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REVIEW

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Overview: The history and pediatric perspectives of severe acute respiratory syndromes: Novel or just like SARS

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Abstract

Many respiratory viral infections such as influenza and measles result in severe acute respiratory symptoms and epidemics. In the spring of 2003, an epidemic of coronavirus pneumonia spread from Guangzhou to Hong Kong and subsequently to the rest of the world. The WHO coined the acronym SARS (severe acute respiratory syndrome) and subsequently the causative virus as SARS-CoV. In the summer of 2012, epidemic of pneumonia occurred again in Saudi Arabia which was subsequently found to be caused by another novel coronavirus. WHO coined the term MERS (Middle East respiratory syndrome) to denote the Middle East origin of the novel virus (MERS-CoV). In the winter of 2019, another outbreak of pneumonia occurred in Wuhan. China which rapidly spread globally. Yet another novel coronavirus was identified as the culprit and has been named SARS-CoV-2 due to its similarities with SARS-CoV, and the disease as coronavirus disease-2019. This overview aims to compare and contrast the similarities and differences of these three major episodes of coronavirus outbreak, and conclude that they are essentially the same viral respiratory syndromes caused by similar strains of coronavirus with different names. Coronaviruses have caused major epidemics and outbreaks worldwide in the last two decades. From an epidemiological perspective, they are remarkably similar in the mode of spread by droplets. Special focus is placed on the pediatric aspects, which carry less morbidity and mortality in all three entities.

KEYWORDS

acute respiratory distress syndrome, COVID-19, MERS-CoV, Middle East respiratory syndrome, SARS-CoV, SARS-CoV-2, severe acute respiratory syndrome

1 | INTRODUCTION

The term "SARS" was coined by the World Health Organisation (WHO) in 2003 and stands for severe acute respiratory syndrome in patients with a relevant travel/contact history and severe acute respiratory symptoms.¹⁻³ The outbreak was caused by a novel SARS coronavirus (SARS-CoV). In 2012, another epidemic of novel coronavirus broke out in the Middle East region and spread globally; and in the winter of 2019, yet another novel coronavirus outbreak occurred. This overview aims to compare and contrast the similarities and differences of the these three major episodes of coronavirus epidemics. We also aim to highlight the pediatric perspective of these entities, which generally has received less attention in current literature.

2 | SARS 2003

2.1 | Origin of the virus

SARS is a viral respiratory disease of zoonotic origin caused by the SARS coronavirus (SARS-CoV). The origin of SARS-CoV is still unsettled and remains a controversial subject to date. SARS-CoV is phylogenetically divergent from other coronaviruses associated with human infections such as OC43, NL63, 229E, and HKU1, but is closely related to civet and bat CoVs.⁴ However, none of the currently known bat severe acute respiratory syndrome-related coronaviruses (SARS-CoV) is thought to be the direct ancestor of SARS-CoV.⁵ SARS was the first severe and readily transmissible new communicable disease of the 21st century.⁶

2.2 | History of the disease

The epidemic first started around mid-November 2002 in Guangzhou where at least two patients had atypical pneumonia of unknown cause.⁷ The initial cases were meat handlers who had regular contact with wild game.⁴ Shortly after, similar cases were reported in five cities in Guangdong province, however, no escalation of public health measures was announced. By February 2003, the outbreak had unfolded and there were 305 cases reported with five mortalities.⁷ Later in the same month, the SARS outbreak started in Hong Kong, initiated by a physician who traveled from Guangzhou to Hong Kong. The virus quickly spread within his admission hospital and into the broader community.

