Coronavirus Disease 2019 (COVID-19) in Neonates and Children From China: A Review

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At the end of 2019, a novel coronavirus began to spread in Wuhan, Hubei Province, China. The confirmed cases increased nationwide rapidly, in part due to the increased population mobility during the Chinese Lunar New Year festival. The World Health Organization (WHO) subsequently named the novel coronavirus pneumonia Coronavirus Disease 2019 (COVID-19) and named the virus Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). Soon, transmission from person to person was confirmed and the virus spread to many other countries. To date, many cases have been reported in the pediatric age group, most of which were from China. The management and treatment strategies have also been improved, which we believe would be helpful to pediatric series in other countries as well. However, the characteristics of neonatal and childhood infection still have not been evaluated in detail. This review summarizes the current understanding of SARS-CoV-2 infection in neonates and children from January 24 to May 1, as an experience from China.

Keywords: neonates, children, coronavirus, COVID-19, SARS-CoV-2

INTRODUCTION

From 2002 to 2003, the outbreak of severe acute respiratory syndrome (SARS) in Guangzhou, China, caused a global epidemic, which brought widespread concern about a coronavirus epidemic (1). Later, another zoonotic coronavirus pathogen, known as the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), spread in the Middle East from 2012, and the disease was named Middle East respiratory syndrome (MERS) (2). A new type of coronavirus was recently reported in Wuhan, Hubei Province, China, which also causes severe respiratory disease. The outbreak of the disease began in China, and has brought a heavy burden on the whole world (3). Considering that newborns and children are susceptible to infectious diseases, the prevalence of the disease among them is the subject of much attention. The strategy in dealing with the cases in neonates and children, as well as a healthy pediatric age group, form elaborate plans in fighting against the novel coronavirus disease. Such experience from the Chinese government and hospitals may also benefit the rest of the world. Here, we review the advances of current research from January 24 to May 1 in the epidemiology, clinical manifestations, management, and treatment of this disease in newborns and children. Cases and recommendations in the pediatric age group from China, published either in English or Chinese, are included.

SEARCH STRATEGY

References for this review were identified through searches of PubMed for articles published from January 1, 2003, to May 1, 2020, by use of the terms "coronavirus," "neonate," "children," "COVID19," and "SARS-CoV-2." Relevant articles published between 2003 and 2020 were identified through searches in the authors' personal files. We further searched the recent online articles from the COVID-19 Academic Research Communication Platform of Chinese Medical Journal Network, where the latest relevant Chinese articles are published. Some news and policies from WHO are also involved for the latest information of COVID-19. Articles published in English and Chinese were included. Articles resulting from these searches and relevant references cited in those articles were reviewed.

EPIDEMIOLOGY OF COVID-19

Background

In late December 2019, Wuhan, Hubei Province, China reported for the first time a large cluster of patients with unexplained pneumonia associated with the wholesale Huanan Seafood Market (4). Subsequently, the Chinese Center for Disease Control and Prevention (China CDC) sent a rapid response team to identify the source of the pneumonia virus cluster, and then isolated and sequenced a new coronavirus, named 2019 novel coronavirus (2019-nCoV) (5). The World Health Organization (WHO) subsequently named the novel coronavirus pneumonia Coronavirus Disease 2019 (COVID-19) and named the virus Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). Since the virus was transmitted to additional family members by a family (including a 10-year-old asymptomatic child) returning to Shenzhen from Wuhan, widespread transmission had quickly emerged from person to person (6). As the Chinese Lunar New Year festival approached, population mobility had increased and the virus had spread rapidly throughout the country (7). Although the incubation period values are very similar to SARS or MERS, the transmission of COVID-19 may be more rapid, because of the possibility of transmission during the incubation period (8, 9). Specifically, some patients may be completely asymptomatic carriers who have passed symptom-based screening, but RT-PCR was positive for SARS-CoV-2

Abbreviations: 2019-nCoV, 2019 Novel coronavirus; ACE2, angiotensin-converting enzyme 2; ARDS, acute respiratory distress syndrome; BALF, bronchoalveolar lavage fluid; CARVER, Cas13-assisted viral expression and read restriction; China CDC, Chinese Center for Disease Control and Prevention; China NHC, National Health Commission of the People's Republic of China; CoVs, Coronaviruses; COVID-19, Coronavirus Disease 2019; DIC, disseminated intravascular coagulation; hSIOs, human small intestinal organoids; IUGR, intrauterine growth restriction; IVIG, intravenous immunoglobulin; MERS, Middle East respiratory syndrome; MERS-CoV, Middle East Respiratory Syndrome Coronaviruses; mNGS, metagenomic next-generation sequencing; NRDS, neonatal respiratory distress syndrome; NICUs, neonatal intensive care units; PHEIC, public health emergency of international concern; PICUs, pediatric intensive care units; PROM, premature rupture of membranes; S, spikes; SARS, severe acute respiratory syndrome; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus-2 wryip; SGA, small-for-gestational-age; ssRNA, single-stranded sense RNA; rRT-PCR, real-time reverse transcription PCR; WHO, World Health Organization.

