) and for some influenza A viruses M2-channel blockers (amantadine and rimantadine). Due to rapid development of antiviral resistance, M2-channel blockers have currently become virtually obsolete in regular clinical practice.

The most effective and cost-effective way to combat influenza is vaccination if indeed a vaccine is available. Seasonal influenza vaccines are therefore updated twice a year to accommodate for the never-ending antigenic drift. The efficiency of seasonal vaccination to prevent seasonal influenza has been estimated to be between almost nonexisting to over 80%, depending on age and risk groups of the population vaccinated but also on the match of the vaccine strains with the actually circulating seasonal influenza viruses (Fiore et al., 2009; Fraaij et al., 2011; Michiels et al., 2011; Osterholm

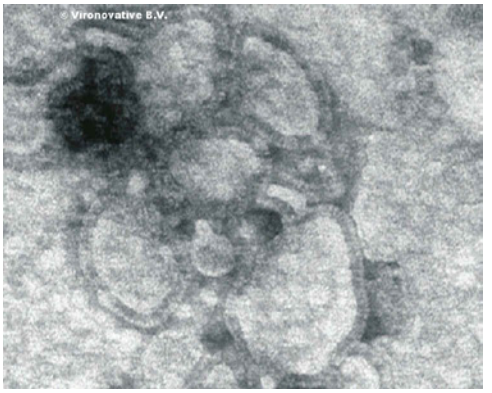

Figure 19.2. **HMPV**. Electron Micrograph of HMPV showing a typical Paramyxovirus morphology (www.vironovative.com).

et al., 2012). For the prevention of human infections with avian H5N1, so-called pre-pandemic candidate vaccines have been developed, which have not been used in the field yet (WHO, 2012d). For pandemics with a previously unknown influenza virus, enormous collaborative endeavors are required from scientists, clinicians, health authorities, and the pharmaceutical industry to manufacture a "new" vaccine in sufficient quantities within a record period of time. The difficulties of this process are probably best illustrated by the course of events during the 2009 H1N1 pandemic. Early in the pandemic, huge efforts were made to develop a pandemic vaccine, initially to vaccinate the highest-risk subjects. Pharmaceutical industry had to produce millions of vaccine doses in a relatively short period of time, which proved to take more than 6 months from the onset of the first efforts to develop the vaccine. Therefore, at the southern hemisphere, the first vaccine produced could only be used after the first wave of the pandemic outbreak was over and at the northern hemisphere well into the autumn wave of the pandemic (Butler, 2010).

19.3 HUMAN METAPNEUMOVIRUS

In 2001 HMPV was first described as the cause of respiratory tract infections of unknown etiology in children (van den Hoogen et al., 2001). They discovered HMPV, a negative single-stranded RNA virus genetically similar to avian metapneumovirus (AMPV) subgroup C, which is a causative agent of respiratory tract illnesses in poultry. Despite its close relationship to AMPV, HMPV does not readily infect birds. Currently, humans are the only known natural hosts. Still several animal models have been identified including hamsters, guinea pigs, ferrets, and nonhuman primates. HMPV has been categorized as a member of the *Metapneumovirus* genus in the subfamily of Pneumovirinae and family Paramyxoviridae (Schildgen et al., 2011). Van den Hoogen identified two lineages of the virus based on sequence homology (HMPV A and B). Both can be further divided into subtypes called A1, A2, B1, and B2 (Schildgen et al., 2011). Co-circulation of these subtypes during outbreaks is common, although predominance of the subtypes may change (Agapov et al., 2006) (see Figure 19.2). People have been shown to be infected several times during their lifetime with this virus (Schildgen et al., 2011).

19.3.1 Epidemiology

After its discovery HMPV has been shown to be a ubiquitous virus. On the northern hemisphere in the period between December and April, "winter" epidemics occur. Serological studies show that most individuals experience their first infection before the age of 1 year (Schildgen et al., 2011). Hereafter reinfections occur repeatedly and frequently (Schildgen et al., 2011). Children (especially <2 years) are at risk for complicated HMPV infection. It causes approximately 5–10% of the lower respiratory tract infections (LRTIs) in infants and is the second leading cause of bronchiolitis after RSV. In addition, patients with underlying medical conditions like neoplasmata and chronic lung disease, immunocompromised patients, and the elderly are at risk for severe disease. In the latter, especially in institutionalized elderly, HMPV infections have been shown to be associated with significant mortality (Schildgen et al., 2011; Te Wierik et al., 2012).

