Coronavirus Infections in Children Including COVID-19

An Overview of the Epidemiology, Clinical Features, Diagnosis, Treatment and Prevention Options in Children

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Abstract: Coronaviruses (CoVs) are a large family of enveloped, single-stranded, zoonotic RNA viruses. Four CoVs commonly circulate among humans: HCoV2-229E, -HKU1, -NL63 and -OC43. However, CoVs can rapidly mutate and recombine leading to novel CoVs that can spread from animals to humans. The novel CoVs severe acute respiratory syndrome coronavirus (SARS-CoV) emerged in 2002 and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012. The 2019 novel coronavirus (SARS-CoV-2) is currently causing a severe outbreak of disease (termed COVID-19) in China and multiple other countries, threatening to cause a global pandemic. In humans, CoVs mostly cause respiratory and gastrointestinal symptoms. Clinical manifestations range from a common cold to more severe disease such as bronchitis, pneumonia, severe acute respiratory distress syndrome, multi-organ failure and even death. SARS-CoV, MERS-CoV and SARS-CoV-2 seem to less commonly affect children and to cause fewer symptoms and less severe disease in this age group compared with adults, and are associated with much lower case-fatality rates. Preliminary evidence suggests children are just as likely as adults to become infected with SARS-CoV-2 but are less likely to be symptomatic or develop severe symptoms. However, the importance of children in transmitting the virus remains uncertain. Children more often have gastrointestinal symptoms compared with adults. Most children with SARS-CoV present with fever, but this is not the case for the other novel CoVs. Many children affected by MERS-CoV are asymptomatic. The majority of children infected by novel CoVs have a documented household contact, often showing symptoms before them. In contrast, adults more often have a nosocomial exposure. In this review, we summarize epidemiologic, clinical and diagnostic findings, as well as treatment and prevention options for common circulating and novel CoVs infections in humans with a focus on infections in children.

Key Words: severe acute respiratory syndrome coronavirus, Middle East respiratory syndrome coronavirus, severe acute respiratory syndrome coronavirus 2, epidemiology, symptoms, laboratory, imaging, treatment, vaccines, prevention, treatment, vaccines, prevention, SARS-CoV, MERS-CoV, SARS-CoV-2

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Coronaviruses (CoVs) comprise a large family of enveloped, single-stranded, zoonotic RNA viruses belonging to the family *Coronaviridae*, order *Nidovirales* (Fig.1).[1] They can infect a variety of animals (including livestock, companion animals and birds), in which they can cause serious respiratory, enteric, cardiovascular and neurologic disease.[2,3] In humans, CoVs mostly cause respiratory and gastrointestinal symptoms ranging from the common cold to more severe disease such as bronchitis, pneumonia, severe acute respiratory distress syndrome (ARDS), coagulopathy, multi-organ failure and death.[4–8] Human coronaviruses (HCoVs) have also been associated with exacerbations of chronic obstructive pulmonary disease,[9] cystic fibrosis[10] and asthma.[11,12]

CoVs are classified into *Alphacoronaviruses* and *Betacoronaviruses* (which are mainly found in mammals such as bats, rodents, civets and humans) and *Gammacoronaviruses* and *Deltacoronaviruses* (which are mainly found in birds).[8,13,14] Four CoVs commonly circulate among humans: HCoV2-229E, -HKU1, -NL63 and -OC43.[15,16] These viruses are believed to have originally derived from bats (NL63, 229E),[17,18] dromedary camels (229E)[19] and cattle (OC43).[20] The origin of HCoV-HKU1 remains unknown. Several CoVs are known to circulate in animals (with bats acting as the main reservoir) but have not been associated with human infection.[3,21,22] CoVs are capable of rapid mutation and recombination leading to novel CoVs that can spread from animals to humans. This occurred in China in 2002 when the novel CoV severe acute respiratory syndrome coronavirus (SARS-CoV) emerged, thought to have been transmitted from civet cats or bats to humans.[22–25] Another novel CoVs emerged in Saudi Arabia in 2012, Middle East respiratory syndrome coronavirus (MERS-CoV), which is transmitted from dromedary camels to humans.[26,27] The 2019 novel CoV (SARS-CoV-2), which originated in China and is currently causing outbreaks globally, is a novel *Betacoronavirus* belonging to the lineage B or subgenus sarbecovirus, which includes SARS-CoV.[28] Sequencing shows that the genome is most closely related (87%–89% nucleotide identity) to the bat SARS-related CoV found in Chinese horseshoe bats (bat-SL-CoVZC45).[28,29] The outbreak of SARS-CoV-2 started in Wuhan city, Hubei province, China, where The Health Commission of Hubei province first announced a cluster of adults with pneumonia of unexplained etiology on December 31, 2019. A local seafood and animal market was identified as a potential source. However, the main driver of the outbreak is symptomatic and asymptomatic humans infected with SARS-CoV-2 from whom the virus can spread to others through respiratory droplets or direct contact.[28] From Wuhan city SARS-CoV-2 has spread to other Chinese cities and internationally, threating to cause a global pandemic. The term COVID-19 is used for the clinical disease caused by SARS-CoV-2.[30]

In this review, we summarize epidemiologic, clinical and diagnostic findings, as well as treatment and prevention options for common circulating and novel CoVs infections in humans with a focus on infections in children.

EPIDEMIOLOGY

Common Circulating HCoVs

Common circulating HCoVs can be isolated from 4% to 6% of children hospitalized for acute respiratory tract infections[11,15,31] and from 8% of children in an ambulatory setting (Table 1).[15,32,33]

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Children under the age of 3 years and children with heart disease are the most frequently affected.[4,15,35,36] Reinfections later in life are common[32,115,116] despite the fact that most individuals seroconvert to HCoVs during childhood.[117–120] In contrast to other respiratory tract viruses [eg, respiratory syncytial virus (RSV)], there is no decrease in the relative prevalence of HCoVs infections with increasing age.[4,5,15,36]

In 11%–46% of cases, common circulating HCoVs are found as coinfections with other respiratory viruses such as adeno-, boca-, rhino-, RSV, influenza or parainfluenza virus.[5,15,16,31–33,36,79,81,121,122] Symptomatic children whose only detectable respiratory virus is a HCoV are reported to more likely suffer from an underlying chronic disease compared with children coinfected with other respiratory viruses.[31]

