Coronaviruses are increasingly recognized as important human pathogens. They cause up to 15% of common colds and have been implicated in more serious diseases, including croup, asthma exacerbations, bronchiolitis, and pneumonia. Evidence also suggests that coronaviruses may cause enteritis or colitis in neonates and infants and may be underappreciated as agents of meningitis or encephalitis. Four coronaviruses are endemic in humans: human coronaviruses (HCoVs) 229E, OC43, NL63, and HKU1. In addition, two epidemics of previously unknown coronaviruses caused significant respiratory distress and high mortality rates among infected individuals. The discoveries of SARS-associated coronavirus (SARS-CoV), the cause of severe acute respiratory syndrome (SARS), and of Middle East respiratory syndrome coronavirus (MERS-CoV) support the potential for coronaviruses to emerge from animal hosts such as bats and camels and become important human pathogens.

**ETIOLOGY**

Coronaviruses are enveloped viruses of medium to large size (80-220 nm) that possess the largest known single-stranded positive-sense RNA genomes. These viruses encode the protein nsp14-ExoN, which is the first known RNA proofreading enzyme and is likely responsible for the
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- coronaviruses
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- severe acute respiratory syndrome (SARS, SARS-CoV)
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- viral pneumonia
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- emerging pathogens
- antivirals
- vaccines
evolution of the large and complex coronavirus genome. Coronaviruses derive their name from the characteristic surface projections of the spike protein, giving a crown or crown-like appearance on negative-stain electron microscopy. Coronaviruses are organized taxonomically by a lettering system based on genomic phylogenetic relationships. Alphacoronaviruses include HCoV-229E and HCoV-NL63. Betacoronaviruses include four human pathogens and are commonly divided into four lineages, without formal taxonomic recognition. HCoV-OC43 and HCoV-HKU1 are in lineage A, whereas SARS-CoV falls in lineage B. Lineages C and D were exclusively comprised of bat coronaviruses until the discovery of MERS-CoV, which aligns with lineage C. Gammacoronaviruses and deltacoronaviruses presently include exclusively nonhuman pathogens.

Coronaviruses received international attention during the SARS outbreak, which was responsible for more than 800 deaths in 30 countries. SARS-CoV, a novel coronavirus at the time of the epidemic, was found to be the causative agent of SARS. The detection of SARS-like coronaviruses in a live animal market in the Guangdong province in Southern China, along with serologic evidence of exposure in food handlers in the same market, suggest that these markets may have facilitated the spread of SARS-CoV to humans from an animal reservoir. Subsequent studies identified SARS-like coronaviruses in fecal specimens from asymptomatic Chinese horseshoe bats that are very closely related, but not direct precursors to, SARS-CoV and are capable of infecting human cells. Thus, although bats are a reservoir for SARS-CoV-like precursors, the precise antecedent to SARS-CoV remains to be identified.

Another novel coronavirus, MERS-CoV, was isolated from a man with acute pneumonia and renal failure in Saudi Arabia. As of March 1, 2017, the WHO had recorded nearly 2000 confirmed cases of MERS, with nearly 700 deaths worldwide (~35% mortality rate). MERS-CoV differs from SARS in that it seems to be less communicable, although human-to-human transmission has been documented. MERS-CoV uses dipeptidyl peptidase 4 and carboxinembryonic antigen–like cell-adhesion molecule 5 as its cellular and co-receptor, respectively; SARS-CoV utilizes ACE-2. With this receptor specificity, MERS-CoV can infect cells from several animal lineages, including human, pig, and bat, suggesting the possibility of movement between multiple species.

Epidemiology

Seroprevalence studies have demonstrated that antibodies against 229E and OC43 increase rapidly during early childhood, so that by adulthood 90–100% of persons are seropositive. Although less information is available for HKU1 and NL63, available studies demonstrate similar patterns of seroconversion to these viruses during early childhood. Although some degree of strain-specific protection may be afforded by recent infection, reinfections are common and occur despite the presence of strain-specific antibodies. Attack rates are similar in different age groups. Although infections occur throughout the year, there is a peak during the winter and early spring for each of these HCoVs. In the United States, outbreaks of OC43 and 229E have occurred in 2- to 3-year alternating cycles. Independent studies of viral etiologies of upper and lower respiratory infections during the same period, but from different countries, have confirmed that all known HCoVs have a worldwide distribution. Studies using both viral culture and polymerase chain reaction (PCR) multiplex assays demonstrate that coronaviruses often appear in coinfections with other respiratory viruses, including respiratory syncytial virus, adenovirus, rhinovirus, and human metapneumovirus. Volunteer studies demonstrated that OC43 and 229E are transmitted predominantly through the respiratory route. Droplet spread appears to be most important, although aerosol transmission may also occur.

