CEP Clin Exp Pediatr Vol. 67, No. 1, 1–16, 2024
https://doi.org/10.3345/cep.2023.00794

Review article

COVID-19 among infants: key clinical features and remaining controversies

Nevio Cimolai, MD, FRCP(C)

Faculty of Medicine, The University of British Columbia and Children's and Women's Health Centre of British Columbia, Vancouver, Canada

Infants aged <1 year represent a seemingly more susceptible pediatric subset for infections. Despite this, coronavirus disease 2019 (COVID-19) infection has not been proven as more serious in this age group (outside the very early neonatal period) than in others. Indeed, a considerable number of asymptomatic infections have been recorded, and the symptoms and morbidity associated with COVID-19 differ minimally from those of other respiratory viral infections. Whether due to an abundance of caution or truly reduced susceptibility, infections in infants have not raised the same profile as those in other age groups. In addition to direct severe acute respiratory syndrome coronavirus 2 diagnostic tests, laboratory markers that differentiate COVID-19 from other viral infections lack specificity in infants. Gastrointestinal presentations are common, and the neurological complications of infection mirror those of other respiratory viral infections. There have been relatively few reports of infant deaths. Under appropriate precautions, breastfeeding in the context of maternal infections has been associated with tangible but infrequent complications. Vaccination during pregnancy provides protection against infection in infants, at least in the early months of life. Multi-inflammatory syndrome in children and multi-inflammatory syndrome in neonates are commonly cited as variants of COVID-19; however, their clinical definitions remain controversial. Similarly, reliable definitions of long COVID in the infant group are controversial. This narrative review examines the key clinical and laboratory features of COVID-19 in infants and identifies several areas of science awaiting further clarification.

Key words: COVID-19, SARS-CoV-2, Infant, Child, Epidemiology, Infection

Key message

- Clinical studies of coronavirus disease 2019 (COVID-19) in infants should be supported by rigorous laboratory diagnostic criteria.
- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spreads to infants similarly to other viral respiratory infections.
- Among infants ≤1 year of age beyond the immediate postpartum period, COVID-19 is relatively mild, but even the low risk of severe disease requires prevention.
- Comorbidities increase infection vulnerability and complications in infants.
- Clinical and laboratory data do not sufficiently distinguish COVID-19 from other respiratory viral infections.
- Coinfection with SARS-CoV-2 is uncommon among infants.
- Unique infection sequelae, including multi-inflammatory syndrome in children and neonates and long COVID require further study and refinement of diagnostic criteria.
- Infection control standards applied to mother-infant dyads should be tempered by standard preventive strategies, maternal input, accommodation potential, and overall safety.
- Maternal vaccination prevents disease in early infancy.

Introduction

Although coronavirus disease 2019 (COVID-19) affected all age groups very early in the pandemic, several studies have proposed that children, especially infants ≤1 year of age, were much less affected and most often experienced relatively minor illness.[1,2] Some studies published well into the pandemic continued to echo the relatively mild nature of infection among young patients.[3] There is now considerable information forthcoming on the state of COVID-19 among children that has extended to include newborn and infant populations. Early features of maternal and newborn infections have largely been confirmed from

Corresponding author: Nevio Cimolai, MD, FRCP(C). Faculty of Medicine, The University of British Columbia and Children's and Women's Health Centre of British Columbia, 4480 Oak Street, Vancouver, B.C. V6H3V4, Canada
✉ Email: ncimolai@mail.ubc.ca, https://orcid.org/0000-0003-2743-0556
Received: 7 June 2023, Revised: 11 August 2023, Accepted: 19 September 2023

earlier analyses.[4] This narrative review examines key aspects of COVID-19 among infants ≤1 year of age outside the immediate postpartum period. In addition to recognizing the important facets of infection in this age group, several controversies and future topics of concern have emerged. These are highlighted in this collation and serve as substrates for further testing.

COVID-19 among infants

1. Risk factors for infection

The risk factors for infection in this age group are not well understood. Most emphasis has been placed on examining the associations of various demographic and clinical factors with hospital admission, illness severity, and mortality. Comorbidities in particular have been analyzed in such studies.[5-11] One confounding issue in this regard is the definition and expressed inclusivity of focused comorbidities given that the enumeration of the latter could conceivably be high. Schober et al.[6] reported that particular comorbidities associated with severe disease, but some individual conditions or the total comorbidities were not. A dilutional effect on the statistical analyses from the overinclusion of variables could be anticipated.

The presence of comorbidities increases a patient's risk of hospital admission.[11] Those with underlying illnesses before COVID-19 also have more serious infections.[6,8-10,12,13] The comorbidities most associated with adversity are prematurity, cardiac, and, to a lesser extent, neurological and chronic lung entities.[6,8,11,12] There is conflicting information on the role of congenital anomalies alone.[6,7,9] What generally emerges is that, while the severity of COVID-19 generally increases with age, greater severity is noted at the younger end of the spectrum including complicated and premature newborns. The latter is consistent with the susceptibility to other respiratory viral infections at a very young age.

2. Role of contact spread

Despite considerable direct studies of SARS-CoV-2 transmission, the mechanisms of spread largely resemble those already known for decades for other respiratory viruses, including other endemic coronaviruses.[14-17] The issues of the degree of respiratory or airborne spread remain contentious, but such discourse is mired in semantics.[14] An infected infant has a known infected close contact in the majority of instances.[11] The contamination of nearby air and solid surfaces is a given; thus, the implementation of respiratory and enteric infection control precautions is essential.

Nosocomial transmission is accepted and includes infants as young as those in the early postpartum period.[2,8,11,18-24] Some groups have experienced a paucity of such transmissions, but institutional outbreaks, including infants, have been cited.[2,19] Furthermore, there may be a very high rate of secondary infections in the outbreak setting affecting newborns, mothers, and healthcare workers.[2] For individual perinatal infections, mothers and healthcare workers can be virus vectors.[21] Despite the subsequent nosocomial transmission, most rationale for institutional care involves reasons other than the proper infection.[21] The latter among very young infants in particular includes prematurity or other noninfectious perinatal events.[8]

Exposure to infected mothers is an established risk factor.[22,23,25] This is especially true when the newborn–maternal contact occurs if the mother first becomes infected in the immediate postpartum phase.[25] Newborn in-rooming may be associated with a higher risk of infection, but no association was found in feeding mode in one study.[8] The dissociation of infants from mothers or other direct caregivers must be considered in the overall context of infant, maternal, healthcare worker, and others' safety. Collective decisions must be tempered by unique circumstances regardless of whether a pre-specified infection control technique is applied. When exceptions arise, consultation with infection control services is a moral obligation and a mandate.

Whether for infected mothers, direct caregivers, family, or other attendees, most infants have a history of close contacts.[5,11,13,23,26-34] The frequency of presumed infected contacts ranges from 36.6% to over 90%. Of the studies that have examined vaginal samples from women with established infection, the finding of a positive test is rare.[24,35-37] Of these studies, only one positive sample was obtained, but live virus was not specifically sought.[36] Regardless, it is firmly established that the live virus can be excreted in stool samples of SARS-CoV-2-infected individuals, and such proximity to the vaginally delivered infant carries a risk.[17] Nucleic acid testing of blood from some infections may identify the presence of the virus. Such positivity might be detected in maternal blood or cord blood and is cited as having the potential to detect the virus in placental samples.[4,38] Many such studies have not sought cultivable viruses; however, at least for the placenta, viral presence has been documented on the fetal and maternal sides through in situ histochemistry techniques.

3. Asymptomatic versus symptomatic disease

Outside the concept that COVID-19 might be a relatively mild illness among infants, a considerable proportion of patients test positive and are deemed asymptomatic for the observed duration.[39,40] The phenomenon of asymptomatic infection has been found for all pediatric ages.[1,41] The frequency of such a state in a given infant population must certainly depend on the cause of the initial testing. Where testing is performed, the bias to include asymptomatic

patients in screening efforts will evidently increase the proportion of apparent asymptomatic infections, as will the testing of contacts of infected patients (e.g., outbreak testing scenario) since most will be asymptomatic at the time of the intervention.[2,42,43] Early in the pandemic, asymptomatic infections were identified in 16%–25% of cases.[28,44] Subsequently, for different age clusters within the infant age group from cumulative reviews or individual reports, the frequency of asymptomatic but test-positive patients was 0.8%–46.2%.[5,8,11,21,24,45-52] When asymptomatic infections gained attention, it was inevitable that some infants would be admitted to the hospital for observation given the then-uncertainty of the clinical course to follow.[24] The inclusion of mild infections among those numbers with presumed asymptomatic infections increases these frequencies to the vast majority of patients in a given study.[2] The meaning of asymptomatic infection must also be considered in the context of the fallibility of the laboratory diagnosis when positive test results are close to the laboratory analysis threshold so chosen as discussed below.

4. Manifestations of infant infection

Distinguishing COVID-19 from other respiratory infections can be challenging. For example, one study found only the nonspecific symptoms of lethargy and poor feeding as being more common among SARS-CoV-2 infections in infants <2 months of age.[53] Servidio et al. determined that patients <3 months of age with COVID-19 infections were more likely to become febrile than those with non-SARS-CoV-2 infections but the latter were more often admitted for intensive care.[3] In a study of bronchiolitis, patients' demographic data, clinical variables, and length of hospital stay were similar for SARS-CoV-2 and other viral causes except for a higher incidence of fever with COVID-19.[27] Evidently, there is little clinical evidence to differentiate COVID-19 from other viral respiratory illnesses for all severities, and where any such differences may exist, the predictive values would be low. The frequency of infected newborns seen in prospective cohorts has been very low.[22,25,54-57] Among these studies, the number of those overtly symptomatic is another lower proportionate fraction. Although this infrequency is rather consistent, some studies have not carefully considered the impact of the close timing of maternal infection on the delivery process.

