Coronavirus

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Name of Virus: Coronavirus

13.1 Brief Introduction

Coronaviruses infect many birds and mammals, including humans, causing respiratory tract, enteric, hepatic, renal, and central nervous system diseases of varying severity. Since the isolation of the prototype murine virus in 1949 (Cheever and Daniels 1949), viruses in the subfamily *Coronavirinae* have been recognized primarily for causing a wide range of economically significant diseases in farm animals and domesticated pets, while the two known human coronaviruses, *Human coronavirus-OC43* (HCoV-OC43) and *Human coronavirus-229E* (HCoV-229E) first described in the mid-1960s (Hamre and Procknow 1966; Tyrrell and Bynoe 1965), were considered a mundane seasonal cause of the common cold. Coronaviruses were catapulted onto the world stage when the World Health Organization (WHO) announced in April 2003 that a new coronavirus, *Severe acute respiratory syndrome-related coronavirus* (SARS-CoV), never seen in humans before, was the cause of Severe acute respiratory syndrome (SARS) (WHO 2003a). Since the SARS epidemic, coronaviruses have been regarded as emerging pathogens, and as a result, three new species in humans, *Human coronavirus-NL63* (HCoV-NL63), *Human coronavirus-HKU1* (HCoV-HKU1), and *Middle East respiratory syndrome coronavirus (MERS-CoV),* have been described (van der Hoek et al. 2004; Woo et al. 2005; Zaki et al. 2012; de Groot 2013).

13.2 Synonyms

There are no synonyms. The term coronavirus is typically used in conjunction with a species designation, for example, *Miniopterus bat coronavirus-HKU8 or human coronavirus-229E, or severe acute respiratory syndrome-related coronavirus.*

13.3 Classification (King et al. 2011; Zaki et al. 2012; de Groot 2013)

Family: *Coronaviridae*
Subfamily: *Coronavirinae*
Genus: *Alphacoronavirus*
Species: *Human coronavirus-229E*
Species: *Human coronavirus-NL63*

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Genus*: Betacoronavirus*
Species: *Human coronavirus-OC43*
Species: *Human coronavirus-HKU1*
Virus: *Middle East respiratory syndrome coronavirus*
Species: *Severe acute respiratory syndrome-related coronavirus*

13.4 Epidemiology

SARS-CoV is the most aggressive human coronavirus known to date, and its epidemiology is quite different from that of the five non-SARS human coronaviruses. Between November 2002 and July 2003, SARS-CoV emerged, swept around the globe via routes of international air travel, and caused 8,098 SARS cases in 26 countries with 774 deaths. This strained the healthcare system in the countries with infections and led to travel restrictions and significant effects on the global economy (WHO 2004a). On July 5, 2003, the WHO declared the chain of person-to-person transmission of SARS-CoV in the epidemic broken (WHO 2003c). Since July 2003, SARS infection has been documented on several occasions. Three incidents were attributed to breaches in laboratory biosafety. The fourth incident involved four community-acquired cases attributed to animal or environmental exposure in three and an undetermined source of infection in the fourth (Liang et al. 2004).

In contrast, most of the non-SARS human coronaviruses have been in continuous circulation globally since their initial isolation. They emerge in winter and spring and demonstrate periodicity with epidemics occurring at 2 to 3 year intervals. They primarily cause upper respiratory tract infections that are more common in children than in adults, and they account for an estimated 15 % of adult colds and up to 35 % of upper respiratory tract infections during peak viral activity. Less commonly, they are associated with lower respiratory tract disease in infants, immunocompromised patients, and the elderly (Gerna et al. 2006; Principi et al. 2010; van der Hoek 2007). In late 2012, HCoV-EMC was isolated in a 60-year-old male who presented with acute pneumonia, subsequently developed renal failure, and had a fatal outcome (Zaki et al. 2012). From discovery to mid-September 2013, HCoV-EMC, renamed MERS-CoV, (de Groot 2013) caused 132 laboratory-confirmed cases of severe acute pneumonia including 58 deaths. (WHO 2013).

