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Review

Covid-19 in pregnant women and babies: What pediatricians need to know

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Educational aims

The reader will come to appreciate that:

- SARS-CoV-2 virus can cause Covid-19 in pregnant women, but that there may also be asymptomatic carriers.
- The prevalence of positive tests for SARS-CoV-2 in women presenting for delivery varies from 3% to 13%, and may be dependent on the prevalence in the general population.
- Up to 3% of newborns may have detectable virus but it is not clear when it was acquired. Most newborns do well.
- Based on 26 reported cases, affected neonates generally do well and need only supportive therapy.

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ABSTRACT

Beginning in late 2019, a novel coronavirus labeled SARS-CoV-2 spread around the world, affecting millions. The impact of the disease on patients and on health care delivery has been unprecedented. Here, we review what is currently known about the effects of the virus and its clinical condition. Covid-19 in areas of relevance to those providing care to neonates. While aspects of pregnancy, including higher expression of the cell receptor for the virus, ACE2, could put these women at higher risk, preliminary epidemiological information does not support this. Viral carriage prevalence based on universal screening show that rates vary from 13% in “hot spots” such as New York City, to 3% in areas with lower cases. Vertical transmission risks are unknown but 3.1% of 311 babies born to mothers with Covid-19 were positive within a week of birth. The clinical description of 26 neonates <30 days of age showed no deaths and only one requiring intensive care. Risks for breast-feeding and for milk banks are discussed.

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INTRODUCTION

In late 2019, a respiratory infection began to spread amongst residents in the city of Wuhan China. It was quickly attributed to a previously unknown coronavirus, which was given the name novel SARS-CoV-2. The clinical disease was subsequently named Covid-19 and as of this writing (late May, 2020), has affected over 5.7 million people in virtually every country and region in the world, accounting for over three hundred and sixty thousand deaths. Initial epidemiological reports indicate that those over 65 years of age and/or who have pre-existing conditions are at

increased risk for Covid-19. These risk factors including asthma and other chronic lung diseases, diabetes, morbid obesity, significant cardiovascular disease, or immune compromise [1]. Some have included pregnancy as a risk factor for Covid-19 [2]. The purpose of this review is to describe the current information available at the time of writing regarding the potential and known effects of this novel SARS-CoV-2 in pregnant women, their fetuses, and their newborns, to help inform neonatologists who might be called upon to counsel expectant mothers and to care for their babies. Like all information about this disease, this is a rapidly developing field. After initial case reports, enough data and experience have rapidly accumulated to inform their clinical care. However, it is very important to note that virtually all reports to date are based on selective, often anecdotal case accrual, primarily using only hospitalized patients or those sick enough to seek hospital care. There

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are limited data at present about the prevalence of affected individuals in the population as a whole, which may differ from current estimates, as the estimated number of asymptomatic individuals may be as high as 52% [3]. It is likely, therefore, that any estimate rates or proportions will be lower than what is currently reported. It must also be noted that, while rapid dissemination of medical information has been very beneficial during this pandemic, the careful peer review process has, of necessity, been placed on hold, for example, by rapid releases of pre-prints. It is therefore likely that some of our current understanding may change as further data are more carefully scrutinized.

PREGNANCY AS RISK FACTOR

SARS-Cov-2 closely resembles the original coronavirus species which caused the SARS epidemic of 2002–03, with 79% gene sequence homology [4]. That epidemic affected nearly 8500 individuals with an overall case fatality rate estimated to be 9% [5]. In a case series from Hong Kong of a dozen pregnant women, there was a 25% mortality rate, along with three first trimester miscarriages, and two of the infants were growth restricted [6]. As a result, some authors suggested that pregnancy was a significant risk factor for SARS morbidity and mortality. This was true during the last world-wide pandemic, Spanish flu of 1918–19 [7] as well as during the 1957 H2N2 influenza season, where half the women between 18 and 49 who died did so from influenza [8]. For these historical precedents, there are possible biological factors that might explain the amplified risk of coronavirus infection during pregnancy. Diabetes is more common during pregnancy; there is relative immunosuppression of the TH1 response, making pregnant women more susceptible to viral infections [9]; and expression of the ACE2 membrane protein, the receptor for both SARS-Cov and SARS-Cov-2, is relatively increased during pregnancy [10].

