COVID-19 in Children, Pregnancy and Neonates: A Review of Epidemiologic and Clinical Features

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Abstract: The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has spread rapidly across the globe. In contrast to initial reports, recent studies suggest that children are just as likely as adults to become infected with the virus but have fewer symptoms and less severe disease. In this review, we summarize the epidemiologic and clinical features of children infected with SARS-CoV-2 reported in pediatric case series to date. We also summarize the perinatal outcomes of neonates born to women infected with SARS-CoV-2 in pregnancy. We found 11 case series including a total of 333 infants and children. Overall, 83% of the children had a positive contact history, mostly with family members. The incubation period varied between 2 and 25 days with a mean of 7 days. The virus could be isolated from nasopharyngeal secretions for up to 22 days and from stool for more than 30 days. Co-infections were reported in up to 79% of children (mainly mycoplasma and influenza). Up to 35% of children were asymptomatic. The most common symptoms were cough (48%; range 19%–100%), fever (42%; 11%–100%) and pharyngitis (30%; 11%–100%). Further symptoms were nasal congestion, rhinorrhea, tachypnoea, wheezing, diarrhea, vomiting, headache and fatigue. Laboratory test parameters were only minimally altered. Radiologic findings were unspecific and included unilateral or bilateral infiltrates with, in some cases, ground-glass opacities or consolidation with a surrounding halo sign. Children rarely needed admission to intensive care units (3%), and to date, only a small number of deaths have been reported in children globally. Nine case series and 2 case reports described outcomes of maternal SARS-CoV-2 infection during pregnancy in 65 women and 67 neonates. Two mothers (3%) were admitted to intensive care unit. Fetal distress was reported in 30% of pregnancies. Thirty-seven percent of women delivered preterm. Neonatal complications included respiratory distress or pneumonia (18%), disseminated intravascular coagulation (3%), asphyxia (2%) and 2 perinatal deaths. Four neonates (3 with pneumonia) have been reported to be SARS-CoV-2 positive despite strict infection control and prevention procedures during delivery and separation of mother and neonates, meaning vertical transmission could not be excluded.

Key Words: 2019 novel coronavirus, SARS-CoV-2, epidemiology, symptoms, clinical presentation, laboratory, imaging, infant, child, outcome, perinatal

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The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes the disease termed coronavirus disease 2019 (COVID-19), emerged in China in early December 2019.[1] The outbreak was declared a public health emergency of international concern by the World Health Organization on January 30, 2020.[2] The virus has rapidly spread causing a global pandemic with a major burden on the health care system and economy.

During the early stages of the outbreak, it was thought that children were rarely affected by SARS-CoV-2 which could have been as a result of their lower nosocomial exposure and less frequent contact with animals.[3] However, a number of reports suggest that children are just as likely as adults to become infected with SARS-CoV-2 but have fewer symptoms and less severe disease, as well as a much lower case-fatality rate.[4,5] Many of the initial studies in China were done in adults hospitals, so it is not surprising that the numbers of children reported were small.[3,6] Furthermore, as many children with mild disease might not be tested, the true rate of infection and viral carriage is likely underestimated.

In this review, we summarize the epidemiologic characteristics and clinical features of children infected with SARS-CoV-2 reported in pediatric case series to date. We also summarize perinatal outcomes of infants born to women infected with SARS-CoV-2 during pregnancy. Understanding the clinical presentation of this virus in this age group is important for early identification of children with SARS-CoV-2 to provide optimal medical care and to help control the pandemic.

PEDIATRIC CASE SERIES

We found 11 case series, including a total of 333 children (range 6–171 children) with confirmed SARS-CoV-2 infections (Tables 1–4).[7–17] All of the series are from China. One case series included only infants[13] and one only children who were admitted to an intensive care unit.[16] In 2 of the studies, there were patients that overlapped[7,16] and further duplicate reporting of patient could not be excluded in 2 other studies.[7,11] We did not include single case reports,[18–23] publications which did not give enough clinical details[17,24–26] or studies which were retracted.[27] The age of the children ranged from 1 day to 16 years, 55% (183) were male. The majority of diagnoses were made by real-time polymerase chain reaction on nasopharyngeal or other respiratory samples. Overall, 83% (275, range 52%–100%) of children had a positive contact history, mostly with family members. Three studies reported incubation periods which varied between 2 and 25 days (mean 7 days, median 6 and 11 days, respectively).[9,15,16] Several studies reported that the nasopharyngeal or throat swabs can be positive before the onset of symptoms.[7,11,14] However, false-negative swabs have also been described.[11] There were 4 studies which did consecutive sampling: real-time polymerase chain reaction on respiratory samples remained positive between 1 and 22 days and in stool between 5 and over 30 days.[8,9,14,17] Viral shedding from the gastrointestinal tract might last longer and also be greater than that from the respiratory tract.[14]