Clinical manifestations of infected infants have been collated in many studies from a considerable diversity of

Table 1. Key clinical manifestations of coronavirus disease 2019 infection among infants

Ref. No.	Country	Age	No.	Fever[a]	LRT	URT	Resp. distress	GI general	Poor feeding	Emesis	Diarrhea	Irritability	Apnea	Lethargy/ hypotonia	Skin	Neuro.	Eye
3	Italy	<90 day	29	66	31	31	14	-	-	3	-	0	-	-	-	-	-
5	Italy	<6 mo	39	87	-	38	-	20	-	-	-	-	-	-	5.1	-	-
9	USA	<28 day	918	11.4	-	1.1	22.3	-	-	0.5	0.8	-	0.3	-	-	-	-
10	USA	<1 yr	206	-	47.1	35.4	-	49	-	-	-	-	-	-	11.2	12.1	-
11	Canada	<1 yr	531	66.5	37.3	60.5	10.4	30.3	25	17.5	14.7	8.7	-	10	9.2	1.3	2.4
13	Poland	<1 yr	940	65	51	45	9	-	37	11	24	-	-	31	9	1	4
21	Spain	<27 day	40	50	23.1	-	15.4	-	-	11.5	3.8	-	3.8	11.5	3.8	-	-
23	UK	<30 day	66	35	11	26	24	33	-	-	-	-	8	23	2	-	-
24	Italy	<3 mo	216	79.6	19.4	26.9	3.2	-	23.6	6.9	13	4.6	1.8	4.2	-	0.9	2.3
26	Turkey	<30 day	11	81.8	-	36.4	63.6	-	45.5	-	-	-	-	-	-	-	-
30	Canada	<1 yr	27	81	37	59	-	85	-	-	-	-	-	-	15	41	-
31	USA	<90 day	18	78	44	28	6	22	28	-	-	22	-	-	6	-	11
32	Bangladesh	<28 day	26	50	11.5	-	65.4	-	23.1	-	3.8	3.8	-	26.9	-	26.9	-
34	Switzerland	<28 day	73	71	14	44	26	-	15	11	14	-	-	-	3	-	-
41	Turkey	<1 yr	34	88.2	41.2	8.8	0	-	-	32.4	29.4	-	-	-	-	-	-
45	Kuwait	<26 day	40	37.5	-	-	12.5	-	37.5	-	-	-	-	37.5	-	-	-
46	Saudi Arabia	<90 day	36	69.4	-	-	63.9	27.8	-	-	-	-	-	-	-	-	-
48	China	<1 yr	46	34.8	58.7	6.5	4.4	-	-	10.9	2.2	-	-	-	-	-	-
51	USA	<6 mo	473	60.6	45.5	45.9	27.6	-	33.9	19.3	12.2	-	6.3	9.2	6.6	-	-
53	USA	<57 day	20	All by definition	20	55	-	-	65	20	0	20	-	30	15	-	-
58	India	<6 day	20	10	-	-	55	30	-	-	-	-	-	-	-	10	-
59	Turkey	<30 day	68	85.3	5.9	-	-	-	13.3	-	7.4	-	-	-	-	2.9	-
60	Israel	<90 day	96	77	-	44	-	16	-	-	-	10	-	14	19	-	-

Ref., reference; LRT, lower respiratory tract symptoms (mainly cough); URT, upper respiratory symptoms (mainly rhinorrhea); Resp. distress, respiratory distress (mainly dyspnea and/or tachypnea); GI general, any general gastrointestinal symptom; Skin, dermatological manifestations; Neuro., neurological manifestations; Eye, ophthalmological manifestations.

[a]Frequencies are expressed as percentages.

geographic regions and with now considerable cumulative numbers.[3,5,9-11,13,21-24,26,30-32,34,41,45,46,48,51-53,58-62] Table 1 details the more common disease features cited to date. Small case series, case reports, and reviews have mostly been consistent.[28,29,62-66] Definitions of symptom categories are inconsistent among these studies, and not all categories of disease manifestations are necessarily considered. These studies tally their findings variably in retrospective and prospective manners. With some exceptions, the pattern of clinical manifestations is relatively consistent across geographically variable populations and ethnic groups. Although fever is relatively common, a consistent association between it and other clinical manifestations is less apparent. Nevertheless, it is surprising that respiratory manifestations are much less appreciated. Although less common, gastrointestinal symptoms can be prominent and may be the chief complaint. Skin manifestations are also common. Neurological events are variably categorized and may be associated with relatively weak signs, such as poor feeding, irritability, and/or inactivity. All of the latter are necessarily complicated by the appreciation of the same patient population for whom clinical assessment is complicated by age.

In addition to the above, studies have published unique presentations such as bronchiolitis, parotitis, croup, bradycardia, arrhythmias, cardiomyopathy, acute kidney injury, necrotizing enterocolitis, late-onset sepsis, and coagulopathy/thrombosis.[27,55,61,67-72] The need for ventilator support is rare.[61,73,74] Many reports are complicated by occasional bacterial coinfection early or late in the COVID-19 disease course, and underlying comorbidities may also present with associated overlapping symptoms and signs. Anecdotes of chronic lung disease after infection have emerged, but the latter must be gauged in the context of whether infants have other comorbidities such as lung prematurity.[75]

Early reports of the pandemic highlighted a seemingly unusual presentation of COVID-19 among children, often with a later-timed presentation.[76,77] This clinical entity, however variable, manifested as an acute inflammatory illness with or without fever and mimicked some aspects of Kawasaki disease or toxic shock syndrome. Early reports more commonly cited older children. Fever, rash, conjunctival flare, peripheral edema, gastrointestinal involvement, and extremity pain were common features, and several patients experienced associated vasogenic shock. Respiratory illness, more typical of COVD-19, was present in many patients. Reports of infants with this illness have emerged, and the clinical picture has been labeled "multisystem inflammatory syndrome in children" (MIS-C). Later, there also emerged some concern of a similar potential illness among neonates (i.e., birth to 1 month) to which the term "multisystem inflammatory syndrome in neonates" (MIS-N) was applied. The variations inherent in such illnesses have become more apparent; therefore, several clinical definitions have emerged. Overall, it is suggested that very few SARS-CoV-2-infected children suffer from MIS-C.[59,78,79] Among all pediatric MIS-C in 2 of the latter studies, some 1.7%–2.6% were <1 year of age. MIS-N among infants <1 month of age was estimated to account for only 0.1% of all infections.[9] MIS-C may be a milder illness for those <1 year of age.[80] These entities are discussed further below.

Laboratory studies are not generally and sufficiently discriminative for COVID-19 versus other viral infections, and there are minor and inconsistent laboratory markers to distinguish between milder and severe COVID-19.[9,10,21,24,48,53,60,81-83] While some patients present with relative generalized leukocytosis, leukopenia, polymorphonuclear leukocytosis, neutropenia, or lymphopenia, it is difficult to use any such trend to confidently distinguish viral causation or respiratory disease severity. Similarly, any trend alone shown for platelet count, liver function tests, and C-reactive protein, procalcitonin, and troponin levels did not lead to tangile indicators with reasonable predictive values. Minor improvements in prediction may be achieved using combinations of laboratory markers other than specific SARS-CoV-2 testing. Most trends for the association with COVID-19 are, at best, similar to those seen with other viral infections in infancy with some minor exceptions.

Reports on neurological diseases during the course of COVID-19 vary considerably, and it is unclear whether such complications arise due to direct viral infection or any underlying complications. All pediatric age groups are potentially affected.[84] Although most patients have symptoms and/or signs of respiratory infection, some lack such apparent manifestations. Weak neurological signs include lethargy, fussiness or irritability, poor feeding, inactivity, drowsiness, apnea perception, and mild hypotonia. Although there may be reference to "neurological" complications, the details of the latter are relatively nondescript.[58,85-87] It is also not apparent if the collations and their proportionalities are influenced by selection bias, but the proportion of infants meeting soft or hard criteria for neurological presentations reached 12% in larger reviews.[10] Seizures of variable types are common among the more concrete neurological events.[9,24,28,30,49,88-97] As expected, some are particularly detailed as febrile seizures.[24] In a large American multicenter surveillance study, neonatal COVID-19 was accompanied by a 1.9% frequency of seizures; the frequency did not differ significantly between severe and non-severe patient groups.[9] A relatively similar frequency was found in an Italian multicenter study.[24] The latter, however, contrasts with another large review in which the outcome of the neurological presentation was more common among infants with severe COVID-19.[10] Other

infants reportedly had encephalopathy or meningitis or meningoencephalitis.[9,49,88,92,93] Intraventricular hemorrhage has arisen during the course of infection.[9] Cerebral venous thrombosis has also been described.[98]

Neurological complications accompanying MIS-N and MIS-C have also been reported.[49,58,80,85,86,91,92,94] As stated above, these complications include seizures. One review cited an incidence of central nervous system involvement as high as 50% in these patients.[85] Two infants aged 4 and 9 months presented with bulging fontanelles.[99,100] One of the latter had evidence from imaging suggestive of increased intracranial pressure.[100] The illnesses of both patients resolved without other neurological sequelae.

Cerebrospinal fluid (CSF) examinations in the context of COVID-19 are usually part of a sepsis workup for infants. There are relatively few reports on CSF analyses. Of the studies reporting on the cell counts of CSF, 25 were reportedly acellular.[30,34,58,89,90,92,93,95-101] Two reports citing pleocytosis in the CSF documented a monocytic or mixed count.[34,102] One of the latter was assessed directly for SARCoV-2 by amplification technology and deemed negative.[34] Of the 5 CSF direct viral assays, 4 were negative and 1 was positive but in the context of an acellular count.[34,89,90,93,97] None of these CSF analyses were assessed for live viruses.

Imaging during the course of or follow-up for patients with neurological manifestations is variable.[87] Pathology from magnetic resonance imaging identified cystic cavitation or acute hemorrhagic necrotizing encephalitis.[87,90,96,97,102] Computed tomography may be suggestive of encephalitis or ischemic lesions.[93.95]

Long-term assessments after neurological events are scarce.[45,103,104] One study of the neurodevelopmental score status at 6 months reported that those born during the pandemic had lower scores, whereas the variable of maternal infection at any time during pregnancy had no such association.[104] The same authors did not find that maternal infection was associated with adverse long-term neurological outcomes.[103]

Infants born to mothers who had prenatal COVID-19 presenting for care can receive a lower rate of acuity or concern than those born to mothers with no history of infection.[105] The latter most likely represents greater diligence assessing infants in the context of infection with the assumption that they might be more at risk for complications. When infected infants are <1 month of age, there is a higher rate of intensive care admission, and there is generally a greater tendency to admit very young infected infants.[106,107] The mean hospital stay is relatively short.[26]

5. Potential for infant mortality

Mortality in infants with COVID-19 has been frequently reported. From reports with small numbers of infected patients <1 year of age, the frequency of death seems alarmingly high at first glance.[7,12,32,46,49,55,58,108] However, it is unclear whether such frequencies reflect patient access to medical care. It is difficult to ascertain reporting biases in other respects. These findings also contradict the negligible mortality that was determined in a very early review of infections through April 2020, at which point the mortality rate was only 0.006%.[44] Other studies reported no deaths among reasonably sized patient pools.[27,34,106] Consistent with the latter, other studies that stratified patients by age into <30 days, <6 months, and <1 year groups reported mortality rates of approximately 0.1%–0.5%, 0.4%–0.7%, and 0.5%–2.2%, respectively.[9,10,11,13,23,48,51,52,61,80,109] These studies should also be individually viewed given the heterogeneity of whether the mortality rates were ascribed to all patients with infections versus only those admitted to the hospital. Overall, considerable data suggest that infant deaths from COVID-19 are relatively infrequent. Where any such death does arise, it is inconsistent whether the event could be directly related to viral infection or other preceding or post-infection complicating factor(s).

