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Human Coronaviruses SARS-CoV, MERS-CoV, and SARS-CoV-2 in Children



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ABSTRACT

The novel coronavirus, known as 2019-nCoV or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has caused an epidemic with high mortality and morbidity since December 2019, in Wuhan, China. The infection has now been transmitted to more than 210 countries worldwide and caused more than 200,000 deaths. Similar to other coronaviruses such as Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), SARS-CoV-2 appears to less commonly affect pediatrics and to cause less severe disease along with fewer symptoms compared to adults. Available data suggest that the pediatric population is just as likely as adults to become infected with SARS-CoV-2. However, they may be asymptomatic or have milder symptoms than adults; they can be potential carriers of the disease. This article reviews the present understanding of SARS-CoV-2 infection in the pediatric age group in comparison with MERS-CoV and SARS-CoV.

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Introduction

Coronaviruses (CoVs) are single-stranded positive-sense RNA viruses belonging to the family Coronaviridae and the order Nidovirales (Chen, Liu, & Guo, 2020; Wu et al., 2020a; Yang et al., 2020). These enveloped viruses possess a non-segmented genome and have the potential to cause respiratory diseases, with varying severity in humans and animals (Guy, Breslin, Breuhaus, Vivrette, & Smith, 2000). They fall into the four genera: alpha, beta, gamma, and delta. Both alpha and beta coronaviruses can infect humans (hCoVs) (Zhu et al., 2020). Of these, three beta CoVs have been epidemic causes: SARS-CoV, MERS-CoV, and SARS-CoV-2.

Severe acute respiratory syndrome (SARS) develops as a sudden onset unusual type of viral pneumonia. The 2002–2003 SARS outbreak started from one of the southern states of China and spread to more than 30 East Asian countries. The incubation period takes between 2

and 7 days up to 10 days. Cold symptoms, such as low-grade fever, muscle aches, and dry cough, are the first signs of illness. There might be unilateral or bilateral pneumonia in chest imaging. Lymphopenia, hypoxia, and elevated creatine phosphokinase (CPK) and lactate dehydrogenase (LDH) (Alsaad et al., 2018; Luk, Li, Fung, Lau, & Woo, 2019; Momattin, Al-Ali, & Al-Tawfiq, 2019) commonly occur in patients with SARS-CoV.

The 2012 MERS coronavirus (MERS-CoV) outbreak is associated with a wide range of diseases, from mild fever and respiratory symptoms to upper respiratory tract infection, diarrhea, weakness, and lethargy. In severe cases, it can lead to progressive infection of the lungs and respiratory failure, renal failure, or multiple organ failure (Bosch, Raj, & Haagmans, 2013; Drosten et al., 2014; Widagdo, Okba, Stalin Raj, & Haagmans, 2017).

COVID-19 is a recently emerged coronavirus disease first reported from Wuhan, China. Due to the worldwide spread of the disease, the World Health Organization has declared COVID-19 a global epidemic on March 21 (Hanaei & Rezaei, 2020; Huang et al., 2020; Hui et al., 2020). The causative pathogen of COVID-19 shares structural similarities with that of SARS and therefore has adopted the name SARS-CoV-2. Pneumonia is the most common manifestation of COVID-19 in the early stages, characterized by fever, cough, shortness of breath, and bilateral infiltration in chest imaging (Lotfi & Rezaei, 2020). Moreover,

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COVID-19 can lead to fatal lung injury, multiple organ failure, and death (Huang et al., 2020).

Children are differently affected by COVID-19. Compared to adults, children are more asymptomatic and develop a severe form of COVID-19 at an incomparably lower rate (Rezaei, 2020a; Shen et al., 2020). Despite this, children are generally one of the most susceptible groups to infectious diseases of viral origin. Mainly related to the subject is the recently reported development of a multi-system inflammatory syndrome in children (MIS-C) affected by COVID-19. This review mainly focuses on the clinical manifestations of the MERS, SARS, and COVID-19 and, in the meantime, aims to compare these three hCoVs in terms of prognosis, epidemiology, prevention, transmission, and treatment in children.

Epidemiology of SARS, MERS, and COVID-19

In the last two decades, the world has faced three epidemics caused by coronaviruses, resulting in significant global health concerns (Guarner, 2020).

In 2002–2003, SARS-CoV emerged in Guangdong, China. It spread rapidly to other areas and countries, including Hong Kong, China's particular administrative area, Singapore, Vietnam, and Canada (Mao, Lin, Weng, & Chen, 2020). After having infected more than 8000 people and resulting in 774 deaths with a mortality rate calculated at 9.5%, the latest patient diagnosed with SARS-CoV occurred in September 2003 (Guarner, 2020). The first pediatric patients with SARS-CoV were hospital staff contacts (Li & Ng, 2005a). Stockman et al. (Stockman et al., 2007) state that of the 135 pediatric cases with SARS documented in the six publications, 80 had laboratory-confirmed SARS, and 27 existed in the SARS-affected regions (3%). There was no known source of SARS in less than 2% of pediatric patients.