PREGNANCY

With rapid publication, several series of Covid-19 infection in pregnancy cases have now been published. Table 1 presents data from fifteen studies that included more than 3 subjects [11–26]. These include 511 subjects, 82.5% diagnosed by SARS-Cov-2 RT-PCR, the others by current clinical criteria. The vast majority presented with symptoms and were then diagnosed, meaning that those who are asymptomatic or who have mild disease are most likely under-represented. This, therefore, might be best viewed as a current snapshot of the most significantly affected pregnant women.

As shown in Table 1, a small proportion were in the first or second trimester (10 and 20 subjects respectively). There were eight spontaneous miscarriages and seven elective terminations due to concerns about the potential effects of SARS-CoV-2 on the fetus. In pregnancies beyond 23 weeks gestational age, one report from Iran noted that five out of nine had intrauterine fetal demise [14], but this has not been replicated in any other published studies to date. More than two thirds (68.1%) of the births were by caesarian section, most probably reflecting the fact that these reports preferentially included symptomatic mothers.

To understand SARS-CoV-2 and pregnancy in a more comprehensive manner, it will be important to acquire more data from asymptomatic and mildly affected mothers. Estimates of asymptomatic rates in pregnant women are preliminary and quite variable. One study from New York reported that, in the first five days of universal testing for women presenting to the Labor and Delivery unit, 12 women were lab-test positive but were asymptomatic [27]. Of note, 8 of them (67%) developed intrapartum or post-partum fever. It was not possible to differentiate the cause

of the fever between clinical chorioamnionitis or Covid-19 but other reports also suggest that fever occurs after delivery in affected mothers. In another, larger series from New York, 33 of 215 screened women were positive (15.3%) [28]. However, only four (1.9% of the whole screened population or 12.1% of the positive group) were symptomatic, although three (1.4%, 9.1% respectively) of the asymptomatic patients did develop fever perinatally or post-natally. Another study from New York screening asymptomatic women scheduled to deliver during the first two weeks of April also had a 15% positive rate (24/155) [29].

In contrast, of 635 pregnant women admitted to Northwestern Hospital in Chicago, only 23 (3.6%) were positive, including ten who were asymptomatic [30]. This is similar to the experience in Richmond Virginia where 6 of 177 (3.4%) patients undergoing general screening upon presentation to the labor and delivery unit were positive. Virginia has approximately the same population as New York City but only one fifth the number of confirmed cases [31]. These observations probably reflect how the prevalence of SARS-Cov-2 colonization in pregnant women is likely to reflect that of the general population.

The risk: benefit analysis for administration of antenatal corticosteroids in mothers with Covid-19 for the benefit of the neonate should they be born prematurely is not very clear [32]. There are no systematic data available as yet for this infection, so recommendations are primarily based on our experience with other viruses, especially pneumonia due to influenza virus, where corticosteroid use was associated with a higher mortality rate and higher rates of ICU admission [33]. These considerations have led to the recommendation that treatment decisions be individualized, based on the risk to and condition of the mother and the potential benefit to the infant. An asymptomatic or mildly symptomatic mother at 24–26 weeks' gestation is a very different scenario compared to a mother who is in the Intensive Care Unit (ICU) on a ventilator at more than 34 weeks gestational age.

TERATOGENICITY

Many viruses, including rubella, cytomegalovirus, varicella zoster and zika, are well known to be teratogenic to the fetus. Coronaviruses are associated with 20% of upper respiratory tract infections, involving the four main sub-types but none of these are of specific concern during pregnancy [34]. There were two cases of intrauterine growth restriction in babies born during the 2002–03 SARS outbreak, although the underlying etiology was not investigated [6]. In the other human coronavirus epidemic, Middle East Respiratory Syndrome MERS-CoV, there was no reported evidence for teratogenicity among the 12 pregnant patients [35]. Similarly, up to mid-May 2020, there have not been any reports of congenital abnormalities in infants born to mothers with Covid-19 or who are positive for SARS-CoV-2. Whilst these data are encouraging, additional data accumulation is urgently required to confirm these observations.