Three studies investigated for co-infections (Table 1).[11,16] One study only for influenza A and B, which was found in 1 of 8 children[16] and the other 2 studies for a broader range of pathogens, which were found in 45% and 79% of children.[11,15]

TABLE 1. Epidemiologic Features of Pediatric Patients With COVID-19 (as of March 27, 2020)

	Lu et al[7]	Qiu et al.[8]	Cai et al[9]	Tang et al[10]*	Xia et al[11]†	Liu et al[12]	Wei et al[13]	Xu et al[14]	Zhang et al[15]*	Sun et al[16]‡	Xing et al[17]*
Number of children	171	36	10	26	20	6	9	10	34	8	3
Location	Wuhan Children's Hospital, China	3 hospitals in Zhejiang, China	Shanghai Children's Hospital, China	Shenzhen Third People's Hospital, China	Wuhan Children's Hospital, China	Tongji Children's Hospital, China	Nationwide study in China	Guangzhou Children's Medical Center, China	4 hospitals in Western China	Wuhan Children's Hospital, China	Qingdao, Shandong Province, China
Time period	Jan 28 to Feb 26, 2020	Jan 17 tp March 1, 2020	Jan 19 to Feb 3, 2020	Jan 16 to Feb 8, 2020	Jan 23 to Feb 8, 2020	Jan 7 to Jan 15, 2020	Dec 8 to Feb 6, 2020	Dec to Feb 20, 2020	Jan 1 to Feb 25, 2020	Jan 24 to Feb 24, 2020	Jan 17 to Feb 23, 2020
Age	Median 7 y	Mean 8y	Mean 6 y	Mean 7 y	Median 2 y	Median 3 y	Median 7 m	Median 6 y	Median 3 y	Median 8 y	Median 5 y
Range	1 d–15 y	1-16y	3 m–11 y	1–13 y	1 d–15 y	1–7 y	2–11 m	2 m–15 y	1 m–12 y	2 m–15 y	1–6 y
Male	61% (104)	36% (13)	40% (4)	65% (17)	65% (13)	33% (2)	22% (2)	70% (7)	41% (14)	63% (5)	66% (2)
Specimens for RT-PCR or RNA sequencing	NP (<2 y) or throat (>2 y)	NP	NP or throat	NP or rectal, sputum, blood	Pharyngeal	Throat	NP	NP or rectal	Throat or lower respiratory	NP	Throat, stool
Transmission	90% (154) family contact	89% (32) family contact 33% (12) endemic area 22% (8) both	80% (8) adult contact (of these 70% (7) family) 20% (2) endemic area	100% (26) contact history	65% (13) family contact	NR	100% (9) family contact	60% (6) family contact 70% (7) endemic area	52% (18) contact history	60% (6) family contact	100% (3) family contact
Incubation period	NR	NR	Mean 7 d	NR	NR	NR	NR	NR	Median 11 d	Median 6 d	NR
Range			2–10 d						8–25 d	5–10 d	
Shedding duration											
Nasopharyngeal	NR	10	Median 12 d	NR	NR	NR	NR	NR	NR	NR	Median 13 d
Range		3-22d	6–22 d					1–15 d			10–15 d
Stool	NR	NR	18–30 d	NR	NR	NR	NR	NR	NR	NR	Median 30 d
Range								5–>28 d			23–33 d
Co-infections											
Total	NR	NR	NR	NR	45% (9)	0	NR	NR	79% (27)	NR	NR
Mycoplasma	NR	NR	NR	NR	20% (4)	0	NR	NR	26% (9)	NR	NR
Influenza A/B	NR	NR	NR	0	15% (3)	0	NR	0	35% (12)	13% (1)	NR
RSV	NR	NR	NR	NR	5% (1)	0	NR	0	6% (2)	0	NR
CMV	NR	NR	NR	NR	5% (1)	NR	NR	NR	0	NR	NR
EBV	NR	NR	NR	NR	NR	NR	NR	NR	6% (2)	NR	NR
Parainfluenza	NR	NR	NR	NR	NR	NR	NR	NR	3% (1)	0	NR
Adenovirus	NR	NR	NR	NR	NR	NR	NR	NR	3% (1)	0	NR

*Preprint.