Other unique findings have been reported by other studies. Cozzi et al.[27] found no deaths among 18 patients whose diagnosis was initially COVID-19-associated bronchiolitis. COVID-19 has been associated with an increase in all-cause mortality, but the association is minimized when the data were controlled for lethal newborn malformations.[7] For an American study of infected children <6 months of age and admitted to the hospital, the mortality rate was not significantly different during the delta (0%) versus omicron (0.75%) periods.[51] The frequency of all-cause mortality may be higher when maternal infection occurs much closer to delivery.[110] Another study found no difference in mortality between nonsevere (0%) versus severe (0.96%) disease among infants admitted to the hospital.10) Comorbidities may be associated with mortality, but it must also be considered that, in the face of congenital anomalies and other significant comorbidities, the cause of death may not always be truly ascribed to SARS-CoV-2.[23,32,111] Deaths among children with MIS-C or MIS-N presentations have been published.[9,46,49,112,113]

Autopsy studies of deceased infants are meager, and most accumulation of COVID-19-related autopsy information stems from the findings among deceased adults.[114,115] Reviews for pediatric autopsy tend to focus on older children, and the proportionate number of infants aged <1 year has been <50%.[116-118] A single case report in the context of an infant with infection with the omicron variant detailed only pulmonary findings.[119] A report of neuropathology in 4 infants is also available.[120] In contrast, there are considerable studies on placental and stillbirth pathology. Most other autopsy reports on infants focused on pulmonary findings.[112,121-123]

Given that the infant mortality rate is considerably low, it is important to question the affinity of the virus for the relatively immature respiratory tract of infants in the context of innate immunity and its variations with age. There is an age-related variation in respiratory ACE2 virus receptor expression, but there are conflicting views on how such variations in the context of other infection-modulating factors may truly influence age susceptibility, especially for pediatric and infant cohorts.[124,125] There are several examples of other respiratory infections in which infants are much less likely to suffer infections than older children (e.g., Streptococcus pyogenes pharyngitis and Mycoplasma pneumoniae lower respiratory infections).

Controversy regarding infants

1. Diagnostics limitations

Generally speaking, it is common for the academic readership to accept scientifically published data with the assumption that diagnoses of SARS-CoV-2 infection or COVID-19 are veritable. However, diagnostic methods have matured since the onset of the pandemic. Surprisingly, even by 2023, many such publications have not established more definitive diagnostic criteria. The latter causes jeopardy, especially when reviews are attempted in the form of meta-analyses.

The majority of the diagnostic studies cited depend on viral genome amplification and detection. Although these are generally considered to be state-of-the-art methods that have undergone many improvements, they have several inherent limitations. For any laboratory diagnostic method, it is assumed that the specimen quality is sufficient for testing. Not only is there the potential to obtain a poor sample that is not truly representative of the infected site, but the contamination of newborn surfaces by maternal contact remains possible.

The threshold for determining a positive result in an automated genetic amplification test is relatively arbitrary, and while there is a good correlation between quantitative determinations and live virus presence, ambiguity may arise when the determined values are close to the strict threshold.[126] The quality of such testing has matured. Early during the pandemic, some centers established genetic amplification diagnoses based on a single subgenomic target. Since multiple targets were used thereafter to improve the specificity of a positive test, the reliability of the research matured (improved); however, aboratories could vary the targets used, causing interlaboratory variability in diagnosis. The subgenomic presence of a virus does not necessarily indicate the existence of a live virus; rather, it can continue past the absence of a live virus for a considerable number of days, when the patient is no longer infectious. The direct culture determination of live viruses can also vary among laboratories and has largely been avoided because of the high level of laboratory containment that is deemed imperative.[127] Both serological diagnostics and antigen detection have interpretive limitations, especially when used in isolation.

Overall, in understanding case reports, single-institutional small or large series, or multicenter studies, it is essential to estimate the veracity of diagnostic methods.

2. Age-related susceptibility

Well-designed studies that examine the age-related susceptibility of infants, either for infection alone or for determining disease intensity, are lacking. Early in the pandemic, it was suggested that infants were more vulnerable than older children, but published data were relatively sparse.[1,44,48] Most further analyses are usually retrospective and often do not control for critical variables that would enable the proper determination of age-related susceptibility.

Regardless of the limitations of existing analyses, several themes have emerged. Among children with COVID-19, some 20%–35% are <1 year of age.[10,12,78,111,128,129] The rate of hospital admission may be higher for younger infected patients.[11,128,130] Admission, however, may also occur commonly for reasons other than the infection proper.[12] The rate of medically attended COVID-19 may be higher among younger patients.[33] Prematurity may be a risk factor for hospital admission.[12] A European multicenter study found that the risk for intensive care increased with young age.[107] Another study suggested that the latter risk was more so for those <1 month of age.[78] Whereas younger age may be at higher risk of hospital admission, those infants may not necessarily require more hospital interventions.[128]

In contrast, in Scottish registries, there was no evidence of increased infection at a younger age; indeed, infants <1 month of age had among the lowest infection frequencies.[106,130] Some researchers found that age was not an independent risk factor for medical attention, hospital admission, or intensive care requirement after infection.[6,41,111] For infants <1 month or <1 year, more illnesses were non-severe than severe.[10,41] In a study from Italy, the frequency of presenting illnesses per week did not significantly differ among infants <1 month old.[24]

Regarding the above differences, it is inevitable that younger age will attract bias in terms of vulnerability. Infants may be more likely to attract greater attention or require hospital admission even when relatively asymptomatic. Such concerns would likely have been more common in the early phases of the pandemic, when more questions about COVID-19 remained unanswered. The benefits of

determining whether there is truly age-related susceptibility to infection and/or disease may be valuable for understanding the pathogenesis.

3. Coinfections

Infections that coexist with COVID-19 may be acquired fortuitously or arise in the context of complicating existing SARS-CoV-2 infections. For the latter, early coinfections comprise typical bacterial respiratory flora as secondary invaders or late opportunistic infections arising as a consequence of prolonged COVID-19 or secondary infections due to physiological or immune compromise.

For concomitant infections with other viruses, understanding the mechanisms of current laboratory diagnostics is critical. In searching for the breadth of viruses that may potentially infect the respiratory tract, multiplex genome amplification assays are commonly applied; indicators for a positive diagnosis are set at a given threshold of automation indicators but are not guaranteed for live virus presence. Effectively, the codetection of 2 or more viruses in a clinical sample does not guarantee the actual simultaneous presence of 2 live infecting viruses.[131] Moreover, some positive signals for detection, at an arbitrarily defined threshold limit of positivity, may not truly be indicative of viral presence, especially when secondary corroborative testing is not routinely applied. This dilemma was evident when considering codetection in the face of other coronavirus epidemiologies and where it was suspected that high frequencies of coinfection were implied.[132] Therefore, codetection does not necessarily imply coinfection. This does not diminish the potential, however, for codetection to imply that, although not simultaneously infected, the first hit-second hit of consequent infections may suggest one active infection shortly following another. The circumstances for secondary bacterial or fungal infections usually differ because these categories of infections are determined using culture methods. The latter is more common, with prolonged hospital stays and complicated COVID-19 features.

It has been generally accepted that quarantine measures during the COVID-19 pandemic reduced the frequencies of other common respiratory infections among infants. With the lifting of preventive measures, a rebound has occurred in other common viral infections alongside COVID-19. Two studies found viral codetection rates of 10%–53% of diagnostic samples among infants presenting to hospitals.[12,24] Doná et al.[24] reported that such codetection was not associated with severe disease. In any such codetection, the rhinovirus/enterovirus category seems overrepresented. Other studies, however, reported a much lower frequency of codetection, including 0% at times.[27,53] A small patient series of infants admitted to the hospital reported that two of 18 patients had a secondary late bacterial infection.[26] For infants seen in emergency departments, secondary bacterial infections were not detected in any patient at the same time or bacterial infections were not seemingly secondary as COVID-19-related complications.[53,81,133] A similar study reported no significant difference in frequency of secondary infections when infants presented with versus without COVID-19.[60] Of note, another study of the entire pediatric age group with COVID-19 proposed that co-detections were associated with a greater probability of the need for hospital intensive care.[107]

4. Breastfeeding

The contamination of an infant through direct skin-skin contact during the course of breastfeeding will inevitably occur, as it may spread through respiratory droplets given the infant-mother proximity. However, does the latter result in considerable secondary spread from an infected mother and overall considerable medical peril? For example, a study from Peru found that vaginal delivery, breastfeeding, and patient isolation did not affect patient complications during the hospital stay.[50] Breast milk samples may test positive for virus detection with genetic amplification technologies but no live virus.[134] If breast milk is not the direct source of live virus, post-milk excretion contamination, other infant contact, or respiratory spread remain potential modes of transmission. Rooming-in with an infected mother increases a neonate's risk of secondary infection.[8]

The practical experience is that mothers are quite likely to initiate breastfeeding during a postpartum hospital stay and continue thereafter, but they have been less likely to breastfeed if infected within 2 weeks before delivery.[20,135,136] For those infants infected within the first 3 months, many will have been breastfed.[25,30,43] However, the frequency of such breastfeeding does not carry a considerable risk.[20,43] Of further interest, when infected mothers are separated from newborns until postpartum discharge, the feeding of unpasteurized milk was not associated with proximal infant infections.[137] When infected mothers and their infants room together, the use of infection control precautions including masking, appropriate hand hygiene, and contact vigilance are associated with negligible secondary infections.[20,136] In practical terms, maternal-infant dyads are not uncommonly separated at birth.[25] The frequency of such separation was much higher earlier in the pandemic, presumably out of an abundance of caution. Very few infants were cared for in the absence of infection control precautions.[25] Notably, the diagnostic test results of the newborns did not appear to influence dyad separation, isolation precautions, or infant feeding patterns.

The benefits of breastfeeding for nutrition, psychosocial outcomes, and immunity are not disputed.[138] The timing