Of the 4 common circulating HCoVs, NL63 and OC43 are the most frequently isolated species.[4,11,15,35,36] Cyclical patterns have been observed for 229E and OC43, with outbreaks occurring every 2–4 years.[4,15,32,35,82,116,119] Seasonal patterns have also been observed: in the Northern Hemisphere, common circulating HCoVs mostly cause infections in humans between December and May, and in the Southern Hemisphere between March and November with peaks in late winter/early spring for 229E and OC43 and in autumn for NL63.[4,5,11,15,32,123] HCoV-HKU1 has been reported to mainly occur in spring and summer in Hong Kong,[11,124] but in winter and spring in the United Kingdom and Brazil.[4,15]

SARS-CoV and MERS-CoV

SARS-CoV is a novel group 2b *Betacoronavirus* which initially emerged in Guangdong province, south China in 2002,[23–25] then spread to Hong Kong and from there rapidly to many other countries.[125] It caused severe lower respiratory tract infection with a severe morbidity and a high case-fatality rate (approaching 50% in individuals over 60 years of age, overall 10%).[63,106,107,126] Person-to-person transmission of SARS-CoV is well established.[55] The virus has spread to 29 countries and has been estimated to have caused more than 8000 infections and 774 deaths worldwide (Table 1).[52]

MERS-CoV is a novel group 2c *Betacoronavirus* which first appeared in Saudi Arabia in 2012.[26,27,127] It can spread from person-to-person[128] and can cause severe lower respiratory tract infections with a case-fatality rate of 20% to 40%.[67,106,108–112] Apart from being endemic in the Middle East, there was a nosocomial outbreak of MERS-CoV in South Korea in 2014, involving 16 hospitals and 186 patients, caused by a medical doctor returning from the Middle East.[49,68] MERS-CoV spread to 27 countries causing an estimated 2494 infections and 858 deaths (Table 1).[53]

The overall reproductive number (R0) for SARS-CoV was estimated to be 0.3–2.9[37,39,40,42,43,47] and for MERS-CoV to be 0.5–3.5 (Table 1).[39,46,48] R0s largely depend on geographic location, stage of the outbreak and inclusion of only nosocomial versus general transmission. Both viruses have been associated with early super-spreading events with R0s of up to 22 for SARS-CoV[39,40,43] and up to 30 for MERS-CoV.[39,49] These large numbers of secondary infections have been mostly associated with nosocomial outbreaks: 30% of all SARS-CoV cases (mostly health care workers) and 44%–100% of all MERS-CoV cases (mostly patients) occurred from nosocomial transmissions.[39,55,56] These super-spreading events were followed by reduced spread in the following generations of viruses with a decrease in the R0s to 0.8 for SARS-CoV[39] and to 0.7 for MERS-CoV (Table 1).[128] Therefore, both SARS-CoV and MERS-CoV have low potential for long-term sustained community transmission. No human SARS-CoV infections have been detected since July 2003. However, SARS-CoV-like viruses can be found in bats, which are known to be able infect human cells without adaptation, making it possible for SARS-CoVs to reemerge[84] (as has now happened with SARS-CoV-2). The zoonotic transmission of MERS-CoV to humans has continued, attributed to the role of dromedary camels as a reservoir and their close contact with humans (in contrast to human-bat-interactions).[21]

SARS-CoV-2

Early in the SARS-CoV-2 outbreak, it was shown that person-to-person transmission was the main driver.[28] The R0 for

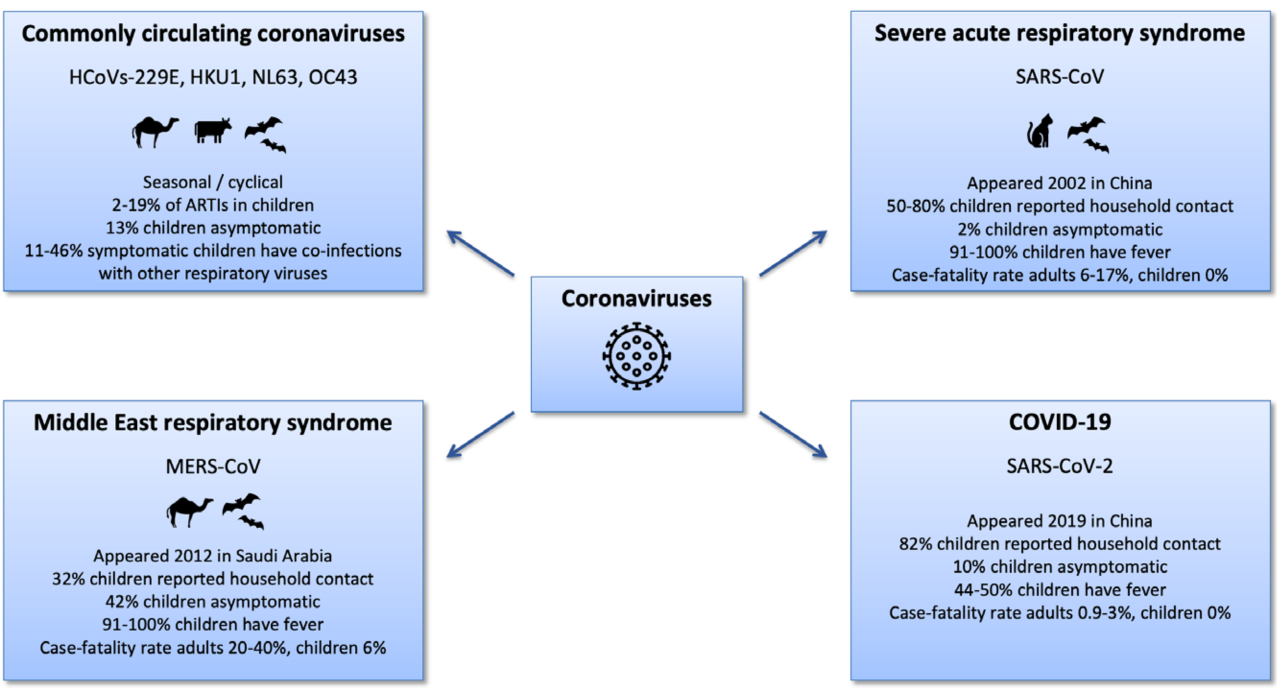

FIGURE 1. Summary of coronavirus diseases. COVID-19 indicates coronavirus disease 2019.