†Patients in this study are possibly also reported in the study by Lu et al.[7]

‡Three patients overlap with the study by Lu et al.[7]

CMV, cytomegalovirus; EBV, Epstein-Barr virus; NR, not reported; NP, nasopharyngeal; RSV, respiratory syncytial virus; RT-PCR, real-time polymerase chain reaction.

TABLE 2. Clinical Symptoms of Pediatric Patients With COVID-19

	Lu et al[7]	Qiu et al[8]	Cai et al[9]	Tang et al[10]*	Xia et al[11]†	Liu et al[12]	Wei et al[13]	Xu et al[14]	Zhang et al[15]*	Sun et al[16]‡	Xing et al[17]*
Asymptomatic	23% (39) (12/39 radiologic pneumonia)	28% (10)	0	35% (9)	10% (2)	0	11% (1)	10% (1)	0	0	NR
Fever	32% (55)	11% (4)	70% (7)	42% (11)	60% (12)	100% (6)	44% (4)	60% (6)	76% (26)	75% (6)	100% (3)
Definition	>38°C	>38.5°C	≥38°C	ns	>37.3°C	>39°C	ns	>38°C	ns	ns	>38.5°C
Median duration	3 d	3 d	1 d			6 d					
Range	1–16 d	2–5 d				3–11 d					
Cough	49% (83)	19% (7)	60% (6)	46% (12)	65% (13)	100% (6)	22% (2)	50% (5)	59% (20)	75% (6)	NR
Pharyngitis	46% (79)	11% (4)	40% (4)	0	5% (1)	100% (6)	0	40% (4)	0	13% (1)	NR
Nasal congestion	5% (9)	NR	30% (3)	0	0	0	0	20% (2)	0	0	NR
Rhinorrhea	8% (13)	NR	20% (2)	8% (2)	15% (3)	17% (1)	0	20% (2)	0	0	NR
Tachypnoea	29% (49)	3% (1)	0	0	10% (2)	17% (1)	0	0	9% (3)	100% (8)	NR
Wheezing	0		0	0	0	33% (2)	0	0	0	0	NR
Diarrhea	9% (15)	6% (2)	0	8% (2)	15% (3)	0	0	30% (3)	12% (4)	38% (3)	NR
Vomiting	0	6% (2)	0	8% (2)	10% (2)	67% (4)	0	0	12% (4)	50% (4)	NR
Headache	NR	8% (3)	NR	NR	NR	NR	NR	NR	NR	13% (1)	NR
Fatigue	8% (13)	NR	NR	NR	5% (1)	NR	NR	NR	NR	13% (1)	NR

*Preprint.
†Patients of this study are possibly also reported in the study by Lu et al.[7]
‡Three patients overlaps with the study by Lu et al.[7]
NR, not reported; ns, not specified.

Mycoplasma (20%, 26%) and influenza A and B (15%, 35%) were the most common co-infections, followed by respiratory syncytial virus (5%, 6%) and Epstein-Barr virus (6%). Cytomegalovirus, parainfluenza and adenovirus were also isolated.[11,15]

Depending on the study design, up to 35% of children were asymptomatic (Table 2). The most common symptoms were cough in 48% (160, 19%–100%), fever in 42% (140, 11%–100%, mean duration 3–6 days, range 1–16 days) and pharyngitis in 30% (99, 11%–100%). Further symptoms were tachypnoea (0%–100%), nasal congestions (0%–30%), rhinorrhea (0%–20%), wheezing (33%), diarrhea (8%–23%), vomiting (8%–50%), headache (8%–13%) and fatigue (8%–13%).

Typical laboratory findings were minor changes in white blood cell counts (reports of both increased and decreased lymphocyte and, less commonly, neutrophil counts), as well as mildly elevated inflammatory markers (erythrocyte sedimentation rate, C-reactive protein or procalcitonin), liver enzymes, creatine kinase, lactate dehydrogenase or D-dimers (Table 3).

Radiologic findings were unspecific and milder compared with those in adults.[28] They included unilateral or bilateral infiltrates on chest radiograph or computer tomography and, sometimes, additional ground-glass opacities or consolidations with a surrounding halo sign in the latter (Table 3).

