The Resilient Child: Sex-Steroid Hormones and COVID-19 Incidence in Pediatric Patients

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Coronavirus disease–2019 (COVID-19), a disease caused by Severe Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection, has become an unprecedented global health emergency, with fatal outcomes among adults of all ages in the United States, and the highest incidence and mortality in adult men. As the pandemic evolves there is limited understanding of a potential association between symptomatic viral infection and age. To date, there is no knowledge of the role children (prepubescent, ages 9-13 years) play as "silent" vectors of the virus, with themselves being asymptomatic. Throughout different time frames and geographic locations, the current evidence on COVID-19 suggests that children are becoming infected at a significantly lower rate than other age groups—as low as 1%. Androgens upregulate the protease TMPRSS2 (type II transmembrane serine protease-2), which facilitates efficient virus-host cell fusion with the epithelium of the lungs, thus increasing susceptibility to SARS-CoV-2 infection and development of severe COVID-19. Owing to low levels of steroid hormones, prepubertal children may have low expression of TMPRSS2, thereby limiting the viral entry into host cells. As the world anticipates a vaccine against SARS-CoV-2, the role of prepubescent children as vectors transmitting the virus must be interrogated to prepare for a potential resurgence of COVID-19. This review discusses the current evidence on the low incidence of COVID-19 in children and the effect of sex-steroid hormones on SARS-CoV-2 viral infection and clinical outcomes of pediatric patients. On reopening society at large, schools will need to implement heightened health protocols with the knowledge that children as the "silent" viral transmitters can significantly affect the adult populations.

In February 2020 the World Health Organization (WHO) formally named the novel coronavirus outbreak triggered by 2019-nCoV as *coronavirus disease–2019* (COVID-19). The Internal Committee of Taxonomy of Viruses then named the disease *severe respiratory*

syndrome coronavirus 2 (SARS-CoV-2), another β-coronavirus cluster related to the severe acute respiratory syndrome (SARS) of 2003 and Middle East respiratory syndrome (MERS) of 2012 (1, 2). As of May 5, 2020, the global pandemic had caused more than 3.5 million cases and 240 000 deaths, with numbers rising each day [3].

Person-to-person transmission of the virus includes droplet inhalation transmission and contact transmission through oral, nasal, and eye mucous membrane contacts [4]. Symptoms of the virus vary depending on the patient but often include fever and dry cough, whereas others suffer from fatigue, dyspnea, nasal congestion, nausea, or diarrhea [5]. The inflammation-driven damaging phase involves viral-induced tissue destruction, compounded by the development of cytokine-release syndrome causing debilitating effects [6]. Cases worsen and lead to acute respiratory distress syndrome or the development of pneumonia. However, diagnosis is often complicated by a large portion of patients who are asymptomatic [7]. Those with preexisting conditions, such as diabetes, hypertension, and pulmonary, cardiac, and kidney disease, are considered to be at higher risk of developing a severe form of the disease [8-10]. Sex and age have also been important risk factors because men and older populations are most at risk of contracting the infection and developing more serious disease [11-14]. The potential involvement of certain human leukocyte antigen haplotypes in increasing susceptibility to infection supports a genetic predisposition [6]. This review discusses the current evidence on the incidence of COVID-19 in children and the role of sex-steroid hormones in the rate of SARS-CoV-2 infection and the clinical outcomes in pediatric patients.