In 2012, MERS-CoV first happened in Saudi Arabia. To date, most patients with MERS-CoV have occurred in or nearby the Arabian Peninsula. Whereas a low reproduction number of about 1 indicates that each patient with MERS-CoV transfers the disease to one other individual only, models estimate an R_0 of 4 for SARS-CoV that corresponds to relatively higher transmissibility of this virus (Guarner, 2020; Schwartz & Graham, 2020). However, as compared to SARS-CoV, MERS-CoV is more deadly, with the death rate of about 35%.

There are at least 31 pediatric patients with MERS-CoV reported to WHO from June 2012 to April 19, 2016. The mean age of the patients was 9.8 years. More than 80% of pediatric patients with MERS-CoV registered in Saudi Arabia, and other cases were reported in Korea, Jordan, and the United Arab Emirates (Bartenfeld, Griese, Uyeki, Gerber, & Peacock, 2017a).

In December 2019, the novel coronavirus disease (COVID-19) was recognized in Wuhan, China, in some patients with an unknown form of viral pneumonia, along with a common history of being in the Huanan seafood market (Peeri et al., 2020). By March 22, the new coronavirus pandemic has been spread to over 185 countries from China and appears not to be more fatal than other similar viruses, such as MERS and SARS (Andersen, Rambaut, Lipkin, Holmes, & Garry, 2020; Pal & Bhansali, 2020). The director-general of the WHO, Tedros Adhanom Ghebreyesus, at a meeting on February 17, stated that over 80% of cases with COVID-19 have "mild disease and will recover", and in 2% of reported patients, it appears to be fatal (Mahase, 2020). Although the case fatality rate is lower in COVID-19 infected individuals, COVID-19 has resulted in about 3 million confirmed cases as well as more than 200,000 deaths by April 26, 2020. It forms a contrast with SARS and MERS that were totally accounted for less than 2000 deaths (1632). During the pandemic of COVID-19, the older population, people with comorbid conditions, such as cardiovascular diseases and cancer, and individuals with a certain genetic background appear as the most vulnerable populations (Ahmadi, Saffarzadeh, Habibi, Hajiesmaeili, & Rezaei, 2020; Darbeheshti & Rezaei, 2020; Shamshirian & Rezaei, 2020; Yousefzadegan & Rezaei, 2020). In the early stages of the

COVID-19 epidemic, pediatric SARS-CoV-2 infected individuals appeared infrequent. Therefore, the pediatric age group is not yet considered at high risk of this disease. However, the pediatric population infected by SARS-CoV-2 was gradually increased in line with the increase of familial clusters (Pal & Bhansali, 2020). By February 11, 2020, the Chinese Centers for Diseases Control and Prevention has reported 44,672 confirmed SARS-CoV-2 infected cases, 549 cases (1.2%) of whom were 10–19 years old and 416 cases (0.9%) of whom were 0–10 years old. Of these infected children, 134 cases had clinical records (今井由美子, 2020). There have been two reported deaths in the pediatric age group, who tested positive for SARS-CoV-2 infection in China; however, no deaths have been reported in the published papers from other countries (Sinha et al., 2020). Furthermore, a cohort of 31 patients (under the age of 18, with 28 patients under the age of 14) who were hospitalized with SARS-CoV-2 infection in Shenzhen city of China reported that apart from some common characteristics between children and adults, a few epidemical characteristics were found in children that sharply differed from what was formerly known about adult patients. Accordingly, no gender preference was revealed in the pediatric patients (Chen et al., 2020).

Clinical manifestations of SARS, MERS, and COVID-19

SARS

According to the reported results of the disease, the virus has occurred in adults between 25 and 70 years. Moreover, there have been reported a few cases in adolescents (15 years old). The latent period of the disease is between 2 and 7 days, and sometimes up to 10 days. During this period, patients might have a low-grade fever, which may be accompanied by chills and flu-like symptoms (including rapid and high fever, muscle pain, headache, and sore throat). After 3–7 days, lower respiratory problems begin with a dry cough. It can lead to shortness of breath, and in some cases (10–20%), blood oxygen depletion. Two clinical phases characterize SARS. In the first phase, the symptoms are mild and related to the upper part of the respiratory system (symptoms of cold, cough, shortness of breath). In the second phase, by the invasion of the virus to the lower respiratory system, it causes cough, shortness of breath, and, ultimately, a decrease in blood oxygenation (Lau et al., 2004). All of these symptoms exist in adults and children, and only symptom severity varies between them.

According to research reports, clinical manifestations in children include a low-grade fever or no fever, fatigue, and dry cough. Also, in the early stage of the disease, the number of white blood cells and the number of lymphocytes may decrease. Children with suspected SARS have shown clinical manifestations, including cough, chills, fatigue, vomiting, diarrhea, rhinorrhea, and respiratory distress, and laboratory abnormalities, including leukopenia, elevated AST, elevated ALT, and lymphopenia. Laboratory results such as thrombocytopenia, lymphopenia, and elevation in CPK and liver transaminase levels appeared mild in young children. Results suggest that SARS is a relatively mild and non-specific respiratory illness in young children. The clinical features observed in teenagers resemble those of adults (Bitnun et al., 2003; Leung & Chiu, 2004).