(10, 11). WHO then identified the incident as a public health emergency of international concern (PHEIC) on January 30, and on March 11 assessed that COVID-19 could be characterized as a pandemic (12, 13).

Epidemiology in Pediatric Group

Among the previously diagnosed family from Shenzhen, the 10-year-old asymptomatic boy was the first child confirmed infected with the virus (6) Later, on January 19, 2020, a 7-year-old boy with a fever and cough was reported in Shanghai after visiting his grandfather in Wuhan (14). The symptoms of COVID-19 appear to be less severe in infants and children than in adult patients, similar to the SARS-CoV infection (15–17). The first case series report in children showed that the interval between symptom onset and exposure to index symptomatic case ranged from two to 10 days (mean 6.5 days), which suggests a longer incubation period for SARS-CoV-2 infection in children (18). Furthermore, the mean number of secondary symptomatic cases in a household exposure setting was 2.43, similar to the basic reproductive number in earlier research on adults (18, 19). Most cases in children were likely to expose themselves to family members or other children with COVID-19, and linked directly or indirectly to Hubei Province, indicating that extra protection of children in families is urgently needed, especially those linked to Wuhan (16, 20). A 13-month-old child was reported as the first severe case on February 8 (21). Furthermore, a 17 day-old newborn was reported as the first neonatal infection on February 5, testing positive with SARS-CoV-2 in pharyngeal swabs and anal swabs (22). In another case, pharyngeal swab testing was positive 36 h after birth (23). China CDC reported that, as of February 8, 2020, of 2,135 pediatric patients <18-years old, 728 (34.1%) were laboratory-confirmed with COVID-19 and 1,407 were (65.9%) suspected (16). Nearly 1% of the total population of patients reported were children under 10-years old (24). Two deaths were reported in children. One was a 14-year-old boy and the other was a 10-month-old child (16, 25). Seven neonates were reported with a positive nucleic acid test, and three with elevated IgM antibodies to SARS-CoV-2 and negative nucleic acid tests (22, 23, 26–30). Therein, no death but one severe case was involved (26). Therefore, we call for preventive and protective measures for pregnant women, newborns, and children against the spread of the disease as soon as possible.

Global Response

The rapid and close collaboration between epidemiologists, virologists, biologists, clinicians, and drug researchers during the COVID-19 outbreak is commendable. Early in the disease outbreak, different models estimated the basic reproduction number R0 of SARS-CoV-2, calling for public health interventions and preparation plans (31–34). The Chinese government had taken emergency measures, such as organizing medical teams to support Wuhan, controlling population movements, establishing more hospitals for the treatment of COVID-19, and developing specific vaccines (35). A nationwide school closure had also been ordered, and children were confined in their homes with online courses offered (36). Based on the epidemiological data, different countries have adopted different

measures to limit the spread of the novel coronavirus as well, such as issuing travel warnings, interrupting flights, prohibiting nationals from going to severely affected countries, and adopting 14 day quarantine rules for nationals from affected areas (37, 38).

VIROLOGY AND PATHOGENESIS

Virology

Coronaviruses (CoVs) are pathogens that can infect humans, domestic animals, and much wildlife, and can invade multiple organ systems such as the respiratory, gastrointestinal, liver, and central nervous systems. This subfamily includes four genera: *alpha-coronavirus*, *beta-coronavirus*, *gamma-coronavirus*, and *delta-coronavirus* (39). SARS-CoV-2 is the seventh CoV known to infect humans and cause respiratory diseases. It belongs to the clade 2 of the subgenus sarbecovirus, Orthocoronavirinae subfamily of *beta-coronavirus*, and is different from SARS-CoV and MERS-CoV (5, 40).

The novel coronavirus was first isolated from human airway epithelial cells and observed under a transmission electron microscope (5). Electron micrographs showed the distinctive spikes(S) (about 9–12 nm) and corona of the virus particles. In ultrathin sections of the human airway epithelium, virus particles were filled in membrane-bound vesicles in the cytoplasm or distributed in the extracellular matrix (5). Researchers had found that the genome had 89% nucleotide homology with bat SARS-like CoVZXC21, and even 96.2% sequence identity with BatCoV RaTG13 (41, 42). Another study also suggests that pangolins may be possible hosts of SARS-CoV-2 (43).

In addition, the SARS-CoV-2 genomic sequence is far from SARS-CoV (about 79%) and MERS-CoV (about 50%) (40, 41). The amino acids in different proteins have also been replaced accordingly, which further explains the structural and functional differences between SARS-CoV-2 and SARS-CoV (44). However, SARS-CoV-2 has a similar receptor-binding domain structure to SARS-CoV, which is located in the S1 conserved domain and critical for determining host tropism and transmission capabilities (40). They may use the same cell-targeted receptor angiotensin-converting enzyme 2 (ACE2), and Cryo-EM showed that SARS-CoV-2 S had 10- to 20-fold higher affinity to bind with ACE2 than SARS-CoV S (41, 45, 46). Further research and understanding of the structure of SARS-CoV-2 would better facilitate the development of vaccines as well.