Twenty (6%) children were reported to require oxygen (Table 4). Other treatments used were oseltamivir, ribavirin (±lopinavir), interferon, glucocorticoids, immunoglobulin, antibiotics and traditional Chinese medicine.[8,10,12,15–17] The hospital stays ranged from 5 to more than 28 days with means of 13–14 days.[8,10–12,16]

Nine children (3%) needed admission to an intensive care unit[7,12,16] (there was an overlap of the reporting of 3 patients between 2 studies).[7,16] Of these 9 children, only 2 were described to have a preexisting condition (leukemia and hydronephrosis, respectively). A 10-month-old girl admitted to an intensive care unit developed intussusception, encephalopathy, septic shock and multiple organ dysfunction, and died.[7] A further death due to COVID-19 of a 14-year-old boy has been reported in an epidemiologic study from China[29] and further deaths have now been reported in Europe and the USA.

SARS-COV-2 INFECTION DURING PREGNANCY, VERTICAL TRANSMISSION AND PERINATAL OUTCOMES

There are 9 small case series (all from China) and 2 case reports including a total of 65 pregnant women (67 neonates) who were infected with SARS-CoV-2 during pregnancy (Table 5).[30–39] The number of women in each case series varied between 2 and 16 (median 7). Two women were infected at 25 and 27 weeks of pregnancy, the remaining during the third trimester. Three women were discharged, the remaining delivered between 30 and 40 weeks of pregnancy, mostly by Cesarean section 88% (56). Fetal distress was reported in 31% (20). A total of 38% (724) women delivered preterm. Maternal complications included premature rupture of membranes 12% (8), pre-eclampsia 3% (2), gestational hypertension 6% (4), gestational diabetes 5% (3), hypothyroidism 3% (2), tachycardia 2% (1) and abnormal umbilical cord 3% (2). Two women (3%) were admitted to intensive care unit for mechanical ventilation, one of whom developed multi-organ failure and was still on extracorporeal membrane oxygenation at the time of the publication.[35,36] Neonatal complications included respiratory distress or pneumonia 18% (12), low birth weight 13% (9), rash 3% (2), disseminated intravascular coagulation 3% (2), asphyxia 2% (1) and perinatal death 3% (2).[34,36] SARS-CoV-2 could not be isolated from amniotic fluid, placenta tissue, vaginal swabs, cord blood or breast milk, or from neonatal nasopharyngeal and throat swabs in 27 mother-infant pairs.[30–36,38,39] However, 1 healthy neonate and 3 neonates who developed pneumonia tested positive on throat, nasopharyngeal and anal swabs on days 2 and 4 of life.[37] This was despite strict infection control and prevention procedures during delivery and separation of mother and neonates. Additionally, three neonates whose mother presented with COVID-19 infection 23 days before delivery were found to have immunoglobulin M and G against SARS-CoV-2 at birth.[39,40] Therefore, vertical transmission could not be excluded.

DISCUSSION

This review confirms that, compared with adults, children with SARS-CoV-2 infection have milder clinical symptoms and fewer laboratory and radiologic abnormalities. The same findings