MERS

MERS-CoV can cause a wide range of symptoms from mild fever and respiratory symptoms (upper respiratory tract infection), diarrhea, weakness, and lethargy, to progressive respiratory failure, renal failure, or multiple organ failure in severe cases. The most common manifestations of the disease are fever and respiratory symptoms, and all patients develop respiratory symptoms during their illness (Bartenfeld et al., 2017a; Schwartz & Graham, 2020). Cases of anemia, coagulopathy, and intravascular coagulation have also been reported in patients with MERS-CoV. There have also been reports of increased levels of serum

transaminases, lactate dehydrogenase, potassium, creatine kinase, troponin, C-reactive (CRP) protein, and procalcitonin, and decreased serum sodium and albumin levels (Das et al., 2015; Moniri, Marjani, Tabarsi, Yadegarynia, & Nadji, 2015). The MERS-CoV virus produces symptoms similar to SARS, but with a distinct clinical course and high mortality rates of between 35 and 50%. The rate of death from MERS is higher in men as well as in patients with underlying diseases. The average time from the onset of symptoms to hospitalization is approximately four days, and the average time from admission to hospital to admission to the ICU is one day. The ICU admission period is approximately 30 days. However, death occurs, on average, 12 days after the onset of symptoms (Mohd, Al-Tawfiq, & Memish, 2016; Omrani et al., 2014; Scobey et al., 2013).

Furthermore, out of 701 patients with confirmed MERS-CoV, only 14 were pediatric cases (2%). Compared to adult patients, MERS-CoV in children is less frequent and seems to be associated with less mortality unless the patient has an underlying disease or a history of infection with other respiratory viruses. Based on the results of the screening, it has been found that one of the children (9-month-old child) with MERS-CoV disease has nephrotic syndrome. Different results show that although few cases of MERS-CoV in children have been reported, MERS remains mainly a disease of adults.

COVID-19

According to the first study of patients with new coronavirus (SARS-CoV-2), the incubation period of the virus was, on average, five days, with a range between 4 and 7 days (Li et al., 2020). According to the present epidemiological evidence, the incubation period of COVID-19 infections varies from 1 to 14 days, generally ranging from 3 to 7 days. SARS-CoV-2 tends to locate and replicate in the cells of the lower respiratory tract (Heymann & Shindo, 2020). At the initial stage of infection with SARS-CoV-2, people have general nonspecific symptoms such as fatigue, body aches, fever, dry cough, nausea, and diarrhea. Also, patients may develop neurological manifestations, such as headach and anosmia (Jahanshahlu & Rezaei, 2020a; Saleki, Banazadeh, Saghazadeh, & Rezaei, 2020; Yazdanpanah, Saghazadeh, & Rezaei, 2020; Zu et al., 2020).

Infected children might appear asymptomatic or present with a dry cough, fever, and fatigue, and gastrointestinal symptoms such as diarrhea, abdominal discomfort, nausea, and vomiting. Most children infected with SARS-CoV-2 have mild clinical manifestations. Most children recover within 1 to 2 weeks after disease onset. Few may progress to lower respiratory infections (Zimmermann & Curtis, 2020). According to the results of research on 26 children with COVID-19 infection, nine patients had no apparent clinical symptom. The most common symptom was fever found in 11 patients. Less common symptoms included cough, diarrhea, rhinorrhea, and vomiting. Few children had lymphocytopenia and elevated alanine transaminase. According to the chest CT scan, 11 patients showed unilateral pneumonia, and eight patients had no pulmonary infiltration. No severe complications such as acute respiratory syndrome and acute lung damage have occurred in children with COVID-19. Also, the leukocyte counts in children were the same as in adults, and most of them appeared normal or decreased. Lymphocyte counts in adult patients decreased significantly (Fathi & Rezaei, 2020), while they increased beyond the normal range in most children with COVID-19. It might reflect the fact that children have a higher percentage of lymphocytes that gradually decrease with age (Lai, Shih, Ko, Tang, & Hsueh, 2020a; Li et al., 2020).

At the disease onset, some cases show fever, cough, and fatigue that is accompanied by nasal congestion, expectoration, runny nose, headache, and diarrhea. The majority of children have a low-grade fever or no fever at all (Stockman et al., 2007). As the condition progresses, dyspnea, cyanosis, and other signs may arise after typically one week of the disease, along with systemic toxic signs, including restlessness or malaise, decreased appetite, poor feeding, and less activity. Children's

condition might progress quickly and turn to respiratory failure, which cannot be improved by conventional oxygen (nasal catheter, mask) within 1–3 days. Metabolic acidosis, septic shock, irreversible bleeding, and coagulation dysfunction can take place in such severe cases (Hui & Sung, 2003). Xia et al. (Ng et al., 2003) reported that 7 of 20 pediatric cases had a history of acquired or congenital diseases, indicating that children with underlying diseases can be more vulnerable to COVID-19. Pediatric patients usually have a better prognosis, with an average stay of 12.9 days in the hospital. As for adults, COVID-19 can rapidly spread in children. However, it is more likely to remain asymptomatic in children than adults (Zeng et al., 2020).