Between November 2002 and July 2003, this outbreak of SARS in southern China caused an eventual 8098 cases worldwide, resulting in 774 deaths reported in 29 countries, with the majority of cases in China and Hong Kong (9.6% case-fatality rate) according to the WHO.⁸ In Hong Kong, 1755 people were infected and 299 died; 386 infected cases were healthcare workers and eight of them died.^{8,9} No case of SARS has been reported worldwide since 2004. However, suspicious cases were reported from time to time.³

2.3 | Transmission, disease course, and symptoms

The incubation period for SARS-CoV is between 2 and 10 days with a mean of 5 days and up to 13 days, symptoms usually develop 2 to 10 days after the initial infection. The immune response includes immunoglobulin M (IgM) antibody to the SARS-CoV-this peaks during the acute or early convalescent phase (week 3), and declines by week 12. IgG antibody is produced later and peaks at week 12.¹⁰

The first symptom of SARS is fever of 38°C (100.4°F) or higher, followed by nonspecific flu-like symptoms such as chills/rigor, muscle aches and pain, headaches, diarrhea, sore throat, runny nose and malaise. The symptoms usually last about 2 to 7 days. Affected patients may develop a dry cough, shortness of breath, and pneumonia.

In severe cases, the patient can develop respiratory failure and acute respiratory distress syndrome (ARDS). In the SARS outbreak of

2003, about 9% of patients with confirmed SARS infection died.¹¹ The mortality rate was much higher for those over 60 years old, with mortality rates approaching 50% for this subset of patients.¹¹

2.4 | Pediatric perspectives

In the SARS epidemic, there were around 135 pediatric SARS cases reported worldwide, the majority of them in Hong Kong.¹²⁻¹⁶ In pediatric cases, the presenting features can be nonspecific, hence a postive contact history and environmental exposure became very important diagnostic clues. Fever was a consistent symptom in all affected children, and lasted for a median duration of 6 days, while other common symptoms included cough (60%) and nausea or vomiting (41%).^{12,13,17} Teenage patients present with symptoms of malaise, myalgia, chill, and rigor in addition to cough and respiratory symptoms similar to those of adults, while the younger children presented mainly with cough and runny nose.¹³ The symptoms and clinical course were milder and shorter in young children. Lymphopenia was an important laboratory finding but more severe among teenagers.¹³ The most prominent radiological features included patchy infiltrates, opacities, and areas of consolidation predominantly in the lower lobes.¹⁴

No pediatric mortalities were reported in the literature.¹² In a case series of 43 children with SARS in Hong Kong, five required PICU care and one patient required invasive ventilatory support.^{17,18} Children who were 12 years of age or younger generally had a milder illness and more favorable outcome.¹² The pathophysiology of a milder disease course in children is not clear, and proposed yet putative mechanisms include relatively low dosage of ribavirin, shorter course of corticosteroids, and a less mature immune system, resulting in less autoinflammatory injury in the young.¹⁹

Follow-up of SARS patients at 6 months after the illness only showed mild residual changes in exercise tolerance and pulmonary function.¹² Osteonecrosis was reported in children whose SARS treatment included steroids; they remained mostly asymptomatic and managed conservatively.¹⁶

There were two reported cases of transmission from children to adults and no reports of transmission from children to children.⁶ As to vertical transmission, in all reported cases of maternal SARS during pregnancy, the infants survived and no perinatal transmission was detected.⁶

In summary, respiratory symptoms are milder and nonrespiratory symptoms are present in pediatric patients.

3 | MERS 2012

3.1 | Origin of the virus

Middle East respiratory syndrome (MERS) is a viral respiratory infection caused by the MERS-coronavirus (MERS-CoV). Like SARS-CoV, MERS-CoV is a betacoronavirus likely derived from bats with camels as an intermediate host. A strain of MERS-HCoV known as Erasmus Medical Center (EMC)/2012 that was isolated from an infected person in London in 2012 was found to have a 100% match to a virus that affected Egyptian tomb bats. Camels have been shown to have antibodies to MERS-CoV, and are believed to be involved in its spread to humans but it is still unclear how and to what extend this contributed to the outbreak.²⁰