TABLE 3. Laboratory and Radiologic Findings of Pediatric Patients With COVID-19

	Lu et al[7]	Qiu et al[8]	Cai et al[9]	Tang et al[10]*	Xia et al[11]†	Liu et al[12]	Wei et al[13]	Xu et al[14]	Zhang et al[15]*	Sun et al[16]‡	Xing et al[17]*
Laboratory findings											
Leucocytosis	0	NR	20% (2) (>12 G/L)	15% (4) (ns)	10% (2) (>12 G/L)	0	NR	0	NR	13% (1) (>12 G/L)	0
Leukopenia	26% (45) (<5.5 G/L)	19% (7) (<4 G/L)	20% (2) (<5.5 G/L)	50% (13) (ns)	20% (5) (<5.5 G/L)	83% (5) (<5.5 G/L)	NR	30% (3) (<5.5 G/L)	NR	13% (1) (<5.5 G/L)	0
Neutrophilia	0	NR	10% (1) (>7 G/L)	NR	NR	0	NR	10% (1) (>7 G/L)	NR	13% (1) (>7 G/L)	0
Neutropenia	0	NR	20% (2) (<1.5 G/L)	NR	NR	50% (3) (<1.5 G/L)	NR	10% (1) (< 1.5 G/L)	NR	26% (2) (<1.5 G/L)	33% (1) (<1.5 G/L)
Lymphocytosis	0	NR	20% (2) (>4 G/L)	NR§	15% (3) (>65%)	0	NR	20% (2) (>4 G/L)	50% (17) (ns)	26% (2) (>4 G/L)	100% (3) (>4 G/L)
Lymphopenia	4% (6) (<1.2 G/L)	31% (11) (<1.1 G/L)	0	NR§	35% (7) (>45%)	100% (6) (<1.8 G/L)	NR	40% (4) (<1.6 G/L)	NR	13% (1) (>1.6 G/L)	0
Thrombocytosis	NR	NR	20% (2) (>350 G/L)	Abnormal in 31% (8)	NR	0	NR	0	NR	25% (2) (>350 G/L)	67% (2) (>350 G/L)
Thrombopenia	NR	NR	10% (1) (<150 G/L)	Abnormal in 31% (8)	NR	0	NR	10% (1) (<150 G/L)	NR	38% (3) (<150 G/L)	0
Elevated ESR	NR	0	NR	27% (7) (>15 mm/h)	NR	33% (2) (>20 mm/h)	NR	30% (3) (>15 mm/h)	NR	0	0
Elevated CRP	20% (33) (>10 mg/L)	3% (1) (>8 mg/L)	20% (2) (>10 mg/L)	19% (5) (>5 mg/L)	35% (7) (>3 mg/L)	83% (5) (>10 mg/L)	NR	30% (3) (>5 mg/L)	NR	63% (5) (>5 mg/L)	33% (1) (>10 mg/L)
Elevated PCT	64% (105) (>0.05 ng/mL)	17% (6) (>0.5 ng/mL)	0	0	80% (16) (>0.05 ng/mL)	NR	NR	50% (5) (>0.1 ng/mL)	NR	63% (5) (>0.05 ng/mL)	33% (1) (>0.1 ng/mL)
Elevated ALAT	12% (21) (>45 U/L)	6% (2) (>40 U/L)	10% (1) (>45 U/L)	12% (3) (>45 U/L)	25% (5) (>40 U/L)	17% (1) (>40 U/L)	NR	10% (1) (>45 U/L)	NR	50% (4) (>45 U/L)	NR
Elevated ASAT	15% (25) (>50 U/L)	8% (3) (>40 U/L)	20% (2) (>45 U/L)	12% (3) (>45 U/L)	NR	67% (4) (>40 U/L)	NR	20% (2) (>45 U/L)	NR	0	NR
Elevated CK	NR	3% (1) (>170 U/L)	NR	0	NR	0	NR	0	NR	25% (2) (>170 U/L)	0
Elevated CK-MB	NR	31% (11) (>18 U/L)	50% (5) (>25 U/L)	NR	75% (15) (>25 U/L)	NR	NR	NR	NR	NR	NR
Elevated LDH	0	NR	30% (3) (>300 U/L)	46% (12) (>250 U/L)	NR	50% (3) (>300 U/L)	NR	20% (2) (>300 U/L)	82% (28) (ns)	63% (5) (>300 U/L)	33% (1) (>250 U/L)
Elevated D-dimers	14% (21) (>0.6 mg/L)	8% (3) (>0.5 mg/L)	0	NR	NR	50% (3) (>0.6 mg/L)	NR	10% (1) (>0.5 μg/L¶)	NR	25% (2) (>0.6 mg/L)	33% (1) (>0.6 mg/L)
Prolonged PT	0	NR	NR	NR	NR	0	NR	0	NR	NR	NR
Chest CT findings											
Normal	0	NR	NR	0	20% (4)	17% (1)	NR	50% (5)	18% (6)	0	33% (1)
Ground-glass opacities	33% (56)	53% (19)	NR	31% (8)	60% (12)	33% (2)	NR	50% (5)	3% (1)	75% (6)	33% (1)
Unilateral infiltrates	19% (32)	NR	NR	42% (11)	30% (6)	0	NR	NR	41% (14)	25% (2)	33% (1)
Bilateral infiltrates	12% (21)	NR	NR	27% (7)	50% (19)	50% (3)	NR	NR	41% (14)	75% (6)	0
Interstitial abnormalities	2% (2)	NR	NR	0	0	0	NR	NR	0	0	0
Consolidation with surroundding halo sign	0	NR	NR	0	50% (10)	0	NR	NR	0	0	0
Nodules	0	NR	NR	0	15% (3)	0	NR	NR	0	0	0
Pleural effusion	0	NR	NR	0	0	0	NR	NR	0	13% (1)	0
'White-lung'	0	NR	NR	0	0	0	NR	NR	0	13% (1)	0

*Preprint.

†Patients in this study are possibly also reported in the study by Lu et al.[7]

‡Three patients overlap with the study by Lu et al.[7]

§Specified norm values incorrect.

¶Likely the wrong unit was specified.

ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; CRP, C-reactive protein; CK, creatinine kinase; CT, computer tomography; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; NR, not reported; ns, not specified; PCT, procalcitonin; PT, prothrombin time.