VERTICAL TRANSMISSION

As shown in Table 1, 322 offspring of Covid-19 mothers were tested after birth, and 10 were noted to be positive (3.1%). It is not possible, however, to know when and by which route (prenatal, perinatal like herpes simplex, or postnatal) the virus passed to the neonate, as few samples were reported to have been obtained immediately after birth or was sampling done serially. In addition, it is not clear if the infants who tested positive were separated from their mothers beginning immediately after birth, so it is not possible to determine if these were cases of postnatally acquired virus.

Table 1
SARS-Cov-2 in Pregnancy.

Country (n)	Period	Dx	Gestation (wks)	Maternal Sx	Delivery	Maternal Outcome	Neonatal Outcome	Newborn Test/+
China (5) ¹¹	1/10–2/10/20	5 PCR	38–41	Postpartum fever (1), Cough, coryza (1), Lymphopenia (4)	CS (2) Vag (3)	No Complications	No Complications	5/0
China (9) ¹²	1/10–1/20/20	9 PCR	36–39	Prepartum fever (7), Postpartum fever (2), Cough (4), GI (1), Myalgia (1), Lymphopenia (5)	CS (9) Vag (0)	Nasal Cannula (6) PPROM (2), Fetal Distress (2), Pre-Eclampsia	SGA (1) to mother with Pre-Eclampsia	9/0
China (13) ¹³	12/8/19–2/25/20	13 PCR	24–30 (2), 31–36 (8), >36 (3)	Fever (13), Cough (8), Fatigue (9)	CS (10) Pregnancy Continued (3)	PPROM (1), Fetal Distress (3), MODS (1)	Preterm < 37 weeks (6), IUFD (1),	10/0
Iran (9) ¹⁴	2/15–3/15/20	9 PCR	24–30 (3), 31–36 (5), >36 (1)	Fever (8), Cough (5), Dyspnea (3), Pneumonia (4)	CS (3) Vag (1)	Death (7), Still in ICU (1)	IUFD (4*), Preterm < 37 weeks (4)	6/1
China (10) ¹⁵	1/20–3/2/20	10 Clinical	36–40	Fever (5), Cough (4)	Vag (10)	None	Preterm < 37 weeks (1)	7/0
China (116) ¹⁶	1/20–3/24/20	65 PCR 51 Clinical	<14 (4), 14–27 (6), 28–36 (30), >36 (76)	Fever (59), Cough (33), Fatigue (15), Sore throat (10), Dyspnea (12), Lymphopenia (44), No Sx (27)	CS (85) Vag (14) SAB (1) Continued (16)	Severe pneumonia (8)	Preterm < 37 weeks (21), Birth asphyxia (1), Death (1)	86/0
China (16) ¹⁷	1/30–2/17/20	16 PCR	35–41	Pneumonia (1)	CS (16)	Severe pneumonia (1)	Preterm < 37 weeks (1)	10/0
China (28) ¹⁸	1/15–3/20/20	28 PCR	1st Trimester (3), 2nd Trimester (1), 3rd Trimester (24)	Fever (5), Cough (7), Dyspnea (2), Lymphopenia (8)	EAB (4), CS (17), Vag (5), Continued (2)	7 hospitalized for average 14 days. No deaths	Preterm < 37 weeks (1)	23/0
China (118) ¹⁹	12/8/19–3/20/20	84 PCR 34 Clinical		Fever (84), Cough (82), Chest tightness (20), Severe Covid-19 (9)	EAB (4), SAB (3), Ectopic (2), CS (63), Vag (5), Continued (41)	1 Severe, all discharged	Preterm < 37 weeks (14)	8/0
China (13) ²⁰	1/20–3/5/20	13 PCR		Prenatal fever (2), Postnatal fever (8)	CS (9) Vag (4)	?	Respiratory distress (3)	20/0
China (16) ²¹	1/24–2/29/20	16 PCR	33–40	Prenatal fever (4), Postnatal fever (8), Lymphopenia (2)	CS (14) Vag (2)	Fetal distress (2)	Preterm < 37 weeks (2)	3/0
China (7) ²²	1/1–2/8/20	7 PCR	37–41	Fever (6), Cough (1), Dyspnea (1), Diarrhea (1), Lymphopenia (5)	CS (7)	None	Respiratory distress (1)	3/1
UK (9) ²³	3/7–4/20/20	9 PCR	24–30 (1), Term (8)	Fever (4), Cough (8), Lethargy (6), Dyspnea (4), Anosmia (7)	CS (8) Vag (1)	Mechanical ventilation (1), ECMO (1)	Viral pneumonia (1), Preterm < 37 weeks (1)	9/1
China (23) ²⁴	12/31/19–3/7/20	19 PCR 4 Clinical	<14 (3), 28–36 (3), >36 (17)	Fever (5), Cough (5)	SAB (3) CS (18) Vag (2)	None	None	4/0
Italy (42) ²⁵	3/1–3/20/20	42 PCR	<34 (4), 34–37 (7), >37 (31)	Prenatal fever (20), Postnatal fever (6), Cough (18), Dyspnea (8), Lymphopenia (6)	CS (24) Vag (18)	ICU (4)	NICU (3)	42/3
Italy (77) ²⁶	2/23–3/28/20	77 PCR	1st Trimester (4), 2nd Trimester (13), 3rd Trimester (50)	Fever (57), Cough (62), Dyspnea (27), Lymphopenia (24)	CS (22) Vag (34) Continued (20)	ICU (5), ECMO (1)	NICU (9)	77/4