Multi-system inflammatory syndrome in children with COVID-19

Unlike adults, most children with COVID-19 have mild symptoms. However, COVID-19 may cause an inflammatory reaction in some children (release WFOPlCCSm, 2020; Riphagen, Gomez, Gonzalez-Martinez, Wilkinson, & Theocharis, 2020). In late April 2020, a group of children was admitted to the intensive care unit for a multi-system inflammatory disease. It appeared that the disease could be related to COVID-19. Also, there were eight children from England, in whom excessive hyperinflammatory shock was observed (Riphagen et al., 2020) and COVID-19 related antibodies were present as well (Abrams et al., 2020). The so-called multi-system inflammatory syndrome in children (MIS-C) is very similar to a type of childhood disease known as Kawasaki disease. Kawasaki disease causes inflammation in the blood vessel walls (Prevention CfDca, 2020; Verdoni et al., 2020). Coronary artery aneurysm is a major complication of Kawasaki disease. The diagnosis is based on the persistent presence of symptoms such as eczema, lymphadenopathy, fever, conjunctival injection, and changes in the mucous membranes and organs (Dietz et al., 2017; McCrindle et al., 2017). Examination of the clinical and laboratory characteristics of MIS-C shows that the syndrome is distinct from Kawasaki's disease. Children with MIS-C are older and systemic inflammation is more severe in them, and they have more myocardial damage than patients with Kawasaki's disease (Whittaker et al., 2020). Children with MIS-C show both the symptoms of COVID-19 and toxic shock syndrome (TSS) and Kawasaki disease (Prevention CfDca, 2020; PICS PICS, 2020). MIS-C can affect different parts of the including the heart, lungs, kidneys, brain, skin, eyes, or gastrointestinal tract. Children with MIS-C mostly have abdominal pain or sometimes diarrhea, neck pain, rash, bloodshot eyes, and vomiting. They may also experience excessive fatigue (Network CHA, 2020; Toubiana et al., 2020). Cases of MIS-C have been reported in several countries (Bahrami, Vafapour, Moazzami, & Rezaei, 2020a; Cheung et al., 2020; Organization WH, 2020). This syndrome appears to occur two to four weeks after infection with COVID-19. In countries where the prevalence of COVID-19 is high, more cases of MIS-C have been reported in children (Control ECfDpa, 2020; Riphagen et al., 2020). Children with this syndrome might suffer from heart problems and need immediate care (Belhadjer et al., 2020). It is not yet fully understood what causes MIS-C (Riphagen et al., 2020).

Virology and pathogenesis of coronaviruses

Coronaviruses (CoVs) are a family of enveloped RNA viruses (Scobey et al., 2013) that display crown-like spikes on their surfaces (Birmingham et al., 2012; Cowling et al., 2015; Ksiazek et al., 2003). In particular, SARS-CoV-2 possesses a typical RNA that encodes 27 proteins. The orf1ab and orf1a genes, which are located at the 5' end of the genome, encode the pp1ab and pp1a proteins, respectively. Together, these two genes express 15 nonstructural proteins nsp1–nsp10 and nsp12–nsp16. On the other hand, at the 3' end of the genome, four structural proteins, including the spike surface protein (S), an envelope protein (E), membrane protein (M), nucleocapsid protein (N), and eight subunit proteins, including 3a, 3b, p6, 7a, 7b, 8b, 9b, and orf 14 are coded (Mou et al., 2013; Wu et al., 2020b).

Although coronaviruses are more common in animals, seven of them can affect humans (hCoVs). Four coronaviruses, including HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1, regularly cause respiratory infections in children and adults. Some coronaviruses, such as SARS-CoV, MERS-CoV, and SARS-CoV-2, are highly pathogenic to humans and can cause more severe symptoms leading to fatal cases of pneumonia (lung infection), renal failure, multiorgan failure, and death.

HCoVs can invade the respiratory tract, intestine, and stomach and cause respiratory and gastrointestinal diseases. Usually, coronaviruses first infect the respiratory mucosa in the pharynx and nose and produce symptoms similar to the common Cold. coronaviruses cause about 15% of cases of colds. Occasionally, colds that coronaviruses cause can progress to infantile bronchitis, ear infections, or exacerbation of asthma in children and adolescents, and even pneumonia in adults, the elderly, and people with pre-existing conditions. Symptoms of respiratory coronavirus infections in humans are partly similar to those of rhinovirus infections and include nasal congestion and restlessness.

Transmission and source of infection

SARS-CoV and MERS-CoV can be transmitted through the fomite route, aerosol transmission, and droplet transmission (Jahanshahlu & Rezaei, 2020b; Li & Ng, 2005b; Perlman, 2020; Zumla, Hui, & Perlman, 2015a). Person-to-person transmission of MERS-CoV occurs by large droplets (Zumla et al., 2015a). People who have exposure to health care centers, for example, hospitals or clinics, are at increased risk for MERS infection. Some MERS outbreaks are related to these centers as one occurred in Jeddah (Saudi Arabia), due to contact transmission in 2014 (Zumla et al., 2015a). There are MERS cases that at first appear as primary cases, but after more consideration, they are confirmed as secondary because they have a history of contact with patients (Zumla et al., 2015a). In another study by Schuster et al., pediatric cases could be infected with MERS-CoV secondarily as they were contacts of adults with MERS. Adults become infected with MERS-CoV at the workplace or due to contact with intermediate host animals (Schuster & Williams, 2018).