TABLE 1. Characteristics of Human Coronaviruses

	Commonly Circulating HCoVs	Novel Coronaviruses		
		SARS-CoV	MERS-CoV	SARS-CoV-2
Prevalence (for 229E, HKU1, NL63, and OC43, unless otherwise specified)	Eight countries: 6% in children with ARTIs (ambulatory, >1 yr)[33] Brazil: 5% in children with ARTIs (ambulatory and hospitalized, >9 yr)[4] China: 2% in children with fever and upper ARTIs (ambulatory and hospitalized, >5 yr)[35] France: 6% (HCo-OC43) in children and adults with ARTIs (ambulatory and hospitalized, October to April)[5] Hong Kong: 4% (HCoV-229E, -OC43, -NL63) in children with ARTIs (hospitalized, >1 yr)[11] Israel: 10% in children and adults with ARTIs (ambulatory and hospitalized, September to April)[36] Nepal: 8% of infants < 6 mo with upper ARTIs (ambulatory, >3 yr)[32] United Kingdom: 5% in infants 7–12 mo with ARTIs (ambulatory and hospitalized, over 3 yr)[15] United States: 19% in adolescents with ARTIs (ambulatory, October to January),[16] 6% in children with ARTIs (hospitalized, >1 yr)[31]	Unknown	Saudi Arabia: 0% of 2235 children with ARTIs (ambulatory and hospitalized, over 2 yr, 2012–2013)[34]	Unknown
Mean reproductive number		Worldwide: overall 2.9 (95% CI: 2.2–3.6)[37] Singapore plus Toronto: overall 1.0 (95% CI: 0.7–1.2)[39] Beijing: overall 0.9 (90% CI: 0.3–1.5)[40], early phase 1.9 (90% CI: 0.4–3.32)[40] Hong Kong: overall 0.7 (95% CI: 0.7–0.8),[42] early phase 3.6 (95% CI: 3.1–4.2),[42] overall 1.7 (IQR, 0.4–2.3),[43] overall 0.9 (95% CI: 0.7–1.1),[44] early phase 2.7 (95% CI: 2.2–3.7)[44] Singapore: overall 1.6 (90% CI: 0.5–2.7),[40] early phase 2.6 (90% CI: 0.5–4.5),[40] overall 0.7 (95% CI: 0.6–0.9),[42] early phase 3.1 (95% CI: 2.3–4.0),[42] 1.8 (IQR, 0.5–2.5),[43] early phase 22,[39] range 2.2–3.6[45] Taiwan: overall 2.6 (90% CI: 0.3–5.3)[47] Toronto: overall 1.0 (95% CI: 0.9–1.2),[42] early phase 2.7 (95% CI: 1.8–3.6),[42] overall 0.9 (IQR, 0.2–1.2),[43] early phase 7[39] Vietnam: overall 0.3 (95% CI: 0.1–0.7),[42] early phase 0.7 (95% CI: 0.7–0.8),[42] overall 2.4 (95% CI: 1.8–3.1)[42]	Worldwide: overall 1.0 (95% CI: 0.6–1.3)[37] Saudi Arabia plus South Korea: overall 0.9 (95% CI: 0.4–1.4)[39] Jeddah: overall range 3.5–6.7[41] Riyadh: overall range 2.0–2.8[41] Middle East: overall 0.5 (95% CI: 0.3–0.8),[46] early phase 3[39] Saudi Arabia: overall 0.5 (95% CI: 0.3–0.6)[48] South Korea: early phase 30,[39] range 2.0–8.1[49]	Wuhan: 2.7 (2.5–3.9) (as of February 2020)[38] 2.2 (2.0–2.6)–3.6 (2.9–4.4) (as of January 2020)[50]
Zoonotic origin	Bats (NL63, 229E)[17,18] Dromedary camels (229E)[19] Cattle (OC43)[20]	Civet cats[24,25] (bats as reservoirs)[21,22]	Dromedary camels[27] (bats as reservoirs)[21]	Pangolin suspected but unproven[51]
Outbreak extent and numbers (adults and children)	Unknown	29 countries[52] 8000 infections[52] 774 deaths[52]	27 countries[53] 2494 infections[53] 858 deaths[53]	102 countries[54] 105,586 infections[54] 3584 deaths[54] (as of March 9, 2020)
Transmission in adults	Unknown	30% nosocomial (mostly health care workers)[55] 13%–21% household contacts[55]	44%–100% nosocomial (mostly patients)[39,55,56] 22%–39% household contacts[39,55,56]	Unknown
Transmission in children	Unknown	50%–80% household contacts[57–59] 30% nosocomial contacts[57]	32% household contacts[60] 23% other contacts[60] 19% nosocomial infections[60]	82% household contacts[61]
Incubation period	2–5 d[20,62]	4–6 d (range 2–10 d)[63–66] 95% develop symptoms within 13 d[63,64]	5–7 d (range 4–13 d)[64,67–71] 95% develop symptoms within 13 d[64,67–70]	5–6 d (range 2–14 d)[38,64,72]

(Continued)

TABLE 1. (*Continued*)