Pathogenesis

It has to be mentioned that the specimens from the respiratory and gastrointestinal tracts were detected as SARS-CoV-2, which indicates the potential multiple ways of SARS-CoV-2 transmission, including fecal-oral transmission, and the possibility of targeting different organs (47). Cases in adults with active virus replication in the upper respiratory tract display a shed pattern that resembles patients with influenza (48, 49). Furthermore, from biopsy samples taken from the lung, liver, and heart tissues of infected and dead adult patient, similar pathological features to SARS and MERS coronavirus infections have been found (50, 51). The lungs showed evidence of acute respiratory distress syndrome (ARDS), while the liver showed moderate microvascular steatosis and mild lobular and portal activity. The heart tissue was infiltrated with mononuclear inflammatory cells, without substantial damage (50). A recent study also found highly expressed ACE2 in proximal and distal enterocytes (52). In human small intestinal organoids (hSIOs), enterocytes were readily infected by SARS-CoV-2 (53). These all reflect the complexity of this novel virus, and we still need more data on transmission dynamics and pathology in neonates and children to further explain the virologic characteristics.

COVID-19 IN PREGNANT WOMEN AND NEONATES

Pregnant Women

During the rapid spread of COVID-19 in China and other countries, SARS-CoV-2 infection in pregnant women seems inevitable. However, there are only several reports of infection in pregnant women and of neonates born to infected mothers in China. Of the 34 pregnant women who were confirmed with the SARS-CoV-2 infection in multiple hospitals in Wuhan, including one pregnant woman with a negative nucleic acid test result, 30 had a fever and 16 had a cough (54–57). Other symptoms included diarrhea in eight patients, myalgia in seven, fatigue in six, sore throat in five, shortness of breath in five, chest pain in three, headache in three, and rashes in two (54–57). Among them, 30 were in their third trimester and the other four were in the second trimester. Fetal distress was monitored in eight of the pregnant women. One case had vaginal bleeding during the third trimester, and six had premature rupture of membranes (PROM). In addition, one patient had gestational hypertension and another had preeclampsia (55). Other comorbidities included hypothyroidism and polycystic ovary syndrome (57). All patients had an epidemiological history and had been exposed to COVID-19. Most patients showed typical features of chest CT images, such as multiple plaque-like ground glass shadows in the lungs, plaque consolidation, and blurred borders (54, 55). Finally, 26 of the pregnant women delivered their babies by cesarean section, and three of them delivered vaginally. One case with a gestational age of 28 weeks had a benign outcome and did not give birth, with conserved treatment to prolong gestation (56). Furthermore, there was one miscarriage at 26 gestational weeks within the onset of bipolar disorder, and the woman required the termination of her pregnancy. It was unknown whether the outbreak of COVID-19 influenced her onset of bipolar disorder. Noticeably, four of these 34 patients developed severe pneumonia, in which one developed worse and was transferred into ICU (55, 56). The clinical characteristics of COVID-19 in pregnant women appear to be similar to those reported in non-pregnant adult patients with COVID-19, which could be further confirmed with recent cases outside Wuhan (55, 58–61). According to the recent report of 118 pregnant women with COVID-19 in Wuhan, the risk of severe disease compared favorably with the risk in the general population of patients in mainland China (62). No maternal death has been reported. Comparably, the clinical outcome of pregnant women during SARS in Hong Kong was worse than that of infected women who were not pregnant

(63–65). Pregnant women infected with MERS-CoV might also develop serious diseases, and even the maternal outcome was fatal (66). Considering the relationship between SARS-CoV-2 and SARS-CoV or MERS-CoV, more cases need to be observed, and COVID-19 in perinatal pregnant women needs treatment with more caution.

Neonates Born to Mothers With COVID-19

Of the 30 pregnant women in the third trimester mentioned above, 29 of them gave birth to 30 babies, including one set of twins (54–57). Of these, 12 were premature infants (gestational age ranging from 31 weeks to 36 weeks plus 3 days), among them three were low-birth-weight infants, and two were small-for-gestational-age (SGA) infants (54–56). The 1- and 5-min Apgar scores of all live births were 8–10, except for one LGA infant who had a 1-min Apgar score of 7- and a 5-min Apgar score of 8. Pharyngeal swab specimens were collected from 22 of the 30 neonates, and only one was positive at 36 h after birth (54–57). Six of the newborns developed shortness of breath, in which five were premature and intrauterine fetal distress was found in mothers of four neonates, but no severe neonatal asphyxia was observed. Other symptoms included vomiting, moaning, edema and skin damage, fever, milk rejection, and gastrointestinal bleeding (54). The newborn with positive SARS-CoV-2 had no fever and cough, with only mild shortness of breath (23, 57). So far, three patients developed disseminated intravascular coagulation (DIC) in two case series, possibly because of immature immune function of the neonates and suspected sepsis (26, 54). One of them eventually died, one improved with antibiotic treatment, and the other also improved after receiving intravenous immunoglobulins (IVIG) transfusion (26, 54). It suggests that gamma-globulin may be effective in severe cases. However, the dose of IVIG was not mentioned in the case and needed further exploration (54). Radiographic findings were non-specific. Within the 33 neonates born to affected mothers reported recently, chest radiographic images in the three with positive SARS-CoV-2 showed pneumonia (26). Recently, another case of neonatal death within 2 hours of birth was reported because of severe neonatal asphyxia. The mother developed severe pneumonia and septic shock after admission (60). Therefore, the severity of neonatal symptoms is closely related to the maternal condition (54). Moreover, maternal chronic illness or complications and effective treatment of the newborns may also affect their outcome (58).