19.3.2 Clinical manifestations

HMPV is a respiratory pathogen causing a wide spectrum of disease ranging from mild ARTI to profound LRTIs including pneumonia. The clinical spectrum of disease is very similar to that of RSV (Brodzinski and Ruddy, 2009). Common symptoms are rhinorrhea, cough, and fever. Other respiratory symptoms can (infrequently) occur and include conjunctivitis, vomiting, diarrhea, and rash. The lower respiratory illnesses caused by HMPV mostly include bronchiolitis, pneumonia, and asthma exacerbation (Schildgen et al., 2011).

19.3.3 Diagnosis

RT-PCR-based techniques are generally the methods of choice for the detection of HMPV, but other assays, such as isothermal real-time nucleic acid sequence-based amplification (NASBA), have also been used. Virus isolation by culture proved relatively difficult for HMPV although shell vial cultures could offer an option (Crowe, 2011; Landry et al., 2005). ELISAs have been developed for antibody detection in plasma and serum.

19.3.4 Treatment, prognosis, and prevention

Overall, HMPV is mostly a self-limiting disease of the respiratory tract, although severe infections do occur (Jartti et al., 2012b). Currently there are no antivirals available for the treatment of HMPV infection. In case of severe disease, treatment consists of supportive care. Bronchodilators and corticosteroids have been used empirically, but there are no controlled trials to support or refute their efficacy. The only currently licensed antiviral drug for a related virus, RSV, is ribavirin, but no well-controlled clinical trials have been performed on the treatment of HMPV infection, and its efficacy has been debated (Schildgen et al., 2011). There is no vaccine available yet (Feuillet et al., 2012).

19.4 HUMAN CORONAVIRUSES: SARS AND NON-SARS

HCoV are viruses with a large positive RNA genome that belong to the genus *Coronavirus*. Together with the viruses grouped in the genus *Torovirus*, they constitute the family of *Coronaviridae*, which in turn are part of the order of *Nidovirales* (Abdul-Rasool and Fielding, 2010). Five HCoV have been identified to date. The first two were discovered in the 1960s, HCoV-OC43 and HCoV-229E. Both were found to cause common cold