Patients infected with SARS-CoV-2 may have symptoms or be asymptomatic. Symptomatic patients are the most contagious. The mechanisms to spread the disease are not yet fully elucidated, especially regarding the relative contributions of the airborne versus contact transmission routes to the COVID-19 pandemic (Zhang, Li, Zhang, Wang, & Molina, 2020). Although contact transmission via respiratory droplets was regarded as the main route in transmitting SARS-CoV-2 virus initially (Van Doremalen et al., 2020; Chin & Poon, 2020; CDC CfDcAP, 2020a; WHO WHO, 2020), present experimental and epidemiological evidence has suggested airborne transmission of the virus via respiratory aerosols as one probable route for the spreading of COVID-19 (Liu et al., 2020; Morawska & Milton, 2020; Prather, Wang, & Schooley, 2020; Van Doremalen et al., 2020). A recent study of the COVID-19 pandemic trends in New York City, Italy, and Wuhan suggested that the airborne transmission route dominated the spread of the disease, and face-covering considerably shaped the trends of the outbreak in the three mentioned epicenters (Zhang, Li, et al., 2020). Therefore, presently, the probable transmission routes (i.e., airborne vs. contact) for SARS-CoV-2 is a highly debated topic among the research communities worldwide (Morawska & Milton, 2020).

It might also be possible for SARS-CoV-2 to be transmitted via the oral-fecal route as well. Supporting this, the fecal samples of some patients with COVID-19 were positive for the viral nucleic acid. However, the accuracy of this pattern of transmission needs more investigation (Jahanshahlu & Rezaei, 2020b).

There is documented data about the vertical transmission of SARS-CoV and MERS-CoV (Jahanshahlu & Rezaei, 2020b; Li & Ng, 2005b). A

mother with SARS-CoV is at increased risk for complications such as spontaneous miscarriage, intrauterine growth retardation, pre-term labor, and coagulopathy problems (Li & Ng, 2005b; Mardani & Pourkaveh, 2020). The data from six newborns born from mothers with COVID-19 showed that samples from amniotic fluid and the umbilical cord lacked SARS-CoV-2 RNA. Also, the neonatal pharynx sample and mother breastmilk were negative for the nuclear acid of COVID-19 (Jahanshahlu & Rezaei, 2020b). The results of another study in China on nine mothers who had COVID-19 associated pneumonia were similar to the previous one, and there was no virus detected in all samples. The Apgar score of nine neonates was high, and there were no signs of asphyxia in them (Mardani & Pourkaveh, 2020). The current evidence is not enough to conclude that SARS-CoV-2 can be transmitted from an infected mother to her fetus (Favre et al., 2020; Jahanshahlu & Rezaei, 2020b; Mirbeyk & Rezaei, 2020). Because the perinatal transmission is suspicious, pregnant women who have a history of travel to affected areas or have a history of exposure to infected patients are recommended to be tested for COVID-19, even if they are asymptomatic (Favre et al., 2020).

The outbreak of SARS-CoV is related to wildlife (Daszak, Olival, & Li, 2020). The source of MERS-CoV infections may be related to camels. The origin of the novel coronavirus is not completely clear, but a zoonotic origin of the disease is well-documented. The first confirmed cases of COVID-19 were related to markets that sell seafood, the meat of wild animals (Daszak et al., 2020), snakes, and other animals like livestock animals and live rabbits too. Furthermore, high similarities between the SARS-CoV-2 and bat coronaviruses support the bat origin of SARS-CoV-2 (Perlman, 2020).

Diagnosis

First of all, the history of exposure to infected patients or travel to the affected areas and laboratory data such as procalcitonin (PCT), complete blood count, and C-reactive protein can help us to diagnose this infection (Jahanshahlu & Rezaei, 2020b). A very advantageous instrument for distinguishing SARS infected children from the others is real-time reverse transcription-polymerase chain reaction (RT-PCR). RT-PCR is also used for MERS-CoV nucleic acid detection, too (Schuster & Williams, 2018). It takes a few hours for the test to count the RNA viruses in the serum (Li & Ng, 2005b). However, the value of conventional RT-PCR decreases along the first week of the SARS-CoV infection (Li & Ng, 2005b), and its sensitivity is not acceptable. In a study of pediatric cases with SARS, conventional RT-PCR of fecal and nasopharyngeal specimens could detect less than 50% of real patients (Li & Ng, 2005b). Laboratory findings of SARS-CoV in children include increased lactate dehydrogenase (LDH), decreased neutrophil count, and elevated creatinine phosphokinase (CPK) (Li & Ng, 2005b). Incomplete airspace filling at the edge of the lung indicates the SARS-CoV infection.

Nowadays, the nucleic acid test is the gold standard for the diagnosis of COVID-19 (Jahanshahlu & Rezaei, 2020b). Among the specimens taken for the diagnosis of COVID-19, the most convenient one is nasopharyngeal swab, with the sensitivity rate close to 50% and less (Jahanshahlu & Rezaei, 2020b). Lower respiratory tract secretions such as bronchoalveolar lavage fluid that contains a high amount of viral RNA are more valid specimens for the detection of the novel coronavirus (Jahanshahlu & Rezaei, 2020b; Zumla et al., 2015a). Also, the pharyngeal swab was used one day after labor for an asymptomatic newborn infected with COVID-19 (). Some children who tested negative for COVID-19 might be infected with this virus and could spread the virus among other people, so the test should be repeated for them (). Imaging data could help us with the diagnosis of COVID-19 in children. High resolution computed tomography (HRCT) can be more helpful than a chest X-ray in this regard. Imaging abnormalities related to COVID-19 include ground-glass opacities (GGO) and peribronchial thickening (Li & Ng, 2005b).