There have been no identified natural or laboratory-acquired cases of SARS-CoV since 2004, but the mechanisms of introduction, spread, and disease remain important for potential animal-to-human transmission and disease. The primary mode of SARS-CoV transmission occurred through direct or indirect contact of mucous membranes with infectious droplets or fomites. Aerosol transmission was less common, occurring primarily in the setting of endotracheal intubation, bronchoscopy, or treatment with aerosolized medications. Fecal-oral transmission did not appear to be an efficient mode of transmission, but may have occurred because of the profuse diarrhea observed in some patients. The seasonality of SARS-CoV remains unknown. SARS-CoV is not highly infectious, with generally only two to four secondary cases resulting from a single infected adult. During the SARS epidemic, a small number of infected individuals, “superspreaders,” transmitted infection to a much larger number of persons, but the mechanism for this high degree of spread remains unknown. In contrast, persons with mild disease, such as children younger than 12 yr of age, rarely transmitted the infection to others. Infectivity correlated with disease stage; transmission occurred almost exclusively during symptomatic disease. During the 2003 outbreak, most individuals with SARS-CoV infection were hospitalized within 3–4 days of symptom onset. Consequently, most subsequent infections occurred within hospitals and involved either healthcare workers or other hospitalized patients.

As of March 1, 2017, the WHO had recorded cases of MERS-CoV in 27 countries, all of which were linked to infections in the Arabian Peninsula (~80% in Saudi Arabia). Though the route of transmission between animals and humans is not fully understood, MERS-CoV is proposed to have repeatedly entered the human population through contact with respiratory secretions of dromedary camels and possibly with raw camel products (e.g., unpasteurized milk). Antibodies to MERS-CoV are found in dromedaries throughout the Middle East, and strains identical to human MERS-CoV isolates have been found in camels in Egypt, Oman, Qatar, and Saudi Arabia. These strains do not appear to be highly pathogenic or virulent in camels and have likely circulated within dromedaries for >30 years. Despite well-documented zoonotic transmission, most reported cases occur through linked human-to-human transmission in healthcare settings, including outbreaks in Jordan, South Korea, and Saudi Arabia in 2015 and 2016. Risk factors for nosocomial MERS-CoV outbreaks include overcrowded emergency departments, delayed diagnosis or isolation, and poor infection control practices. Transmission most likely occurs through respiratory droplets and is thus a greater risk during aerosol-generating procedures. Outside of healthcare settings, human-to-human transmission has been infrequently documented and is primarily associated with close contact within households. No sustained human-to-human transmission has yet been reported.

Pathogenesis of SARS and MERS

Severe disease in SARS and MERS likely results from both direct virologic damage and subsequent immunopathology. Studies with SARS-CoV in human airway epithelial cell cultures indicate that ciliated cells are principal targets for infection, whereas MERS-CoV preferentially infects bronchial epithelial cells, type I and II pneumocytes, and vascular endothelial cells. Substantial viral loads can be detected in the lower respiratory tract and in blood for both viruses. However, late progression to severe disease appears independent of the quantity and timing of viremia. Thus, excessive host immune responses likely play an important role in the progression to lower respiratory disease and acute respiratory distress syndrome. CoV infections are associated with massive elaboration of inflammatory cytokines and recruitment of inflammatory cells. The roles for inflammatory cells are controversial, with cytotoxic T cells and macrophages implicated variously in immune protection and immunopathology. Recapitulation of human clinical features in animal models of MERS-CoV infection remains challenging, but promising new models are in development.

Clinical Manifestations

Respiratory Infections

Even though up to 50% of respiratory tract infections with OC43 and 229E are asymptomatic, coronaviruses are still responsible for up to 15% of common colds and can cause fatal disease. Cold symptoms caused by HCoVs are indistinguishable from those caused by rhinoviruses and other respiratory viruses. The average incubation period is 2–4 days, with symptoms typically lasting 4–7 days. Rhinorrhea, cough, sore throat, malaise, and headache are the most common symptoms. Fever occurs in up to 60% of cases. Coronavirus NL63 is a cause of croup in children younger than 3 yr of age. Coronavirus infections are linked to episodes of wheezing in asthmatic children, albeit at a lower frequency...
and severity than observed with rhinovirus and respiratory syncytial virus infections. Lower respiratory tract infections, including bronchiolitis and pneumonia, are also reported in immunocompetent and immunocompromised children and adults. As with respiratory syncytial virus or rhinovirus, coronavirus detection in upper respiratory infections is frequently associated with acute otitis media and can be isolated from middle ear fluid.