SARS-CoV is an animal virus that crossed the species barrier when environmental change increased chances for the virus to enter humans and enable human-to-human transmission (Antia et al. 2003). Supporting this, research has identified a SARS-CoV-like virus in Himalayan masked palm civets, raccoon dogs, and Chinese ferret badgers sold in live-animal markets for human consumption in southern China, as well as, in humans working in the same markets indicating a route of interspecies transmission. Horseshoe bats have been identified as a natural reservoir of SARS-CoV-like viruses (Guan et al. 2003; Li et al. 2005; Song et al. 2005).

SARS-CoV is highly contagious, and spread occurs primarily by close person-to-person contact via droplet transmission or fomite. Virus is shed in respiratory secretions, feces, and urine. At room temperature it retains its infectivity for 4 days in diarrheal stool samples, for up to 6 days when dried, and for more than 7 days in respiratory specimens. The virus is readily inactivated by commonly used disinfectants (Lai et al. 2005; Rabenau et al. 2005).

13.5 Ultrastructure

Coronaviruses are the largest of all RNA viruses and have a positive-sense, single-stranded RNA genome of 30–32 kilobases. Virions are enveloped and spherical with widely spaced club-shaped surface projections that give the virus its unique coronal fringe by negative-staining electron microscopy (Fig. 13.1). Cryo-electron microscopy reveals an outer envelope diameter of 85 ± 5 nm with 20 nm club-shaped surface projections, an exceptionally thick, 7.8 ± 0.7 nm envelope and a loosely wound, helical nucleocapsid separated from the envelope by a 4 nm gap. Certain structural proteins are common to all coronaviruses: the spike glycoprotein S, an envelope glycoprotein that mediates receptor-binding

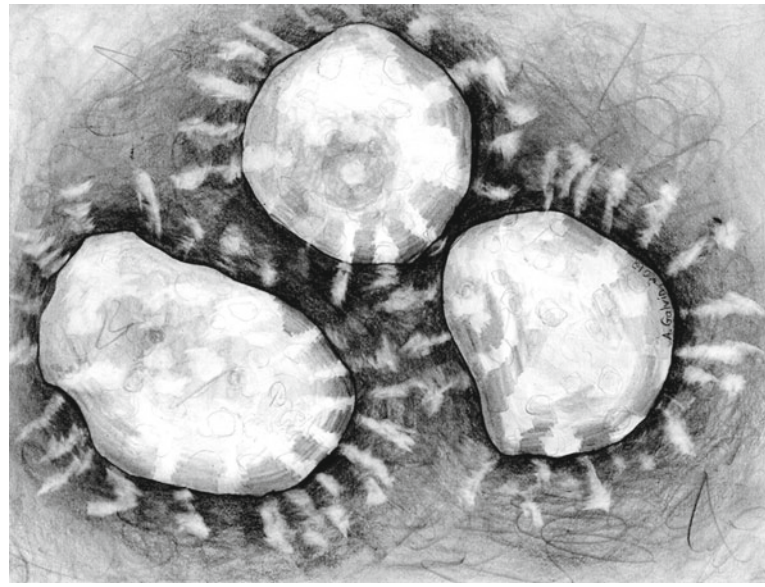

Fig. 13.1 Artist illustration of the club-shaped surface projections (peplomers) that give coronaviruses their unique coronal fringe by negative-staining electron microscopy (Illustration by Adrian Galvin, New York, NY)

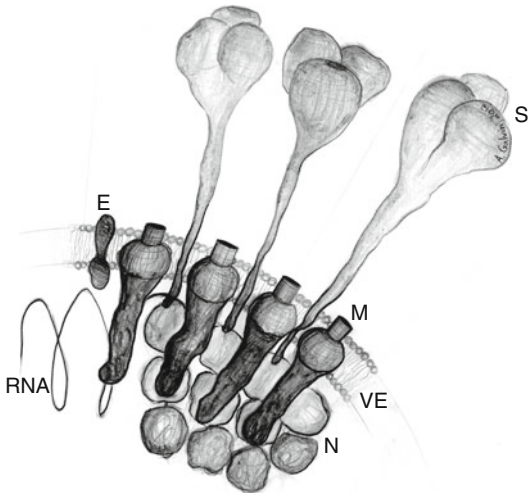

Fig. 13.2 Artist illustration of the major structural proteins and components common to all coronaviruses: *S* spike glycoprotein, *M* primary membrane glycoprotein, *E* envelope protein, *N* nucleocapsid protein enclosing the RNA helix, *RNA* RNA helix, *VE* viral envelope composed of host cell cytoplasm (Illustration by Adrian Galvin, New York, NY)