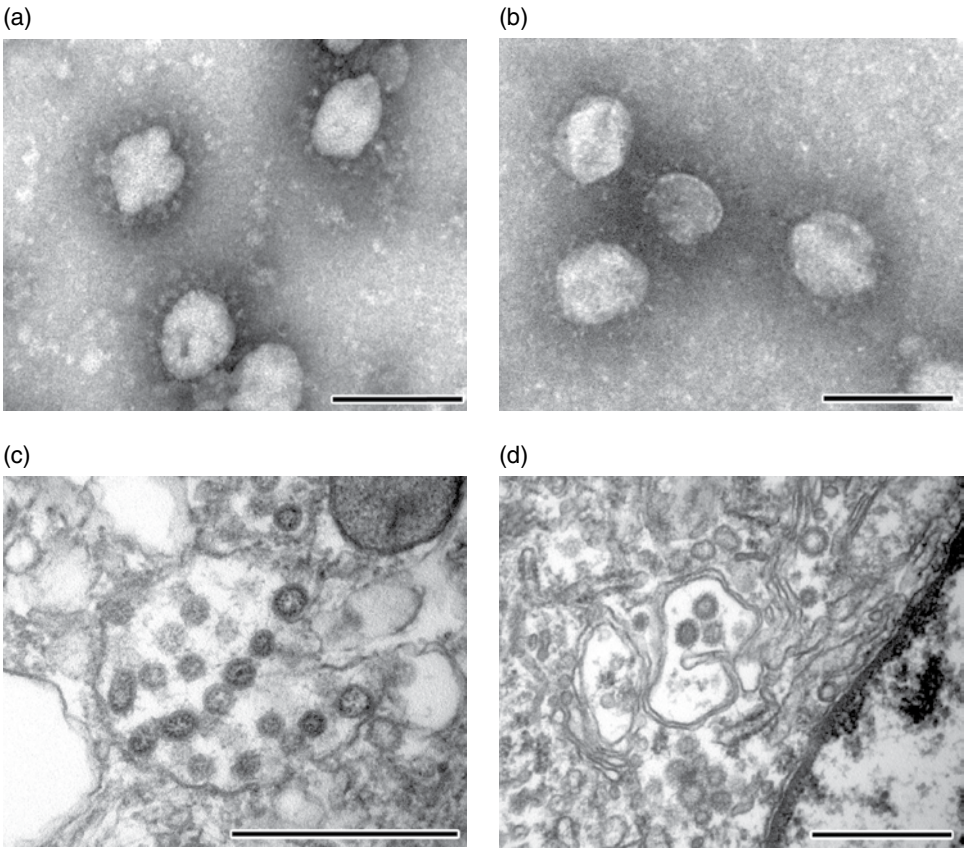

Figure 19.3. **SARS-CoV**. Electron microscopy of SARS-CoV in inoculum, clinical samples, and tissue samples of experimentally infected cynomolgus macaques. (**a**) Negative-contrast electron microscopy of virus stock used to inoculate cynomolgus macaques shows the typical club-shaped surface projections of coronavirus particles; negatively stained with phosphotungstic acid, bar = 100 nm. (**b**) Morphologically identical particles isolated from nasal swabs of infected macaques; negatively stained with phosphotungstic acid, bar = 100 nm. (**c**) Transmission electron microscopy of infected Vero 118 cell shows viral nucleocapsids with variably electron-dense and electron-lucent cores in smooth-walled vesicles in the cytoplasm; stained with uranyl acetate and lead citrate, bar = 500 nm. (**d**) Morphologically similar particles occur in pulmonary lesions of infected macaques, within vesicles of the Golgi apparatus of pneumocytes; stained with uranyl acetate and lead citrate; bar = 500 nm (Kuiken et al., 2003a,b).

(Bradburne et al., 1967). Recently, three new coronaviruses were described. The first was discovered in 2003 and caused the SARS outbreak (Drosten et al., 2003; Rota et al., 2003) (Figure 19.3). Soon thereafter the two other coronaviruses were discovered: human coronavirus NL63 (HCoV-NL63) in 2004 and human coronavirus HKU1 (HCoV-HKU1) in 2005 (Fouchier et al., 2004; van der Hoek et al., 2004; Woo et al., 2005).

19.4.1 The SARS-CoV outbreak

The 2002–2003 SARS outbreak was again an impressive example of how a zoonosis can eventually develop into a pandemic threat to the human population. During this outbreak,

approximately 8000 cases were reported from 29 countries, with an overall staggering mortality of approximately 10% (Pang et al., 2003; Svoboda et al., 2004; WHO, 2003). Due to a quick and well-coordinated international response, the epidemic could be stopped in its wake (Peiris et al., 2004). However, the impact of the outbreak was massive because of reduced air travel and the impact on our globalized economy (Stockman et al., 2006). Since 2004 no new human cases of SARS-CoV have been reported. The masked palm civet (*Paguma larvata*) was initially believed to be the reservoir for SARS-CoV, and elimination was necessary from markets where they were sold for human consumption. However, later the presence of the virus was also demonstrated in other civet species and raccoon dogs, but there reservoir is now thought to be fruit bats. Therefore, ongoing vigilance for reappearance needs to be upheld (Graham and Baric, 2010; Kuiken et al., 2005).

19.4.2 Clinical manifestations of SARS-CoV

The WHO and the Center of Disease Control (CDC) made the following clinical case definition during the outbreak of SARS-CoV: patients with a history of (documented) fever and one or more symptoms of lower respiratory tract illness (cough, difficulty breathing, shortness of breath) and radiographic evidence or autopsy findings of lung infiltrates consistent of pneumonia or ARDS and no alternative diagnosis fully explaining the illness. Most patients with SARS have no upper respiratory symptoms during the first 3–7 days (the prodrome phase), the respiratory phase starts with a nonproductive cough, and dyspnea and respiratory failure occur as the disease progresses. The case description is still applicable if there is suspicion of a new SARS-CoV case; obviously it must always be combined with laboratory confirmation (WHO, 2009a).