However, there is no evidence that the emergence of COVID-19 in the third trimester of pregnancy may result in severe adverse outcomes in neonates, which is caused by vertical transmission in the womb (55). Amniotic fluid, umbilical cord blood, neonatal throat swabs, and even breast milk samples were collected and tested, but no SARS-CoV-2 was found (55). Pathological analysis has also showed no evidence of viral infection or chorioamnionitis in placental tissue (67). In addition, one study used public single-cell RNA sequencing databases to analyze mRNA expression profiles and found that the expression of ACE2 in different cell types in the early maternal-fetal interface was very low, which may provide an explanation of low risk of vertical transmission in COVID-19 and SARS (68). However, at least five neonates born to COVID-19 pregnant women tested positive for SARS-CoV-2 (23, 26, 27). Three infants born to mothers with COVID-19 had elevated IgM antibodies to SARS-CoV-2 (29, 30). They were delivered in negative-pressure isolation rooms, and the mothers wore masks in delivery. These results remind us that more evidence is still needed to evaluate whether vertical transmission could be a possible way of coronavirus transmission (58, 63).

Neonatal COVID-19 From the Community

In addition, a neonate was diagnosed as having COVID-19 17 days after birth and he had a history of close contact with two confirmed cases (parents of the newborn) (22, 58). The patient's early clinical symptoms were mild, such as transient fever and diarrhea, without any severe complications. X-ray imaging of the lungs showed inflammatory changes. Repeated positive nucleic acid test results of pharyngeal and anal swabs indicated that the virus could appear in the respiratory and digestive tracts of newborns (22). This case also indicates that there is a possibility that family members or the community may be a source of neonatal infection. Another case recently reported was a 19 day-old baby boy, who also showed gastrointestinal symptoms (28). Although the symptoms could be mild, protection of the newborns still needs to be strengthened. They may show different symptoms from adults, therefore, either the parents or the doctors should be more aware of any abnormal conditions when breastfeeding.

Additionally, no cases of SARS-CoV-2 infection have been reported in women in the first trimester of pregnancy. Given that the fetus of a mother infected with SARS-CoV in the first trimester of pregnancy would develop intrauterine growth restriction (IUGR), more attention should be paid on the prevention of COVID-19 in the first trimester of pregnancy (63).

CLINICAL, RADIOLOGICAL, AND LABORATORY FEATURES IN INFANTS AND CHILDREN

The proportion of infants and children diagnosed with COVID-19 is currently small, which may be related to the lack of pathogen detection among them. It may be because they have a lower risk of exposure, or that they either have mild symptoms or are asymptomatic, which is not easily identified, rather than them being less susceptible than adults (16, 25, 69). The early stages of the COVID-19 epidemic mainly involve adults over the age of 15, indicating confirmed childhood cases are more likely transmitted from family members or the community (19). In addition, the ability of children to transmit the virus may be limited, and no clear report has been found that children can be the source of infection in adults (70).

Clinical Features

The most common symptoms of COVID-19 in children were a fever and cough. Other symptoms included fatigue, myalgia, nausea, vomiting, and diarrhea, which seems to be milder than adults with COVID-19 (**Table 1**) (20, 25, 81, 82). Within 2,135

TABLE 1 | Epidemiologic and clinical characteristics in pediatric series of COVID-19.

Characteristic	Neonates (0–28 d)	Infants (28 d–1 y)	Children[&] (1 y–18 y)
Case number (n)	7	16	44
Sex			
Male	7	3	22
Female	0	13	22
Frequency of symptoms			
Fever	4	7	31
Cough	2	8	21
Nausea/vomiting	4	2	8
Diarrhea	2	0	6
Milk rejection	1	0	0
Feeding intolerance	1	0	0
Sneezing	0	1	4
Stuffy nose	0	1	4
Running nose	0	4	2
Fatigue/malaise	0	0	1
Lethargy	1	0	0
Sore throat	0	0	10
Shortness of breath	1	2	8
None	1	1	9
Case severity[&&]			
Mild	2	0*	3
Moderate	4	5*	33
Severe	0	1*	4
Critical	1	1*	4
Epidemiologic history			
Linkage to Wuhan**	6	14	30*
Contact with infected family member	2	15*	16*
Complication	1	3	3
Radiographic evidence	5	6*	28*
Positive nucleic acid test			
Pharyngeal swab	7	16	43
Stool/anal swab	5*	4*	5*
Sputum	NA	NA	1*
Urine	NA	0*	0*
Blood	NA	0*	0*
Treatment			
Oxygen therapy	1*	3	6*
Antiviral therapy	1*	5*	19*
Use of corticosteroid	0*	1*	9*
Antibiotic therapy	2*	4*	16*

(Continued)

TABLE 1 | Continued

Characteristic	Neonates (0–28 d)	Infants (28 d–1 y)	Children[&] (1 y–18 y)
Outcome			
Discharge	6	13	27
In hospital	1	3	17
Died	0	0	0
References	(22, 23, 26–28)	(15, 18, 71–74)	(6, 14, 18, 21, 73–79)

COVID-19, 2019 novel coronavirus disease. NA, not available.