and membrane fusion; the envelope spanning glycoprotein M, which contributes to the thickness of the envelop; the envelope protein E, which has been identified as a virulence factor SARS-CoV; and the nucleocapsid protein N, with its function in genome encapsidation, RNA synthesis and translation, and as a type I interferon antagonist (Fig. 13.2). Additional accessory proteins vary by species; for SARS-CoV, structural proteins 3a, 6, and 7 and nonstructural proteins nsp2–5 and nsp9 have been described (Goldsmith et al. 2004; King et al. 2011; Neuman et al. 2006).

13.6 Immunology

SARS-CoV is internalized through binding of the spike glycoprotein to the host cell surface receptor angiotensin-converting enzyme 2 (ACE2) (Wang et al. 2004). Binding initiates conformational change in the spike that mediates fusion of the viral and host cell membranes and release of the nucleocapsid into the target cell allowing for disassembly and replication of the genome. Spike-mediated cell-to-cell fusion can occur and promotes syncytium formation and viral spread (Cheng et al. 2007).

Once internalized, the specific mechanism by which the human immune system responds to SARS-CoV is not well understood, and a particular area of controversy is the role of interferon (IFN). Cameron and colleagues measured plasma levels of IFN during the natural history of SARS in 40 patients. They found high IFN-alpha, IFN-gamma, and IFN-stimulated chemokine levels,

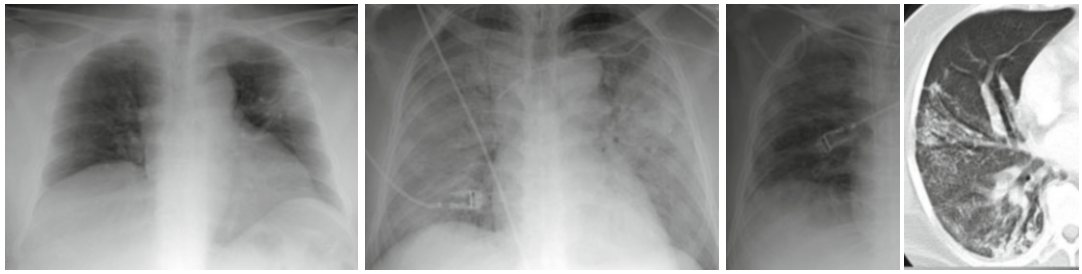

Fig. 13.3 Sequential chest radiographs in SARS patient. Anteroposterior portable chest radiograph (*left*) demonstrates focal consolidation in the left upper lobe. Anteroposterior portable chest radiograph (*center*) acquired 3 days later demonstrates consolidation of all five lobes with the patient intubated. Anteroposterior chest radiograph (*right*) acquired 3 months later demonstrates reticular opacities in the lung periphery. A chest CT acquired at the same time confirms the presence of fibrosis with traction bronchiectasis and reticular opacities

and robust antiviral IFN-stimulated gene (ISG) expression was present early in the course of illness. Patients entered a crisis phase starting at approximately day 8, and most patients resolved IFN responses at crisis and expressed adaptive immune genes as they recovered. In contrast, patients with poor outcomes demonstrated deviated ISG and immunoglobulin gene expression levels, persistent chemokine levels, and deficient anti-SARS spike antibody production, suggesting a malfunction in the switch from innate to adaptive immunity (Cameron et al. 2007).