Abbreviations:

PCR = Polymerase chain reaction.

EAB = Elective termination.

SAB = Spontaneous termination.

CS = Cesarean section.

Vag = Vaginal delivery.

On the other hand, an initial case report from China described elevated IgG and IgM against SARS-CoV-2 drawn at 2 h of age, born to a mother with Covid-19. However, the baby had 5 negative RT-PCR nasopharyngeal tests [36]. In another study of six infants born to Covid-19 mothers who had blood and nasopharyngeal samples obtained at birth [37] two had elevations in their IgG and IgM antibodies against SARS-CoV-2, although neither had viral RNA detected. These results taken together raise the possibility that the fetus responds with an immune response to virus at some point prior to delivery, but this needs to be confirmed by larger,

more systematic studies, using validated serological assays to establish the true nature of the associations between SARS-CoV-2 and neonatal infections [38].

NEONATAL DISEASE AND CLINICAL IMPLICATIONS

Overall, children are a small minority of diagnosed Covid-19 cases. The incidence in South Korea among children as of May 16, 2020 was 3.4 cases/100,000, one eighth the rate in the elderly population. There were also no deaths reported in those under

Table 2
SARS-Cov-2 Positive Neonates.

Country (n)	Age at Dx	Gest. Age (weeks)	Gender	Bwt (g)	Delivery Mode	Testing source	Contact	Symptoms	Therapy
UK (1) ²²	< 6 days	39	?	4165	CS	NP	Mother	Fever, signs of pneumonia	Antibiotics, Supportive
China (1) ²³	36 hrs	40	M	3250	CS	OP	Mother	Tachypnea	Supportive
China (3) ⁴¹	DOL 2	40	?	3250	CS	NP, anal	Mother	Lethargy	Supportive
	DOL 2	41	M	3360	CS	NP, anal	Mother	Fever, pneumonia, lethargy	Supportive
	DOL 2	31	?	1580	CS	NP, anal	Mother	RDS, sepsis, thrombocytopenia	Antibiotics, mechanical ventilation
China (1) ⁴²	36 hrs	40	M	3205	CS	OP	Mother	Emesis, mild lymphopenia abnormal chest CT	Antibiotics, Supportive
Peru (1) ⁴³	16 hrs	33	M	2970	CS	NP	Mother	Tachypnea, cough	Nasal cannula
China (1) ⁴⁴	19 Days	38	M	3030	Vag	OP, anal	Both parents	Vomiting, poor feeding, diarrhea, fever, mild thrombocytopenia	Interferon
China (1) ⁴⁵	17 Days	39	M	?	?	NP, anal	Both parents with Sx	Sneezing, vomiting, poor feeding	Supportive
USA (1) ⁴⁶	25 Days	Full term	M	?	?	NP	Both parents with Sx	Fever	Antibiotics, Supportive
Korea (1) ⁴⁷	27 Days	39	F	3730	Vag	NP, oral, anal	Multiple family	Vomiting, fever, cough	Supportive
China (5) ⁴⁸	18 days	Term	?	?	?	NP	Mother	Spitting, choking, fever	Antibiotics, Supportive
	DOL 1	Term	?	?	?	NP	Mother	Choking, lethargy	Supportive
	OL12	Term	?	?	?	NP,	Mother	Spitting up, diarrhea, sneezing	Supportive
	DOL 3	Term	?	?	?	anal	Mother	Fever, lethargy, abnormal chest CT	Supportive
	DOL 1	Term	?	?	?	NP	Mother	Poor feeding, lethargy, abnormal chest CT	?
Iran (1) ⁴⁹	15 Days	Term	M	3460	CS	NP	Both parents with Sx	Fever, lethargy, mottling	Antibiotics, oseltamivir
Spain (1) ⁵⁰	26 Days	?	M	?	?	?	Multiple family with Sx	Seizure, fever, nasal discharge, vomiting	Antibiotics, Supportive
Spain (1) ⁵¹	8 Days	38	F	2800	CS	NP	Mother + on DOL 3	Mild respiratory distress and abnormal CXR	Supportive
USA (1) ⁵²	3 weeks	36	M	?	?	NP	Multiple family with Sx	Nasal congestion, tachypnea, reduced feeding, progressed to hypotension, pneumonia, pneumothorax	Antibiotics, mechanical ventilation × 5 days, hydroxychloroquine and azithromycin, crystalloid, pressors