1. Coronavirus Disease–2019 Clinical Presentation in Pediatric Patients

The incidence of COVID-19 in children has been significantly lower compared to adults, with clear underrepresentation when taking into account the age proportions of the overall population. Comprehensive Centers for Disease Control and Prevention (CDC) data reported that between February 12 and April 2, 2020, patients younger than 18 years accounted for only 1.7% of US cases [11]. Among all 2572 COVID-19 cases in children younger than 18 years, the median age was 11 years (range, 0-17 years); 59% were age 10 to 17 years, 26% were age 1 to 9 years, and 15% were younger than 1 year [11]. Early reports from China echoed the recent US findings. A study presenting the 72 314 cases diagnosed by the Chinese Center for Disease Control and Prevention showed that most cases were in the adult age range of 30 to 79 years (87%), with only 1% age 10 to 19 years, and 1% age 9 years or younger. There were also no deaths that occurred in children younger than 9 years [15]. The current evidence on COVID-19 indicates that children are becoming infected at a significantly lower rate than other age groups—as low as 1% of reported cases in most case studies [11, 16, 17]. Similar trends were seen during the SARS epidemic, as children younger than 12 years had less-severe cases of the disease, no deaths reported, and the disease was seen to increase in severity with age [18].

This trend may be due in part to the lack of testing in pediatric patients, as a large number of infected individuals are asymptomatic [5, 11, 16, 19, 20]. Children are just as likely to be exposed to and contract SARS-CoV-2 but are less likely to be symptomatic for COVID-19 and thus are less likely to be tested as well [21]. As similar rates were detected among the pediatric population during the SARS epidemic, there may also be an underlying molecular mechanism decreasing the susceptibility of children to developing a severe form of COVID-19 disease. Thus, case count is not always an accurate measurement of incidence, because there are asymptomatic children who are affected by COVID-19 but are not part of the case count because of the lack of testing [19, 20]. Among symptomatic children who were tested, the incidence of COVID-19 was still low. In an early report from the Wuhan Children's Hospital, 1391 children who had upper respiratory symptoms resembling those of SARS-CoV-2 infections were assessed and only 171 (12.3%) had COVID-19, with the median age of COVID-19–positive patients being 6.7 years, a younger median age than the CDC report from the United States because of the younger population studied [17]. Death

count, which is another more standardized measurement that has been used to control for testing capabilities, has also been low in the pediatric population, with some case reports reporting 0% to 0.2% deaths in patients younger than 19 years [11, 22]. Furthermore, 80% of the CDC-reported severe cases in children were those who had an underlying condition, with the most common being chronic respiratory problems like asthma [11]. The incidence, case count, severity of symptoms, and death rate are all lower in pediatric patients compared to adult populations (Table 1) [22-28].

The pediatric experience at Mount Sinai supports the concept that children are less severely affected by COVID-19 than adults. Between March 1 through April 24—representing the height of the pandemic in New York City—29 children were admitted to the Kravis Children's Hospital at Mount Sinai with COVID-19. Ages ranged from 4 weeks to 21 years. There were 16 male and 13 female patients. The average length of stay for this group was 4.5 days. Five of the 29 patients received intensive care unit (ICU)-level care. None required intubation and there were no deaths in the cohort. Two of the patients were babies in the neonatal intensive care unit, where the average length of stay was 2 days. At the end of April 2020, past the initial adult peak in New York City, reports began emerging of children with symptoms unlike the respiratory symptoms of cough and shortness seen in adults. Children have presented with skin rashes, conjunctivitis, and an inflammatory vascular phenomenon that involves the heart. Initially high fever, tachycardia, and hypotension were noted, in some cases precipitous decompensation requiring ICU admission occurred. As of this report, 7 patients with this syndrome have required ICU care, including 1 who required extracorporeal membrane oxygenation; no fatalities have been seen. Resemblance to the pediatric illness Kawasaki disease has been noted. Interestingly, one of these patients tested negatively on 3 occasions for COVID-19, only to have a later bronchial lavage sample be positive. On May 3, 2020, an international conference confirmed the pathophysiology in a similar cohort of pediatric patients in Europe.