13.7 Clinical Features

The mean incubation period for SARS is 5 days with a range of 2–10 days. The clinical course of SARS follows a typical pattern that parallels viral load. The first week of illness is an influenza-like prodrome with fever, malaise, myalgia, headache, and rigors that coincide with increasing viral load. A decreasing viral load accompanies the second week of illness that is characterized by dry cough, dyspnea, and hypoxemia. Up to 70 % of patients develop large volume watery diarrhea. Clinical deterioration with rapidly progressive respiratory distress occurs in severe cases with approximately 20 % requiring intensive care. Progression to respiratory failure is the most common cause of death. Transmission occurs primarily in the second week (Hui and Chan 2010).

Chest radiographic and CT changes occur 3–4 days after onset of illness in most patients despite the lack of respiratory signs. Initial unilateral peripheral areas of ground glass and consolidation progress to multiple bilateral areas involving more than 80 % of lung characteristic of diffuse alveolar damage. In patients who survive the acute episode, traction bronchiectasis heralds the development of fibrosis and honeycomb lung (Fig. 13.3) (Chang et al. 2005).

13.8 Pathologic Changes

SARS-CoV affects multiple organs but the major pathology is in the lungs. Diffuse alveolar damage (DAD) is the primary histologic finding, and the phase of DAD varies based on duration of illness. Cases of short duration, 10 days or less, demonstrate acute-phase DAD characterized by hyaline membranes lining alveolar walls, interstitial and airspace edema, mild chronic interstitial inflammation, and vascular congestion (Fig. 13.4). Bronchiolar injury is evidenced by luminal collections of fibrin associated with loss of cilia, denudation of bronchiolar epithelium, and deposition of fibrin on exposed basement membranes. Cases of more than 10 days duration exhibit organizing-phase DAD characterized by interstitial and airspace fibroblast proliferation accompanied by repair including type II pneumocyte hyperplasia and airway-centered squamous metaplasia. Hyperplastic type II cells show marked cytologic change, including cytomegaly, nucleomegaly, clearing of nuclear chromatin, and prominent nucleoli. Alveolar spaces contain a combination

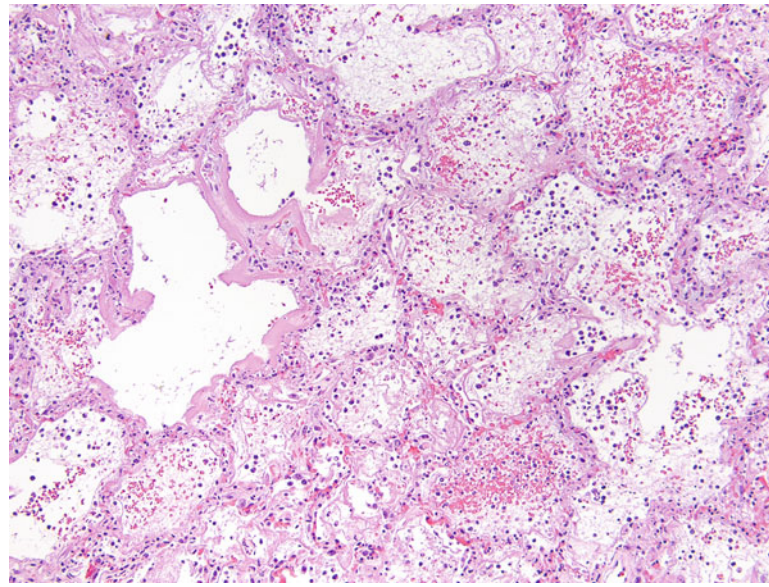

Fig. 13.4 Acute-phase DAD in SARS patient. Acute-phase DAD is characterized by eosinophilic hyaline membranes plastered against alveolar walls, interstitial and airspace edema, and mild chronic interstitial inflammation (100×, hematoxylin-eosin stain)

of macrophages and desquamated pneumocytes including multinucleated forms of both. Acute bronchopneumonia is a common feature in organizing-phase DAD, and fibrin thrombi may also be present. Intranuclear and intracytoplasmic inclusions have been variably reported, but SARS lacks a unique tissue response and cytopathic effect, making diagnosis by light microscopy alone difficult. After several weeks there can be progression of the organizing phase to the fibrotic phase, with extensive restructuring of the lung parenchyma and development of honeycomb lung (Franks et al. 2003).