3.2 | History of the disease

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The first identified case occurred in 2012 in Saudi Arabia and most cases have occurred in the Arabian Peninsula.²⁰ On 22 September, 2012, the United Kingdom informed WHO of a case of "acute respiratory syndrome" with renal failure in a previously healthy, 49-year-old male Qatari national with travel history to Saudi Arabia and Qatar. The Health Protection Agency confirmed the presence of a novel coronavirus (human betacoronavirus 2C). WHO coined the interim case definition of "severe respiratory disease associated with novel coronavirus" on 25 September, which was revised on 29 September to "Severe Acute Respiratory Infections associated with novel coronavirus infection" (SARI associated with nCoV). Notably, the definition of SARS for surveillance is not used, while the symptoms and viral etiology all fulfilled the SARS definition. The Department of Health in Hong Kong included "Severe Respiratory Disease associated with Novel Coronavirus" as a statutorily notifiable disease. Originally named "human coronavirus EMC/2012," the virus was finally given the name Middle East respiratory syndrome coronavirus (MERS-CoV).

From September 2012 to January 2020, WHO has been informed of a total of 2519 laboratory-confimed MERS cases globally, including 858 associated deaths (34.4% case-fatality rate) from 27 countries. It is not known if this staggering mortality is related to elusive milder cases that had escaped identification. Cases of MERS mainly originated from countries in the Middle East and 84% of human cases have been reported in Saudi Arabia.²¹ Cases have also been reported in France, Germany, and the United Kingdom, with all European cases having had a direct or indirect connection to the Middle East. In France and the United Kingdom, there had been limited local transmission among close contacts who had not been to the Middle East but had been in contact with a traveler who recently returned from the Middle East. The largest outbreak outside Middle East occurred in the Republic of Korea in 2015, resulting in 186 cases and 39 deaths.²¹ No cases of MERS have been reported in Hong Kong.

3.3 | Transmission, disease course, and symptoms

The mean incubation period for MERS-CoV is 5.2 days, and ranges from 2 to 13 days. Symptoms may range from mild to severe and include fever, cough, diarrhea, and shortness of breath.

Spread between humans typically involves close contact with an infected person. Human-to-human transmission has been limited and

mainly among family members and healthcare workers. There have been clusters of cases in healthcare facilities, where infection prevention and control practices were suboptimal, however, its spread was uncommon outside of hospitals.^{20,22} Overall, 17.9% of the cases reported were healthcare workers.²¹ There have been no reports of sustained human-to-human transmission; thus, its risk to the global population is currently deemed to be fairly low.²⁰ The high morbidity associated with MERS may be spurious due to bias of inadequate sampling that had missed a much larger denominator with elusive milder cases.²³

As of 2019, there was no specific vaccine or treatment for the disease; a number of antiviral medications were being studied.²⁰ The WHO recommends that those who come in contact with camels wash their hands frequently and not touch sick camels, and that camelbased food products should be appropriately cooked. In essence, symptomatic and supportive treatments constitute therapies.

Of the cases reported to WHO, 20.8% had mild to no symptoms while 46.5% had severe disease or died.²¹ MERS is typically more severe in those with other health problems, more than half of the reported cases had had comorbidities (eg, diabetes mellitus, hypertension, heart disease, chronic renal failure, or lung disease), which might explain the high mortality rate.^{20,21} The overall risk of death may be lower than reported as those with mild symptoms may be undiagnosed.²⁴

3.4 | Pediatric perspectives

The rate of pediatric MERS-CoV infection is relatively low in comparison to adults.²³ A large Saudi Arabian study that screened for MERS-CoV by polymerase chain reaction (PCR) testing in a selected at-risk population, including 8032 children (<14 years old) found 0.1% who tested positive when compared with 0.7% in adults.²⁵ The most common source of infection was household contact and acquired infection within a healthcare facility.²⁶

Approximately 42% of affected children are asymptomatic.²⁶ The most common presenting symptoms are fever (57%), vomiting (28%), diarrhea (28%), and cough (14%).²⁶ The severity is lower in comparison to the adult population. In one series of 31 pediatric cases, only one patient required intensive care support and there were no deaths.²⁶ Only two fatal pediatric MERS-CoV cases were found in the literature, and both cases had comorbidities (infantile nephrotic syndrome and cystic fibrosis).²⁷