USA (1) ⁵³	2 weeks	39	M	?	CS	NP	Mother with Sx	Fever, lethargy, poor feeding, Transient neutropenia, abnormal chest X-ray	Antibiotics, acyclovir
Italy (2) ⁵⁴	18 Days	41	M	4440	?	NP	Mother	No Sx	None
	10 Days	39	F	3120	?	NP	Mother	Cough, poor feeding, diarrhea	Supportive
Iran (1) ⁵⁵	DOL 2	32	F	2350	CS	NP	Mother	Fever	Antibiotics, Supportive
China (2) ⁵⁶	5 Days	40	F	?	CS	NP	Mother	No Sx	None
	30 h	40	M	?	CS	NP	Mother	Respiratory distress	Supportive

Abbreviations:

DOL = Day of life.

M/F = male/female.

CS = Cesarean section.

Vag – vaginal delivery.

NP = nasopharyngeal.

OP = oropharyngeal.

Sx = symptoms.

9 years of age [39]. This is consistent with observations from other countries. In the United States, as of April 2, 2020, only 398 (0.3%) of the 149,370 Covid-19 patients were under 1 year of age [40].

Current recommendations in most countries, including the US, are to test all babies born to mothers who are either positive for or who are suspected of having Covid-19 [41]. The US Centers for Disease Control adopted this approach in late May, 2020 due to concerns that the disease may be more severe in neonates. Over

two dozen neonates (less than 30 days old at presentation) have been reported in the medical literature as of May 21, 2020. Table 2 summarizes the available information [22–23,41–56]. Two thirds were born to mothers with Covid-19, the others presumably acquired the virus from household contacts. Three were preterm. Fever was noted in 48%, respiratory symptoms in 30%, and emesis or diarrhea in 37%. Many reports listed lethargy or changes in neurological status, poor feeding, and other non-specific symptoms.

Notably, three (11%) were asymptomatic. Only one baby, who presented at 3 weeks of age with nasal congestion, poor feeding, and lethargy, progressed to hypotension and respiratory failure requiring intensive care [52]. Encouragingly, there were no deaths.

CLINICAL GUIDELINES AND CONSIDERATIONS

One question that frequently arises is whether those called to attend at the delivery of a newborn should wear coronavirus-resistant personal protective equipment since positive pressure ventilation, which can generate aerosols, is a potential intervention at each delivery. Considerations include the availability of the equipment, whether mothers presenting for delivery are being routinely screened, and what is known regarding the baseline rate of positive tests in the general population, including those who are asymptomatic.

For newborn infants born to mothers who have or are suspected to have Covid-19, viral RT-PCR testing from the nasopharynx, oropharynx or nares is recommended beginning after 24 h of life [57]. Until proven negative with at least two tests 24 h apart, these babies should be kept separate from any other neonates. Separation of SARS-CoV-2 positive mothers and negative or status-unknown babies is still encouraged, but it is acknowledged that this is not based on evidence-based data of post-natal transmission. If the decision is made to keep the mother-baby pair together, there are guidelines for physical distancing, maternal hand hygiene and face mask use. Breast-feeding should still be encouraged, which will affect whether the mother and infant are separated (unless expressed breast milk is considered as an option) [58].