Predisposing factors

Among children affected by SARS-CoV and MERS-CoV, females are infected slightly more than males (Al-Sehaibany, 2017; Chang et al., 2004; Hon et al., 2003; Memish et al., 2014; Thabet, Chehab, Bafaqih, & Al, 2015). Most of the children with SARS did not have underlying conditions except for two children reported with epilepsy and spontaneous pneumothorax. In contrast, children with MERS showed underlying diseases, like renal failure, cystic fibrosis, and Down syndrome. Also, coinfection with influenza is reported in children with MERS (Bartenfeld, Griese, Uyeki, Gerber, & Peacock, 2017b; Chang et al., 2004; Memish et al., 2014; Thabet et al., 2015). Searching the exposure history of contaminated children, the majority of them had at least one of the history of traveling to endemic areas, contact with health care workers, household contact, or experiencing community outbreaks in 14 days before the initiation of the disease (Bartenfeld et al., 2017b; Chang et al., 2004; Hon et al., 2003; Memish et al., 2014; Ng, Leung, Chiu, Wong, & Hon, 2004; Thabet et al., 2015).

Previously it was thought that among children with COVID-19, female ones are affected more than male ones. However, recent reports show the reverse, raising the need to further surveys to investigate the issue. The manifestations of COVID-19 vary from asymptomatic, mild, and moderate to severe and critical ones. Some of the underlying conditions like malnutrition, congenital heart disease, and hydronephrosis might make children susceptible to severe COVID-19. Moreover, children may develop respiratory coinfections like mycoplasma pneumonia, influenza virus, Epstein-Barr virus, respiratory syncytial virus, parainfluenza virus, and adenovirus (Lu & Shi, 2020; Shen & Yang, 2020; Wong, Leo, & Tan, 2020; Xia et al., 2020; Zhang et al., 2020).

Possible sources of infection in children affected by COVID-19 include contact with infected adults (with the history of travel to endemic areas or contact with a person living in such areas), having at least one family member infected with COVID-19, presence in population clusters, living in or traveling to affected areas, having visited a hospital or a history of contact with animals (Cai et al., 2020; Chen et al., 2020; Shen & Yang, 2020; Wang, Wang, Chen, & Qin, 2020; Yang, Liu, Li, & Disease, 2019). Vertical transmission from infected mothers needs further investigations to be clarified as a predisposing factor (Chen et al., 2020; Liu et al., 2020; Lu & Shi, 2020; Zhu et al., 2020).

Prevention

In a case-control study in five hospitals in Hong Kong, Seto et al. revealed that the use of masks could markedly reduce the risk of SARS-CoV infection among healthcare workers. Among surveyed noninfected staff members who wore masks, 15.3% of them were reported to have used paper masks, 30.7% surgical masks, and 54.4%, N95 masks. Contact and droplet precautions alone were shown to be sufficient to protect against SARS-CoV infection. Additionally, no marked difference was revealed between the surgical and N95 masks (Seto et al., 2003). In its May 2003 interim Domestic Guidance on the use of respirators to prevent transmission of SARS, the US Centers for Disease Control and Prevention (CDC) reported that disposable N95 respirators are sufficient for routine airborne isolation precautions. However, in case N95 masks were not available, a surgical mask should be worn ((CDC) CfDcaP, 2003). Regarding SARS, children with mild symptoms and patients with the common flu-like manifestations of the disease at the initial phase could transmit the infection, which demanded early detection and separation of these children (Tian et al., 2020; Yang et al., 2019). Also, suspension of schools, contact tracing, preparing wards with negative pressure ventilation for the infected patients, and practicing hygiene preventions by schools were recommended (Leung, Wong, Hon, & Fok, 2003; Li & Ng, 2005c).

Additionally, WHO supported the use of surgical (procedure) masks when caring for suspects with either possible or confirmed MERS-CoV infection as well as particulate respirators in case of aerosol-generating

procedures ((WHO) WHO, 2013). CDC also supported the use of particulate respirators additional to airborne precautions for all MERS patient care activities ((CDC) CfDcaP, 2014). For MERS prevention, besides points stated for SARS, cooking or pasteurization of camel products and avoidance of contact with camels and their products, touching nose, eyes, and mouth while working with camels were considered (Al-Tawfiq & Memish, 2015; Disease-a-month : DM, 2017; Zumla, Hui, & Perlman, 2015b).

