Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Epilogue

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Since the start of the 21st century, several viral epidemics have occurred throughout the world, including severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1), Middle East respiratory syndrome (MERS), avian influenza, pandemic H1N1 influenza, Zika virus, and Ebola [1–7]. These outbreaks demonstrated the capacity of emerging viruses to wreak havoc on human populations that lack preexisting immunity, but thankfully, through a combination of public health efforts, novel treatments, vaccines, and luck, the impact on global human health could be mitigated in each outbreak [7]. However, in late 2019, a novel coronavirus, SARS-CoV-2 was identified in China and has subsequently led to a global pandemic of **CO**rona**VI**rus **D**isease **2019 (COVID-19)** [8,9]. This virus has spread ubiquitously across all human populations to the point that the rapid dissemination led to healthcare systems becoming overwhelmed with critically ill patients [9]. In response, many communities and nations temporarily closed schools, public gathering locations, and places of employment in order to prevent the exponential spread of SARS-CoV-2, colloquially known as "flattening the curve" [9,10].

For SARS-CoV-1 and SARS-CoV-2, infected children are relatively spared from the complications observed in older adults [11–17]. This contrasts with outcomes with other viral respiratory diseases, including influenza, respiratory syncytial virus, and human metapneumovirus, where increased morbidity and mortality are observed at both extremes of age (young infants and the elderly) [18–22]. A small proportion of children do develop severe complications of COVID-19, as the Centers for Disease Control and Prevention (CDC) analysis of pediatric COVID-19 cases diagnosed by nasopharyngeal polymerase chain reaction (PCR) between February–April 2020 estimated that 5.7–20% of pediatric cases required hospitalization [13]. In a meta-analysis of published pediatric COVID-19 cases, only 3.3% required admission to the intensive care unit [15]. These percentages are likely overestimates because many cases go unrecognized and were not well captured during the initial surge of cases in the United States because many children developed either no or mild symptoms of infection [13]. Symptoms of pediatric COVID-19 can be nonspecific and have precluded the development of a clinical diagnostic tool based solely on symptoms. Children may present with fever, cough, myalgia, rhinorrhea, shortness of breath, headache, nausea/vomiting, or diarrhea, but many of these symptoms are present in less than half of symptomatic children [11–16].

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Various hypotheses have been proposed to explain the differences in the clinical outcomes of COVID-19 in children and adults [23–25]. Children have fewer comorbidities that increase the risk of poor outcomes, including lower rates of obesity, heart disease, chronic lung disease, and diabetes [11–16]. Conversely, children are frequently exposed to seasonal coronaviruses (229E, NL63, OC43, and HKU1), which may confer cross-protective immunity [25,26]. Cross-reactive CD4+ T cell responses to SARS-CoV-2 in unexposed individuals have been identified, supporting the potential for cross-protective immunity to be induced by infection of other non-SARS coronaviruses [26]. The immune response to SARS-CoV-2 may also be altered in children compared to adults, as significant dysregulation occurs with increased age [24]. This leads to an increased risk of development of a hyperimmune response often referred to as a "cytokine storm," and these age-dependent differences have been observed in mouse models of SARS-CoV-1 infection [27–29]. Children might be at lower risk for becoming infected and transmitting the virus to others, as they may have a reduced expression of angiotensin-converting enzyme 2 (ACE2), the host cell receptor utilized by SARS-CoV-2 to gain entry to cells [30,31]. All of these hypotheses may contribute to the observed differences in COVID-19 in children when compared to adults.

While the vast majority of children recover from SARS-CoV-2 without significant sequalae, a unique pediatric presentation of COVID-19 has been recognized and has been named multisystem inflammatory syndrome in children (MIS-C) [32–34]. This condition was first recognized in children weeks after an initial surge of COVID-19 cases in a community, providing an epidemiological link between this disease and SARS-CoV-2 infection [32–34]. The CDC has defined this condition as a recent SARS-CoV-2 infection by PCR, antigen test, serology, or recent exposure to a known case of COVID-19; the presence of fever, laboratory evidence of inflammation (defined as elevated C-reactive protein, erythrocyte sedimentation rate, fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase, interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes, or low albumin), and multisystem (≥2) organ involvement (cardiac, renal, hematologic, respiratory, gastrointestinal, dermatologic, or neurological) [32]. In a cohort of 186 MIS-C patients in the United States, cases were identified from children <1 year of age to age 20, with a higher proportion of cases occurring in males (62%) and 73% were previously healthy [32]. A majority (71%) of children had four or more organ systems involved with the gastrointestinal (92%), cardiovascular (80%), hematologic (76%), mucocutaneous (74%), and respiratory (70%) systems being the most frequently involved [32]. Cardiac injury is one of the most severe complications of MIS-C as 50% of children had elevations of troponin, 73% had elevated B-type natriuretic peptide, and 48% required vasoactive medications to support their blood pressure [32]. The long-term consequences of MIS-C remain unknown and four children with MIS-C had died by the time of publication [32].