4 | COVID-19

4.1 | Origin of the virus

The culprit of the recent pandemic in 2020, termed by the WHO as coronavirus disease-2019 (COVID-19), is yet another novel coronavirus; now named SARS-CoV-2. The ultimate origin of SARS-CoV-2 is believed to be bats with a possible unknown intermediate host (possibly pangolins) transmitting the virus to humans.^{28,29}

4.2 | History of the disease

In December 2019, a provincial health commission in China reported a cluster of pneumonia cases with unknown cause in Wuhan of Hubei province. The symptom onset date for the first patient identified was 1 December, 2019.³⁰ According to Wuhan health officials, the pneumonia appeared to be viral in nature and patients were placed in isolation. Potential causes including influenza, avian influenza, adenovirus, SARS-CoV, and MERS-CoV were ruled out.³¹ Since there was highly suggestive evidence that the outbreak was associated with exposure in Wuhan's Huanan Seafood Wholesale Market, the market was closed on 1 January, 2020.³² From 31 December, 2019 to 3 January, 2020, a total of 44 cases of pneumonia of unknown etiology from Wuhan of Hubei province were reported to the WHO. The virus was identified to be a new type of coronavirus on 7 January, 2020. Thailand reported the first case outside China on 13 January, 2020. Subsequently, cases were reported from other provinces in China, Japan, and South Korea. The epidemic has since been spreading rapidly and exponentially worldwide. The first known serious outbreak outside mainland China happened on the "Diamond Princess" cruise ship, where more than 700 people were infected and six died. The first case in Hong Kong was confirmed on 22 January, 2020 in a patient who returned from Wuhan.³³ At the time of writing, there are in excess of 3.6 million confirmed COVID-19 cases and more than 257 000 deaths globally, the case-fatality rate being 7%,³⁴ however, in the absence of sufficient testing to determine the true levels of morbidity, this number should be viewed as an approximation.

4.3 | Transmission, disease course, and symptoms

The mean incubation period for SARS-CoV-2 is estimated to be between 2 and 14 days, with an average of 5 days.³⁵ There is evidence of humanto-human transmission through droplets or direct contact; and precautions should be practiced in the healthcare settings to prevent airborne transmission, which may be underestimated, among many uncertainties about this novel virus.³⁶ There have been confirmed cases in healthcare workers, and the reported cases were 3.8% and 20% of the total confirmed cases in China and Italy, respectively.^{31,37,38} With the ascertainment of asymptomatic carriage, the risk of transmission within the community is very high.³⁹ The most common symptoms include fever, cough, dyspnea, myalgia, or fatigue.³⁰ In a series of 41 cases, only a few patient had prominent upper respiratory tract signs even though abnormalities in chest computed tomography (CT) images were detected among all patients.³⁰ CT chest scans have a higher sensitivity for diagnosis of COVID-19 as compared with PCR swab samples; and the findings include bilateral, subpleural, ground-glass opacities with air bronchograms, ill-defined margins, and a slight predominance in the right lower lobe.^{40,41} Indeed, CT chest abnormalities are now diagnostic criteria in the latest "Novel coronavirus diagnosis and treatment plan" published by the National Health Commission of the People's Republic of China.42

In a report of 72 314 cases prepared by the Chinese Center for Disease Control and Prevention (CDC), a majority (80.9%) of the

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cases were classified as mild, while 4.7% were critical cases.³¹ The age group \geq 80 years old had the highest case-fatality rate at 14.8%.³¹

Treatment is mainly supportive, as no antiviral treatment has been clinically proven to be effective against SARS-CoV-2 and there are no standard treatment guidelines recommended by the WHO. The protease inhibitors lopinavir-ritonavir can be considered, but the results of a recent clinical trial are discouraging.⁴³ Remdesivir and chloroquine have been shown to have good inhibitory effect on SARS-CoV-2 in vitro.⁴⁴ Remdesivir is now undergoing phase II clinical trials in treating patients with COVID-19.⁴⁵ Hydroxychloroquine, sometimes in combination with azithromycin, has been widely used in both Europe and the US with little evidence of efficacy, and early analyses point to increased risk and higher mortality.^{46,47}

Long-term outcome for COVID-19 patients is yet to be determined. The Guangdong Centre of Disease Control and Prevention reported that about 14% of recovered patients were tested postive for SARS-CoV-2 in follow-up checks several weeks after discharge. This is deemed most likely due to residual RNA in clinical samples rather than reinfection.⁴⁸ Given that a robust test has yet to be developed, speculations about results of the testing include false negativity at the time of discharge, inadequate specimen, less desirable site of specimen acquisition (eg, specimen taken from the throat vs the nasopharynx), testing discrepancies, new tests finding the virus in the lower respiratory tract, and reinfection.