*Some data may not be available in some cases and are not counted in the table as well.

**Residing in or visiting Wuhan or contact with visitors from Wuhan ≤2 weeks before the onset of infection.

[&]*We define the age of children from 1 to 18-years old, including 1-year old.*

[&&] *Definitions of clinical types of COVID-19 in pediatric patients: (80).*

Mild disease: Mild upper respiratory symptoms for a short duration, without abnormal radiographic presentation.

Moderate disease: Mild pneumonia or asymptomatic with radiographic evidence.

Severe disease: Rapid breath (≥70 breaths per min for infants aged <1-year; ≥50 breaths per min for children aged >1-year); Hypoxia; Difficulty in feeding with dehydration; Lack of consciousness, depression, coma, convulsions.

Critical illness: Respiratory failure with need for mechanical ventilation; Septic shock; Organ failure that needs monitoring in the ICU.

pediatric patients <18-years old who reported with COVID-19, groups of all ages were susceptible (16). The median age of all patients was 7-years, and no statistically significant difference was shown in gender (16). Among both confirmed and suspected cases, 94 (4.4%), 1088 (51.0%), and 826 (38.7%) were diagnosed as asymptomatic, mild, or moderate, respectively (16). Another report in 171 children with SARS-CoV-2 infection showed the median age was 6.7-years (25). Fever was present in 41.5% of the children at any time of the illness (25).

Specifically, symptoms could be mild in infants (28 days to 1-year), with only fever or mild upper respiratory symptoms (15, 71). However, the proportion of severe and critical cases amongst pediatric groups was highest in infants <1-year old, which reveals that young children, particularly infants, were vulnerable to SARS-CoV-2 infection (16). According to the case of a 55 day-old female infant, multiple organ damage affecting the lungs, liver, and heart may be present (72). Both the nasopharyngeal swab and stool specimen tested positive for SARS-CoV-2. The symptoms were initially mild but progressed rapidly later. Therefore, frequent and careful monitoring, as well as timely and appropriate treatment, are important in infant cases (72).

Similarly, children with SARS-CoV-2 infection may also have severe symptoms. The first severe case of childhood infection was reported on January 27, 2020, in Wuhan (21). He was a 13-month-old child, with frequent vomiting and diarrhea at first, which rapidly progressed to other acute symptoms including shortness of breath and oliguria 6 days later, which turned to ARDS, septic shock, and acute renal failure at last. He had no comorbidities. Nucleic acid tests were not positive until it was performed for the third time. Given that his immune system may be overreacted, and it was necessary to maintain acid-base balance and improve organ function in

the critically ill patient, continuous renal replacement therapy (CRRT) was used and finally improved his symptoms. In severe or critically ill pediatric patients, the most common symptom is shortness of breath, and invasive mechanical ventilation may be indicated for effective respiratory support (73). Children with cancer could also be exposed to SARS-CoV-2 infection. An 8-year-old boy with acute lymphoblastic leukemia was confirmed with COVID-19 recently (73). The symptoms included pancytopenia and fever. The conditions turned critical regardless of assisted ventilation. Therefore, development of standardized guidance for prevention in children with cancer and collaboration among the pediatric oncology community are urgently required (83).

In addition, another situation also needs to be paid attention to. This was a case of a child diagnosed with COVID-19 with acute appendicitis (75). He was initially prepared for abdominal surgery for "acute appendicitis," but he developed a fever before the operation. His mother told the doctor that he had dinner with his grandmother before, who was earlier confirmed to be SARS-CoV-2 positive. Therefore, it has to be considered that children and infants may not cooperate with the examination, and the description may be unclear. Respiratory symptoms and physical signs are not obvious among them as well. When the emergence of surgical related symptoms happens, such as acute abdominal pain as the first manifestation, the possibility of SARS-CoV-2 infection needs to be discussed, and more concern is also needed on the reasonable arrangements for surgical operations during the epidemic.

Radiological and Laboratory Features
In addition to atypical clinical symptoms, early radiographic findings of children with pulmonary infections were also milder than those of adults, and most were nodular ground-glass changes or unilateral patchy lesions (18, 25, 76, 84). The CT characteristics were atypical, with a more localized ground glass opacity (GGO) extent, lower GGO attenuation, and relatively rare interlobular septal thickening (85). Furthermore, the CT imaging of severe cases of COVID-19 may be similar to the findings of adults, such as pulmonary parenchymal ground-glass lesions and consolidative pulmonary opacities in the lung (21, 86, 87).