TABLE 4. Management and Outcomes of Pediatric Patients With COVID-19

	Lu et al[7]	Qiu et al[8]	Cai et al[9]	Tang et al[10]*	Xia et al[11]†	Liu et al[12]	Wei et al[13]	Xu et al[14]	Zhang et al[15]*	Sun et al[16]‡	Xing et al[17]*
ICU admission	1.8% (3) Two co-existing conditions§	0	0	0	0	17% (1)	0	0	0	100% (8)	0
O_2 requirement	2% (4)	17% (6)	0	NR	NR	17% (1)	NR	NR	9% (3)	75% (6)	NR
Drug treatment	NR	Interferon-alpha nebulization 100% (36) Lopinavir/ribavirin 39% (14)	Antibiotics (ns)	Interferon (ns) Lopinavir/ribavirin (ns) Oseltamivir (ns) Traditional Chinese medicine (ns)	NR	Ribavirin 33% (2) Oseltamivir 100% (6) Glucocorticoids 66% (4) Immunoglobulin 17% (1) Antibiotics (ns)	NR	NR	Interferon-alpha nebulization 82% (28) Antivirals 82% (28) Glucocorticoids 15% (5) Antibiotics 89% (30)	Interferon 100% (8) Ribavirin 100% (8) Oseltamivir 100% (8) Glucocorticoids (ns) Immunoglobulin (ns) Antibiotics (ns) Traditional Chinese medicine (ns)	Interferon-alpha nebulization 100% (3) Ribavirin 100% (3) Traditional Chinese medicine (ns)
Duration of hospitalization Range	NR	14 d 10–20 d	NR	Mean 14 d	Mean 13 d 8–20 d	Median 8 d 5–13 d	NR	NR	NR	NR 12–>28 d	Median 26 d 16–27 d
Deaths	0.6% (1) 10m-old	0	0	0	0	0	0	0	0	0	0

*Preprint.
†Patients of this study are possibly also reported in the study by Lu et al.[7]
‡Three patients overlaps with the study by Lu et al.[7]
§Hydronephrosis 1, leukemia on maintenance chemotherapy 1.
NR, not reported; NP, nasopharyngeal; ns, not specified.

have previously been reported for SARS- and Middle East respiratory syndrome (MERS)-CoV.[41–46]

There are several hypotheses for why children infected with SARS-CoV-2 have less severe symptoms (Table 6). One potential explanation is differences in the immune system between children and adults, especially elderly adults.[47] Mice models of infections with SARS-CoV show that both CD4 and CD8 T cells, as well as antibodies, play an important role in virus clearance.[48–50] Children have a stronger innate immune response, higher proportion of total lymphocytes and absolute numbers of T and B cells, as well as natural killer cells, which might help to fight the virus.[51] However, children are often described to have an 'immature' immune system and, for infections with other respiratory tract viruses, for example, respiratory syncytial virus or influenza, infants and children are at higher risk for serious disease and hospital admission.[52] This suggests that protective immunity against SARS-CoV-2 differs to that against other common respiratory viruses.

Furthermore, children have a less proinflammatory cytokine response and are less prone to develop acute respiratory distress syndrome.[51,53] It is therefore possible that the cytokine storm which plays an important role in the pathogenesis of severe COVID-19 in adults, is attenuated in this age group.[54]

The second factor that may contribute to the reduced severity of COVID-19 is the lower prevalence in children of the co-morbidities that have been associated with severe disease, such as diabetes, chronic lung, heart and kidney problems or arterial hypertension.[55]

The third potential explanation for the milder symptoms of SARS-CoV-2 infections in children is that common circulating coronaviruses are frequent in this age group, responsible for approximately 8% of acute respiratory tract infections.[56–58] Pre-existing immunity and cross-reacting antibodies to SARS-CoV-2 may play a protective role. Despite the fact that most individuals develop antibodies to common circulation coronaviruses during childhood,[59–62] reinfections later in life occur,[56,63,64] suggesting waning immunity against coronaviruses and increased susceptibility in adults.