13.9 Diagnosis

There are no clinical or laboratory findings that reliably diagnose SARS-CoV infection early or rapidly enough to inform management decisions that must be made soon after a patient enters the healthcare system in order to contain potential infection. The Centers for Disease Control and Prevention (CDC) recommends that the diagnosis of SARS-CoV infection and initiation of isolation and stringent infection control measures should be based on risk of exposure. In the absence of person-to-person transmission of SARS-CoV anywhere in the world, the diagnosis of SARS-CoV infection should be considered only in patients who require hospitalization for radiologically confirmed pneumonia and who have an epidemiologic history that raises suspicion of SARS-CoV infection. Suspicion is heightened when the patient, within 10 days of onset of illness, has a history of recent travel to mainland China, Hong Kong, or Taiwan, or close contact with ill persons with a history of travel to these areas, or is employed in an occupation at risk for SARS-CoV, or is part of a cluster of cases of atypical pneumonia without an alternative diagnosis. Laboratory testing for SARS-CoV is available, including antibody detection by enzyme immunoassay (EIA) and reverse transcription polymerase chain reaction (RT-PCR). However, the positive predictive value of a diagnostic test is very low in the absence of person-to-person transmission worldwide, and the CDC recommends testing be performed judiciously and in consultation with local or state health departments (CDC 2005).

13.10 Differential Diagnosis

Initial signs and symptoms of SARS are nonspecific and common, which generates a wide differential diagnosis of respiratory pathogens including influenza virus, parainfluenza

viruses, respiratory syncytial virus, *Haemophilus influenza, Mycoplasma pneumonia, Chlamydia* species, *Legionella* species, *Coxiella burnetii,* and other human coronaviruses (WHO 2004b).

13.11 Prevention

At the time of this writing in October 2013, the world is in an interepidemic period for SARS. The greatest risk of recurrence is from emergence or introduction of SARS-CoV from laboratories and emergence of SARS-CoV-like viruses from wildlife or other animal reservoirs. If SARS recurs, early detection of infected individuals is essential to contain local spread of infection and prevent international dissemination. Primary responsibility for risk assessment and management of SARS is with national health authorities, for example, the CDC in the United States. However, in its role coordinating global and regional surveillance, the WHO has revised its guidelines for global surveillance and reporting of SARS and has provided a framework of activities at national and international levels for risk assessment of SARS (WHO 2004b, c).

13.12 Treatment and Outcome

Many drugs were empirically tried during the epidemic, but no treatment has been shown to consistently improve the outcome of SARS patients, and supportive medical care remains the primary therapy. The case fatality ratio for SARS ranges from 0 % to more than 50 % depending on age group, with an overall estimate of 11 %. Case fatality is estimated to be less than 1 % for people aged 24 years and younger, 6 % for 25–44 years, 15 % for 45–64 years, and over 50 % for people aged 65 years and older (WHO 2003b).

13.13 Vaccine

Efforts to develop a SARS vaccine have been ongoing since the epidemic of 2002–2003, and significant advances have been made in our understanding of SARS-CoV. Notably, the domains of the S glycoprotein that allow for viral infection have been identified, ACE2 has been determined to be a surface receptor for binding the S glycoprotein, and the regions of interaction between the S glycoprotein and ACE2 have been mapped. All of these present targets for vaccine development. However, much of the immunology and pathogenesis of SARS is incompletely understood. Of particular concern is the potential for a SARS vaccine to trigger immunopathogenic mechanisms which could lead to more severe disease in vaccines, as has been observed with some veterinary coronavirus vaccines. Additionally, coronaviruses are notorious for their frequent mutations which further complicate development of a suitable vaccine. Currently there are no licensed vaccines for use in SARS (NIAID 2012).