	Commonly Circulating HCoVs	Novel Coronaviruses		
		SARS-CoV	MERS-CoV	SARS-CoV-2
Serial interval mean	Unknown	6 d (interquartile range, 4–9 d)[40] 8 d (95% CI: 1.6–19.2 d)[37] 8 d (SD 4 d)[45]	7 d (SD 4 d)[48] 8 d (95% CI: 2.5–23.3 d)[37] 12 d (SD 3 d)[70]	8 d[38]
Shedding duration	6 d (3–10 d) in children in daycare[73]	Mostly after onset of symptoms[74,75]	Mostly after onset of symptoms[70]	Unknown
Asymptomatic proportion of children	13% asymptomatic[16]	2% asymptomatic[57–59]	42% asymptomatic[60,76]	9%–11% asymptomatic[61,77]
Clinical features in children	Fever,[5,11,32] rhinitis,[5,11] conjunctivitis,[78] otitis,[5] pharyngitis,[5,11] laryngitis,[5] croup,[11,79,80] headache,[5,16,81] bronchitis,[5,11] bronchiolitis,[5,11] wheezing,[4,11,32] asthma exacerbations,[11,12] pneumonia,[5,81,82] gastrointestinal symptoms,[5–7] febrile seizures,[7,11] neurologic disseminated[83]	Fever (91%–100%),[57–59] myalgia (10%–40%),[57,84] rhinitis (33%–60%),[38,57,84] sore throat (5%–30%),[38,57,84] cough (43%–80%),[38,57,84] dyspnea (10%–14%),[38,84] headache (14%–40%),[38,57,84] vomiting (20%),[38,57] abdominal pain (10%),[57] diarrhea (10%,)[38,84] febrile seizures (10%)[57]	Fever (57%),*[76] vomiting (28%),*[76] diarrhea (28%),*[76] cough and shortness of breath (14%)*[76]	Fever (44%–50%),[61,72,77] cough (38%),[61,72] rhinitis,[72] fatigue,[72] headache,[72] diarrhea,[72] dyspnea,[72] cyanosis,[72] poor feeding[72]
Laboratory findings in children	Not reported	 Decreased neutrophil count[85] Decreased lymphocyte count[57–59,86] Thrombocytopenia[57–59,86] Increased alanine aminotransferase[57–59,86] Increased lactate dehydrogenase[57] Deranged coagulation and increased D-dimers in severe cases[57–59,86]	Normal WBC[76] Thrombocytopenia[76] Normal liver function tests[76] Normal urea and creatinine levels[76]	Normal or reduced WBC[61,72] Decreased neutrophil count[61] Decreased lymphocyte count[61,72] CRP and PCT levels usually normal[61,72] Abnormal liver function tests[72] Increased lactate dehydrogenase[61] Increased D-dimers in severe cases[72]
Imaging findings in children	Not reported	Chest radiography: bilateral patchy airspace consolidations at the periphery of the lungs and in upper lobes, linear atelectasis, peribronchial thickening, ground-glass opacities[57–59,86,87] Chest CT: ground-glass opacities, airspace consolidation[89]	Chest radiography: bilateral airspace consolidations[76]	Chest CT: bilateral multiple patchy, nodular ground-glass opacities, speckled ground-glass opacities and/or infiltrating shadows in middle and outer zone of the lung or under the pleura[61,88]
Diagnostics (adults and children)	Multi- or monoplex RT-PCR or RNA sequencing on nasopharyngeal or oropharyngeal swabs, sputum, endotracheal aspirate or bronchoalveolar lavage[5,15,90] Monoplex RT-PCR on stool (not routine)[98]	RT-PCR or RNA sequencing on nasopharyngeal or oropharyngeal swabs, sputum, endotracheal aspirate or bronchoalveolar lavage[91–93] RT-PCR on stool (not routine)[91] Serology (not in acute phase)[100–102]	RT-PCR or sequencing of RNA on nasopharyngeal or oropharyngeal swabs, sputum, endotracheal aspirate or bronchoalveolar lavage[94–96] RT-PCR on stool (not routine)[99] Serology (not in acute phase)[103]	RT-PCR or sequencing of RNA sequencing from nasopharyngeal or oropharyngeal swabs, sputum, endotracheal aspirate or bronchoalveolar lavage[28,97] Serology only when RT-PCR not available[97]
Case-fatality rate in adults	Sporadic cases reported in immunosuppressed adults[104,105]	6%–17%[63, 66, 106, 107]	20%–40%[67, 106, 108–112]	<3%[113] 2.3%[114] 0.9% (95% CI: 0.4%–2.9%)[54]
Case-fatality rate in children	Unknown	0%[57–59,86]	6%[60]	0%[72]

*Case series consisted of 7 children only.
ARTI indicates acute respiratory tract infection; CI, confidence interval; CRP, C-reactive protein; IQR, interquartile range; PCT, procalcitonin; WBC, white blood cell.

SARS-CoV-2 is currently estimated at 2.7.[38] The incubation period is estimated at 5–6 days, which is similar to that for SARS-CoV and MERS-CoV.[38,63–65,67–72] The serial interval is estimated to be 8 days, also similar to the other novel CoVs (Table 1).[38,45,48,70] By March 2020, the World Health Organization reported that SARS-CoV-2 had spread to over 100 countries and caused over 100,000 infections and over 3500 deaths.[54] At that time the case-fatality rate was uncertain but estimated at 0.9%–3%,[54,113,114] which is much lower than for SARS-CoV and MERS-CoV (6%–17% and 20%–40%, respectively).[63,67,106–112]

SYMPTOMS

Common HCoVs

In children, common circulating HCoVs can cause common cold symptoms such as fever,[5,11,32] rhinitis,[5,11] otitis,[5] pharyngitis,[5,11] laryngitis[5] and headache,[5,16,81] but also bronchitis,[5,11] bronchiolitis,[5,11] wheezing,[4,11,32] pneumonia,[5,81,82] and, in up to 57% of cases, gastrointestinal symptoms (which are more common in children than adults).[5–7] In a study including children and adults, fatigue, headache, myalgia and sore throat were more common in HCoV-infected patients compared with RSV-infected patients, while fever, cough and dyspnea were more frequent in the later.[36] Fewer patients infected with HCoVs had fever compared with those infected with RSV or influenza.[36]

In children, HCoV-NL63 has been associated with conjunctivitis,[78] croup,[11,79,80] asthma exacerbations,[11,12] febrile seizures[11] and HCoV-HKU1 with febrile seizures.[7] Rare cases of neurologic diseases have also been described (eg, the detection of HCoV in cerebrospinal fluid in a child presenting with acute disseminated encephalomyelitis[83] or in cerebrospinal fluid of adults with multiple sclerosis.)[129,130] A suspected association between HCoVs and Kawasaki disease could not be confirmed.[131,132] Common HCoVs can be isolated from asymptomatic individuals.[16] During an infection, the viral load is high in the first 2 days and decreases thereafter.[29] A correlation between viral load and severity of disease has not been observed[29] This contrasts with SARS-CoV for which a higher initial viral load is independently associated with a worse prognosis, including a higher case-fatality rate.[133,134] Virus particles can be isolated from nasopharyngeal secretions up to 14 days after the onset of infection.[135]