Regarding breast-feeding, there are no extensive reports about whether SARS-CoV-2 is present in breast milk. Two publications indicate that the virus can be detected in breast milk [59,60]. Further information may modify current guidelines that breastfeeding may be advisable in Covid-19 mothers under strict measures of infection control (physical distancing when not feeding, mother wearing mask, thorough cleaning) [58,61]. Human milk banks have added Covid-19 questions to their donor screening and requirements for pre-donation quarantine. During the common Holder pasteurization process, the breast milk is raised to 62.5 °C for thirty minutes. The infectivity of the SARS-CoV-2 virus was eliminated when the virus was exposed to temperature of 56 °C for thirty minutes [62].

A definitive recommendation for adding testing for the presence of SARS-CoV-2 by RT-PCR to the evaluation for early- or late-onset neonatal sepsis is not yet possible, given the paucity of data, especially in the absence of any known risk. As outlined in Table 2, neonates are affected, both before 72 h and after. Note that all the neonates reported in Table 2 had a history of exposure to either tested or symptomatic Covid-19 contacts. Until more extensive epidemiologic studies are published, health care professionals will have to factor the prevalence in the obstetric and general population as well as local testing practice to decide. Overall, it may be that children are relatively protected from Covid-19 in general and in the severity of disease when they do acquire due to the observation that there is a linear relationship between age and the ACE2 receptor [63]. Of note, this was only sampled from the nasal epithelium, and did not include any neonates.

Although the attack rate in children is far lower than in any other age group, a worrisome complication has become apparent. Termed multiorgan inflammatory syndrome – children (MIC-S), over a hundred children have had this Kawasaki Syndrome-like condition, including some who were asymptomatic for Covid-19 but tested positive, by RT-PCR or serology [64]. To date, we are unable to find any cases in a child under the age of one year.

Because there are so few neonates who have been diagnosed with Covid-19, therapeutic recommendations or guidelines based on evidence or clinical experience are not possible. Most of the cases listed in Table 2 received supportive or routine care. At this point, if a baby is critically ill and either positive for SARS-CoV-2 by RT-PCR (not serology), or strongly suspected of having the disease based on exposure history and symptoms, consulting experts in adult disease is advised, given their larger accumulated experience. Any recommended drug therapy will require risk-benefit assessment including adjustments for dose and timing considerations for this specific population. The best hope for the longer term is for a long-lasting effective vaccination together with an effective serology test that will identify both recent and past infection with SARS-CoV-2.

DIRECTIONS FOR FUTURE RESEARCH

The rapidity with which SARS-CoV-2 has spread, and the number of cases, and deaths, from Covid-19 is unlike anything seen since at least the Spanish flu pandemic of 1918–19, but a hundred years later, international cooperation and rapid dissemination of experience has permitted those facing the need to care for a patient with a disease they have never seen before to tap into the experience of others. We can expect case reports and small series to be replaced by larger and more systematic studies, followed by prospective trials and long-term follow-up reports. For anyone who may have a patient with SARS-CoV-2 or Covid-19, it is important to follow the medical literature, including consensus expert guidelines.

KEY POINTS

- With an altered immune system, the pregnant woman may be at risk of acquiring Covid-19 but most evidence has been based on critically ill pregnant women; although screening seems to show lesser prevalence, clearly pregnant women will continue to be vulnerable to SARS-CoV-2.
- Additional accumulation of data on teratogenicity of SARS-CoV-2 is required despite early reassuring data.
- Vertical transmission of SARS-CoV-2 from the mother to the baby seems limited.
- Covid-19 infection in babies and infants of less than one year of age seems to be low and acquisition in most cases seems to be postnatal.

RESEARCH DIRECTIONS

- More data from both hospital and community-based acquisition of SARS-CoV-2 by pregnant women is required.
- Since the prevalence of Covid-19 is lower in infants, studying the underlying mechanisms and immune system of the newborn may lead to better understanding of how the virus may be controlled.
- An adequate blood test to identify current and previous infection is urgently required.
- Any vaccine developed will need to be tested on children. To protect neonates, maternal immunization programs may be necessary.

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