Table 2. Exemplary diagnostic criteria for MIS-C and MIS-N

Variable	MIS-C							MIS-N		
	CDC[80,86]	revised CDC[142]	WHO[78,86]	United Kingdom[143,144]	New York[145]	Mexico[113]	Multicentre[143]	India[58]	India, Qatar[85]	Multi-centre[143]
Age	<21 yr	<21 yr	<19 yr	-	<21 yr	-	<21 yr	<28 day	<28 day	<28 day
Fever	>38˚C, >24 hr	>38˚C	>3 day	>38.5˚C	Present	Present	>38˚C, >3 day	-	Yes	-
Hospital admission	-	Yes (or death)	-	-	Yes	Yes	-	-	-	Yes
Systems inclusive	2 or more: Cardiac Renal Respiratory Hematological Gastrointestinal Dermatological Neurological	2 or more: Cardiac Mucocutaneous Shock Gastrointestinal Hematological (does not mandate respiratory)	2 or more: Mucocutaneous Hypotension/shock Cardiac Coagulopathy Gastrointestinal (does not mandate respiratory)	Single or multisystem dysfunction Most have oxygen requirements or hypotension Additional features may include abdominal pain, cough, confusion, conjunctivitis, rash, diarrhea, headache, sore throat, lymphadenopathy, respiratory, syncope, emesis, neck swelling, mucosal change, swollen digits	one of: Hypotension/shock Cardiac Other severe end-organ disease OR: 2 or more of: Rash Conjunctivitis Acute gastrointestinal Mucocutaneous	2 or more systems (including respiratory)	2 or more: Cardiac Gastrointestinal Mucocutaneous Hematological Renal Respiratory Neurological	2 or more: Cardiac Gastrointestinal Mucocutaneous Hematological Renal Respiratory Neurological	2 Organ systems	'Severe' and 2 organ systems or cardiac
Laboratory criteria	Evidence of inflammation: ↑CRP, ↑ESR, ↑fibrinogen, ↑procalcitonin, ↑D-dimer, ↑LDH, ↑ferritin, ↑lactic acid	Evidence of ↑CRP AND: ↓platelets or ↓lymphs	Inflammation marker: ↑CRP ↑ferritin ↑ESR ↑procalcitonin	One laboratory abnormality of: ↑fibrinogen, ↑CRP, ↑D-dimer,↑ferritin, ↓albumin, ↓lymphs, ↑neutrophils Additional features may include acute renal, anemia, coagulopathy, ↑IL-6, ↑IL-10, proteinuria, ↑neutrophils, ↑CK, ↑LDH, ↑triglycerides, ↑troponin, ↓platelets, transaminitis	2 more of: ↑CRP, ↑neutrophils, ↑ESR, ↑fibrinogen, ↑procalcitonin, ↑IL-6, ↓lymphs, ↓platelets, ↑D-dimer, ↑ferritin, ↓albumin, ↑LDH	1 or more of: ↑CRP, ↑ferritin, ↑procalcitonin, ↑fibrinogen, ↑D-dimer, ↓lymphs, ↑neutrophils, ↓albumin	1 or more of: ↑CRP, ↑ESR, ↑D-dimer, ↑IL-6, ↑fibrinogen, ↑ferritin, ↑procalcitonin, ↑LDH, ↑lactic acid, ↓lymphs, ↓albumin, ↑neutrophils	1 or more: ↑CRP, ↑ESR, ↑fibrinogen, ↑procalcitonin, ↑D-dimer, ↑IL-6, ↑ferritin, ↑LDH, ↑neutrophils, ↓lymphs	1 or more: ↑CRP, ↑ESR, ↑fibrinogen, ↑procalcitonin, ↑D-dimer, ↑IL-6, ↑ferritin, ↑LDH	1 or more: ↑CRP, ↑ESR, ↑fibrinogen, ↑procalcitonin, ↑D-dimer, ↑IL-6, ↑ferritin, ↑LDH, ↓albumin, ↓lymphs
Absence of other diagnoses	Yes	-	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Diagnostic methods	Any of: PCR or serology or antigen detection or exposure <4 weeks	Any of: PCR or serology or antigen detection	Any of: PCR or serology or antigen detection or confirmed contact	SARS-CoV-2 PCR may be positive or negative	PCR or serology	PCR or serology or contact <4 weeks	Any of: PCR or serology or antigen detection or confirmed contact	Maternal serology or PCR or consistent symptoms or confirmed exposure	Maternal or newborn serology	Maternal or newborn PCR or serology

MIS-C, multi-inflammatory syndrome in children; MIS-N, multi-inflammatory syndrome in neonates; -, not cited; CDC, Centers for Disease Control; WHO, World Health Organization; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; IL-6, interleukin-6; IL-10, interleukin-10; CK, creatine kinase; PCR, polymerase chain reaction.

of maternal infection relative to birth is important because live virus excretion during infection may persist for 5–14 days.[139-141] The benefits of breastfeeding, when necessarily interrupted for several days, do not excessively compromise its long-term benefits. Breast milk may be pasteurized successfully to minimize contamination.[4] Infant-maternal interactions can be guided by proper infection control techniques and personal choices made available. The management of infant-maternal interactions must also be considered in terms of the care setting, healthcare workers, secondary nosocomial infections, and newborn fragility.

5. Multisystem inflammatory syndrome in children and neonates

Furthermore, some ambiguity emerged in the analysis of MIS-C and MIS-N. Its inflammatory and multisystem nature suggests a distinction from the more common respiratory-dominant illness. Although suggestive of an altered pathogenesis, a clear pattern and series of complications led to the creation of several formats for diagnostic criteria (Table 2). The uniting all of such diagnostic criteria involved the inclusion of age specification, with or without hospital admission, fever, the involvement of 2 or more body systems, laboratory evidence of inflammation, the exclusion of other microbial causes, and proof of SARS-CoV-2 infection. Similar criteria were used for MIS-N, including age <1 month and evidence of maternal infection. Although SARS-CoV-2 infection documentation of some form unites these clinical groups, the nonspecificity of many of these criteria detracts from the establishment of a coherent and unified clinical entity. Otherwise, there did not appear to be a secondary diagnostic marker with high specificity. This is akin to the use of clinical diagnostic criteria and associated perils for several other syndromic illnesses.[146] Such heterogeneity is especially illustrated by variations in case reporting.[91,94,101,147-150]

Where details have been provided, it is possible to exemplify several potential problems. For patients who were previously administered antibiotics, a noninfectious cause of the patients' manifestations is possible as an adverse

Table 3. Prevention of infant infection and hospital admission by maternal (2-dose) coronavirus disease 2019 vaccination regimen

Country	Vaccine	Infection risk reduction			Hospital admission risk reduction				Reference
		Delta	Omicron	Single dose	Delta	Omicron	Late vaccination[a]	Early vaccination[b]	
USA	mRNA	-	-	-	80	38	69	38	109
Canada	mRNA	95	43	-	97	53	-	-	160
Israel	mRNA	62 (total)		0		-	-	-	161
USA	mRNA	84	21 (assessed over 0–2 months)		-	-	-	-	162
		62	14 (assessed over 0–4 months)		-	-	-	-	
		56	13 (assessed over 0–6 months)		-	-	-	-	

[a]Vaccination late in pregnancy but more than 2 weeks before delivery. [b]Vaccination early in pregnancy relative to delivery.

reaction, such as rash, pyrexia, ocular manifestations, diarrhea, and vasomotor instability. The latter is more likely to be mitigated or altered by the coadministration of systemic corticosteroids, which have been used to treat COVID-19. When alternative infectious diagnoses are sought by multiplex respiratory laboratory panels, some relevant pathogens, such as parvoviruses, may be forgotten. However, other noninfectious diseases may be causative in whole or in part.

For the clinical manifestations that are recommended as diagnostic criteria, variations may cause considerable interstudy differences. Gastroenteritis is a common feature of pediatric COVID-19, including some patients with a predominance of the same.[17] Among reported MIS-C cases, mild gastrointestinal symptoms occurred in up to 20%.[5] Therefore, if the respiratory system is included as a clinical diagnostic criterion, the respiratory and gastrointestinal body systems would allow the inclusion of many more patients. For laboratory markers of inflammation, the potential choices are considerable; thus, the potential is high for a patient to have any one above the diagnostic threshold at some time during their illness. However, the latter markers alone yielded relatively low predictive values. When defining MIS-N, the sole dependence on a marker of maternal infection preceding birth involves jeopardy, especially when such a diagnosis is dependent solely on serological criteria and may be timed variably before birth.[58,151] A proposal that MIS-C and MIS-N are SARS-CoV-2 antibody-dependent draws interest but remains unproven.[72,93] Other studies of pathogenesis have emerged.[85,86,152-154] The similarities to Kawasaki disease and toxic shock syndrome continue to be explored, and rightfully so.[155] Some data suggest the possible difference in MIS-C incidence depending on the SARS-CoV-2 strain dominance.[79]

6. Protective role of maternal vaccination

The role of maternal antibodies in newborn and infant protection against various infections, including those predominantly of a respiratory nature, is most often undisputed. Whether transplacental as more quantitatively derived by the end of pregnancy or via breast milk thereafter, maternal antibodies can be delivered systemically or mucosally to impart protection, which is usually time-limited and progressively diminishes from birth or after the cessation of breastfeeding. Such concepts of protection have been reasonably well-established for many coronaviruses, especially in the veterinary field.[156] In parallel to the latter, breast milk anti-SARS-CoV-2 antibody declines in the first year.[157] In keeping with past experience from other respiratory virus infections, there is a strong correlation between increased circulating maternal antibody levels, increased quantities of circulating infant antibody levels, and increased breast milk antibody levels.[157] The move to protect mothers from serious disease and protect their infants via the latter through vaccination was justified on theoretical grounds early but then corroborated specifically for COVID-19. It was later shown that vaccination during pregnancy did not overtly affect common delivery or neonatal outcomes.[158,159]

Given the novelty of SARS-CoV-2 infections, large population studies to date of the impact of maternal vaccination on newborns and infants are relatively experimental, but success as measured in the prevention of infection or mitigation of disease severity has become evident (Table 3).[109,158-162] The latter studies included retrospective analyses of sizable populations and focused on mRNA vaccination protocols. Two maternal vaccinations generally provided protection against infection and hospital admission among infants throughout the first 6 months of life. Such protection was greater for the delta variant, which is closer to the ancestral strain used for vaccine derivation, than for the omicron variant, which captures an evidently distinct serological profile.[163] Vaccinations given closer to the time of delivery (but >2 weeks before delivery) were associated with better infant protection. Whether for delta or omicron immunophenotypes, protection waned over 6 months. Single maternal vaccination provides minimal protection. Children of vaccinated mothers had less severe COVID-19 when admitted to the hospital for care. Three vaccine doses improved protection against the omicron immunophenotype. One study group's finding that all-cause infant (<6 months) mortality was reduced when mothers

suffered COVID-19 in pregnancy more than 2 weeks prior to birth is also consistent with the aforementioned findings.[110]

Many concerns should be addressed in future studies of maternal vaccination and infant protection. Would infants <6 months of age benefit from direct vaccination when their mothers were appropriately vaccinated during pregnancy? How do non-mRNA SARS-CoV-2 vaccinations compare to mRNA vaccines? Is infant vaccination warranted when mothers contract COVID-19 during pregnancy? Do maternal vaccination and/or infection provide protection to infants during subsequent pregnancies? Although of great relevance, such concerns regarding the key questions to be raised in this context are not overly exhaustive. Such concern may also be viewed in the context of how the presence and quality of antibody may have varying roles for mother or infant.[164] In addition, a more precise definition of what constitutes "protection" is generally lacking, although studied by several authors.[165] There is also ambiguity in the definition of protection for infection versus serious or otherwise advanced illness.

7. Long COVID

Whether expressed as long COVID or other late manifestations, the longitudinal impact of maternal COVID-19 on infants remains concerning.[166] Also, whether fulfilling a well-designed definition of long COVID or not, some potential long-term consequences of maternal-neonatal infection continue to surface.[167] Like the designations of MIS-C and MIS-N, precise definitions of long COVID are controversial, and many variations on this theme prevail. It must be emphasized that the severity of a viral illness largely determines the nature of the convalescence required and, to some degree, the pattern of complications. These conditions are often referred to as postviral syndrome or postviral fatigue.[168] Most patients resolve postviral illness sequelae over variable courses with supportive treatment alone. In this context, the nature of infants and the need for caregiver observation to dominate the main clinical complaints probably reduce the frequency of perceived long-term COVID-19-related issues.

Common case definitions for long COVID, if taken literally, would encompass a very broad and overwhelming working basis for patient inclusion. From copious past examples, such overarching clinical and predominantly syndromic definitions often add to the confusion.[146] Outside of attributing subsequent diseases to a former laboratory diagnosis of SARS-CoV-2 infection, there are few other more tangible credible diagnostic confirmations. It is likely that overinclusion or overgeneralization has the potential to muddle the study of those who may have a bona fide long-term virus-specific illness. With the vast number of confirmable diseases in the community, it is more likely that confounders can be partially avoided by studying well-defined post-infectious clinical entities rather than using the overly inclusive World Health Organization or similar definitions. Most studies of long COVID will inevitably emerge in older patient populations, but it is unlikely that this topic will escape the field of infant care regardless of how much less an impact it seems to have.