SARS-CoV

There are 3 case series that report a total of 41 children who were affected by SARS-CoV.[57–59] The virus was associated with milder disease in children compared with adults, and no deaths have been reported in children.[57–59,86] Symptomatic children with SARS-CoV infection were reported to have fever (91%–100%),[57–59] myalgia (10%–40%),[57,58] rhinitis (33%–60%),[57–59] sore throat (5%–30%),[57–59] cough (43%–80%),[57–59] dyspnea (10%–14%),[38,84] headache (14%–40%)[57–59] and, less commonly, vomiting (20%),[57,59] abdominal pain (10%),[57] diarrhea (10%)[58,59] and febrile seizures (10%).[57] In total, 50%–80% of children had other family members who were infected[57–59] and 30% had a nosocomial contact with SARS-CoV.[57] Most children recover quickly from an infection with SARS-CoV.[86] However, abnormalities on chest computed tomography (CT) can persist for several months (eg, air trapping and ground-glass opacifications).[136]

There is no evidence that SARS-CoV can be vertically transmitted to the fetus.[137] However, SARS-CoV infections during pregnancy have been associated with possible miscarriage, intrauterine growth retardation and preterm delivery.[137,138]

MERS-CoV

Most case series of patients infected with MERS-CoV report a low proportion (0.1%–4%) of children.[34,76,109,110,139,140] In a large case series of 2235 children with acute respiratory tract infection who presented to a tertiary hospital in Saudi Arabia during the MERS-CoV epidemic (2012–2013), none tested positive for MERS-CoV (Table 1).[34] There are 2 small case series of children infected with MERS-CoV: one including 31 children with a mean age of 10 years[60] and the other one only 7 children.[76] In both studies, 42% of children were asymptomatic.[60,76] In the case series of 7 children, 57% suffered from fever, 28% from vomiting and diarrhea and 14% from cough and shortness of breath.[76] Two children required oxygen supplementation and one mechanical ventilation.[76] In the other case series, 2 died (6%).[60] The main sources of MERS-CoV infection in children were household (32%) and other contacts (23%), followed by nosocomial transmission (19%).[60]

Eight cases of MERS-CoV maternal infections during pregnancy have been reported (occurring between 20 and 28 weeks of pregnancy), three of the affected infants died.[141–144]

SARS-CoV-2

Different case definitions for COVID-19 cases in adults and children from authoritive sources as of March 2020 are detailed in Table 2. Children are less commonly affected by SARS-CoV-2, the Chinese Centers for Disease Control and Prevention reports that of the 72,314 cases reported as of February 11, 2020, only 2% were in individuals of less than 19 years of age.[114] There are 3 case series of children who have been infected with SARS-CoV-2.[61,72,77] The first included 20 children up to January 31, 2020, in the Province of Zhejiang,[72] the second 34 children between January 19, 2020, and February 7, 2020, in the Province of Shenzhen,[61] and the third 9 infants from different provinces in China.[77] The case series with 34 children provides the most clinical details: none of the children had an underlying disease, 65% had common respiratory symptoms, 26% had mild disease and 9% were asymptomatic.[61] The most common symptoms were fever (50%) and cough (38%).[61] In the case series of 20 children, presentation was with low to moderate or no fever, rhinitis, cough, fatigue, headache, diarrhea and, in more severe cases, with dyspnea, cyanosis and poor feeding, but the numbers were not specified.[72] In the series of 9 infants, only 4 were reported to have fever. One infant was asymptomatic.[77] Additional asymptomatic children infected with SARS-CoV-2 outside these case series have also been described (eg, a 10-year-old asymptomatic child with radiologic ground-glass lung opacities on chest CT).[28] Most infected children recover 1–2 weeks after the onset of symptoms and no deaths from SARS-CoV-2 had been reported by February 2020.[72]

From these series, it appears that children have milder clinical symptoms than adults[61,72] (as has been reported for SARS-CoV and MERS-CoV infections),[57–60,76,86] which could mean children might not be tested for SARS-CoV-2 as frequently as adults. It has therefore been suggested that asymptomatic or mildly symptomatic children might transmit the disease.[147] However, the majority of children infected with SARS-CoV-2 thus far have been part of a family cluster outbreak [100% in the infants series, in which other family member had symptoms before the infants in all cases; 82% in the case series of 34 children;[61] and the majority in the one with 20 children (exact number not specified)].[72] This is similar to SARS-CoV, in which 50%–80%[57–59] of children were reported to have an affected household contact[60] and to MERS-CoV in which it was 32%.[60]

A study prepublished in early March 2020 suggests that children are just as likely as adults to become infected with SARS-CoV-2 but are less likely to be symptomatic or develop severe symptoms.[246] However, the importance of children in transmitting the virus remains uncertain.

From a small case series of 9 mothers who were infected with SARS-CoV-2, there is, to date, no evidence that SARS-CoV-2 can be vertically transmitted to the infant.[148]

TABLE 2. Case Definitions for SARS-CoV-2 Infections in Adults and Children (as of February 2020)

Adults: Original case definition from the Chinese CDC[38]

A suspected or probable case is defined as a case that meets: (1) three clinical criteria or (2) two clinical criteria and one epidemiologic criterion
Clinical criteria:
1. Fever
2. Radiographic evidence of pneumonia or acute respiratory distress syndrome
3. Low or normal white blood cell count or low lymphocyte count

Epidemiologic criteria:
1. Living in Wuhan or travel history to Wuhan within 14 d before symptom onset
2. Contact with patients with fever and symptoms of respiratory infection within 14 d before symptom onset
3. Link to any confirmed cases or clusters of suspected cases

Adults: Case definition from the US CDC (February 13, 2020)[145]

A. Fever or signs/symptoms of lower respiratory illness (eg, cough or shortness of breath) AND close contact with a laboratory-confirmed SARS-CoV-2 patient within 14 d of symptom onset
B. Fever and signs/symptoms of lower respiratory illness (eg, cough or shortness of breath) AND a history of travel from Hubei Province, China within 14 d of symptom onset
C. Fever or signs/symptoms of lower respiratory illness (eg, cough or shortness of breath) requiring hospitalization AND a history from mainland China within 14 d of symptom onset

Adults: Case definition from the World Health Organisation (WHO) (27th February 2020), which also form the basis for the European Centre for Disease Prevention and Control (ECDC) case definition[146]

Suspected case
A. Patient with acute respiratory infection [fever and at least one sign/symptom of respiratory disease (eg, cough, shortness of breath)] AND with no other etiology that fully explains the clinical presentation AND a history of travel to or residence in a country/area or territory reporting local transmission of COVID-19 during the 14 days prior to symptom onset; OR
B. A patient with any acute respiratory illness AND having been in contact with a confirmed or probable COVID-19 case in the last 14 days prior to onset of symptoms; OR
C. A patient with severe acute respiratory infection (as above) AND requiring hospitalization AND with no other etiology that fully explains the clinical presentation.