COVID-19 has now turned into an endemic matter, which is spreading rapidly. In order to break this cascade of distribution, some preventive measures are needed both in society and healthcare levels. Some of the precautions needed to be considered by the healthcare system include early identification and isolation of the infected patients in wards with appropriate environmental ventilation, isolation of the neonates born from infected mothers and examining them for COVID-19, training the health care personnel to use adequate personal protective equipment, and optimization of medical intervention and personnel visiting in order to reduce nosocomial transmission. Besides, carrying patients with special vehicles and by fully protected staffs, standard elimination of the dischargeable productions of the patients, and isolation of the infants with the underlying disease early after delivery is necessary to be considered. For the public preventive measures, training via trustable sources, travel controlling and inhibition of the entry from endemic areas, the boundary of the population clusters and canceling the family unions, protection of the susceptible population, and probing the children of the families with at least one contaminated member should be regarded. Also, people should be trained to practice hand hygiene and surface cleaning, use protective outfits when visiting and taking care of the patients, control the source of infection and the route of transmission, and use protective tools while having contact with animals. It is required to disinfect the toys and provide specific protective equipment for children younger than 12 months (Chen, Fu, et al., 2020; Lai, Shih, Ko, Tang, & Hsueh, 2020b; Liu, Wang, et al., 2020; Lu & Shi, 2020; Shen & Yang, 2020; Wang et al., 2020; Wei et al., 2020; Wong et al., 2020; Xu et al., 2020; Yang, Liu, et al., 2020). Furthermore, due to the immunologic and phylogenetic similarities between SARS-CoV, MERS-CoV, and SARS-CoV-2, infection control precautions may be extrapolated from the previous experience with MERS and SARS (Jabbari, Jabbari, Ebrahimi, & Rezaei, 2020). Moreover, Esposito et al. stated that the common use of facial masks is necessary for people's everyday outdoor lives. Masks of different sizes capable of perfectly adapting to the face should be available. Moreover, it is crucial that by strong parental work as well as school lessons on this issue, child cooperation is obtained, and thus, the use of masks in children is preceded (Esposito & Principi, 2020). However, protecting healthy children with mask faces difficulties. Children younger than two years of age are recommended not to wear any type of masks since their very small airways might then struggle to breathe. Furthermore, since without assistance, they may be unable to remove the masks, they can be at high risk of suffocation ((CDC) CfDcaP, 2020b). Surgical masks suitable for children from 3 to 12 years old are now widely marketed, and they can also be prepared at home from commonly available materials at low cost, according to the US Centers for Disease Prevention and Control (Balasubramanian, Rao, Goenka, Roderick, & Ramanan, 2020).

During the process of delivery in the infected mothers, merely essential staff with appropriate personal protective equipment should be present, and the mother has to wear masks and maintain hand hygiene. The resuscitation personnel should keep a distance of at least 2 m between the newborn and the mother. After the delivery, the mother should be encouraged to breastfeeding while wearing a mask (Balasubramanian et al., 2020). Tele triaging patients and quarantines are important strategies to be provided by the health care system (Moazzami, Razavi-Khorasani, Dooghaie Moghadam, Farokhi, & Rezaei, 2020). People should be educated to practice appropriate interpersonal distance and to restrain themselves from touching their eyes and mouth with unwashed hands (Adhikari et al., 2020; Unni, 2020).

Treatment

There is no specific antiviral drug to treat COVID-19, SARS, and MERS. The primary treatment of these conditions involves the correction of electrolyte and acid-base imbalance and oxygenation. In this context, there are no adequate clinical trials in pediatric cases. The treatment protocols for children are, therefore, similar to those for adults (Jahanshahlu & Rezaei, 2020b).

Studies recommend a combination of drug therapy for patients with MERS infection. This combination therapy consists of a nucleoside inhibitor named Ribavirin and subcutaneous interferons (IFNs) such as IFN α -2b and IFN β . It could decrease pulmonary damage and boost the 14-day survival but failed to improve 28-day survival (Schuster & Williams, 2018; Zumla et al., 2015a). Broad-spectrum antibiotics were considered for children with SARS who had symptoms of fever and pneumonia. In phase 2 of SARS infection, systemic corticosteroids might be administered to regulate the immune system and reduce lung damage. Intravenous methylprednisolone pulse therapy was associated with better clinical and radiological outcomes in children with severe SARS infection (Li & Ng, 2005b).

Corticosteroid therapy is also used in patients with severe COVID-19 (; Saghazadeh & Rezaei, 2020a), even though the incorrect use of broad-spectrum antibiotics and corticosteroids could increase the mortality rate in adults with COVID-19. However, patients with severe COVID-19 disease might develop hyper inflammation and a cytokine storm (Bahrami, Vafapour, Moazzami, & Rezaei, 2020b; Nasab, Saghazadeh, & Rezaei, 2020; Rokni, Hamblin, & Rezaei, 2020; Saghazadeh & Rezaei, 2020b; Yazdanpanah, Hamblin, & Rezaei, 2020). Interestingly, COVID-19 seems to happen and become severe in people with primary immune deficiency disorders less than in the general population (Ahanchian et al., 2020; Babaha & Rezaei, 2020). This suggests the role of the immune system in contributing to COVID-19 (Yazdanpanah, Hamblin, & Rezaei, 2020) and therefore indicates the diagnosis and treatment of hyperinflammatory state as crucial for reducing mortality. Hence for this subgroup, immunosuppression using corticosteroids, Janus kinase (JAK) inhibitors, selective cytokine blockade, and intravenous immunoglobulin can be considered (Jahanshahlu & Rezaei, 2020b; Mansourabadi, Sadeghalvad, Mohammadi-Motlagh, & Rezaei, 2020; Mehta et al., 2020; Pashaei & Rezaei, 2020; Pourahmad, Moazzami, & Rezaei, 2020; Ritchie & Singanayagam, 2020).