13.14 Clinicopathologic Capsule

Of the six human coronaviruses recognized to date, SARS-CoV is the most aggressive. Four of the non-SARS coronaviruses mainly cause upper respiratory tract infections that are more common in children than in adults. The fifth non-SARS coronavirus, MERS-CoV, reportedly causes severe acute pneumonia similar to SARS-CoV. SARS-CoV has been identified as the etiologic agent for SARS, which caused 8,098 infections in 26 countries with 774 deaths during the 2002–2003 epidemic. Initial signs and symptoms of SARS are nonspecific and common, thereby generating a wide differential diagnosis of more commonly occurring lower respiratory tract pathogens. SARS primarily targets the lungs and produces a viral pneumonia with a high mortality rate. DAD is the histopathologic hallmark of SARS and the phase of DAD varies with the duration of illness: acute-phase DAD is seen in illnesses of 10 days or less, whereas organizing-phase DAD is associated with illnesses greater than 10 days in duration. SARS has no vaccine and no treatment.

Currently, the world is in an interepidemic period for SARS. Resurgence of SARS remains a distinct possibility, as the circumstances that allowed a SARS-COV-like virus to cross the species barrier from animals to humans in the

live-animal markets of southern China still exist. All countries must be vigilant for reemergence of SARS because, in the absence of a vaccine and specific therapy, containment through the classical epidemiologic procedures of early case detection, isolation, and infection control, contact tracing, and follow-up surveillance remain our only tools to contain local spread of infection and prevent international dissemination.

References

Antia R, Regoes R, Koella J et al (2003) The role of evolution in the emergence of infectious diseases. Nature 426:658–661

Cameron MJ, Ran L, Xu L et al (2007) Interferon-mediated immunopathological events are associated with atypical innate and adaptive immune responses in patients with severe acute respiratory syndrome. J Virol 81:8692–8706

CDC (2005) In the absence of SARS-CoV transmission worldwide: guidance for surveillance, clinical and laboratory evaluation, and reporting, version 2. http://www.cdc.gov/sars/Surveillance/absence.html. Accessed 10 Oct 2013

Chang Y-C, Yu C-J, Chang S-C et al (2005) Pulmonary sequelae in convalescent patients after severe acute respiratory syndrome: evaluation with thin-section CT. Radiology 236(3):1067–1075

Cheever F, Daniels J (1949) A murine virus (JHM) causing disseminated encephalomyelitis with extensive destruction of myelin: I. Isolation and biological properties of the virus. J Exp Med 90(3):181–194

Cheng VCC, Lau SKP, Woo PCY, Yuen K-Y (2007) Severe acute respiratory syndrome coronavirus as an agent of emerging and reemerging infection. Clin Microbiol Rev 20(4):660–694

de Groot RJ, Baker SC, Baric RS et al (2013) Middle East respiratory syndrome coronavirus (MERS-CoV): announcement of the coronavirus study group. J Virol 87(14):7790–7792

Franks TJ, Chong PY, Chui P et al (2003) Lung pathology of severe acute respiratory syndrome (SARS): a study of 8 autopsy cases from Singapore. Hum Pathol 34(8):743–748

Gerna G, Campanini G, Rovida F et al (2006) Genetic variability of human coronavirus OC43-, 229E-, and NL63-like strains and their association with lower respiratory tract infections of hospitalized infants and immunocompromised patients. J Med Virol 78(7):938–949

Goldsmith CS, Tatti KM, Ksiazek TG et al (2004) Ultrastructural characterization of SARS coronavirus. Emerg Infect Dis [serial online] Feb. http://wwwnc.cdc.gov/eid/article/10/2/03-0913.htm. Accessed 10 Oct 2013

Guan Y, Zheng BJ, He YQ et al (2003) Isolation and characterization of viruses related to the SARS coronavirus from animals in southern China. Science 302(5643):276–278

Hamre D, Procknow JJ (1966) A new virus isolated from the human respiratory tract. Proc Soc Exp Biol Med 121(1):190–193

Hui DSC, Chan PKS (2010) Severe acute respiratory syndrome and coronavirus. Infect Dis Clin North Am 24(3):619–638

King A, Adams MJ, Carstens EB et al (2011) Virus taxonomy: ninth report of the international committee on taxonomy of viruses. Elsevier, London