4.4 | Pediatric perspectives

Fortunately, infants and children have rarely been involved in the recent COVID-19 outbreak. A systemic review of the literature showed that children accounts for 1 to 5% of diagnosed COVID-19 cases.⁴⁹ In the United States, 1.7% of the reported COVID-19 cases were under 18 years old; while in Mainland China and Italy, 1.3% of the reported COVID-19 cases were less than 19 years old.⁵⁰⁻⁵² Contact and travel history are common, in a case series of 28 confirmed pediatric patients in China, all were either family clusters or had a close contact history.⁵³ The first reported pediatric case in Hong Kong was an imported case with a 16-year-old boy returning from the Diamond Princess Cruise.

Most infected children had relatively milder symptoms and recovered within 1 to 2 weeks.⁵³ Several of the patients had no overt clinical symptoms and were found by positive screening of infected close contacts.⁵³ A study reviewing the epidemiology of 2135 pediatric cases in China revealed the proportion of severe and critical illness to be higher in the younger age group, in particular infants.⁵⁴ In the report by the US Centres for Disease Control and Prevention, among the aged less than 1 year with known hospitalized status, 62% were hospitalized; compared to 4.1 to 14% among those aged 1 to 17 years.⁵⁰ Around 2% of the pediatric cases require admission to the intensive care, which is low comparing to the adult population.⁵⁵ There were less than 10 pediatric deaths reported worldwide.^{31,50}

Children may play a major role in community-based viral transmission and there were evidence of COVID-19 infections in children occurring early in the epidemic.^{56,57} There is no convincing evidence WILEY

of vertical transmission to neonates so far with only a couple of studies finding IgM in neonatal blood, but no viral RNA in samples from the respiratory tract.^{58,59} However, early onset COVID-19 disease in neonates has been reported.⁶⁰

The reason for the decreased incidence in childhood is yet to be clarified, but it has been postulated that children are less susceptible to COVID-19 because of lesser maturity and function of ACE2 receptor, the cell entry receptor of SARS-CoV-2, compared to adults.⁶¹⁻⁶³

5 | SIMILARITIES AND DIFFERENCES OF SARS, MERS, AND COVID-19

Officials and experts compared similarities and differences of the acronyms and believed that they are all novel and impactful syndromes. They may have fever, respiratory symptoms, history of contact or travel, an animal vector and a novel coronavirus, and significant mortality and morbidity. There are relatively minimal or no differences in these acronyms except for the nomenclatures (Table 1). The fact that a significant number of patients with COVID-19 are mildly symptomatic vs patients with SARS and MERS, with low mortality rates, reflects that SARS-CoV-2 resembles other common circulating respiratory viruses. However, the lack of any population immunity against SARS-CoV-2 gives it the ability to cause high attack rates, which can overwhelm and cripple healthcare systems if not managed carefully.

Similarities and differences between SARS, MERS, and COVID-19 are tabulated hereunder (Table 1). It is perhaps unnecessary to coin confusing and seemingly different acronyms for each of these recurring epidemics and coronaviruses.^{1,64,65} The virus for COVID-19 could have been called CoV-19, or the epidemic caused by SAR-CoV2 as SARS-19.