On the other hand, laboratory tests of the 13-month-old severe case mentioned above showed similar characteristics to adult cases. In the acute phase of the disease, C-reactive protein was significantly increased, $CD3^+$ T cells and natural killer cells were significantly reduced, and C3 and C4 levels were also significantly reduced (21). The child's T cell activation was inhibited, but the body's immune system can be over-activated, indicating the complex role of the immune system in the progression of COVID-19. Other abnormal laboratory findings in common and severe cases are elevated creatine kinase MB, decreased lymphocytes, and elevated procalcitonin and alanine aminotransferase, which indicates possible damage of multiple organs (20, 88). Noticeably, the older children may have significantly decreased lymphocytes, elevated procalcitonin, and decreased creatine kinase compared

with the younger patients, such as children under 5-years old (20).

DIAGNOSIS AND MANAGEMENT
Diagnostic Methods and Differential Diagnosis
The reliability of real-time reverse transcription PCR (RT-PCR) for the detection of SARS-CoV-2 has been demonstrated, particularly in collected patient saliva or pharyngeal swabs (89, 90). Recommendations from China for the diagnosis of COVID-19 also suggest the use of real-time fluorescent RT-PCR to detect SARS-CoV-2 nucleic acid (80, 91–93). It is important especially in children with atypical symptoms (6). Another method suggested is metagenomic next-generation sequencing (mNGS) of RNA extracted from bronchoalveolar lavage fluid (BALF) or other specimens (80, 94).

However, it has to be mentioned that the first two pharyngeal swab nucleic acid tests of the severe 13-month-old child above-mentioned were negative, and they were not positive until the third nucleic acid test on the 13th day of onset (21). The delay in diagnosis and treatment of children may be fatal, since there have been two deaths in children (16, 25). Therefore, other samples should be actively explored and evaluated for the diagnostic value of SARS-CoV-2 infection in children as in recommendations, such as the upper or lower respiratory tract, blood, stool, and urine, in order to increase the positive rate of nucleic acid detection (80, 92, 93, 95). Given that neonates seem to manifest gastrointestinal symptoms more commonly, persistent anal swab tests might be more useful (22, 28, 52).

However, there are still some atypical cases with epidemiological history, respiratory or gastrointestinal symptoms, and positive chest CT manifestations that may have negative RT-PCR results for SARS-CoV-2 in adults (96–98). In the diagnosis of patients with suspected COVID-19, the positive rate of chest CT imaging may be even higher than that of RT-PCR analysis. The patients may first show a positive chest CT, and the improvement of the chest CT can be reflected earlier in recovery, indicating its better sensitivity in diagnosis of COVID-19 (99). Given that chest radiographic images could also reflect abnormalities in most cases of neonates and children, the combination of imaging and nucleic acid tests may be a better method for comprehensive evaluation of pediatric patients with COVID-19 (25, 26). Additionally, chest X-rays and CTs should be performed with more caution in pediatric patients for protection to this vulnerable population from the risk of radiation (85). Moreover, application of pulmonary ultrasounds in neonates may show pulmonary abnormalities of COVID-19 with better sensitivity and safety than chest X-rays and CTs, which provides more chances in monitoring and evaluation of the disease (100).

In addition, specific antibody tests are available for retrospective diagnostic and epidemiological studies, which have already been used as one of the methods for diagnosis of COVID-19 according to the latest version of New Coronavirus

Pneumonia Prevention and Control Protocol from National Health Commission of the People's Republic of China (China NHC) (80). IgM antibodies to SARS-CoV-2 in neonates may also have indication in vertical transmission (29, 30). Recently, a new platform called Cas13-assisted viral expression and read restriction (CARVER) was developed for rapid diagnosis of ssRNA viruses. It mainly uses Cas13 to detect and destroy viral RNA (101). The CRISPR system seems to illustrate the unique and comprehensive prospect of virus infection diagnosis and treatment in future (101, 102).

Finally, the additive effect of seasonal influenza on the COVID-19 epidemic may interfere with doctors' clinical decisions, so more tests should be considered to distinguish COVID-19 from other acute respiratory infections with similar symptoms in order to strengthen management of COVID-19 (77).

Management

In the prevention and management of COVID-19, pregnant women, neonates, and children should be considered as the main high-risk population (58). China NHC has provided prevention and control protocols for COVID-19 and updated these during the epidemic. The latest 7th version provided on March 3 covered all populations in China (80). Furthermore, specific recommendations for neonates and children were also provided as national consensus guidelines (91–93). The guidelines define the suspected and confirmed cases in different populations, as well as the criteria for discharge (80, 92, 93). **Figure 1** is extracted from these guidelines as a concise protocol for management in pregnant women, neonates, and children. According to the management plan in pregnant women and neonates, newborns of mothers suspected or diagnosed with SARS-CoV-2 infection in delivery should be well-rescued and cared for via the cooperation of the department of obstetrics and neonatology (92). All neonates with suspected or laboratory-confirmed COVID-19 should be admitted to neonatal intensive care units (NICUs) (91, 92). High-risk neonates should be placed in a designated room for medical observation for at least 14 days (91). If a pregnant woman or newborn is diagnosed or suspected of infection, breastfeeding should be avoided (91). Recently, a global guideline for pregnant women with suspected SARS-CoV-2 infection has also been provided (103). Moreover, recent research found that there may be potential risks of SARS-CoV-2 transmission in hospital settings, hence pediatricians and neonatologists should be more careful in treating the patients in NICUs and pediatric intensive care units (PICUs) (104, 105). Home confinement and online courses may have a psychological impact on children and adolescents, emphasizing the importance of the awareness and guidelines provided for students from the government (36, 106). Finally, it must be noted that RT-PCR-positive results may still be found in pediatric patients recovered from COVID-19 (47, 71). In infants and young children, negative pharyngeal swab results may have already been detected, but viral nucleic acid can still be detected in fecal specimens (78). A contingency plan for NICUs recently suggested SARS-CoV-2 negative results of respiratory specimens or anal swabs should be obtained at least 48 h before discharge (91). Further isolation and long-term follow-up of discharged children with positive results of anal swabs should be considered for their potential transmission in public health (107).