Lai MYY, Cheng PKC, Lim WWL (2005) Survival of severe acute respiratory syndrome coronavirus. Clin Infect Dis 41(7):e67–71

Li W, Shi Z, Yu M et al (2005) Bats are natural reservoirs of SARS-like coronaviruses. Science 310(5748):676–679

Liang G, Chen Q, Xu J et al (2004) Laboratory diagnosis of four recent sporadic cases of community-acquired SARS, Guangdong Province, China. Emerg Infect Dis [serial online] Nov. http://wwwnc.cdc.gov/eid/article/10/10/04-0445.htm. Accessed 10 Oct 2013

Neuman BW, Adair BD, Yoshioka C et al (2006) Supramolecular architecture of severe acute respiratory syndrome coronavirus revealed by electron cryomicroscopy. J Virol 80(16):7918–7928

NIAID (2012) The Jordan report: accelerated development of vaccines 2012. NIH Publication No. 11-7778:98–104. http://www.niaid.nih.gov/topics/vaccines/Pages/Jordan2012.aspx. Accessed 10 Oct 2013

Principi N, Bosis S, Esposito S (2010) Effects of coronavirus infections in children. Emerg Infect Dis [serial online]. http://wwwnc.cdc.gov/eid/article/16/2/09-0469.htm. Accessed 10 Oct 2013

Rabenau HF, Cinatl J, Morgenstern B et al (2005) Stability and inactivation of SARS coronavirus. Med Microbiol Immunol 194(1–2):1–6

Song H-D, Tu C-C, Zhang G-W et al (2005) Cross-host evolution of severe acute respiratory syndrome coronavirus in palm civet and human. Proc Natl Acad Sci USA 102(7):2430–2435, Epub 4 Feb 2005

Tyrrell DA, Bynoe ML (1965) Cultivation of a novel type of common-cold virus in organ cultures. Br Med J 1(5448):1467–1470

van der Hoek L (2007) Human coronaviruses: what do they cause? Antivir Ther 12(4 Pt B):651–658

van der Hoek L, Pyrc K, Jebbink MF et al (2004) Identification of a new human coronavirus. Nat Med 10(4):368–373

Wang P, Chen J, Zheng A et al (2004) Expression cloning of functional receptor used by SARS coronavirus. Biochem Biophys Res Commun 315(2):439–444

WHO (2003a) Coronavirus never before seen in humans is the cause of SARS. http://www.who.int/mediacentre/news/releases/2003/pr31/en/. Accessed 10 Oct 2013

WHO (2003b) Update 49 – SARS case fatality ratio, incubation period. http://www.who.int/csr/sars/archive/2003_05_07a/en/#. Accessed 10 Oct 2013

WHO (2003c) Update 96 – Taiwan, China: SARS transmission interrupted in last outbreak area. http://www.who.int/csr/don/2003_07_05/en/. Accessed 10 Oct 2013

WHO (2004a) Summary of probable SARS cases with onset of illness from 1 November 2002 to 31 July 2003. http://www.who.int/csr/sars/country/table2004_04_21/en/index.html#. Accessed 10 Oct 2013

WHO (2004b) WHO guidelines for the global surveillance of severe acute respiratory syndrome (SARS): updated recommendations, October 2004. http://www.who.int/csr/resources/publications/WHO_CDS_CSR_ARO_2004_1/en/index.html. Accessed 10 Oct 2013

WHO (2004c) WHO SARS risk assessment and preparedness framework, October 2004. http://www.who.int/csr/resources/publications/WHO_CDS_CSR_ARO_2004_2/en/index.html. Accessed 10 Oct 2013

WHO (2013) Middle East respiratory syndrome coronavirus (MERS-CoV) – update 19 September 2013. http://www.who.int/csr/don/2013_09_19/en/index.html. Accessed 10 Oct 2013

Woo PCY, Lau SKP, Chu C-M et al (2005) Characterization and complete genome sequence of a novel coronavirus, coronavirus HKU1, from patients with pneumonia. J Virol 79(2):884–895

Zaki AM, van Boheemen S, Bestebroer TM et al (2012) Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. N Engl J Med 367(19):1814–1820