8. Treatment options

Large-scale well-designed placebo-controlled studies of one or more treatment modalities for infants are lacking. Inevitably, the propensity for less severe disease in pediatric patients is contributory. The acquisition of any such trial data for the infant subgroup would require large multicenter studies to attract sufficient patient numbers. The spectrum of virus-specific treatments for older children and adults includes antivirals, monoclonal antibodies, and plasma infusions. Similarly, solid data on the use of non-virus-specific disease modifiers, including corticosteroids, in infants are unavailable.

Various treatments and disease modifiers have been used considerably in pediatric age groups as suggested by observational studies.[52,169,170] Where specific antiviral chemotherapy has been administered, the frequency of included infants is relatively small.[170,171] Administration has been given largely on a compassionate basis with reference to some success in older age groups and in the vacuum of concrete trial data. More often, such treatments have been administered to older age groups with high-risk comorbidities, and interventions to treat other illnesses have already been established. There are many anecdotes in which different individual or combined treatments have been applied; however, these are insufficient to construct a sense of impact given the lack of control groups, even among retrospective studies. Whereas passive immunity would have theoretical justification, its application in infants lacks sufficient experience.[172]

In the face of mild to moderate SARS-CoV-2 infection, the surgical management of other morbidities may be feasible.[173]

Footnotes

Conflicts of interest: No potential conflict of interest relevant to this article was reported.

Funding: This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Acknowledgments: This review is dedicated to the former

tutelage from and collaboration with Dr. Chik H. Pai, then of the University of Calgary, Calgary, Alberta, Canada.
ORCID:
Nevio Cimolai https://orcid.org/0000-0003-2743-0556

References

1. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiology of COVID-19 among children in China. Pediatrics 2020;145:e20200702.
2. Nakwa FL, Thomas R, van Kwawegen A, Ntuli N, Seake K, Kesting SJ, et al. An outbreak of infection due to severe acute respiratory corona virus-2 in a neonatal unit from a low and middle income setting. Front Pediatr 2022;10:933982.
3. Servidio AG, Visentin G, Conti R, Cozzi G, Travan L, Bua J, et al. Mild COVID-19 in hospitalised infants younger than 90 days. Acta Paediatr 2023;112:483-5.
4. Cimolai N. A comprehensive analysis of maternal and newborn disease and related control for COVID-19. SN Compr Clin Med 2021;3:1272-94.
5. Bellini T, Rotuio GA, Caruggi S, Carta S, Bonato I, Piccotti E. Characteristics of COVID-19 patients up to 6 months of age admitted to a pediatric emergency department. Acta Paediatr 2022;111:272-4.
6. Schober T, Caya C, Barton M, Bayliss A, Bitnun A, Bowes J, et al. Risk factors for severe PCR-positive SARS-CoV-2 infection in hospitalized children. BMJ Pediatr Open 2022;6:e001440.
7. Kumar J, Kumar P, Saini SS, Sundaram V, Mukhopadhyay K, Dutta S, et al. Clinical characteristics & outcome of SARS-CoV-2 infected neonates presenting to paediatric emergency. Indian J Med Res 2022;155:189-96.
8. More K, Chawla D, Murki S, Tandur B, Deorari AK, Kumar P, et al. Outcomes of neonates born to mothers with coronavirus disease 2019 (COVID-19) – National Neonatology Forum (NNF) India COVID-19 Registry. Indian Pediatr 2021;58:525-31.
9. Devin J, Marano R, Mikhael M, Feaster W, Sanger T, Ehwerhemuepha L. Epidemiology of neonatal COVID-19 in the United States. Pediatrics 2022;150:e2022056297.
10. Hobbs CV, Woodworth K, Young CC, Jackson AM, Newhams MM, Dapul H, et al. Frequency, characteristics and complications of COVID-19 in hospitalized infants. Pediatr Infect Dis J 2022;41:e81-6.
11. Piché-Renaud PP, Panetta L, Farrar DS, Moore-Hepburn C, Drouin O, Papenburg J, et al. Clinical manifestations and disease severity of SARS-CoV-2 infection among infants in Canada. PLoS One 2022;17:e0272648.
12. Di Pietro GM, Ronzoni L, Meschia LM, Tagliabue C, Lombardi A, Pinzani R, et al. SARS-CoV-2 infection in children: a 24 months experience with focus on risk factors in a pediatric tertiary care hospital in Milan, Italy. Front Pediatr 2023;11:1082083.
13. Pawlowska M, Pokorska-Śpiewak M, Talarek E, Mania A, Hasiec B, Żwirek-Pytka E, et al. Clinical course and severity of COVID-19 in 940 infants with and without comorbidities hospitalized in 2020 and 2021: the results of the National Multicenter Database SARSTer-PED. J Clin Med 2023;12:2479.
14. Cimolai N. The semantics of airborne microbial spread and environmental relevance: back to Anderson and Cox. Environ Res 2021;193:110448.
15. Cimolai N. Disinfection and decontamination in the context of SARS-CoV-2-specific data. J Med Virol 2022;94:4654-68.
16. Cimolai N. Environmental and decontamination issues for human coronaviruses and their potential surrogates. J Med Virol 2020;92:2498-510.
17. Cimolai N. Features of enteric disease from human coronaviruses: implications for COVID-19. J Med Virol 2020;92:1834-44.
18. Harding BR, Vora F. Report of a confirmed SARS-CoV-2 positive newborn with delivery despite negative SARS-CoV-2 testing on both parents. AJP Rep 2021;11:e80-3.
19. Shaiba LA, Hadid A, Abdulghani SH, Hussain SA, Shah PS. SARS-CoV-2 exposure from health care workers to infants: effects and outcomes. Am J Perinatol 2023;40:799-806.
20. Imran S, Gupta R, Sharma R, Mukhopadhyay S, Yadav S. Perinatal transmission of SARS-CoV-2 infection and its clinical attributes: a single-center study from Western Uttar Pradash. Cureus 2023;15:e35824.
21. Fernández Colomer B, Sánchez-Luna M, de Alba Romero C, Alarcón A, Baña Souto A, Camba Longueira F, et al. Neonatal infection due to SARS-CoV-2: an epidemiological study in Spain. Front Pediatr 2020;8:580584.
22. Lim SB, See KC, Law KB, Kamaruddin NIM. Characteristics and outcomes of SARS-CoV-2 positivity in neonates born to mothers with COVID-19 in Klang Valley, Malaysia: a retrospective observational study. IJID Reg 2022;5:146-53.
23. Gale C, Quigley MA, Placzek A, Knight M, Ladhani S, Draper ES, et al. Characteristics and outcomes of neonatal SARS-CoV-2 infection in the UK: a prospective national cohort study using active surveillance. Lancet Child Adolesc Health 2021;5:113-21.
24. Doná D, Montagnani C, Di Chiara C, Venturini E, Galli L, Lo Vecchio A, et al. COVID-19 in infants less than 3 months: severe or not severe disease? Viruses 2022;14:2256.
25. Hudak ML, Flannery DD, Barnette K, Getzlaff T, Gautam S, Dhudasia MB, et al. Maternal and newborn hospital outcomes of perinatal SARS-CoV-2 infection: a national registry. Pediatrics 2023;151:e2022059595.
26. Aydoğan S, Zenciroglu A, Çitli R, Dilli D, Özdem S. Evaluation of newborns diagnosed with COVID-19: a single-center experience. Am J Perinatol 2023;40:567-74.
27. Cozzi G, Cortellazzo Wiel L, Amaddeo A, Gatto A, Giangreco M, Klein-Kremer A, et al. Prevalence of SARS-CoV-2 positivity in infants with bronchiolitis: a multicentre international study. Arch Dis Child 2022 Jun 15:archdischild-2021-323559. doi: 10.1136/archdischild-2021-323559. [Epub].
28. Trevisanuto D, Cavallin F, Cavicchiolo ME, Borellini M, Calgaro S, Baraldi E. Coronavirus infection in neonates: a systematic review. Arch Dis Child Fetal Neonatal Ed 2021;106:330-5.
29. Liguoro I, Pilotto C, Bonanni M, Ferrari ME, Pusiol A, Nocerino A, et al. SARS-CoV-2 infection in children and newborns: a systematic review. Eur J Pediatr 2020;179:1029-46.
30. Panetta L, Proulx C, Drouin O, Autmizguine J, Luu TM, Quach C, et al. Clinical characteristics and disease severity among infants with SARS-CoV-2 infection in Montreal, Quebec, Canada. JAMA Netw Open 2020;3:e2030470.
31. Mithal LB, Machut KZ, Muller WJ, Kociolek LK. SARS-CoV-2 infection in infants less than 90 days old. J Pediatr 2020;224:150-2.
32. Saha S, Ahmed ANU, Kumar Sarkar P, Bipul MRA, Ghosh K, Wasik Rahman S, et al. The direct and indirect impact of SARS-CoV-2 infection in neonates: a series of 26 cases in Bangladesh. Pediatr Infect Dis J 2020;39:e398-405.
33. Griffin I, Irving SA, Arriola CS, Campbell AP, Li DK, Dawood FS,