Children: Case definition by the National Clinical Research Center for Child Health, Zhejiang University School of Medicine (adapted from Chen et al [72])

A suspected or probable case is defined as a case that meets: two clinical criteria and one epidemiologic criterion
Clinical criteria:
1. Fever, fatigue, dry cough; some pediatric patients may have no fever
2. Patients with the following chest imaging findings: multiple small patchy shadows and interstitial changes, mostly in the lung periphery, bilateral multiple ground-galls opacity, infiltrating shadows, pulmonary consolidation on chest radiography or ground-glass opacities, bilateral segmental lung consolidation, especially in the periphery on chest CT
3. White blood cell counts are normal or decreased, or with decreased lymphocyte count

Epidemiologic criteria:
1. Children with a travel or residence history in Wuhan City and neighboring areas, or other areas with persistent local transmission within 14 d prior to disease onset
2. Children with a history of contacting patients with fever or respiratory symptoms who have a travel or residence history in Wuhan City and neighboring areas, or in other areas with persistent local transmission within 14 d prior to disease onset
3. Children with a history of contacting confirmed or suspected cases infected with SARS-CoV-2 within 14 d prior to disease onset
4. Children who are related with a cluster outbreak: in addition to this patient, there are other patients with fever or respiratory symptoms, including suspected or confirmed cases infected with SARS-CoV-2
5. Newborns delivered by suspected or confirmed SARS-CoV-2-infected mothers

A confirmed case is defined as a case that meets any of the following criteria:
1. Throat swab, sputum, stool or blood samples tested positive for SARS-CoV-2 nucleic acid using RT-PCR
2. Genetic sequencing of throat swab, sputum, stool or blood samples being highly homologous with the known SARS-CoV-2
3. SARS-CoV-2 granules being isolated by culture from throat swab, sputum, stool or blood samples

CDC indicates Centers for Disease Control and Prevention.

LABORATORY FINDINGS

Laboratory findings from children are similar with infections caused by different novel CoVs (Table 1). The white blood cell count is typically normal or reduced with decreased neutrophil[85] and/or lymphocyte counts.[57–59,72,86] Thrombocytopenia may occur.[57–59,76,86] C-reactive protein and procalcitonin levels are often normal.[72] In severe cases, elevated liver enzymes,[57–59,72,86] lactate dehydrogenase levels,[57] as well as a abnormal coagulation and elevated D-dimers have been reported.[57–59,72,86]

SARS-CoV-2

The same laboratory findings has above have been observed for children infected with SARS-CoV-2.[61] In the case series of 34 children, the white blood cell count was normal in 83%, neutropenia and lymphopenia were each found in 1 case (3%). The lactate dehydrogenase level was elevated in 30% of cases.[61] C-reactive protein and procalcitonin levels were each elevated in 1 case only (3%).

RADIOLOGIC FINDINGS

Similar to the laboratory findings, radiologic findings from children are also similar across infections with different novel CoVs (Table 1). On chest radiography, children mostly show bilateral patchy airspace consolidations often at the periphery of the lungs, peribronchial thickening and ground-glass opacities.[57–59,76,86,87] Chest CT mostly shows airspace consolidations and ground-glass opacities.[89]

SARS-CoV-2

CT changes observed in children infected with SARS-CoV-2 include bilateral multiple patchy, nodular ground-glass opacities, speckled ground-glass opacities and/or infiltrating shadows in the middle and outer zone of the lung or under the pleura.[61,88] These findings are unspecific and milder compared with those in adults.[88]

DIAGNOSIS

The main basis for diagnosis of infections with HCoVs is real-time polymerase chain reaction (RT-PCR) on upper or lower respiratory secretions.[5,15,90–96] For SARS-CoV, MERS-CoV and SARS-CoV-2, higher viral loads have been detected in samples from the lower respiratory tract compared with the upper respiratory tract.[28,149] Therefore, in clinically suspected cases with an initially negative result on nasopharyngeal or throat swab, repeat testing of upper respiratory tract samples or (preferably) testing of lower respiratory tract samples should be done. RT-PCRs on stool samples can be positive for HCoVs but is not used for routine diagnosis.[91,98,99] For SARS-CoV and SARS-CoV-2, rare cases with positive PCRs in blood have been reported.[28,150] Serology has been used to diagnose infections with SARS-CoV and MERS-CoV, but is not useful in the acute phase of the infection.[100–103] Cross-reactivities between antibodies against SARS-CoV and common CoVs have been observed.[151]

SARS-CoV-2

Whole genome sequencing allowed the rapid development of molecular diagnostic tests for SARS-CoV-2.[28] RT-PCR for genes encoding the internal RNA-dependent RNA polymerase and surface spike glycoprotein are commonly used.[28]

TREATMENT

Supportive treatment including sufficient fluid and calorie intake, and additional oxygen supplementation should be used in the treatment of children infected with HCoVs. The aim is to prevent ARDS, organ failure and secondary nosocomial infections. If bacterial infection is suspected broad-spectrum antibiotics such as second or third generation cephalosporins may be used.

SARS-CoV

In the absence of specific antiviral drugs for CoVs, broad-spectrum antiviral drugs, such as interferon alpha and beta or ribavirin were used for the treatment of SARS-CoV, including in children.[57–59] Ribavirin was subsequently shown to be ineffective or even harmful because it can cause hemolytic anemia or liver dysfunction.[152] In adults, interferon-alpha alone or together with ribavirin also did not consistently improve outcomes.[152,153] There is some evidence that intravenous corticosteroids led to clinical and radiologic improvement in SARS-CoV-infected individuals.[58] However, a systematic review showed that the evidence for this is inconclusive and corticosteroids might also be harmful (delayed viral clearance, avascular necrosis, osteoporosis, new onset of diabetes).[152] There is some evidence from adult studies that lopinavir/ritonavir (Kaletra) started early during infection is associated with improved clinical outcomes (decreased intubation, ARDS and death rates).[154,155] However, a systematic review found inconclusive results for the use of lopinavir/ritonavir because of a possible selection bias in many of the studies.[152] Inconclusive results were also found for intravenous immunoglobulins because studies did not account for comorbidities, stage of illness and effect of other treatments.[152] There is no evidence for the use of monoclonal antibodies against tumor necrosis factor alpha.[156]

