and *Betacoronavirus*. Severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) are betacoronaviruses.

In general, human coronaviruses have been difficult to cultivate in vitro, and some strains grow only in human tracheal organ cultures rather than in tissue culture. SARS-CoV and MERS-CoV are exceptions whose ready growth in African green monkey kidney (Vero E6) cells greatly facilitates their study.

EPIDEMIOLOGY

Human coronavirus infections are present throughout the world. Seroprevalence studies of strains HCoV-229E and HCoV-OC43 have demonstrated that serum antibodies are acquired early in life and increase in prevalence with advancing age, so that >80% of adult populations have antibodies detectable by enzyme-linked immunosorbent assay (ELISA). Overall, coronaviruses account for 10–35% of common colds, depending on the season. Coronavirus infections appear to be particularly prevalent in late fall, winter, and early spring—times when rhinovirus infections are less common.

An extraordinary outbreak of the coronavirus-associated illness known as SARS occurred in 2002–2003. The outbreak apparently began in southern China and eventually resulted in 8096 recognized cases in 28 countries in Asia, Europe, and North and South America; ~90% of cases occurred in China and Hong Kong. The natural reservoir of SARS-CoV appeared to be the horseshoe bat, and the outbreak may have originated from human contact with infected semidomesticated animals such as the palm civet. In most cases, however, the infection was transmitted from human to human. Case–fatality rates varied among outbreaks, with an overall figure of ~9.5%. The disease appeared to be somewhat milder in cases in the United States and was clearly less severe among children. The outbreak ceased in 2003; 17 cases were detected in 2004, mostly in laboratory-associated settings, and no cases have been reported subsequently.

The mechanisms of transmission of SARS are incompletely understood. Clusters of cases suggest that spread may occur via both large- and small-droplet aerosols and perhaps via the fecal–oral route as well. The outbreak of illness in a large apartment complex in Hong Kong suggested that environmental sources, such as sewage or water, may also play a role in transmission. Some ill individuals ("super-spreaders") appeared to be hyperinfectious and were capable of transmitting infection to 10–40 contacts, although most infections resulted in spread either to no one or to three or fewer individuals.

Since it began in June 2012, another extraordinary outbreak of serious respiratory illness, MERS, has been linked with a coronavirus (MERS-CoV). Through May 2014, a total of 536 cases and 145 deaths (27%) have been reported. All cases have been associated with contact or travel to six countries in or near the Arabian Peninsula: Jordan, Kuwait, Oman, Qatar, Saudi Arabia, and the United Arab Emirates. Cases have also been reported in France, Italy, Tunisia, Germany, Spain, and the United Kingdom. Person-to-person transmission has been documented, but sustained spread in communities has not. The source of MERS-CoV has not been established, but it is suspected that bats may be the animal reservoir and that camels serve as an intermediate host.

PATHOGENESIS

Coronaviruses that cause the common cold (e.g., strains HCoV-229E and HCoV-OC43) infect ciliated epithelial cells in the nasopharynx via the aminopeptidase N receptor (group 1) or a sialic acid receptor (group 2). Viral replication leads to damage of ciliated cells and induction of chemokines and interleukins, with consequent common-cold symptoms similar to those induced by rhinoviruses.

SARS-CoV infects cells of the respiratory tract via the angiotensin-converting enzyme 2 receptor. The result is a systemic illness in which virus is also found in the bloodstream, in the urine, and (for up to 2 months) in the stool. Virus persists in the respiratory tract for 2–3 weeks, and titers peak ~10 days after the onset of systemic illness. Pulmonary pathology consists of hyaline membrane formation, desquamation of pneumocytes in alveolar spaces, and an interstitial infiltrate made up of lymphocytes and mononuclear cells. Giant cells are frequently seen, and coronavirus particles have been detected in type II pneumocytes. Elevated levels of proinflammatory cytokines and chemokines have been detected in sera from patients with SARS.

Because MERS-CoV was so recently detected, little is known at present about its pathogenesis. However, it may well be similar to that of SARS-CoV.

CLINICAL MANIFESTATIONS

After an incubation period that generally lasts 2–7 days (range, 1–14 days), SARS usually begins as a systemic illness marked by the onset of fever, which is often accompanied by malaise, headache, and myalgias and is followed in 1–2 days by a nonproductive cough and dyspnea. Approximately 25% of patients have diarrhea. Chest x-rays can show a variety of infiltrates, including patchy areas of consolidation—most frequently in peripheral and lower lung fields—or interstitial infiltrates, which can progress to diffuse involvement. In severe cases, respiratory function may worsen during the second week of illness and progress to frank adult respiratory distress syndrome accompanied by multiorgan dysfunction. Risk factors for severe disease include an age of >50 years and comorbidities such as cardiovascular disease, diabetes, and hepatitis. Illness in pregnant women may be particularly severe, but SARS-CoV infection appears to be milder in children than in adults.

Information regarding the clinical manifestations of MERS-CoV is limited. The case–fatality rate has been high in the initial cases, but this may represent an ascertainment bias, and it is clear that mild cases occur as well. The median incubation period has been estimated to be 5.2 days, and a secondary case was estimated to have an incubation period of 9–12 days. Cases have been reported that begin with cough and fever and progress to acute respiratory distress and respiratory failure within a week. Other cases have manifested as mild upper respiratory symptoms only. Renal failure has been noted, and DPP-4, the host cell receptor for MERS-CoV, is expressed at high levels in the kidney; these findings suggest that direct viral infection of the kidney may lead to renal dysfunction. Diarrhea and vomiting are also common in MERS, and pericarditis has been reported.

The clinical features of common colds caused by human coronaviruses are similar to those of illness caused by rhinoviruses. In studies of volunteers, the mean incubation period of colds induced by coronaviruses (3 days) is somewhat longer than that of illness caused by rhinoviruses, and the duration of illness is somewhat shorter (mean, 6–7 days). In some studies, the amount of nasal discharge was greater in colds induced by coronaviruses than in those induced by rhinoviruses. Coronaviruses other than SARS-CoV have been recovered occasionally from infants with pneumonia and from military recruits with lower respiratory tract disease and have been associated with worsening of chronic bronchitis. Two novel coronaviruses, HCoV-NL63 and HCoV-HKU1, have been isolated from patients hospitalized with acute respiratory illness. Their overall role as causes of human respiratory disease remains to be determined.

LABORATORY FINDINGS AND DIAGNOSIS

Laboratory abnormalities in SARS include lymphopenia, which is documented in ~50% of cases and which mostly affects CD4+ T cells but also involves CD8+ T cells and natural killer cells. Total white blood cell counts are normal or slightly low, and thrombocytopenia may develop as the illness progresses. Elevated serum levels of aminotransferases, creatine kinase, and lactate dehydrogenase have been reported.

A rapid diagnosis of SARS-CoV infection can be made by reverse-transcription PCR (RT-PCR) of respiratory tract samples and plasma early in the illness and of urine and stool later on. SARS-CoV can also be grown from respiratory tract samples by inoculation into Vero E6 tissue culture cells, in which a cytopathic effect is seen within days. RT-PCR appears to be more sensitive than tissue culture, but only around one-third of cases are positive by PCR at initial presentation. Serum antibodies can be detected by ELISA or immunofluorescence, and nearly all patients develop detectable serum antibodies within 28 days after the onset of illness.