et al. Incidence rates of medically attended COVID-19 in infants less than 6 months of age. Pediatr Infect Dis J 2023;42:315-20.
34. Zimmerman P, Uka A, Buettcher M, Fougère Y, Piebani M, Relly C, et al. Neonates with SARS-CoV-2 infection: spectrum of disease from a prospective nationwide observational cohort study. Swiss Med Wkly 2022;152:w30185.
35. Uslu Yuvacı H, Aslan MM, Köse O, Akdemir N, Toptan H, Cevrioğlu AS, et al. Evaluation of the presence of SARS-COV-2 in the vaginal fluid of reproductive-aged women. Ginekol Pol 2021 Mar 10. doi: 10.5603/GP.a2021.0018. [Epub].
36. Barber E, Kovo M, Leytes S, Sagiv R, Weiner E, Schwartz O, et al. Evaluation of SARS-CoV-2 in the vaginal secretions of women with COVID-19: a prospective study. J Clin Med 2021; 10:2735.
37. Nielsen SY, Murra M, Henning Pedersen L, Rohi Kalil M, Hvidman L, Helmig RB, et al. Comparatively low rates of COVID-19 in women admitted in labor and their newborns prior to routine vaccination of pregnant women: insight from Denmark. J Matern Fetal Neonatal Med 2023;36:2229933.
38. Nunes MC, Jones S, Strehlau R, Baba V, Ditse Z, da Silva K, et al. Active intrapartum SARS-CoV-2 infection and pregnancy outcomes. Am J Perinatol 2022;39(S 01):S42-8.
39. Buonsenso D, Costa S, Sanguinetti M, Cattani P, Posteraro B, Marchetti S, et al. Neonatal late onset infection with severe acute respiratory syndrome coronavirus 2. Am J Perinatol 2020; 37:869-72.
40. Eghbalian F, Monsef Esfahani A, Jenabi E. COVID-19 virus in a 6-day-old girl neonate: a case report. Clin Pediatr 2020;59:1288-9.
41. Gençeli M, Metin Akcan Ö, Pekcan S, Akin F, Özdemir M, Kiliç AO, et al. Outcomes of COVID-19 infections in children: a single-center retrospective study. Pediatr Pulmonol 2022;57:2533-9.
42. Ayed M, Alsaffar Z, Bahzad Z, Buhamad Y, Abdulkareem A, AlQattan A, et al. Coronavirus infection in neonates: neurodevelopmental outcomes at 18 months of age. Can J Infect Dis Med Microbiol 2023;2023:6140085.
43. Capozza M, Salvatore S, Baldassarre ME, Inting S, Panza R, Fanelli M, et al. Perinatal transmission and outcome of neonates born to SARS-CoV-2 positive mothers: the experience of 2 highly endemic Italian regions. Neonatology 2021;118:665-71.
44. Raba AA, Abobaker A, Elgenaidi IS, Daoud A. Novel coronavirus infection (COVID-19) in children younger than one year: a systematic review of symptoms, management and outcomes. Acta Paediatr 2020;109:1948-55.
45. Brodin P. Why is COVID-19 so mild in children? Acta Paediatr 2020;109:1082-3.
46. Shaiba LA, Altirkawi K, Hadid A, Alsubaie S, Alharbi O, Alkhalaf H, et al. COVID-19 disease in infants less than 60 days: case series. Front Pediatr 2021;9:674899.
47. Urstemova K, Bozhbanbayeva N, Cetinkaya M, Manzhuova L, Yeraliyeva L, Issayeva A. Features of the clinical course of coronavirus infection in newborn children. Georgian Med News 2022;331:101-8.
48. Liu X, Tang J, Xie R, Li W, Chen J, Guo Y, et al. Clinical and epidemiological features of 46 children <1 year old with coronavirus disease 2019 in Wuhan, China: a descriptive study. J Infect Dis 2020;222:1293-7.
49. Banerjee M, Pal J, Mondal T, Ghosh T, Nayek K. Clinical profile and short-term outcome of SARS-CoV-2-infected neonates from a government medical college in West Bengal, India. J Trop Pediatr 2022;68:fmac002.
50. Dávila-Aliaga C, Torres-Marcos E, Paucar-Zegarra R, Hinojosa-Pérez R, Espinoza-Vivas Y, Mendoza-Ibáñez E, et al. Clinical and epidemiological characterization in the follow-up of newborns with COVID-19: a descriptive study. Medwave 2021;21:e8500.
51. Hamid S, Woodworth K, Pham H, Milucky J, Chai SJ, Kawasaki B, et al. COVID-19-associated hospitalizations among U.S. infants aged <6 months - COVID-NET, 13 States, June 2021-August 2022. MMWR Morb Mortal Wkly Rep 2022;71:1442-8.
52. De Luca D, Perkins E, Tingay DG; European Society of Pediatric and Neonatal Intensive Care COVID-19 Paediatric and Neonatal Registry Group; European society of pediatric and neonatal intensive care covid-19 paediatric and neonatal registry (EPICENTRE) group - group authorship; European Society of Pediatric and Neonatal Intensive Care COVID-19 Paediatric and Neonatal Registry Group and European society of pediatric and neonatal intensive care covid-19 paediatric and neonatal registry (EPICENTRE) group - group authorship. Community Versus Vertically Acquired Neonatal SARS-CoV-2 Infection: The EPICENTRE Cohort Study. Pediatr Infect Dis J 2023;42:685-7.
53. Leibowitz J, Krief W, Barone S, Williamson KA, Goenka PK, Rai S, et al. Comparison of clinical and epidemiologic characteristics of young febrile infants with and without Severe Acute Respiratory Syndrome Coronavirus-2 infection. J Pediatr 2021; 229:41-7.
54. Solis-Garcia G, Gutiérrez-Vélez A, Pescador Chamorro I, Zamora-Flores E, Vigil-Vázquez S, Rodríguez-Corrales E, et al. Epidemiology, management and risk of SARS-CoV-2 transmission in a cohort of newborns born to mothers diagnosed with COVID-19 infection. Ann Pediatr 2021;94:173-8.
55. Babaei R, Bokharaei-Salim F, Khanaliha K, Kiani SJ, Marjani A, Garshasbi S, et al. Prevalence of SARS-CoV-2 infection in neonates born to mothers or relatives with COVID-19. BMC Infect Dis 2022;22:730.
56. Fitzpatrick T, Wilton AS, Chung H, Guttmann A. SARS-CoV-2 infection among maternal-infant dyads in Ontario, Canada. JAMA Netw Open 2021;4:e2120150.
57. Dumitriu D, Emeruwa UN, Hanft E, Liao GV, Ludwig E, Walzer L, et al. Outcomes of neonates born to mothers with severe acute respiratory syndrome coronavirus 2 infection at a large medical center in New York City. JAMA Pediatr 2021;175:157-67.
58. Pawar R, Gavade V, Patil N, Mali V, Girwalkar A, Tarkasband V, et al. Neonatal multisystem inflammatory syndrome (MIS-N) associated with prenatal maternal SARS-CoV-2: a case series. Children 2021;8:572.
59. Elbayiyev S, Şimşek GK, Ceran B, Akın MŞ, Kanmaz Kutman HG, Canpolat FE. Could red cell distribution width be used for predicting cardiac injury in neonates with COVID-19? J Med Virol 2022;94:5739-45.
60. Benenson-Weinberg T, Gross I, Bamberger Z, Guzner N, Wolf D, Gordon O, et al. Severe acute respiratory syndrome coronavirus 2 in infants younger than 90 days presenting to the Pediatric Emergency Department: clinical characteristics and risk of serious bacterial infection. Pediatr Emerg Care 2023 Apr 11. doi: 10.1097/PEC.0000000000002940. [Epub].
61. Krishnan P, Malik A, Isath A, Bandyopadhyay D, Goel A, Parton L, et al. Nationwide analysis of the outcomes and mortality of hospitalized infants with concomitant diagnosis of COVID-19. Am J Perinatol 2023 Sep 8. doi: 10.1055/a-2149-8810. [Epub].
62. Ansari NS, Watson DC, Campbell DM, Sarhan MA, Bitnun A, Gauda EB. SARS-CoV-2 infection in young infants during the Omicron wave: a case series. Biomed Hub 2023;8:10-4.
63. Nakhaei MHA, Moghadam SS, Yaghhoubi S. COVID-19 symptomatic newborns with possible postpartum transmission of

SARS-CoV-2. Case Rep Pediatr 2022;2022:7394175.
64. Lu Q, Shi Y. Coronavirus disease (COVID-19) and neonate: what neonatologists need to know. J Med Virol 2020;92:564-7.
65. De Bernardo G, Giordano M, Zollo G, Chiatto F, Sordino D, De Santis R, et al. The clinical course of SARS-CoV-2 positive neonates. J Perinatol 2020;40:1462-9.
66. Mo Y, Mo J, Liang RY, Xiao GY, Li Y, Wei QF. A case report of neonatal coronavirus disease 2019. Zhongguo Dang Dai Er Ke Za Zhi 2022;24:1266-8.
67. Tatura SNN. Severe COVID-19 with late-onset sepsis-like illness in a neonate. Am J Trop Med Hyg 2022;106:1098-103.
68. Mannix MK, Blood D, Gomez-Duarte OG, Davidson L. Necrotizing enterocolitis in a 34-week premature infant with COVID-19. Case Rep Infect Dis 2021;2021:1442447.
69. Brehm R, Narayanam L, Chon G. COVID-19-associated parotitis in a 10-week-old male. Cureus 2022;14:e31054.
70. Azeka E, Arshad A, Martins C, Dominguez AC, Siqueira A, Silveira Loss A, et al. Dilated cardiomyopathy in a newborn, a potential association with SARS-CoV-2. Front Pediatr 2021;9:674300.
71. Abdulaziz-Opiela G, Sobieraj A, Sibrecht G, Bajdor J, Mroziński B, Kozlowska Z, et al. Prenatal and neonatal pulmonary thrombosis as a potential complication of SARS-CoV-2 infection in late pregnancy. Int J Mol Sci 2023;24:7629.
72. Sidatt M, Sghair YM, Ghaddour T, Ahmed MS, Kader FA, Habib L, et al. Neonatal necrotizing enterocolitis due to COVID-19: a case report. J Neonatal Perinatal Med 2023;16:165-8.
73. Marsico C, Capretti MG, Aceti A, Vocale C, Carfagnini F, Serra C, et al. Severe neonatal COVID-19: challenges in management and therapeutic approach. J Med Virol 2022;94:1701-6.
74. Kaveh M, Sadatinejad SM. Management of neonatal sepsis with COVID-19 infection in a premature neonate – a case report. J Neonatal Nurs 2023;29:409-12.
75. Goussard P, Venkatakrishna S, Frigati L, Janson J, Schubert P, Verster J, et al. Chronic lung disease in children due to SARS-CoV-2 pneumonia: case series. Pediatr Pulmonol 2023;58:2111-23.
76. Cheung EW, Zachariah P, Gorelik M, Boneparth A, Kernie SG, Orange JS, et al. Multisystem inflammatory syndrome related to COVID-19 in previously health children and adolescents in New York City. JAMA 2020;324:294-6.
77. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet 2020;395:1607-8.
78. Swann OV, Holden KA, Turtle L, Pollock L, Fairfield CJ, Drake TM, et al. Clinical characteristics of children and young people admitted to hospital with COVID-19 in United Kingdom: prospective multicenter observational cohort study. BMJ 2020;370:m3249.
79. Stemberger Marić L, Trkulja V, Petrović D, Lah Tomulić K, Bartulović I, Tešović G, et al. Incidence and clinical phenotype of multisystem inflammatory syndrome in children after two SARS-CoV-2 pandemic waves: a Croatian prospective nationwide study. Pediatr Infect Dis J 2023;42:e229-31.
80. Godfred-Cato S, Tsang CA, Giovanni J, Abrams J, Oster ME, Lee EH, et al. Multisystem inflammatory syndrome in infants <12 months of age, United States, May 2020-January 2021. Pediatr Infect Dis J 2021;40:601-5.
81. Guernsey D 3rd, Pfeffer M, Kimpo J, Vazquez H, Zerzan J. COVID-19 and serious bacterial infection in febrile infants less than 60 days old. West J Emerg Med 2022;23:754-9.
82. Mehrpisheh S, Farhadi R, Ghaffari Saravi V, Dastourian F, Memarian A. Evaluation of clinical manifestations of coronavirus delta variant in neonates admitted to a hospital in northern Iran during the sixth wave: a case series. J Neonatal Nurs 2023 Apr 18. doi: 10.1016/j.jnn.2023. 04.008. [Epub].
83. Bechor Ariel T, Ariel B, Lahav Y, Yana M, Ben-Acon M, Sharon N. Clinical outcomes and laboratory values of infants with COVID-19 among several maternal variables: a retrospective cohort. Isr Med Assoc J 2023;25:387-91.
84. Sakuma H, Takanashi JI, Muramatsu K, Kondo H, Shiihara T, Suzuki M, et al. Severe pediatric acute encephalopathy syndromes related to SARS-CoV-2. Front Neurosci 2023;17:1085082.
85. Mascarenhas D, Goyal M, Haribalakrishna A, Nanavati R, Ish P, Kunal S. Multisystem inflammatory syndrome in neonates (MIS-N): a systematic review. Eur J Pediatr 2023;182:2283-98.
86. Shaiba LA, More K, Hadid A, Almagharbi R, Al Marri M, Alnamnakani M, et al. Multisystemic inflammatory syndrome in neonates: a systematic review. Neonatology 2022;119:405-17.
87. Kurokawa M, Kurokawa R, Lin AY, Capizzano AA, Baba A, Kim J, et al. Neurological and neuroradiological manifestations in neonates born to mothers with coronavirus disease 2019. Pediatr Neurol 2023;141:9-17.
88. Wątroba SJ, Bryda J. Meningoenphalitis and postinflammatory hydrocephalus in the course of COVID-19 disease in newborn – the potential role of acetazolamide as add-on therapy to the standard treatment. Ann Agric Environ Med 2022;29:595-602.
89. Sinaei R, Nejadbiglari H, Sinaei R, Zeinaly M, Pezeshki S, Jafari M. Finding positive SARS-CoV-2 RT-PCR in cerebrospinal fluid of two pediatric patients with severe COVID-19: a brief case report. BMC Pediatr 2023;23:49.
90. Tetsuhara K, Akamine S, Matsubara Y, Fujii S, Kashimada W, Marutani K, et al. Severe encephalopathy associated with SARS-CoV-2 Omicron BA.1 variant infection in a neonate. Brain Dev 2022;44:743-7.
91. Nagda A, Sawant V, Rajput K, Malik S, Singh V, Kondekar S. Multisystem inflammatory syndrome in neonates due to severe acute respiratory syndrome coronavirus 2: an emerging entity. Indian J Child Health 2021;8:401-3.
92. More K, Aiyer S, Goti A, Parikh M, Sheikh S, Patel G, et al. Multisystem inflammatory syndrome in neonates (MIS-N) associated with SARS-CoV-2 infection: a case series. Eur J Pediatr 2022;181:1883-98.
93. Abdelbari M, Tilouche S, Hannachi S, Bouguila J, Hannachi N, Boughammoura L. Fulminant encephalitis caused by SARS-CoV-2 in a two-month-old infant. Indian J Pediatr 2023;90:101.
94. Saha S, Pal P, Mukherjee D. Neonatal MIS-C: managing the cytokine storm. Pediatrics 2021;148:e2020042093.
95. Brum AC, Glasman MP, De Luca MC, Rugilo CA, Urquizu Handal MI, Picon AO, et al. Ischemic lesions in the brain of a neonate with SARS-CoV-2 infection. Pediatr Infect Dis J 2021;40:e340-3.
96. Fragoso DC, Marx C, Dutra BG, da Silva CJ, da Silva PM, Martins Maia Junior AC, et al. COVID-19 as a cause of acute neonatal encephalitis and cerebral cytotoxic edema. Pediatr Infect Dis J 2021;40:e270-1.
97. Yildiz H, Yarci E, Bozdemir SE, Ozdinc Kizilay N, Mengi S, Beskardesler N, et al. COVID-19-associated cerebral white matter injury in a newborn infant with afebrile seizure. Pediatr Infect Dis J 2021;40:e268-9.
98. Cursi L, Calo Carducci FI, Chiurchiu S, Romani L, Stoppa F, Lucignani G, et al. Severe COVID-19 complicated by cerebral venous thrombosis in a newborn successfully treated with remdesivir, glucocorticoids, and hyperimmune plasma. Int J