Nonrespiratory Sequelae
There is some evidence to support a role for coronaviruses in human gastrointestinal disease, particularly in young children. Coronavirus-like particles have been detected by electron microscopy in the stools of infants with nonbacterial gastroenteritis. In addition, several outbreaks in neonatal intensive care units of gastrointestinal disease characterized by diarrhea, bloody stools, abdominal distention, bilious gastric aspirates, and classic necrotizing enterocolitis have also been associated with the presence of coronavirus-like particles in stools. In older children and adults, coronavirus-like viruses have been observed with similar frequency in symptomatic and asymptomatic individuals, making it difficult to discern if they are pathogenic in the gastrointestinal tract. Coronaviruses are well-known causes of neurologic disease in animals, including demyelinating encephalitis, but their role in causing human neurologic disease remains unclear. They have been detected by culture, in situ hybridization, and reverse transcriptase PCR (RT-PCR) in brain tissue from a few patients with multiple sclerosis. HCoV-OC43 has been detected by RT-PCR in the spinal fluid, nasopharynx, or brain biopsy specimens of two children with acute encephalomyelitis. However, coronavirus RNA has also been recovered from the spinal fluid and brain tissue of adults without neurologic disease.

Severe Acute Respiratory Syndrome–Associated Coronavirus
SARS-CoV infections in teenagers and adults included a viral replication phase and an immunologic phase. During the viral replication phase, there was a progressive increase in viral load that reached its peak during the second week of illness. The appearance of specific antibodies coincided with peak viral replication. The clinical deterioration that typified the second and third week of illness was characterized by a decline in the viral load and evidence of tissue injury, likely from cytokine-mediated immunity. The explanation for milder clinical disease in children younger than 12 yr of age has not been determined. Seroepidemiologic studies suggest that asymptomatic SARS-CoV infections were uncommon. The incubation period ranged from 1–14 days, with a median of 4–6 days. The clinical manifestations were nonspecific, most commonly consisting of fever, cough, malaise, coryza, chills or rigors, headache, and myalgia. Coryza was more common in children younger than 12 yr of age, whereas systemic symptoms were seen more often in teenagers. Some young children had no respiratory symptoms. Gastrointestinal symptoms, including diarrhea and nausea or vomiting, occurred in up to one third of cases. The clinical course of SARS-CoV infection varied with age. Adults were most severely affected, with initial onset of fever, cough, chills, malaise, nausea or vomiting, following an initial improvement at the end of the first week, fever recurred and respiratory distress developed, with dyspnea, hypoxemia, and diarrhea. These symptoms progressed in 20% of patients to acute respiratory distress syndrome and respiratory failure. Acute renal failure with histologic acute tubular necrosis was present in 6.9% of patients, likely a result of hypoxic kidney damage. Of SARS patients, 28.8% had abnormal urinalysis, with viral genome detectable by quantitative RT-PCR. In contrast, children younger than 12 yr of age had a relatively mild nonspecific illness, with only a minority experiencing significant lower respiratory tract disease and illness typically lasting less than 5 days. There were no deaths or cases of acute respiratory distress syndrome in children younger than 12 yr of age from SARS-CoV infection. Adolescents manifested increasing severity in direct correlation to increasing age; respiratory distress and hypoxemia were observed in 10–20% of patients, one third of whom required ventilator support. The case fatality rate from SARS-CoV infection during the 2003 outbreak was 10–17%. No pediatric deaths were reported. The estimated case fatality rate according to age varied from < 1% for those younger than 20 yr of age to > 50% for those older than 65 yr of age.

Middle East Respiratory Syndrome Coronavirus
The incubation period of MERS-CoV is between 2–14 days. The syndrome usually presents with nonspecific clinical features typical of acute febrile respiratory illnesses, including low-grade fever, rhinorrhea, sore throat, and myalgia. In mildly symptomatic cases, radiographic findings are typically normal. Severe disease is characterized by the acute respiratory distress syndrome with multilobar airspace disease, ground-glass opacities, and occasional pleural effusions on radiography. The median time between hospitalization and ICU transfer for critical illness is 2 days. Risk factors for severe disease include age > 50 yr and comorbidities such as obesity, diabetes, COPD, end-stage renal disease, cancer, and immunosuppression. Specific host genetic risk factors have not been identified. Variation in clinical outcomes does not appear to be explained by viral strain–specific sequence variability. As with SARS, extrapolmonary manifestations are common in severe MERS disease. Gastrointestinal symptoms such as nausea, vomiting, and diarrhea occur in one third of patients, and acute kidney injury has been documented in half of critically ill patients. Encephalitis-like neurologic manifestations have been observed in three cases. Laboratory analyses typically detect leukopenia and lymphopenia, with occasional thrombocytopenia, anemia, and aminotransferase elevations. The case fatality rate remains at 35%, though the true incidence of MERS-CoV infection is likely underestimated by existing data. Most patients have been adults, although children as young as 9 mo of age have been infected. It is not known whether children are less susceptible to MERS-CoV or present with a different clinical picture.