Typical symptoms in children include fever, cough, and shortness of breath (Table 1) [11, 22, 23, 29]. Symptoms among pediatric patients tend to compare in nature to those in adults, though the overall severity of the symptoms and frequency of manifestation is lower [22]. However, the sex discrepancy in the incidence of COVID-19 among adults is not reflected in the pediatric population. Men have a significantly higher risk of ICU admission and death than women diagnosed with COVID-19 [12]. In the pediatric population, there have been no significant differences in the number or severity of COVID-19 cases across sex (Table 1) [16]. Thus, the different incidence rates between sexes appears only with adulthood, suggesting hormonal changes and sexual maturity may affect viral transmission and clinical symptom manifestations.

The low case number for pediatric patients being treated for COVID-19 presents a limitation in determining transmission patterns among this young population. In a case report tracing the transmission cluster of one pediatric case in France, a child who tested positive for COVID-19 visited 3 schools, and 169 individuals had been in contact with the student. Of these contacts, 70 individuals presented with respiratory symptoms. After testing 73 of these contacts, only 13 tested positive for COVID-19 [30]. The low incidence among the contacts of confirmed positive children raises the possibility that SARS-CoV-2 follows a transmission process different in children from that in adults, affecting the rate of viral infection and clinical manifestation of COVID-19 [22, 30]. Moreover, it was reported that the virus in pediatric patients is present in higher levels in stool samples than in the respiratory epithelium, raising the possibility that the virus may be transmitted through fomites from contaminated feces instead of the suspected transmission through respiratory droplets in this population [31].

In efforts to define the transmission dynamic among pediatric patients, one must also consider the potential spread through expecting mothers. A recent systematic review of cases in pregnant women recommended that pregnant women be treated as high-priority patients because of their immunosuppression [32, 33]. Others have reported no severe or lethal cases in pregnancy, with some even suggesting a protective effect of pregnancy [34-37].

In one report, it was suggested that there was no vertical transmission of the viral from mother to fetus because of the absence of the virus in the amniotic fluid, cord blood samples, and breast milk, as well as swabs from the newborns [37]. Of the reported cases of vertical transmission, the positively testing neonates recovered safely [22, 38, 39]. Similar patterns were also shown in SARS, with no evidence of vertical transmission from infected mothers to their children [18].

The question thus arises as to a cutoff age for children for SARS-CoV-2 infections and viral propagation. In addition to the lower case counts among pediatric patients, there is a particularly lower incidence among younger children. In a large CDC cohort, 25% of pediatric patients were age 1 to 10 years, whereas nearly 60% of pediatric patients were age 10 to 19 years [11]. This could be caused by the immunological changes and increasing hormone levels associated with puberty, but it is also important to understand the effects of adrenarche and the production of androgens in this process. Adrenarche is an early stage in sexual maturation in both sexes, in which the adrenal glands secrete increased levels of weak adrenal androgens including DHEA (dehydroepiandrosterone), DHEA-S (dehydroepiandrosterone sulfate), and A4 (androstenedione) without increased cortisol levels [40]. It is a process related to puberty but distinct from hypothalamic-pituitary-gonadal axis maturation and function [41]. Adrenarche occurs on average at age 6 to 8 years and precedes puberty by about 2 years [40]. Puberty in girls usually lasts from around age 8 to 14 years, and for boys, it lasts from age 10 to 16 years on average. The similar sex compositions across ages among COVID-19 pediatric patients suggest effects from adrenarche rather than puberty, as the synchronous hormonal changes increase susceptibility across both sexes until adulthood when men are at increased risk because of higher androgen levels [42, 43].