19.4.3 Diagnosis of SARS-CoV

The diagnosis is based on the clinical picture and the following laboratory tests: RT-PCR assay for detecting viral RNA and eventually virus isolation from a clinical specimen. To confirm an infection, an additional sample should be tested. ELISA and/or immunofluorescence assay (IFA) can be performed for serum antibody detection (Kenneth McIntosh, 2012).

19.4.4 Epidemiology of non-SARS coronaviruses

HCoV OC43 and 229E circulate throughout the year and have a worldwide distribution. In temperate climates, there is an incidence peak in winter, while in other geographical areas such seasonality is not observed (Bastien et al., 2005; Brodzinski and Ruddy, 2009). The prevalence of the two newly discovered HCoV NL63 and HKU1 varies greatly. In both out- and inpatient populations, NL63 virus may be found in as many as 1 to almost 10% in patients with ARTIs. The virus is mostly detected in children, elderly, and immunocompromised patients (Pyrc et al., 2007).

19.4.5 Clinical manifestations of non-SARS coronaviruses

HCoV NL63, HKU1, 229E, and OC43 mostly cause common cold and are usually associated with a relatively mild clinical picture. Still hospitalization as a result of infection with one of the two viruses may occur. In this respect, HCoV-NL63 is often associated with pseudocroup in young children (Abdul-Rasool and Fielding, 2010). Moreover, it has also

been found to cause wheezing and bronchiolitis and is associated with pneumonia. A relation with Kawasaki disease in children has been suggested, but could not be confirmed in two other study groups (Esper et al., 2005). HKU1 was first described among elderly patients with major underlying disease, in particular of the respiratory and cardiovascular systems.

19.4.6 Diagnosis of non-SARS coronaviruses

RT-PCR techniques are used to detect these coronaviruses (Gaunt et al., 2010). Complement-fixing and ELISA antibody assays for coronaviruses 229E and OC43 are available (Gerna et al., 2006). Recently also a novel double-antibody sandwich ELISA based on specific monoclonal antibodies allows detection and differentiation of HCoV-NL63 and HCoV-229E infections (Greenberg, 2011).

19.4.7 Treatment, prognosis, and prevention

Many treatment options for SARS-CoV have been suggested; ribavirin, corticosteroids, lopinavir and ritonavir, type 1 interferon (IFN), intravenous immunoglobulin, and SARS convalescent plasma have been implemented in battling SARS. However, none of these approaches were found to be uniformly effective (Sastre et al., 2011). Especially of note is the use of pegylated IFN-α in macaque studies (Haagmans et al., 2004). Despite all efforts, the prognosis of SARS-CoV remained to be poor during the epidemic with an overall mortality of 10%, which was however largely restricted to older-age categories (Chan et al., 2004; Liang et al., 2004; Liu et al., 2006).

Treatment options for the other coronaviruses are also limited, but in most cases unnecessary since infections are mostly self-limiting. There is no vaccine available to prevent for coronavirus infection.

19.5 HUMAN BOCAVIRUS

HBoV was discovered in 2005 (Allander et al., 2005). It has a single-stranded DNA genome and was classified in the *Bocavirus* genus (family Parvoviridae, subfamily Parvovirinae). To date, four strains have been identified: HBoV 1–4 (Jartti et al., 2012a). The closest relatives of this new parvovirus are *bo*vine parvovirus and minute virus of *ca*nines, hence its name: human bocavirus. It is a parvovirus that is only distantly related to parvovirus B19, the agent of fifth disease and other human disorders (Allander, 2008).

19.5.1 Epidemiology

HBoV has been detected in all continents of the world. It is not clear yet whether there is true seasonal variability for HBoV, but most studies indicate a higher incidence during winter (Chow and Esper, 2009). Seroprevalence of specific antibodies increases with age from >64% at 2–4 years of age to 100% in children 7 years of age (Jartti et al., 2012a).