Environ Res Public Health 2021;18:13201.
99. Schiff J, Brennan C. COVID-19 presenting as a bulging fontanelle. Am J Emerg Med 2021;43:81-2.
100. Sethuraman C, Holland J, Priego G, Khan F, Johnson R, Keane M. Bulging anterior fontanelle caused by severe acute respiratory syndrome coronavirus-2. Pediatr Infect Dis J 2023; 42:e4-5.
101. Eghbalian F, Sami G, Bashirian S, Jenabi E. A neonate infected with coronavirus disease 2019 with severe symptoms suspicious of multisystem inflammatory syndrome in childhood. Clin Exp Pediatr 2021;64:596-8.
102. Mierzewska-Schmidt M, Baranowski A, Szymanska K, Ciaston M, Kuchar E, Ploski R, et al. The case of fatal acute hemorrhagic necrotizing encephalitis in a two-month-old boy with COVID-19. Int J Infect Dis 2022;116:151-3.
103. Firestein MR, Shuffrey LC, Hu Y, Kyle M, Hussain M, Bianco C, et al. Assessment of neurodevelopment in infants with and without exposure to asymptomatic or mild maternal SARS-CoV-2 infection during pregnancy. JAMA Netw Open 2023;6:e237396.
104. Shuffrey LC, Firestein MR, Kyle M, Fields A, Alcántara C, Amso D, et al. Association of birth during COVID-19 pandemic with neurodevelopmental status at 6 months in infants with and without in utero exposure to maternal SARS-CoV-2 infection. JAMA Pediatr 2022;176:e215563.
105. Ungar SP, Solomon S, Stachel A, Demarco K, Roman AS, Lighter J. Impact of prenatal SARS-CoV-2 infection on infant emergency department visits and hospitalization. Clin Pediatr 2022;61:206-11.
106. Goulding A, McQuaid F, Lindsay L, Agrawal U, Auyeung B, Calvert C, et al. Confirmed SARS-CoV-2 infection in Scottish neonates 2020-2022: a national, population-based cohort study. Arch Dis Child Fetal Neonatal Ed 2023;108:367-72.
107. Götzinger F, Santiago-Garcia B, Noguera-Julián A, Lanaspa L, Lancella L, Calò Carducci F, et al. COVID-19 in children and adolescents in Europe: a multinational, multicenter cohort study. Lancet Child Adolesc Health 2020;4:653-61.
108. Mohagheghi P, Hakimelahi J, Khalajinia Z, Sadeghi Moghadam P. COVID-19 infection in Iranian newborns and their mothers: case series. Tanaffos 2021;20:172-9.
109. Halasa NB, Olson SM, Staat MA, Newhams MM, Price AM, Pannaraj PS, et al. Maternal vaccination and risk of hospitalization for COVID-19 among infants. N Engl J Med 2022;387: 109-19.
110. Gosdin L, Wallace B, Lanzieri TM, O'Malley Olsen E, Lewis EL, Chang DJ, et al. Six-month outcomes of infants born to people with SARS-CoV-2 in pregnancy. Pediatrics 2022;150: e2022059009.
111. Fattahi P, Abdi S, Saeedi E, Sirous S, Firuzian F, Mohammadi M, et al. In-hospital mortality of COVID-19 in Iranian children and youth: a multi-centre retrospective cohort study. J Glob Health 2022;12:05048.
112. Duarte-Neto AN, Caldini EG, Gomes-Gouvêa MS, Kanamura CT, de Almeida Monteiro RA, Ferranti JF, et al. An autopsy study of the spectrum of severe COVID-19 in children: From SARS to different phenotypes of MIS-C. EClinicalMedicine 2021;35:100850.
113. Yamazaki-Nakashimada MA, Márquez-González H, Miranda-Novales G, Neme Díaz GA, Prado Duran SA, Luévanos Velázquez A, et al. Characteristics and outcomes of multisystem inflammatory syndrome in children: a multicenter, retrospective, observational cohort study in Mexico. Front Pediatr 2023; 11:1167871.
114. Buja LM, Wolf DA, Zhao B, Akkanti B, McDonald M, Lelenwa L, et al. The emerging spectrum of cardiopulmonary pathology of the coronavirus disease 2019 (COVID-19): report of 3 autopsies from Houston, Texas, and review of autopsy findings from other United States cities. Cardiovasc Pathol 2020;48:107233.
115. Septimiu-Radu S, Gadela T, Gabriela D, Oancea C, Rosca O, Lazureanu VE, et al. A systematic review of lung autopsy findings in elderly patients after SARS-CoV-2 infection. J Clin Med 2023;12:2070.
116. Octavius GS, Wijaya JH, Tan AO, Muljono MP, Chandra S, Juliansen A. Autopsy findings of pediatric COVID-19: a systematic review. Egypt J Forensic Sci 2022;12:32.
117. Khairwa A, Jat KR. Autopsy findings of COVID-19 in children: a systematic review and meta-analysis. Forensic Sci Med Pathol 2022;18:516-29.
118. Bhatnagar J, Gary J, Reagan-Steiner S, Estettter LB, Tong S, Tao Y, et al. Evidence of severe acute respiratory syndrome coronavirus 2 replication and tropisms in the lungs, airways, and vascular epithelium of patients with fatal coronavirus disease 2019: an autopsy case series. J Infect Dis 2021;223:752-64.
119. Goussard P, Schubert P, Parker N, Myburgh C, Rabie H, van der Zalm MM, et al. Fatal SARS-CoV-2 Omicron variant in a young infant: autopsy findings. Pediatr Pulmonol 2022;57:1363-5.
120. Stram MN, Seifert AC, Cortes E, Akyatan A, Woodoff-Leith E, Borukhov V, et al. Neuropathology of pediatric SARS-CoV-2 infection in the forensic setting: novel application of ex vivo imaging in analysis of brain microvasculature. Front Neurol 2022;13:894565.
121. Konopka KE, Nguyen T, Hlavaty L, Rayes O, Schmidt CJ, Dahl J, et al. Utility of CDC screening guidelines and autopsy findings in identifying decedents who die of SARS-CoV-2 infection. Am J Forensic Med Pathol 2021;42:118-20.
122. Mulale UK, Kashamba T, Strysko J, Kyokunda LT. Fatal SARS-CoV-2 and Mycobacterium tuberculosis coinfection in an infant: insights from Botswana. BMJ Case Rep 2021;14: e239701.
123. de Almeida Monteiro RA, Duarte-Neto AN, Ferraz da Silva LF, de Oliveira EP, do Nascimento ECT, Mauad T, et al. Ultrasound assessment of pulmonary fibroproliferative changes in severe COVID-19: a quantitative correlation study with histopathological findings. Intensive Care Med 2021;47:199-207.
124. Chen J, Jiang Q, Xia X, Liu K, Yu Z, Tao W, et al. Individual variation of the SARS-CoV-2 receptor ACE2 gene expression and regulation. Aging Cell 2020;19:e13168.
125. Dioguardi M, Cazzolla AP, Arena C, Sovereto D, Caloro GA, Dioguardi A, et al. Innate immunity in children and the role of ACE2 expression in SARS-CoV-2 infection. Pediatr Rep 2021;13:363-82.
126. Cimolai N. Solidifying diagnostics in SARS-CoV-2 research. Am J Obstet Gynecol MFM 2022;4:100514.
127. Cimolai N. Not all viral culture approaches are equal. Clin Infect Dis 2021;73:e1787-8.
128. Ibrahim L, Wilson C, Tham D, Corden M, Jani S, Zhang M, et al. The characteristics of SARS-CoV-2-positive children in Australian hospitals: a PREDICT network study. Med J Aust 2023;218:460-6.
129. Haraschchenko T, Umanets T, Pololskiy V, Kaminska T, Marushko Y, Podolskiy V, et al. Epidemiological, clinical, and laboratory features of children with SARS-CoV-2 in Ukraine. J Mother Child 2023;27:33-41.
130. Hardelid P, Favarato G, Wijlaars L, Fenton L, McMenamin J, Clemens T, et al. SARS-CoV-2 tests, confirmed infections and