2. Molecular Mechanisms of Severe Respiratory Syndrome Coronavirus 2 Infection

Structural Spike (S) proteins drive entry of coronaviruses SARS-CoV and SARS-CoV-2 into target host cells by engaging the cellular receptor angiotensin-converting enzyme 2 (ACE2) and facilitating the viral attachment to target cells [44]. This step is also functionally associated with activation of cellular TMPRSS2, a type II transmembrane serine protease that drives the entry of virus into the target cell and is regulated by androgen receptor signaling. Successful SARS-CoV infection is dependent on the proteolytic activity of TMPRSS2, which results in cleavage of SARS S protein at multiple sites [45]. Proteolytic cleavage of SARS S protein by TMPRSS2, known as S priming, mediates efficient virus-host cell fusion and decreases virus sensitivity to neutralizing antibodies [46]. ACE2 depletes angiotensin I and II (Ang I and II) levels by directly catalyzing the compounds and converting Ang I to angiotensin 1 to 9 and Ang II to angiotensin 1 to 7, known vasodilators acting through Mas receptor with antifibrotic, antiproliferative, and anti-inflammatory effects [8, 47-49]. ACE2 expression is elevated in patients with cardiovascular conditions, diabetes, and hypertension, comorbidities that confer a higher risk of mortality to COVID-19 [50-52]. Thus, inhibition of the renin-angiotensin system may affect COVID-19 outcomes by decreasing the proinflammatory activity of Ang II or increasing virulence in the heart and lungs because of the increased ACE2 expression [10].

ACE2 and TMPRSS2 are both coexpressed on ciliated bronchial epithelial cells and type II pneumocytes, the epithelium of the small intestine, and podocytes and the brush border of proximal tubule cells of the kidney, facilitating routes for SARS-CoV-2 infection [53]. Compared to women, men have higher ACE2 expression and activity in the kidneys and higher expression of TMPRSS2 in the lungs [54, 55]. There is also the potential for sex hormones to affect levels of activity of these receptors [56]. Not only might this affect the sex disparities in disease incidence, it could also have implications for the infection rate in children who physiologically have low levels of sex hormones [57]. It is critical to understand the underlying mechanisms of the low incidence of COVID-19 in pediatric patients and their capacity to be silent vectors while being asymptomatic [11, 16].

Table 1. Summary of current literature on COVID-19 incidence in pediatric patients

Study	Location	Time frame in 2020	Pediatric count	Ages (range)	Sex	Symptoms	Days to symptom onset (range)	Deaths	Comorbidities
Cai et al, 2020 [29]	Shanghai, China	January 19-February 3	10	Mean 6.1 y (3 mo-11 y)	1:1.5	Fever 8 (80%) Cough 6 (60%) Sore throat 4 (40%) Nasal congestion 3 (30%) Sneezing and rhinorrhea 2 (20%)	Mean 6.5 d (2-10 d)	0	
CDC, 2020 [11]	United States	February 12-April 2	2572/149 802 (1.7%)	Median 11 y (0-17 y)	57% male, 53% female	73% fever, cough, or shortness of breath		3	Of 345 cases with information: 80 (23%) at least 1 40 chronic lung disease (including asthma) 25 cardiovascular disease 10 immunosuppression
Dong et al, 2020 [16]	Mainland China	January 16-February 8	2143	Median 7 y	57% males, 43% female	Asymptomatic 94 (4.4%) Mild 1091 (50.9%) Moderate 831 (38.8%)	Median 2 d (0-42 d)	1	
Liu et al, 2020 [80]	Wuhan, China	January 7-January 15	6	Median 3 y (1-7 y)	33% male, 67% female	High fever 6 (100%) Cough 6 (100%) Vomiting 4 (66.7%)		0	
Lu and Shi, 2020 [38]	Wuhan, China	January 28-February 26	171	Median 6.7 y (1 d-15 y)	61% male, 39% female	Asymptomatic 27 (15.8%) Cough 83 (48.5%) Pharyngeal erythema 79 (46.3%) Fever 71 (41.5) Diarrhea 15 (8.8%) Fatigue 13 (7.6%) Rhinorrhea 13 (7.6%) Vomiting 11 (6.4%) Nasal congestion 9 (5.3%)		1	