MERS-CoV

There are no studies on treatment outcomes for MERS-CoV in children. In adults, as for SARS-CoV, interferon or ribavirin alone or in combination have not been shown to have a clear benefit.[157–159] Mycophenolate mofetil, which inhibits guanine (and therefore RNA) synthesis, was identified as a potential anti-MERS-CoV drug in vitro.[160] However, animal studies showed that the drug leads to worse outcomes with higher viral loads in lung and extrapulmonary tissues.[161] Consistent with this, renal transplant patients on mycophenolate mofetil have been reported to develop severe and sometimes fatal MERS-CoV infections.[162]

SARS-CoV-2

Until the results of on-going clinical trials become available, there is no definitive evidence on which to base treatment of patients infected with SARS-CoV-2. The only treatment recommendation for children, published by the Zhejiang University School of Medicine, suggests the use of nebulized interferon alpha-2b and oral lopinavir/ritonavir together with corticosteroids for complications (ARDS, encephalitis, hemophagocytic syndrome or septic shock) and intravenous immunoglobulin for severe cases.[72]

However, as none of these therapies have shown a clear benefit in the treatment of other novel CoVs, it is questionable whether they will be beneficial in the treatment of SARS-CoV-2. Neither the World Health Organization nor the US Centers for Disease Control and Prevention recommends any specific treatment in children or adults.[97,163] Despite this, in the previously mentioned case series of the 34 children infected with SARS-CoV-2, 59% were treated with lopinavir/ritonavir.[61] None of the children received glucocorticoids or immunoglobulins.[61]

Other Therapeutic Options

Monoclonal Antibodies

Despite their diversity, CoVs share many proteins among different species, which is helpful for the design of new drugs. One of them is the surface structural spike glycoprotein S, which is responsible for virus-cell interaction.[164] Monoclonal antibodies (from convalescent human plasma, animal plasma or manufactured) against the spike glycoprotein S have been shown to inhibit fusion of CoVs with human cells and to decrease mortality rate in SARS-CoV-infected patients.[165–171] A protein, which also inhibits the spike glycoprotein S, although it is not a monoclonal antibody, has been isolated from a red alga called Griffithsia.[172] However, to date, it has only been tested in animal studies.[172]

Angiotensin-converting enzyme 2, dipeptidyl peptidase 4, aminopeptidase N, O-acetylated sialic acid are further host receptors for HCoVs and monoclonal antibodies against these proteins might be useful in treatment of infections.[173–176] However, rapid mutation of CoVs poses a potential problem, which might be diminished by using several monoclonal antibodies targeting different epitopes.[166]

Protease Inhibitors

Endosomal and nonendosomal virus entry into cells can be reduced by inhibiting responsible proteases.[177–179] Papain-like proteases (PLpro) are involved in viral replication in CoVs and are further potential targets for treatment. Numerous PLpro inhibitors have been identified. However, none of them has been validated in in vivo studies.[180,181] Moreover, PLpro enzymes differ between CoVs species, making PLpro inhibitors narrow-spectrum antiviral drugs against CoVs.[182]

A further protein involved in viral replication is CoV main proteinase, which is inhibited by lopinavir. However, as previously mentioned, lopinavir (plus ritonavir) has been shown to be effective against CoVs in animal and nonrandomized studies of SARS-CoV-infected humans.[154,161] However, as previously mentioned, these results are considered inconclusive because of potential selection bias.[152]

Chloroquine

Chloroquine, which is commonly used against malaria and autoimmune diseases, increases the endosomal pH thereby inhibiting virus-cell fusion, and is therefore a potential broad-spectrum antiviral drug.[183] It also interferes with glycosylation of cellular receptors of SARS-CoV.[184] In addition, in vitro studies show that chloroquine inhibits entry and postentry stages of SARS-CoV-2 into cells.[185] Moreover, chloroquine possesses immune-modulating activity, which might enhance its antiviral effect in vivo.[185]

RNA Synthesis Inhibitors

As previously mentioned, ribavirin, a guanosine analog has been shown to be ineffective or even harmful against SARS-CoV[152] and MERS-CoV.[157–159] Immucillin-A, a new adenosine analog that has recently been developed, inhibits the viral RNA polymerase of a wide range of RNA viruses, including SARS-CoV and MERS-CoV,[186] and might be useful in the treatment of other HCoVs. Furthermore, inhibitors of helicase (which are proteins unwinding double-stranded RNA into single strands during replication) might be useful in treatment of CoVs.[187] RNA synthesis inhibitors, which reduce the formation of double-membrane vesicles, a hallmark of CoV2 replication, have been identified as potential antiviral drugs.[188,189] A double-stranded RNA activated caspase oligomerizer (DRACO) that targets long viral double-stranded RNA and induces apoptosis of infected cells, but spares healthy cells, might also be useful in the treatment of CoVs.[190]

VACCINES

Several vaccines against HCoVs are in development with the aim of preventing infection, reducing disease severity and viral shedding. The main antigens for vaccine development are the structural spike glycoprotein S or its receptor-binding domain (RBD).[191] However, the propensity of CoVs to rapidly mutate and recombine poses a potential problem for vaccine development.[192–194] Furthermore, the enhanced disease after viral challenges postvaccination has been observed in animal models after several different vaccines.[195–197]

Live-attenuated Vaccines

The advantage of live-attenuated vaccines is that they usually induce a robust and long-lasting immune response, including cellular and humoral immunity to many different antigens. In SARS-CoV animal studies, attenuated mutants with deletion of the structural E gene have been shown to induce neutralizing antibodies, reduce viral loads and protect from clinical symptoms of SARS-CoV infection.[198–200] In contrast, deletion of open reading frames had little or no effect on viral loads in vitro and in vivo.[201] Other strategies under development for live-attenuated vaccines against CoVs are genome rearrangement or gene knockouts.[202–204] These have the advantage that the vaccine virus cannot recombine with wild viruses.