19.5.2 Clinical manifestations

The clinical impact of this newly discovered virus remains topic for debate, although most papers report a relation between HBoV and ARTI (Allander, 2008). As for most respiratory

viruses, the clinical picture includes fever, cough, and rhinorrhea. In addition, episodes of wheezing, acute obstructive bronchitis, bronchiolitis, and pneumonia have been found to be associated with HBoV infection. Furthermore, HBoV2 has been implicated in some cases of acute gastroenteritis (Jartti et al., 2012a). It has been suggested that most clinical manifestations of HBoV infections are associated with coinfection with other respiratory viruses (Guo et al., 2011).

19.5.3 Diagnosis

RT-PCR is widely used for the detection of HBoV in study setups. Serology for HBoV detection in serum is also used to diagnose acute infection (Chow and Esper, 2009; Jartti et al., 2012a).

19.5.4 Treatment, prognosis, and prevention

Most HBoV-induced disease is non-severe and self-limiting. This renders treatment unnecessary. However, in more severe cases, often in patients with underlying illness, supportive care should be given (Jartti et al., 2012a). The overall prognosis of HBoV infection is good.

19.6 KI AND WU POLYOMAVIRUSES

In the last decade, several new *polyomaviruses* (PyV) have been identified. Two of them were detected in samples taken from children with ARTIs and named KIPyV (Karolinska Institute) and WUPyV (Washington University); another was detected in a rare skin tumor and was named MCPyV (Merkel cell carcinoma) (Babakir-Mina et al., 2011; Jartti et al., 2012b). Whether or not the polyomaviruses KI and WU are indeed true pathogens remains a matter of debate. Still, in some patients with acute respiratory symptoms, they were the only pathogen detected (Han et al., 2007; Mourez et al., 2009).

19.6.1 Epidemiology

Serological studies show that both viruses occur in many geographical areas (Kean et al., 2009). Respiratory tract samples obtained during childhood show that primary exposure occurs early in life (Babakir-Mina et al., 2011). In the adult population, the seroprevalence of KIPyV and WUPyV are 55% and 69%, respectively (Kean et al., 2009).

19.6.2 Clinical manifestations

KIPyV and WUPyV have been detected in children with complaints of the respiratory and gastrointestinal tract. The majority of patients have the following symptoms: rhinitis, cough, bronchiolitis, or pneumonia (Jartti et al., 2012b).

19.6.3 Diagnosis

Most research on the occurrence of KI and WU was performed using PCR-based techniques in different samples including nasopharyngeal aspirates, sera, stool, and solid tissues (Babakir-Mina et al., 2011).

19.6.4 Prognosis

The prognosis is good without intervention.

19.7 NIPAH AND HENDRA VIRUSES

Two new viruses, Nipah virus (NiV) and Hendra virus (HeV), both *paramyxoviruses* derived from animals were discovered in 1994 and 1998. Both belong to the recently defined genus *Henipavirus* (Chua et al., 1999; Young et al., 1996). Fruit bats were found to be the main reservoir for both viruses. HeV was found to cause human infections upon exposure to affected horses in Australia, whereas most human cases caused by NiV took place upon contacts with affected pigs or bats in Southeast Asia (Ksiazek et al., 2011).

19.7.1 Outbreaks

The spread of NiV and HeV is reliant on the presence of the Pteropid fruit bats. Until now 13 outbreaks have been reported for NiV infections, all of which happened in South Asia (WHO, 2009c). Isolated human cases of HeV infection, derived from occupational contacts with diseased horses, have been reported in Australia from the mid-1990s onward and apparently continue to cause severe and fatal cases (Mendez et al., 2012; WHO, 2009b). The recently (2011) reported increase in the incidence of severe HeV infections in horses and isolation of HeV from a dog in Australia are a sharp reminder that the problems with HeV are far from over (Mendez et al., 2012; Young et al., 2011), as an unwanted fear for infection with HeV has caused Australian veterinarians to cease equine practice (Mendez et al., 2012).