Nomenclature Virus	SARS 2003 SARS-CoV ^{8,12,24}	MERS 2012 MERS-CoV ^{21,22,24,27,69}	COVID-19 (previously as SARI then 2019 nCoV) SARS-CoV-2 ^{29,31,34,35,37,38,50,55,70-74}
Epidemic			
Origin	Foshan city, China	Saudi Arabia	Wuhan, China
Source	Likely from bats, via palm civets	Likely from bat, via dromedary camels	Likely from bats, via pangolins
Spread	Animal to human, then human-to-human	Animal to human, limited human-to-human cases	Animal to human, then human-to-human
Duration of epidemic	Nov 2002 to July 2003, no further case since 2004	Since 2012 until today	December 2019 until today
Global effect	29 countries	27 countries, 84% from Saudi Arabia	Pandemic now
Number of cases worldwide	8096	2494 (still escalating)	Over 3.6 million (still escalating)
Pediatric cases	Yes, around 135 reported case	Yes	Yes, estimated around 176,190 (still escalating)
Healthcare workers infected	21%, 1706 cases	17.9%	3.8% - 20%
Age affected	Median 50	Median 52 y	Majority 30-79 y (86.6%)
	Range 1-91 y	IRQ 37-65 y	
Sex (M, F)	M: 43%, F:57%	M: 64.5%, F: 35.5%	M: 51.4%, F:48.6%
Clinical features			
Principal symptoms	Fever, cough, shortness of breath, diarrhea	Fever, cough, diarrhea, and shortness of breath	Fever, cough, dyspnea
Incubation period	2-10 d	Median 5.2 d	Mean: 5 d
		Range 2-13 d	Range 2-14 d
Travel history	Yes	Yes	Yes
Basic reproduction	Approximately 3	<1	Average 4.2
number, R _o		1-5.7, during healthcare associated outbreak	Range: 1.5-6.49
Outcome			
Major morbidity	Osteonecrosis	No data	No data
Mortality	9.6%, 774 deaths	34.4%, 858 deaths	7%, over 257,207 deaths (still escalating)
Pediatricmortality	No death	2 deaths	Less than 10 deaths, mainly teenagers
Treatment			
Antivirals and treatment	Supportive, ribavirin +corticosteroid	Nil, supportive	Supportive Maybe remdesivir, lopinavir/litonavir, hydroxychloroquine

Abbreviations: COVID-19, coronavirus disease-19; MERS, Middle East respiratory syndrome; SARS, severe acute respiratory syndrome.

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Assuming the next CoV epidemic may recur every 8 years in 2027, the epidemic can be called COVID-27 and the virus CoV-27. They are often severe, always acute, and have pneumonia with respiratory tract symptoms among the more severe cases. In other words, severe acute respiratory syndromes presenting with severe acute respiratory symptoms are here to stay and they are just like SARS.^{3,66}

The syndrome approach (as in SARS) as opposed to disease approach (as in COVID) has its pros and cons (Table 2).^{1,67} Health organizations and authorities should provide consistent definitions for index surveillance, epidemiological and prognostication studies, and refrain from the temptation of coining unnecessary new terminology to describe essentially the same conditions when outbreaks of severe respiratory infection occurs.^{13,65} Travel or contact history is pivotal in formulating management protocol during any outbreak when the pathogen is not initially clear.^{2,68} History of travel or contact provide important clues to emerging infections as evidenced during coronavirus outbreaks in 2003 and 2012, swine influenza pandemic in 2009 as well as the avian influenza outbreak in 2013. In 2003, the WHO coined the term SARS for severe acute respiratory syndrome in patients with a relevant travel/contact history and pneumonia symptoms. Any patient in an epidemic area with fever and cough would be diagnosed as SARS by WHO definition in 2003. The clinical features are essentially the same as for any respiratory viral infections or pneumonitis. Toward the end of the 2003 epidemic, SARS-CoV was identified to be the culprit. Subsequently, it was realized that the clinical features of many patients with laboratory SARS (confirmed by laboratory testing) were neither "severe" nor "respiratory" in nature. Nevertheless, imprecise definition carries serious public health implications as patients may be erroneously

TABLE 2 SARS acronym: more cons than pros

Pros

- The clinical definition can be applied to any similar epidemics for surveillance without knowing the culprit pathogen.
- Sensitive.
- The SARS concept of surveillance is easy to apply in epidemics.
- The acronym is used even in afebrile, asymptomatic carriers or patients with mild and extrapulmonary symptoms in some laboratory-confirmed SARS patients.