TREATMENT AND OUTCOME

Treatment

The treatment of neonates and children is similar to that of adults, but it also has its own characteristics. To date, there are no specific drugs that can cure COVID-19, and vaccines are still being studied. The purpose of treatment is to improve the patient's symptoms and provide better support. The most effective treatment is oxygen therapy, which is important in treating symptomatic newborns and critically ill children. It is closely related to the children's final outcome, and early treatment can reduce complications, such as ARDS or respiratory failure (108). In adult COVID-19 cases, severe ARDS is always associated with high mortality (109). Therefore, timely ventilation might be vital in preventing ARDS or respiratory failure in pediatric COVID-19 cases.

Secondly, the effect of antiviral treatment in COVID-19 is still uncertain. The first reported case in the United States benefited from an investigational antiviral drug called remdesivir, which has also proved to have a clinical benefit in the rhesus macaque model of MERS-CoV infection (110, 111). Lopinavir–ritonavir treatment reported no benefit in adult severe cases (112). In 36 pediatric cases, mild cases received interferon alfa by aerosolization twice a day, while most moderate cases were given interferon alfa with lopinavir/ritonavir syrup twice a day (20). However, no specific improvement of such antiviral treatment has been analyzed in pediatric cases, and it would be helpful to provide more clinical trials in the future.

In addition, the use of corticosteroids remains controversial. WHO's current interim guidelines recommended against the use of corticosteroids unless indicated for another reason (113). Different studies have shown that it could be either beneficial or unfavorable for patients with coronavirus infection (such as SARS and MERS) (114, 115). Recently, expert consensus in China has advised against the use of corticosteroids in children under 18-years-old (116).