COVD-19-related hospital admissions in children and young people: birth cohort study. BMJ Pediatr Open 2022;6:e001545.
131. Cimolai N. Co-detections versus coinfections in the context of SARS-CoV-2 diagnostics. J Antimicrob Chemother 2022;77:542.
132. Cimolai N. Complicating infections associated with common endemic human respiratory coronaviruses. Health Secur 2021; 19:195-208.
133. Jacob R, Padeh G, Kaplan O, Koppel JH, Porat D, Weiser G, et al. Bacterial infections and clinical outcomes among febrile infants up to 90 days old with SARS-CoV-2 infection: a multicenter cohort study. Pediatr Infect Dis J 2023;42:905-7.
134. Krogstad P, Contreras D, Ng H, Tobin N, Chambers CD, Bertrand K, et al. No infectious SARS-CoV-2 in breast milk from a cohort of 110 lactating women. Pediatr Res 2022;92:1140-5.
135. Lewis EL, Smoots AN, Woodworth KR, Olsen EO, Roth NM, Yazdy M, et al. Breast milk feeding of infants at birth among people with confirmed SARS-CoV-2 infection in pregnancy: SET-NET, 5 States, March 29, 2020-December 31, 2020. Am J Public Health 2022;112(S8):S787-96.
136. Salvatore CM, Han JY, Acker KP, Tiwari P, Jin J, Brandler M, et al. Neonatal management and outcomes during the COVID-19 pandemic: an observation cohort study. Lancet Child Adolesc Health 2020;4:721-7.
137. Shlomai NO, Kasirer Y, Strauss T, Smolkin T, Marom R, Shinwell ES, et al. Neonatal SARS-CoV-2 infections in breastfeeding mothers. Pediatrics 2021;147:e2020010918.
138. Briana DD, Malamitsi-Puchner A. Breastfeeding provides a protective hug and the benefits have outweighed the risks during the COVID-19 pandemic. Acta Paediatr 2023;112:1177-81.
139. Cimolai N. Reanalysis of quarantine for coronavirus disease 2019 with emerging data. Am J Obstet Gynecol MFM 2021;3: 100291.
140. Cimolai N. In pursuit of the right tail for the COVID-19 incubation period. Public Health 2021;194:149-55.
141. Cimolai N. More data are required for incubation period, infectivity, and quarantine duration for COVID-19. Travel Med Infect Dis 2020;37:101713.
142. Centers for Disease Control. Multisystem inflammatory syndrome (MIS): information for healthcare providers about multisystem inflammatory syndrome in children (MIS-C) [Internet]. Atlanta (GA): 2023 [cited 2323 Apr 2]. Available from: https://www.cdc.gov/mis/mis-c/hcp_cstecdc/index.html.
143. Molloy EJ, Nakra N, Gale C, Dimitriades VR, Lakshminrusimha S. Multisystem inflammatory syndrome in children (MIS-C) and neonates (MIS-N) associated with COVID-19: optimizing definition and management. Pediatr Res 2023;93:1499-508.
144. Royal College of Paediatrics and Child Health. Guidance: paediatric multisystem inflammatory syndrome temporally associated with COVID-19 [Internet]. London: Royal College of Paediatrics and Child Health; 2023 [cited 2023 Apr 14]. Available from: https://www.rcpch.ac.uk/sites/default/files/2020-05/COVID-19-Paediatric-multisystem-%20inflammatory%20syndrome-20200501.pdf.
145. Dufort EM, Koumans EH, Chow EJ, Rosenthal EM, Muse A, Rowlands J, et al. Multisystem inflammatory syndrome in children in New York State. N Engl J Med 2020;383:347-58.
146. Cimolai N. Mast cell biology and linkages for non-clonal mast cell activation and autoimmune/inflammatory syndrome induced by adjuvants. SN Compr Clin Med 2020;2:2310-23.
147. Zaki SA, Hazeem AA, Rashid A. Giant coronary aneurysm in an infant with multisystem inflammatory syndrome. Heart Views 2022;23:108-12.
148. Diwakar K, Gupta BK, Uddin MW, Sharma A, Jhajra S. Multisystem inflammatory syndrome with persistent neutropenia in neonate exposed to SARS-CoV-2 virus: a case report and review of literature. J Neonatal Perinatal Med 2022;15:373-7.
149. Kappanayil M, Balan S, Alawani S, Mohanty S, Leeladharan SP, Gangadharan JP, et al. Multisystem inflammatory syndrome in a neonate, temporally associated with prenatal exposure to SARS-CoV-2: a case report. Lancet Child Adolesc Health 2021; 5:304-8.
150. Khaund Borkotoky R, Banerjee Barua P, Paul SP, Heaton PA. COVID-19-related potential multisystem inflammatory syndrome in childhood in a neonate presenting as persistent pulmonary hypertension of the newborn. Pediatr Infect Dis J 2021;40:e162-4.
151. Gámez-González LB, Escárcega-Juárez Ana Silvia AS, Aguilar-Soto DE, Colmenero Rascón M, García Espinosa AC, Yamazaki-Nakashimada MA. Multisystem inflammatory syndrome in neonates associated with SARS-CoV-2 infection, a different entity? J Neonatal Perinatal Med 2023;16:169-77.
152. Zambrano LD, Wu MJ, Martin L, Malloch L, Chen S, Newhams MM, et al. Risk factors for multisystem inflammatory syndrome in children: a case-control investigation. Pediatr Infect Dis J 2023;42:e190-6.
153. Ryan L, Plötz FB, van den Hoogen A, Latour JM, Degtyareva M, Keuning M, et al. Neonates and COVID-19: state of the art. Pediatr Res 2022;91:432-9.
154. Bodansky A, Sabatino JJ Jr, Vazquez S, Chou S, Novak T, Moffitt KL, et al. A distinct cross-reactive autoimmune response in multisystem inflammatory syndrome in children (MIS-C). medRxiv [Preprint] 2023 [cited 2023 Apr 2]. Available from: https://www.medrxiv.org/content/10.1101/2023.05.26.23290373v1.
155. Klavina L, Smane L, Kivite-Urtane A, Vasilevska L, Davidsone Z, Smitins E, et al. Comparison of characteristics and outcomes of multisystem inflammatory syndrome, Kawasaki disease and toxic shock syndrome in children. Medicina (Kaunas) 2023; 59:626.
156. Cimolai N. Applying immune instincts and maternal intelligence from comparative microbiology to COVID-19. SN Compr Clin Med 2020;2:2670-83.
157. Wachman EM, Snyder-Cappione J, Devera J, Boateng J, Dhole Y, Clarke K, et al. Maternal, infant, and breast milk antibody response following COVID-19 infection in early versus late gestation. Pediatr Infect Dis J 2023;42:e70-6.
158. Ibroci E, Liu X, Lieb W, Jessel R, Gigase FAJ, Chung K, et al. Impact of prenatal COVID-19 vaccination at delivery and neonatal outcomes: results from a New York City cohort. Vaccine 2023;41:649-56.
159. Tripathy GS, Rath TS, Behera S, Lekha KS, Kar D, Pendyala S. Effects of COVID-19 vaccination during pregnancy on the obstetric and neonatal outcomes in a tertiary health care center. J Mother Child 2023;27:72-8.
160. Jorgensen SCJ, Hernandez A, Fell DB, Austin PC, D'Souza R, Guttmann A, et al. Maternal mRNA COVID-19 vaccination during pregnancy and delta or omicron infection or hospital admission in infants: test negative design study. BMJ 2023;380: e074035.
161. Danino D, Ashkenazi-Hoffnung L, Diaz A, Erps AD, Eliakim-Riaz N, Avni YS, et al. Effectiveness of BNT162b2 vaccination during pregnancy in preventing hospitalization for SARS-CoV-2 in infants. J Pediatr 2023:254:48-53.e1.
162. Zerbo O, Ray GT, Fireman B, Layefsky E, Goddard K, Lewis E,

et al. Maternal SARS-CoV-2 vaccination and infant protection against SARS-CoV-2 during the first six months of life. Nat Commun 2023;14:894.
163. Cimolai N. Immunophenotyping of SARS-CoV-2 and vaccine design. Vaccine 2022;40:3985-6.
164. Adhikari EH, Lu P, Kang YJ, McDonald AR, Pruszynski JE, Bates TA, et al. Diverging maternal and cord antibody functions from SARS-CoV-2 infection and vaccination in pregnancy. J Infect Dis 2023 Oct 10:jiad421. doi: 10.1093/infdis/jiad421. [Epub].
165. Cimolai N. A minimalist strategy towards temporarily defining protection for COVID-19. SN Compr Clin Med 2020;2:2059-66.
166. Ockene MW, Russo SC, Lee H, Monthé-Drèze C, Stanley TL, Ma IL, et al. Accelerated longitudinal weight gain among infants with in utero COVID-19 exposure. J Clin Endocrinol Metab 2023;108:2579-88.
167. Roy S, Jha VN, Ranjan B. A case series of coagulopathy in preterm or growth-restricted term neonates born to mothers with antenatal SARS-CoV-2 infection: neonatal post-COVID-19 coagulopathy? J Family Med Prim Care 2022;11:7483-490.
168. Cimolai N. Microvascular hypertensive disease, Long COVID, and end-organ pathology. Hypertens Res 2023;46:2247-8.
169. Derespina KR, Kaushik S, Plichta A, Conway EE Jr, Bercow A, Choi J, et al. Clinical manifestations and outcomes of critically ill children and adolescents with coronavirus disease 2019 in New York City. J Pediatr 2020;226:55-63.e2.
170. Shoji K, Asai Y, Akiyama T, Tsuzuki S, Matsunaga N, Suzuki S, et al. Clinical efficacy of remdesivir for COVID-19 in children: a propensity-score-matched analysis. J Infect Chemother 2023; 29:930-3.
171. Goldman DL, Aldrich M, Hagmann SHF, Bamford A, Camacho-Gonzalez A, Lapadula G, et al. Compassionate use of remdesivir in children with severe COVID-19. Pediatrics 2021; 147:e2020047803.
172. Cimolai N Passive immunity should and will work for COVID-19 for some patients. Clin Hematol Int 2021;3:47-68.
173. Kadian YS, Ali M, Kumar C, Kajal P. Surgical neonates with coronavirus infectious disease-19 infection: an experience with five cases at high-volume tertiary care centre of India. Afr J Paediatr Surg 2022;19:228-32.

How to cite this article: Cimolai N. COVID-19 among infants: key clinical features and remaining controversies. Clin Exp Pediatr 2024;67:1-16.