Moreover, a recent study investigated the role of extracorporeal membrane oxygenation (ECMO) in the management of severely ill individuals with confirmed COVID-19 who develop acute respiratory and cardiac compromise refractory to conventional therapies. This analysis of 32 COVID-19 patients with severe pulmonary compromise supported with ECMO stated that ECMO could be useful in salvaging critically ill participants with COVID-19. However, further studies are necessary to enhance our understanding of the role of ECMO in patients with COVID-19 and ARDS (Jacobs et al., 2020).

Except in critical cases, children with COVID-19 did not require antiviral drug treatment because they could be recovered on their own (). The administration of Remdesivir seems to have positive effects (Mohamed, Yazdanpanah, Saghazadeh, & Rezaei, 2020), but its efficacy has not been proven for children.

Current concerns on pediatric COVID-19

Debate on the epidemiology of COVID-19 in children

In the early stages of COVID-19, it was thought that children were rarely affected by the virus (Wu & McGoogan, 2020). However, current reports suggest that children are just as affected as adults but with milder symptoms, lower disease severity, and lower mortality (Bi et al., 2020; Zimmermann & Curtis, 2020). SARS-CoV-2 is transmitted through human-to-human contact and occurs within both family and social relationships (Lotfi, Hamblin, & Rezaei, 2020). It is difficult for

children, especially toddlers, to follow the principles of hygiene, and baby carriers are expected to transmit the COVID-19. The lack of awareness of the disease in affected children is another possible explanation for the high rate of disease transmission (Fan et al., 2020). Children are likely to expose themselves to other children, friends, and family members, and this directly correlates with the person to person transmission of COVID-19 (Phan et al., 2020).

PCR limitation and antibody detection

There are many limitations to the PCR method, such as high rates of people with false-negative tests. It also takes a long time for the PCR test to tell us the result, so rapid tests are needed to prevent the spread of the coronavirus from suspect cases to the general population (Basiri et al., 2020).

Serological testing based on antibodies can be used for patients with asymptomatic infection. Recently studies reported the development of rapid antibody tests with the use of nucleocapsid and spike proteins as antigens. These tests work based on the detection of both IgG and IgM antibodies in whole blood or serum samples simultaneously. They might take about 15 min and have reasonable specificity and sensitivity (GeurtsvanKessel et al., 2020; Li et al., 2020; Long et al., 2020).

Asymptomatic infection in children

6.7% of children get the infection severely, and the rest is known as asymptomatic carriers. It is, therefore, essential to identify asymptomatic or mild infected children to prevent the virus from spreading (Tezer & Bedir, 2020). Based on the current evidence, viral load in symptomatic cases and asymptomatic carriers is approximately the same. The late identification of asymptomatic carriers makes them a source of uncontrollable infection (Yu & Yang, 2020). As a result, paying attention to children who get the infection less severe than adults and identifying early asymptomatic ones will help prevent the transmission of the virus (Ciuca, 2020).

Social-emotional functioning in children during the pandemic

According to the recommendations of the WHO, it is better not to separate children from their families during this pandemic and ask children to speak about their emotions to give them a sense of calm. There are simple but effective ways to entertain children, such as painting or playing with them. Depending on the age of the children, it is appropriate to provide them with useful disease-related information to the extent of their understanding because they will become more curious during the crisis and ask more questions of their parents (WHO, 2020). According to the behavioral research conducted on children aged between 3 and 18 in Shaanxi, clinginess is the most prevalent problem, especially in younger children (3–6 years old). Since children in epidemic areas suffer from fear, using media as a hobby could help them to forget about their bad feelings (Jiao et al., 2020).

Conclusion

In the past two decades, the world has witnessed three outbreaks caused by coronaviruses: SARS-CoV, MERS-CoV, and SARS-CoV-2. Studies propose a zoonotic origin for these three coronaviruses. These pathogens can affect pediatrics as well as adults. However, the majority of the children show mild manifestations except for the ones with underlying conditions. Among pediatrics, the main signs and symptoms include fever, respiratory symptoms, and other flu-like manifestations. Nucleic acid tests and imaging techniques are used for the diagnosis. Serological tests have reasonable specificity and sensitivity and can also be used for diagnosis of a new infection, recent infection, and re-infection as well (Jabbari & Rezaei, 2020). Public education for practicing hygiene and contact avoidance with infected patients, as well as isolation of the

contaminated people, should be taken into consideration. As no precise drug treatment has been discovered up to date, supportive and symptom alleviating treatments are the principal therapies. However, regenerative medicine and targeted therapies pose potentials to the COVID-19 (Basiri et al., 2020; Fathi & Rezaei, 2020; Mansourabadi et al., 2020; Pashaei & Rezaei, 2020; Rabiee, Rabiee, Bagherzadeh, & Rezaei, 2020; Rezaei, 2020b; Sharifkashani et al., 2020). The potentials need testing at large, and this would be well-achieved when all collaborate (Kafieh et al., 2020; Mohamed et al., 2020; Momtazmanesh et al., 2020; Moradian et al., 2020; Rzymiski et al., 2020).

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E.A.D., F.S., N.D., and Z.R. conceptualized the study and prepared the initial draft. A.S. prepared the final draft. N.R. supervised the project and critically appraised the manuscript.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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