Moreover, traditional Chinese medicine may have a therapeutic effect on COVID-19, but it is not fully recommended for children as well, because childhood toxicity is uncertain (117, 118). Intravenous immunoglobulin (IVIG) is used to rescue newborns and critically ill children and may improve the disease (21, 54). Finally, recent studies on the structure of SARS-CoV-2 spike glycoprotein and cell entry have provided possible solutions for vaccine design and the application of protease inhibitors (119, 120). The blocking effect of cross-neutralizing antibodies may also indicate the feasibility of developing convalescent plasma therapy from healthy donors as a clinical trial in China, which has already been used in severe and critically ill pediatric and adult cases (77, 119–122).
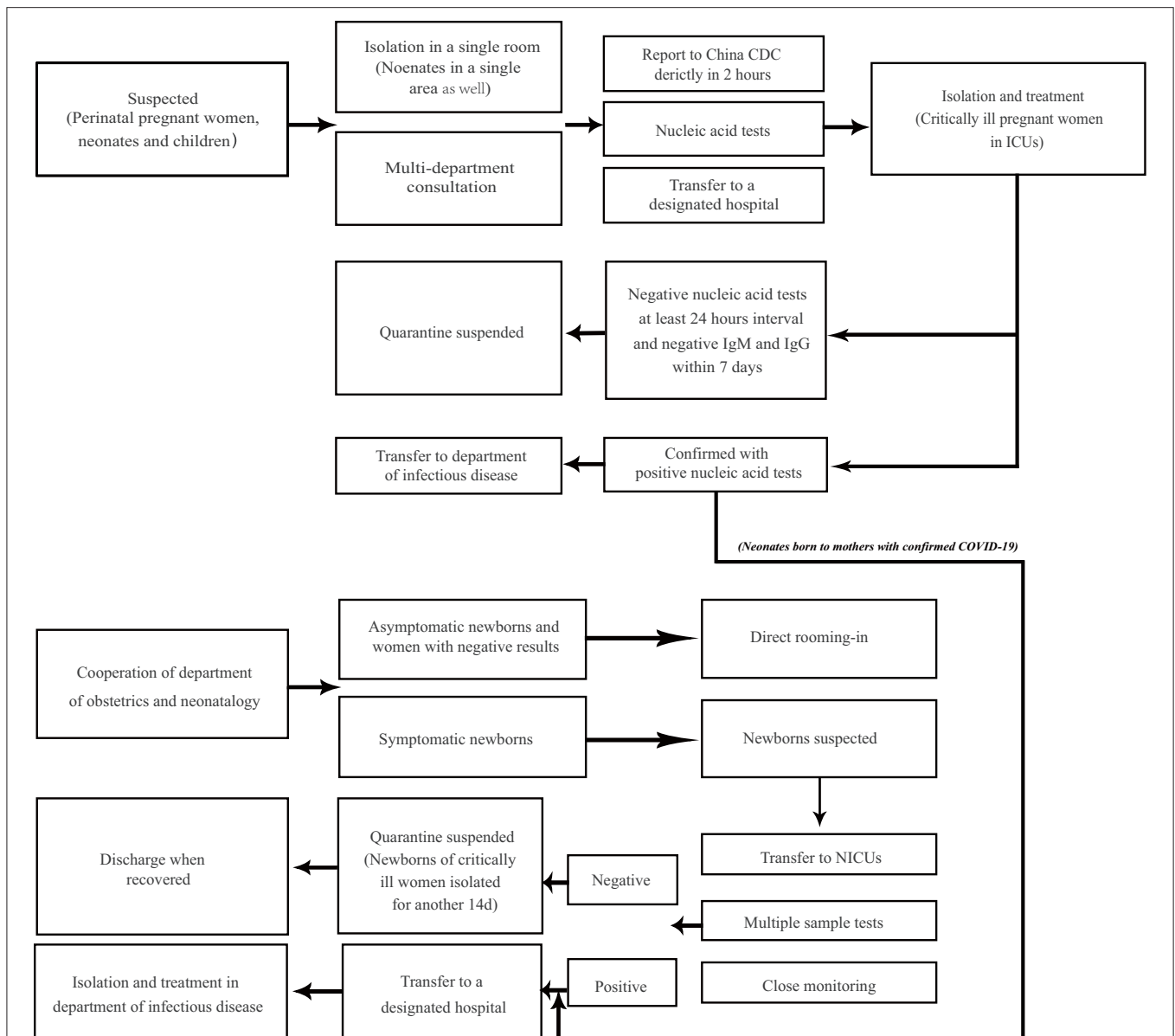
FIGURE 1 | Management plan for prevention and control of COVID-19 in perinatal pregnant women, neonates, and children. Neonates and children of high risk need medical observation for 14 days, which can be terminated in advance based on epidemiology history, clinical characteristics, and laboratory tests. Neonates from women with confirmed COVID-19 should be treated according to the management of neonatal confirmed case, although they may not be infected. Perinatal pregnant women refer to women in peripartum. Pregnant women at birth with suspected infection follow the diagram below. Neonates with epidemiology history such as being born to SARS-CoV-2 infected mothers within 14 days before and 28 days after delivery, or direct exposure to family members, caregivers, medical staff, or visitors with COVID-19 should be suspected with infection, whether with or without symptoms. Suspected cases with both negative nucleic acid tests at least 24 h interval and negative IgM and IgG to SARS-CoV-2 within 7 days will be suspended quarantine. The management plan in perinatal pregnant women, neonates, and children from the community is from the latest New Coronavirus Pneumonia Prevention and Control Protocol from China NHC (80). The management plan in neonates born to the mothers is from the national guideline of perinatal and neonatal management plan of SARS-CoV-2 infection (92).

Outcome

In elderly patients with COVID-19 (>65-years), especially those with comorbidities, clinical outcomes are usually poor (123). However, to date, only two neonates born to mother with COVID-19 and two children with COVID-19 have been reported to have died in China, and most newborns and children have eventually recovered. Some patients were still isolated in hospital for further observation (81). Further analysis is needed to better understand the prognosis of COVID-19 in neonates and children. Neonates born to mothers with COVID-19 in the first and second trimester need close monitoring and further assessment. In addition,

follow-up studies have shown that some children with SARS had deficiencies in lung function assessment and decreased exercise capacity (124). Therefore, we call for long-term follow-up and comprehensive assessment of infected newborns and children after discharge to determine the prognosis of COVID-19.

CONCLUSIONS

Since 2003, the Chinese government has gained many lessons from the SARS outbreak. In the COVID-19 epidemic, besides China, the global response has been more timely, including coordination among different countries, sharing of disease information and cases, government and media reports, and public response (24, 125). The Chinese government has taken effective measures to control the epidemic. The experts also made recommendations for high-risk groups including pregnant women, newborns, and children. In addition, compared to adults, children have milder conditions, a faster recovery, and a better prognosis (126). A series of improvements to date have been applied to prevent the prevalence of COVID-19 in the global community. However, given that the symptoms of COVID-19 in neonates and children are atypical, and transmission within family members is quite common, more effort should be made to protect this high-risk population. Although there is still no direct evidence of vertical transmission, the rescue of newborns of infected pregnant women in delivery should not be delayed. Furthermore, development of vaccines and effective treatments like novel antiviral drugs is also urgent and necessary. Current outbreak will be restricted only if the whole world stands together and cooperates constantly.

AUTHOR CONTRIBUTIONS

YY and PC contributed to the conception of the review. YY contributed to the literature search and writing of the manuscript. Final integration and editing were done by PC. The table and figure were drafted by YY.

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