Table 1. Continued

Study	Location	Time frame in 2020	Pediatric count	Ages (range)	Sex	Symptoms	Days to symptom onset (range)	Deaths	Comorbidities
Qiu et al, 2020 [28]	Zhejiang, China	January 17-March 1	36	Mean 8.3 y (1-16 y)	64% male, 36% female	None 10 (28%) Dry cough 7 (19%) Dyspnea or tachypnea 1 (3%) Pharyngeal congestion 1 (3%) Sore throat 2 (6%) Vomiting or diarrhea 2 (6%) Fever 13 (36%) Headache 3 (8%)		0	None
Tang et al, 2020	Shenzhen, China	January 16-February 8	26	Mean 6.9 y (0-13 y)	35% male, 65% female	None 9 (35%) Fever 11 (42%) Cough 12 (46%) Rhinorrhea 2 (8%) Vomiting 2 (8%) Diarrhea 10 (38%)		0	None had underlying conditions
Wang et al, 2020	6 provinces in mainland China	January 25-February 21	31	Mean 7.1 y (6 mo-17 y)	48% male, 52% female	Fever 20 (65%) Cough 14 (45%) Fatigue 3 (10%) Diarrhea 3 (9%)	Mean 5 d	0	
Xia et al, 2020	Wuhan, China	January 23-February 8	20	Median 2.13 y (1 d-14.6 y)	65% male, 35% female	Fever 12 (60%) Cough 13 (65%) Diarrhea 3 (15%) Nasal discharge 3 (15%) Sore throat 1 (5%) Fatigue 1 (5%) Vomiting 2 (10%) Tachypnea 2 (10%)		0	Seven (35%) had history of congenital or acquired disease
Xu et al, 2020	Guangzhou, China	February 20	10	(2 mo-15 y)	60% male, 40% female	Asymptomatic 1 (10%) Coughing 5 (50%) Sore throat 4 (40%) Nasal congestion/rhinorrhea 2 (20%) Diarrhea 3 (3%)		0	

Abbreviations: CDC, Centers for Disease Control and Prevention; COVID-19, coronavirus disease–2019.

3. Mechanistic Considerations in Diagnosis in Children

ACE2 has been a common target of potential therapies against COVID-19; however, it is unknown whether this important viral receptor contributes to the lower incidence of COVID-19 in pediatric patients [58, 59]. Several studies have reported no significant differences in lung ACE2 expression levels across sexes, implying that sex-related differences in ACE2 expression are not driving the sex-related difference in disease severity [55, 56]. Of the 3984 exomes for ACE2 obtained from a large Italian cohort, there were no significant differences in the burden of rare deleterious variants as compared to European and East Asian cohorts [55]. The most common single-nucleotide polymorphism difference in variants between the European populations and East Asian populations was rs2285666 (also called G8790A) [55]. This variant has been studied as a potential risk factor for hypertension, type 2 diabetes, and coronary artery disease—comorbidities that increase susceptibility to SARS-CoV-2 infection and severe virulence [60, 61]. Therefore, ACE2 and genetic variations of its target genes are important to the predisposition of certain populations to higher SAS-CoV-2 infection, although independent of sex-steroid hormones.

TMPRSS2 is essential for entry of a variety of viruses, such as SARS-Cov-2, MERS-Cov, human coronavirus 229E (HCov-229E), influenza A virus, and influenza B virus, in the primary human type II pneumocytes and enhances the virulent effects on the host [46, 62, 63]. Subsequently, there is emerging therapeutic potential of TMPRSS2 inhibitors in the treatment of COVID-19 [46, 64]. The *TMPRSS2* gene, located on human chromosome 21, has several androgen receptor elements and TMPRSS2 protein is expressed in an androgen-dependent manner both in prostate and lung cancer cells [65, 66]. Androgen-regulated TMPRSS2 in prostate cells has been demonstrated to play a role both in normal male reproduction and in the progression and metastasis of prostate cancer [67]. Its expression in the lung and sputum has been found to be higher in men than in women [62, 68]. This is consistent with the increased susceptibility of men to COVID-19 because the increased TMPRSS2 allows for increased viral entry [64]. *TMPRSS2* also has an estrogen-responsive promoter, a mechanistic step that may be of significance in the hormonal control in pediatric patients as compared to adults [69]. Because prepubertal children have lower levels of sex-steroid hormones, they have lower TMPRSS2, resulting in a lower disease incidence and severity in this age population.