The fourth potential explanation is the higher mucosal colonization by viruses and bacteria, which could limit colonization and growth of SARS-CoV-2 through microbial interactions and competition.[65,66]

A fifth hypothesis for the less severe symptoms in children is that children are usually infected by an adult, which means that they are infected by a second or third generation of the virus. For SARS- and MERS-CoV, these following generations have been described to have decreased pathogenicity.[67,68]

The sixth potential explanation related to angiotensin-converting enzyme 2 (ACE2) receptors that are one of the main receptors for the entry of SARS- and SARS-CoV-2 into human cells.[69,70] It has been suggested that adults who are taking ACE inhibitors or angiotensin receptor blockers for arterial hypertension might have a higher number of ACE2 receptors, potential making them more susceptible to SARS-CoV-2.[71,72] However, this theory remains controversial.[73] It has been postulated that children have less ACE2 receptors with lower affinity compared with adults and therefore might be less affected by SARS-CoV-2.[74] ACE2 is important in regulating the immune response, especially in the lungs. In animal studies, it has been shown to protect against SARS-CoV- and influenza-associated lung injury.[75–77] For Pseudomonal lung infections, it has been shown that a dynamic variation of pulmonary ACE2 is required for protection against lung injury.[78] The interaction between ACE2 concentration and the number and affinity of ACE2 receptor is likely complex and might also be influenced by genetics.[79,80]

TABLE 5. Case Series of Pregnant Women With COVID-19 (as of March 27, 2020)

	Chen et al[30]	Liu et al[35]*	Li et al[31]*	Chen et al[32]	Fan et al[33]	Zhu et al[34]	Wang et al[36]	Yu et el[38]	Zeng et al[37]
Number of women	9	13	16	4	2	9	1	7	3
Number of infants	9	13	17	4	2	10	1	7	3
Location	Wuhan University Hospital, China	Different hospitals in China outside Wuhan	Hubei Provincial Maternal and Child Health Center, Wuhan, China	Tongji Medical College, Wuhan, China	Renmin Hospital of Wuhan University, China	Maternal and Child Health Hospital of Hubei Province, China	Suzhou Municipal Hospital, China	Tongji Medical College, Wuhan, China	Wuhan Children's Hospital, China
Time period	Jan 20 to Jan 31, 2020	Dec 8 to Feb 25, 2020	Jan 24 to Feb 29, 2020	ns	17 Jan to Feb 19, 2020	20 Jan to Feb 5, 2020	Feb 2, 2020	Jan 1 to Feb 8, 2020	Dec to Mar 10, 2020
Gestational age	Median 37+2	Median 35	Mean 38+0	Median 38+6	36+5 and 39+0	Median 34+5	30	Mean 39+1	Median 40
Range	36+0 to 39+4	25–38	33+6 to 40+4	37+2 to 39+0		31+0 to 39+0		37+0 to 41+2	31+2 to 40+4
Maternal complications	44% (4) PROM 22% (2) Pre-eclampsia 11% (1) Gestational hypertension 11% (1)	16% (2) PROM 8% (1) Admission to ICU for mechanical ventilation, multi-organ failure 8% (1)	69% (11) PROM 6% (1) Pre-eclampsia 6% (1) Gestational hypertension 19% (3) Gestational diabetes 19% (3) Hypothyroidism 12% (2) Tachycardia 6% (1)	0	0	56% (5) PROM 33% (3) Abnormal umbilical cord 22% (2)	Admission to ICU for mechanical ventilation 100% (1)	0	33% (1) PROM 33% (1)
Fetal distress	22% (7)	23% (3)	6% (1)	0	0	60% (6)	100% (1)	0	67% (2)
Cesarean section	100% (9)	77% (10)	88% (14)	75% (3)	100% (2)	70% (7)	100% (1)	100% (7)	100% (3)
Preterm deliveries (<37 weeks)	44% (4)	46% (6)	24% (4)	0	50% (1)	60% (6)	100% (1)	0	67% (2)
Specimens for RT-PCR	Amniotic fluid, cord blood, breast milk, neonatal throat swabs in 6, all negative	NR	Neonatal throat swabs in 3, all negative	Neonatal throat swab in 3, all negative	Vaginal swabs, amniotic fluid, placenta tissues, maternal serum, cord blood, breast milk, neonatal nasopharyngeal swabs in 2, all negative	Pharyngeal swabs in 9, all negative	Amniotic fluid, placenta tissues, cord blood, neonatal throat swab, gastric juice and stool negative	Neonatal throat swab in 3, 1 positive on day 2	Neonatal nasopharyngeal and anal swab positive in 3, positive on day 2 and 4
Fetal complications									
Low birth weight	22% (2)	NR	18% (3)	0	0	20% (2)	NR	0	67% (2)
Rash	0	NR	0	50% (2)	0	0	0	0	0
Asphyxia	0	0	0	0	0	0	0	0	33% (1)
Resp distress or pneumonia	0	0	0	25% (1)	100% (2)	60% (6)	0	0	100% (3)
O_2 requirement	0	0	0	25% (1)	NR	NR	0	0	NR
Mechanical ventilation	0	0	0	25% (1) (noninvasive)	NR	NR	0	0	33% (1)
DIC	0	0	0	0	0	20% (2)	0	0	0
Death	0	8% (1)	0	0	0	10% (1)	0	0	0

*Preprint.