One of the most provocative findings of MIS-C is the overlap in the signs and symptoms that are observed in Kawasaki disease, a medium-vessel vasculitis that can lead to aneurysm of the coronary blood vessels [35,36]. Children with Kawasaki disease commonly present with

persistent fever, rash, conjunctivitis, hand/feet swelling or erythema, lip/tongue changes, and lymphadenopathy [36,37]. In a subset of children, coronary aneurysms will develop, and similar changes have also been observed in 8% of children with MIS-C [32,35]. Currently, the etiology of Kawasaki disease remains unknown despite being first described nearly 50 years ago, with some of the epidemiological data being suggestive of an undiscovered virus [37]. Coronaviruses have been previously associated with cases of Kawasaki disease, including coronavirus species 229E and NL63; however, further follow-up studies did not confirm the same association [38–45]. Given the recent emergence of SARS-CoV-2, this virus cannot be the exclusive cause of Kawasaki disease, but given the emergence of a condition that mimics several of the features of Kawasaki disease, SARS-CoV-2 may provide the important insights into common pathways in the pathogenesis of each disease. Autopsy series of fatal cases of COVID-19 have demonstrated the virus in the predicted tissues of the upper and lower respiratory tracts [46,47]. SARS-CoV-2 has also been detected in endothelial cells of many organs, including the lungs, heart, and kidneys, and is associated with an extensive disruption and inflammation of endothelial cells [48]. The ACE2 receptor is highly expressed on the surface of many cells of the cardiovascular system, including cardiac myocytes and endothelial cells, providing a mechanistic connection between the viral infection and cardiovascular complications like myocarditis or development of coronary aneurysms [49]. While SARS-CoV-2 has been considered primarily a respiratory infection, viral infection of the cardiovascular system is likely an important determinant of COVID-19 morbidity and mortality. Further study is needed to better understand the consequences of cardiovascular inflammation induced by coronaviruses and may lead to the elucidation of the mechanisms of coronary aneurysm formation in MIS-C and Kawasaki disease.

The diagnostic approach for COVID-19 is the same across the age spectrum, with utilization of a reverse transcription PCR for detection of viral RNA in nasopharyngeal or saliva samples during the acute phase of infection [50]. Other body sites are being examined for detection of SARS-CoV-2 to enhance sensitivity or provide prognostic function as many pediatric patients can have prolonged shedding of viral RNA in stool samples [14]. Utilization of serological testing has been mostly beneficial in categorizing children who were recently infected with SARS-CoV-2 and subsequently developed symptoms consistent with MIS-C [32]. Many of the initial commercial antibody assays used for COVID-19 utilize the nucleocapsid antigen, which may lead to false positives due to the detection of cross-reacting antibodies from other coronaviruses and confound studies of the seroprevalence in regions with low rates of infection [50].

Other biomarkers have been used to quantify inflammation from pediatric COVID-19 cases and have been used in the case definition of MIS-C, including C-reactive protein, erythrocyte sedimentation rate, fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase, IL-6, albumin, and complete blood cell counts [15]. Some of these biomarkers have prognostic function in predicting outcomes in adult COVID-19 cases, including IL-6 and other

cytokines, but the utility of these tests in children are unknown, especially given that the few pediatric fatalities have occurred [51,52]. These tests may provide some benefits in identifying patients with high risk of cardiovascular and hematological complications, as up to 70% of adult fatalities have evidence of hypercoagulable state, 7–28% of hospitalized adults have evidence of myocardial injury, and up to 50% of deaths exhibit concomitant evidence of heart failure [52,53].

The SARS-CoV-2 pandemic triggered an unprecedented mobilization of medical providers, scientists, epidemiologists, and experts across many scientific fields to rapidly redirect the efforts to study all the aspects of SARS-CoV-2 and COVID-19. The lessons learned from this pandemic will hopefully serve as an important foundation on how to prevent and mitigate future emerging infections in modern society, as SARS-CoV-2 will not be the last global threat to human health.

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