Although there is evidence that estrogens may influence TMPRSS2 activity, the main driver of expression of TMPRSS2 appears to be androgens [62]. Adrenarche, as mentioned previously, is then an important time marker for increasing susceptibility in pediatric patients. Data support that children ages 10 years and older of both sexes have a higher incidence of COVID-19, suggesting the entrance into adrenarche and production of androgen may increase susceptibility to the virus [11]. The presence of androgens may be even more important than preexisting conditions, such as asthma, in the pediatric population. The TMRPSS2 expression in sputum was found to be no different in asthma patients as compared to healthy patients, yet was still increased in adult men as compared to adult women [68]. Because of these androgenic effects, there is the potential to decrease the viral entry of host cells and prevent severe disease in high-risk individuals through the use of androgen-synthesis inhibitors, used in the treatment of advanced prostate cancer [70]. The evidence so far supports the idea that with lower levels of androgens and estrogens, pediatric patients have a low expression of TMPRSS2, limiting the extent of viral entry into host cells because of decreased protease activity; the lower viral load would lead to less-severe symptoms among children [71].

4. Severe Respiratory Syndrome Coronavirus 2 Infection in Children: Environmental and Hormonal Reasoning

In addition to the potential molecular mechanisms contributing to the decreased incidence and severity of COVID-19 in pediatric patients, other physiological and environmental

factors may be at play. In general, the pediatric population is exposed to fewer harmful environmental factors, such as smoke and air pollution, which allows them to have healthier respiratory tracts [72]. However, prior studies in low-income communities have shown differential susceptibility to some infectious diseases in children based on existing environmental, economic, and psychological factors [73, 74]. Psychological stress is higher among low-income families and their children, resulting in impaired immune function and hence higher susceptibility to epidemic diseases [75, 76]. Malnutrition in children is also a driving mechanism for acute respiratory infection and related mortality [77-79]. Disparities in vaccine uptake rates could cause differential susceptibility once exposed to the virus. Vaccine uptake rates are likely to differ by socioeconomic status, including access to health insurance [73, 74].

The child population is constantly exposed to a variety of coronaviruses that make up colds and flus that circulate endemically. These prior exposures could increase the resilience of children's immune systems [18]. A study in France tracking infections spread among schools and family clusters found greater dissemination of picornaviruses and influenza among the pediatric population of both groups. The results suggest these infections are more easily transmitted and potentially more infectious than COVID-19 in children [30]. These results were confirmed in a hospital study of pediatric patients in a hospital in Wuhan, China. Of 366 patients with respiratory infections, 6.3% were detected to have influenza A, 5.5% had influenza B, and only 1.6% tested positive for COVID-19 [80]. Inversely, exposure to other viruses and viral interference could potentially make these patients *more* susceptible to contracting the novel coronavirus, a trend seen by the interaction between H1N1 influenza virus and respiratory syncytial virus [81].

5. Coronavirus Disease–2019 and Educational and Psychosocial Health Challenges in Pediatric Patients

Despite the lower incidence in the pediatric population, children have suffered from the disease in other indirect ways. Global preventive measures of COVID-19 through social distancing have prompted the closure of schools [82]. Though reducing COVID-19 incidence and mortality rates, the impact of school closures can have significant health, economic, and societal consequences for children [85, 86]. These effects are likely to be more prominent in disadvantaged families and their children and may result in mental health challenges, more compromised nutrition, and economic costs to families who have suffered wage loss because of COVID-19 [84, 87]. For many children, the COVID-19 crisis will mean falling academically further behind their peers, further increasing existing gaps in educational inequalities because of the lack or limitation of internet access and availability of learning materials. In spite of the reduced COVID-19 risk in children, reopening schools may increase the risk of this disease in teachers and ultimately increasing the risk for the larger community [86].