DIAGNOSIS
In the past, specific diagnostic tests for coronavirus infections were not available in most clinical settings. The use of conserved PCR primers for coronaviruses in multiplex RT-PCR viral diagnostic panels now allows widely available and sensitive detection of the viruses. Virus culture of primary clinical specimens remains a challenge for HCoVs HKU1, OC43, 229E, and NL63, even though both SARS-CoV and MERS-CoV can successfully be grown in culture from respiratory samples. Serodiagnosis with complement fixation, neutralization, hemagglutination inhibition, enzyme immunoassay, and Western blots have been used in the research setting. The diagnosis of SARS-CoV infection can be confirmed by serologic testing, detection of viral RNA using RT-PCR, or isolation of the virus in cell culture. Even though the serology for SARS-CoV has a sensitivity and specificity approaching 100%, antibodies are not detectable until 10 days after the onset of symptoms, and immunoglobulin G seroconversion may be delayed for up to 4 wk. In addition, the SARS epidemic resulted in the inclusion of coronavirus-conserved primers in many diagnostic PCR multiplex assays such that coronaviruses may be more readily detected.

The diagnosis of MERS-CoV should be guided by clinical features and an epidemiologic link. The mainstay for laboratory confirmation of MERS-CoV infection is real-time RT-PCR. Screening should target the region upstream of the envelope gene (upE), followed by confirmation with an assay targeting open reading frame 1a. The best diagnostic sensitivity is achieved from lower respiratory tract samples collected within the first week of infection, though MERS-CoV RNA can be detected in upper respiratory and blood samples. Alternatively, seroconversion can be documented by screening enzyme-linked immunosorbent assays followed by immunofluorescence microscopy. For all known endemic and emerging HCoVs, respiratory specimens (nasopharyngeal swabs or aspirates) are most likely to be positive, but in a setting of a possible novel coronavirus, serum or stool may be positive.

TREATMENT AND PREVENTION
Coronavirus infections of humans are acute and self-limited, although persistent infection and shedding occurs in multiple animal models in the setting of minimal or no symptoms. There are no available antiviral agents for clinical use against coronaviruses, although strategies targeting conserved coronavirus proteases and coronavirus polymerases have
been shown to block replication of the viruses in vitro and are in the
drug development pipeline. Thus, treatment of SARS-CoV and MERS-
CoV infections is primarily supportive. The role of antiviral and
immune-modulating agents remains inconclusive, though several clinical
trials are ongoing. Ribavirin was extensively used during the 2003
SARS-CoV outbreak, but is of questionable benefit given its poor in
vitro activity against SARS-CoV at clinically relevant concentrations.
The identification of the proofreading nsp14-exonuclease in multiple
coronaviruses suggests that this activity may be important in resistance
to antiviral nucleosides and RNA mutagens such as ribavirin. Systemic
corticosteroid therapy may be associated with increased mortality rates
in SARS-CoV and MERS-CoV and is thus not recommended unless
indicated for another clinical condition. Meta-analysis of observational
studies suggests that human convalescent plasma may reduce SARS
mortality rates; the use of blood products has not been well-studied in
MERS. Several monoclonal antibody preparations have shown positive
results against SARS-CoV and MERS-CoV in animal studies.

Challenges for the development of effective vaccines targeted against
OC43, 229E, HKU1, and NL63 include the fact that infections are rarely
life-threatening and reinfection is the rule, even in the presence of
natural immunity from previous infections. The durability of immunity
to SARS-CoV and MERS-CoV is poorly understood. Nevertheless,
effective vaccines for SARS-CoV and MERS-CoV are highly desirable
but not yet available. A potential vaccine target is the viral spike protein,
which could be delivered as a recombinant protein or by viral or DNA
vectors. This approach appears to be effective against closely related
strains of SARS-CoV but not necessarily early animal or human variants.
A SARS-CoV vaccine approach that recently has shown success in animal
models used a live recombinant SARS-CoV mutant with inactivated
ExoN, demonstrating attenuation and protection in aged, immuno-
compromised mice. Approaches for the rapid development of stably
attenuated live viruses or broadly immunogenic and cross-protective
protein immunogens continues to be a key area for future research.
Although SARS-CoV demonstrated characteristics of symptomatic
transmission that made it controllable by public health measures such
as quarantine, these characteristics cannot be assumed for future novel
HCoVs. The recent discovery of MERS-CoV serves as a reminder that
coronavirus emergence is both likely and unpredictable, making it
important to continue studies of the replication, emergence, and
transmission of coronaviruses. Additionally, strategies for rapid recovery,
testing, and development of vaccines and neutralizing human monoclonal
antibodies may be essential to prevent the high morbidity and mortality
rates associated with previous epidemics.

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