Cons

- Stigmatizing many patients because the definition is too nonspecific or too sensitive.
- May not be used for a non-coronavirus (eg, influenza or measles) or another novel coronavirus (eg, MERS) even if the symptoms are severe, acute and respiratory.
- May miss nonfebrile patients or patients with extrapulmonary symptoms.
- Contact or travel history is only good in early phase of an epidemic.
- New acronym has to be coined (eg, MERS for Middle East respiratory syndrome, WARS for Wuhan acute respiratory syndrome, CARS for Canton and MARS for Macau or Moscow acute respiratory syndrome, and COVID-19 for coronavirus disease in 2019).

Abbreviation: SARS, severe acute respiratory syndrome.

quarantined and cities stigmatized. Conceptually, we could think of the infections as a confluence of factors: pathogens (viral, bacterial); exposure (travel, contact history); vector (bat, camel); infectious status (exposed but not infected, asymptomatic carrier, infectious, disease); syndrome (during early phrase of disease as in SARS and MERS); and disease (during late stage when the process becomes apparent as in COVID-19).

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6 | CONCLUSIONS

Apart from the epidemics and novelty of names, these coronavirus are similar in nature and not particularly novel in their clinical presentation. Lower prevalence of these coronavirus diseases in children might be explained by lower exposure in the pediatric population; and as the symptoms are less severe and can even be asymptomatic in children, some cases are not diagnosed. Research to compare the immunopathogenesis of children and adults in responding to SARS-CoV-2 infection might lead to discovery of the possible pathogenesis and treatment strategies for these "recurrent" novel coronavirus diseases. If the opportunity to study this is missed during this epidemic, we might need to wait for another few years before this mystery can be solved—the most vulnerable population of the society might be the answer to the treatment of coronavirus.

Lessons to learn in the past 17 years since the first SARS outbreak include: (a) coronavirus could cause a major global public health crisis every 8 to 9 years; (b) SARS, MERS, and COVID-19 are overlapping syndromes that may be associated with severe ARDS and associated with different coronaviruses; (c) pediatric infection by novel coronaviruses is milder; and (d) treatment is primarily symptomatic in nature. At the time of writing, the most urgent issue at present is to control the COVID-19 pandemic. Vaccination could be an answer to this crisis, but it is likely to take more than a year to develop and manufacture at scale for the worldwide population. As the global battle against the coronavirus continues, alertness in personal hygiene, mass mask-wearing in the community, early prompt quarantine, vigilant contact tracing, surveillance program for testing suspected cases and measures to prevent healthcare related transmission are all the key factors to our success in the global management of coronavirus disease pandemic.

This review compares three distinct entities sharing a commonality of a virus. The pediatrician's view is relief that children are globally far less affected by these infections, and the threat is predominantly that asymptomatic children may transmit the virus to vulnerable adults. The larger view, however, is that the current epidemic is by far more concerning in its impact on morbidity and mortality around the globe. It stands to reason that some of the pernicious profile of today's pandemic is related to delayed recognition of its magnitude and virulence that allowed for spread that went out of control starting in China and followed by the US. However, the disturbing questions about this apparent evolution from relatively smallscale epidemics to a global pandemic are whether this has to do with a serendipitous evolution of a virus with inherently more potent infectivity and transmissibility, and if so what are the determinants of WILEY-

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these characteristics. Whether beyond the virus there might be environmental changes that have occurred over the two-decade history of these infections, that enhance its spread, such as rising temperatures, or other yet to be determined atmospheric changes. It is hoped that because of the devastation that COVID-19 carries in its wake, large efforts will be invested in a search for answers to these questions, and with that, we will all be able to be wiser in dealing with the threats of the future. This will require the combined efforts of a global community, since the current events clearly manifested our interconnectedness and interdependence and hence shared vulnerability in the face of a calamity of previously unexperienced magnitude.

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