According to the Human Rights Watch, even though children are less likely to experience severe symptoms of or die with COVID-19 compared to different age groups, job and income loss and economic insecurity among families are likely to increase rates of child labor and sexual and physical exploitation (87). The high rates of COVID-19 mortality are also likely to result in large numbers of children losing close family members, thereby increasing their psychological and physical vulnerability. For children living in institutional environments such as refugee camps, justice systems, immigration detention centers, or orphanages, the risk of COVID-19 and its physical and psychological consequences are higher because of the close proximity to other infected individuals, limited access to water and sanitation, and other environmental and health conditions that contribute to the lack of proper health care [87].

6. Future Directions

The concept that androgens correlate directly with TMPRSS2 activity and vulnerability to severe SARS-CoV-2 infection requires evaluation at the cellular and epidemiological level. It will be significant to determine whether children with higher androgen levels—whether endogenous, as in intersex/disorders of sex development conditions (congenital adrenal hyperplasia) or exogenous, as in transgender adolescents who undergo cross-sex induction of puberty—demonstrate increased susceptibility to COVID-19 compared to their age- and chromosomal–sex-matched peers. Conversely, children with hypogonadism, whether natural or induced by puberty blockade, may be relatively protected from infection. If patients with hyperandrogenism are determined to be more vulnerable to infection, they and their families would be empowered to assume extra precautions.

When proposing the study of sex-gender minority populations, especially children who cannot provide their own informed consent to research, it is vital to consider not only the scientific merit of the project, but also its moral ramifications. For patients with intersex/disorders of sex development and transgender conditions, COVID-19 reinforces the social isolation and alienation from a culture that conflates sex with gender and perceives both as male/female binary. Historically, many of these patients experienced their involvement in research and clinical care as stigmatizing and traumatic, issues that are further challenged by the isolating measures of the ongoing pandemic [88].

As the COVID-19 pandemic evolves globally, the current knowledge at the molecular level implies that this disease is biologically under sex-steroid control, allowing investigators to better understand why most children are clinically "silent" carriers of the virus. In addition to TMPRSS2 activity, driving increased susceptibility to and cell internalization of SARS-CoV-2, further mechanistic insights into the hormonal regulation of immunological responses also invite an exploration of sex- and age-related differences. The direct action of androgens (driven by local precursor synthesis and metabolic alterations) in human lungs must be investigated. The strategy to address these issues will involve the potential use of induced pluripotent stem cell technology as a means to develop individual-specific lung epithelial cell lines and organoids that could be used to exploit SARS-CoV-2 entry into human cells directly. Infected patients' specific derived alveolar cells dully differentiated under "reprogramming factors" could potentially populate tissue-engineered lungs, providing a cell model for functional interrogation of lungs from COVID-19 patients and drug testing against the disease [89]. Induced pluripotent stem cells can be differentiated to alveolar epithelium through exposure to a variety of different culture conditions and growth media. The ultimate success of differentiated cells for translational medicine applications will depend on further advances in the understanding of the effect of steroid hormones and SARS-CoV-2 infection in human lungs, using in vitro cultures and organoids, from different induced pluripotent stem cells to cells resembling respiratory epithelium in vitro.

At the time of submission of this review (early May 2020), there were emerging reports on a pediatric multisystem postinfectious inflammatory syndrome (myocarditis, high fever, and hypotension) resembling the pediatric Kawasaki disease in SARS-CoV-2–infected children; this clearly merits further investigation immediately. Global initiatives and policies are needed to understand the COVID-19 pandemic to strengthen the health protection and social wellness for the most innocent and yet apparently most resilient members of our population, the children.

Additional Information

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Data Availability: Data sharing is not applicable to this article because no data sets were generated or analyzed during the present study.

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