Inactivated Vaccines

In mouse models, inactivated vaccines successfully induce cellular and humoral immunity (with many different neutralization antibodies) against SARS-CoV[191,205–207] and humoral immunity against MERS-CoV.[208,209] In a human phase 1 trial, inactivated vaccines against SARS-CoV were well tolerated and elicited neutralizing antibodies.[210] However, no challenge studies have been done in humans, and in monkey challenge studies, no clear evidence of protection was shown despite the induction of strong cellular and humoral responses.[211] Moreover, concerns have been raised that inactivated vaccines against SARS-CoV and MERS-CoV may lead to harmful immune and/or inflammatory responses postchallenge.[195,209]

Subunit and Recombinant Vaccines

Subunit vaccines are purified antigens, usually combined with adjuvants and are the most popular method in the development of vaccines against novel CoVs. For SARS-CoV and MERS-CoV, these are mostly developed from spike glycoprotein S, RBD or nucleocapsid protein.[212–216] Some studies show that subunit vaccines given intranasally might induce stronger immune responses and mucosal immunity.[217] Several subunit vaccines have shown to be successful in animal challenging studies.[218–220]

In a study in monkeys, recombinant RBD protein was used to successfully reduce viral loads in lungs and oropharynx and to prevent MERS-CoV pneumonia.[218] In mice, similar results were achieved using recombinant RBD protein vaccines from SARS-CoV.[221]

Viral Vectors Vaccines

Adenovirus-based vectors encoding SARS proteins (eg, nucleocapsid protein, spike glycoprotein S and other membrane proteins) have been shown to be immunogenic in mice and rhesus macaques in whom they induced humoral and cellular vaccine responses.[222,223] Adenovirus-based vaccines carrying parts MERS-CoV have been shown to reduce morbidity and mortality (undetectable or reduced pulmonary viral loads) in mouse models.[196,224] Initially, pulmonary hemorrhages were observed postviral challenge.[196] However, adding a CD40 ligand to the vaccine enhanced immunogenicity and efficacy, and also prevented inadvertent pulmonary pathology, which makes this vaccine a promising strategy.[196] Nonetheless, preexisting immunity against adenovirus might reduce efficacy. This might be addressed by giving a viral-based vaccine followed by a recombinant vaccine as a booster.[225] A adenovirus-based MERS-CoV vaccine has moved into a phase I clinical trial.[226]

One study, comparing an inactivated SARS-CoV vaccine with an adenovirus-based vaccine against SARS-CoV, found that the first led to higher humoral responses.[227] Adenovirus-based vaccines administered intranasally led to immunoglobulin A antibody production which has been associated with superior protection from virus replication in lungs.[227] This indicates that measuring serum neutralizing antibodies might not be a sufficient way of assessing vaccine efficacy for HCoV as mucosal immunity might be more important.

For SARS-CoV, a poxvirus has also been used as a vector for an intranasally and intramuscularly administered vaccine. This vaccine-induced neutralizing antibodies and reduced viral loads in the respiratory tract of challenged mice.[228] However, a similar vaccine used in ferrets led to increased liver damage after SARS-CoV challenge.[197]

Further vector vaccines for SARS-CoV that have been tested in animals are based on recombinant parainfluenza virus,[229,230] live-attenuated recombinant measles virus,[231] attenuated rabies virus[232] and attenuated *Salmonella*.[233]

DNA Vaccines

Vaccines containing DNA encoding the spike glycoprotein seem to induce a more robust response of neutralizing antibodies against MERS-CoV than vaccines only containing the RBD protein. They have been shown to protect rhesus macaques from MERS-CoV pneumonia.[234,235] Three DNA vaccines against MERS-CoV have advanced into clinical trials.[236–238]

OTHER STRATEGIES FOR CONTROLLING EMERGING CORONAVIRUSES

After quickly spreading across the globe, SARS-CoV was contained in 2003 after a highly effective global public health response. This highlights the urgent need for rapid and effectful strategies of infection control. One of the main challenges with novel CoVs is the high potential for nosocomial transmission.[239] Health care settings seem to increase the risk of viral transmission due to aerosol-generating procedures such as intubation and bronchoscopy. Appropriate hospital hygiene practices are therefore crucial to limit nosocomial outbreaks. The main aims are to effectively triage patients with fever, respiratory symptoms and a contact history[240] and to apply stringent infection control measures such as isolating patients and quarantine contacts as early as possible. Ideally, each patient is placed in a single negative pressure room. If this is not possible, patients and health care workers should be cohorted.[241] Protective gear should include water-resistant gowns, disposable gloves, N95 masks and goggles or face shields.[240] Only suction catheters and mechanical respirators with a closed-circuit system and viral filters should be used.[240] In contrasts, nebulizers, oxygen masks or nasal continuous positive airway pressure systems should not be used on an open ward.[240,241] Needless to say, strict hand hygiene needs to be applied and visitors should be avoided or limited to an absolute minimum. HCoVs have been shown to persist on dry surfaces for up to 9 days.[242–244] The persistence depends on temperature (shorter duration at 30–40°C) and humidity (longer at higher humidity).[245] HCoVs, including novel CoVs, can be inactivated by heating to 56°C for 30 minutes or by using lipid solvents such as ethanol (>75%), isopropanol (>70%), formaldehyde (>0.7%), povidone-iodine (>0.23%), sodium hypochlorite (>0.21%), hydrogen peroxide (>0.5%), but not chlorhexidine.[72,244]

SUMMARY

SARS-CoV, MERS-CoV and SARS-CoV-2 infections seem to affect children less commonly and less severely as compared with adults. This might be because children are less frequently exposed to the main sources of transmission (which until now has been disproportionally nosocomial) or because they are less exposed to animals. However, it could also be that children are less frequently symptomatic or have less severe symptoms and are therefore less often tested, leading to an underestimate of the true numbers infected. In relation to SARS-CoV-2, a study prepublished in early March 2020 suggests that children are just as likely as adults to become infected with this virus but are less likely to be symptomatic or develop severe symptoms.[246] However, the importance of children in transmitting the virus remains uncertain. The majority of children infected by a novel CoVs reported thus far have a documented household contact, often showing symptoms before them, suggesting the possibility that children are not an important reservoir for novel CoVs. The clinical, laboratory and radiologic features in children are similar for all novel CoVs, except more children infected with SARS-CoV presented with fever compared with SARS-CoV-2 or MERS-CoV. To date, no deaths in children have been reported for SARS-CoV or SARS-CoV-2, except (in the case of the former) for infants of mothers who were infected during pregnancy.

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