19.7.2 Clinical manifestations and prognosis

NiV infection can cause both respiratory and neurological signs and symptoms. Disease onset is characterized by fever, headache, myalgia, and dizziness. Within a few days, drowsiness, confusion, and other neurological signs like hyporeflexia or areflexia, segmental myoclonus, gaze palsy, and limb weakness may develop. NiV is known to cause encephalitis and virus can be detected in the cerebrospinal fluid (Ksiazek et al., 2011). During the outbreak in Malaysia, the fatality rate was 30–40% and during several outbreaks in Bangladesh over 70% (Goh et al., 2000; Hossain et al., 2008). HeV has a high fatality rate of almost 60% (4 out of 7 patients identified have died). Disease symptoms initially are influenza-like with fever, myalgia, headache, lethargy, sore throat, nausea, and vomiting. Within days the central nervous system gets involved with meningitis and (late-onset) encephalitis (Tulsiani et al., 2011).

19.7.3 Diagnosis

PCR is performed on urine, respiratory, and cerebrospinal fluid samples. In addition serology can be performed. Virus isolation should only be performed in biosafety level 4 laboratories (the highest biosafety classification). The "gold standard" for HeV detection is the serum neutralization test, but during an outbreak the other methods are more commonly used. Currently, new methods are being developed like antigen-capture ELISA and Luminex-based tests (Tulsiani et al., 2011).

19.7.4 Treatment and prevention

Supportive care is given to patients infected with NiV and HeV. The use of antivirals such as ribavirin showed inconclusive outcomes. New and promising developments include the use of humanized monoclonal antibodies (Bossart et al., 2009). A number of vaccines have been developed for animal use only. Although their use may be beneficial in livestock, also with regard to animal welfare, surveillance and culling remain to be most cost-effective (Ksiazek et al., 2011; Tulsiani et al., 2011).

19.8 CONCLUSION

As discussed earlier, new, emerging, and re-emerging infectious diseases will continue to pose a challenge for health authorities worldwide. Frequently they are the direct result of ecological changes that may at least in part be climate driven. Research efforts to mitigate their effects on the human population concentrate on four main areas: improved surveillance, improved diagnostic methods, the development of vaccines, and the development of antiviral agents. Detection of a new, emerging, or reemerging virus starts with its first detection in animals or humans; therefore, vigilance of clinicians and veterinarians to recognize newly emerging disease entities is of great importance. We should realize that viruses not only cross species barriers but also geographical borders. Therefore, it is in the best interest of public and animal health programs to invest in international and preferably global surveillance programs. Diagnostic methods combining old and new advanced techniques such as random RT-PCR assays, nucleotide sequencing, and phylogenetic analysis have led to fast detection of new or modified known viruses. As discussed earlier, recent outbreaks have shown that there is an urgent need for (antiviral) treatment, as for most viral infections safe and effective specific treatment usually is lacking. Furthermore, public awareness programs concerning viral threats should be available and easy to access worldwide. In our current society, information can be spread fast via the Internet and social media. This may give us a head start facing new viral threats by early detection of a starting epidemic, early alerts, and easy access to this information by efficient communication. This may then result in extensive collaboration between expert laboratories, as shown previously with the successful identification and elimination of SARS-CoV (Peiris et al., 2004).

19.9 LIST OF ABBREVIATIONS

Viruses:

AMPV	avian metapneumovirus
CDV	canine distemper virus
HBoV	human bocavirus
HeV	Hendra virus
HIV	human immunodeficiency virus
HMPV	human metapneumovirus
HPAI	highly pathogenic avian influenza virus
HCoV	human coronavirus
KIPyV	Karolinska Institute polyomavirus
NiV	Nipah virus
PyV	polyomavirus

RSV	respiratory syncytial virus
SNV	Sin Nombre virus
WUPyV	Washington University polyomavirus
Others:	
AIDS	acquired immunodeficiency syndrome
ARDS	acute respiratory distress syndrome
ARTI	acute respiratory tract infection
CDC	centers for disease control and prevention
DNA	deoxyribonucleic acid
EIA	enzyme immunoassay
ELISA	enzyme-linked immunosorbent assay
HA	hemagglutinin
IFA	immunofluorescence assay
IFN	interferon
LRTI	lower respiratory tract infection
NA	neuraminidase
NASBA	nucleic acid sequence-based amplification
p	pandemic
RNA	ribonucleic acid
RT-PCR	reverse transcriptase polymerase chain reaction
SARS	severe acute respiratory syndrome
URTI	upper respiratory tract infection
WHO	World Health Organization

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