DIC, disseminated intravascular coagulation; ICU, intensive care unit; ns, not specified; PROM, premature rupture of membranes; RT-PCR, real-time polymerase chain reaction.

TABLE 6. Hypotheses Suggested to Date for Why Children Infected With SARS-CoV-2 Have Less Severe Symptoms

Hypothesis	Details
1. Differences in the immune system	Children have stronger innate immune response, higher proportion of total lymphocytes, absolute numbers of T and B and NK cells and lower proinflammatory cytokine responses
2. Lower prevalence of co-morbidities	Children have lower prevalence of diabetes, chronic lung, heart and kidney problems, arterial hypertension
3. Differences in pathogen exposure, e.g. higher prevalence of infections with common coronaviruses	Children are more likely to have preexisting immunity to common coronaviruses, including potential cross-reacting antibodies to SARS-CoV-2
4. Microbial interactions and competition limiting colonization and growth of SARS-CoV-2	Children have higher mucosal colonization by viruses and bacteria
5. Infection with second or third generation of virus might have decreased pathogenicity	Children predominantly infected by transmission from adults
6. Differences in ACE2 receptors	Children might have less ACE2 receptors with lower affinity
7. Protection through off-target effects of BCG vaccination	Possible correlation between BCG vaccination policies and severity of COVID-19 in children

ACE2, angiotensin-converting enzyme 2; NK, natural killer; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; BCG, Bacillus-Calmette-Guérin.

The majority of children included in this review had a reported adult or family contact infected with SARS-CoV-2. It is still uncertain whether asymptomatic children transmit the virus and therefore the role of children as a reservoir for SARS-CoV-2 and for transmission of the virus remains unclear. However, it has been reported that even asymptomatic children can have high viral loads of SARS-CoV-2[20] and can excrete the virus in stool for a prolonged period.[9,14,17]

Unpublished data suggests that the clinical features of COVID-19 in children varies in different countries. While in Asian countries and Europe children have been reported to have milder disease, recent data from the US reports that, by March 27, 2020, at least 35 children needed mechanical ventilation and one infant died. It has been suggested that this could be due to differences in Bacillus-Calmette-Guérin vaccination policies, as this vaccine's off-target immunomodulatory effects might alter the immune response to SARS-CoV-2.[81–83]

The influence of SARS-CoV-2 infection on pregnancy and neonatal outcomes is also unclear. SARS- and MERS-CoV cause more severe disease in pregnant women compared with non-pregnant women.[84,85] To date, this has not been reported for SARS-CoV-2.[25,86] Nevertheless, 3% of pregnant women infected were admitted to intensive care unit.[35,36] There is no evidence that SARS-CoV or MERS-CoV can be vertically transmitted to the fetus, however, maternal infections have been associated with intrauterine growth retardation, preterm delivery, stillbirths and perinatal deaths.[85,87–91] Similarly, low birth weight, preterm delivery and 2 perinatal deaths have been reported in association with SARS-CoV-2.[30,31,33–37] It is unclear if some of the reported maternal and neonatal complications are due to the virus or were iatrogenic (eg, decision for a Cesarean leading to preterm delivery and neonatal respiratory problems). Nevertheless, 1 case-control study reported that the number of pre-term deliveries were higher in SARS-CoV-2-infected women compared with non-infected women.[31] Furthermore, fetal distress and preterm ruptures of membranes have been reported in SARS-CoV-2 infected women.[30,31,34,37]

The one healthy neonate and 3 neonates who developed pneumonia and tested positive for SARS-CoV-2 on day 2 of life and the three neonates who had immunoglobulin M against SARS-CoV-2 at birth, despite strict infection control and prevention procedures during delivery and separation of mother and infants, suggests the possibility of vertical transmission of SARS-CoV-2.[37–40]

There is no evidence for the presence of SARS-CoV-2 in genital fluids.[33] However, the virus can be isolated from feces, meaning it is possible that vaginal delivery poses a greater risk for infection of the infant. Most of the women delivered by Cesarean section as recommended in Chinese guidelines. It is still unclear whether the virus can be transmitted through breast milk. However, close contact during breast-feeding, might risk droplet or contact transmission from the mother to the neonate.

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