

Review Article

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Coronavirus disease 2019 in children: Clinical & epidemiological implications

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Despite the global spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, there are limited data emerging in children. This review provides an update on clinical features, diagnosis, epidemiology, management and prevention of coronavirus disease 2019 (COVID-19) in children. Specific characteristics noted in children and their implications in disease management as well as transmission control are highlighted. Besides respiratory symptoms, gastrointestinal and atypical features such as chilblains, neurological symptoms and multisystem inflammation are also reported. Younger infants and those with comorbidity were found to be at risk of severe illness. Infected pregnant women and neonates were reported to have good prognosis. It is possible to manage the children with mild disease at home, with strict infection prevention control measures; severely affected require respiratory support and intensive care management. There are anecdotal reports of using antiviral and immunomodulatory drugs, benefit of which needs to be confirmed in clinical trials. A significant percentage of asymptomatic infection in children has epidemiological implication as these may act as links in transmission chain in the community. There is a need for systematic data on extra-pulmonary manifestations and atypical features, risk factors of severity, role of imaging and biomarkers, testing and management strategies and trials with antivirals and immunomodulatory drugs in children. The psychosocial effects of quarantine, closure of schools, lack of play activities and impact of lockdown need to be addressed. Understanding the biological basis for the profound age-dependent differential outcome of COVID-19 infection is important. Elucidating the protective mechanisms in children may aid in developing novel treatment strategies.

Key words Children - clinical features - COVID-2019 - epidemiology - prevention - SARS-CoV-2 - severity of illness - treatment

Introduction

Coronavirus disease 2019 (COVID-19), since its origin in Wuhan city of Hubei Province in China in December 2019, became pandemic in less than

100 days. Globally, 11.5 million confirmed cases have been reported with mortality of 0.53 million by July 7, 2020¹. In India, the first case was detected on January 30, 2020 who was a student returned from Wuhan, China,

to Kerala². Subsequent to this, several cases were reported from different States of the country, mainly from travellers returning from abroad and then local transmission happened in many areas. A salient facet of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic is that children and adolescents are found to be less affected³⁻⁶. However, children as a vulnerable group pose unique challenges during the unprecedented pandemic. This review describes transmission characteristics, clinical manifestations, diagnostic, treatment and preventive aspects of COVID-19 in children. It also emphasizes on the need for conducting studies to understand the protective mechanisms in children as this has significant implications for the development of future therapeutics.

SARS-CoV-2 and its origin

The causative agent of the COVID-19 pandemic is SARS-CoV-2, which belongs to the *Betacoronaviruses* of the family *Coronaviridae*. Some coronaviruses, such as HCoV-229E, -HKU1, -NL63 and -OC43, are known to circulate among humans causing mild respiratory illness⁷. However, coronaviruses are known to undergo rapid mutation and recombination forming novel viruses that may jump from animals to humans, resulting in severe disease. In December, 2019, a cluster of adults with pneumonia of unexplained aetiology was announced by the Health Commission of Hubei province, China. Further investigation confirmed the causative agent to be a novel coronavirus (n-CoV-2019), with 85 per cent genomic identity with a bat SARS-like coronavirus (MG772933.1, bat-SL-CoVZC45)^{8,9}.

Transmission characteristics and pathogenesis of SARS-CoV-2

SARS-CoV-2 infection is transmitted predominantly through the respiratory route by droplets and by surface contact with fomites⁹. Transmission of infection to healthcare staff may happen during aerosol-generating events such as intubation, ventilation, suction and nebulization in critical care units. Gastrointestinal (GI) route of transmission is also speculated as virus shedding has been reported in faecal samples, especially in children, but needs further confirmation¹⁰⁻¹². Transmission to neonates from infected mothers is known, but vertical transmission is not yet documented^{13,14}. Most children acquire infection by close contact with infected adults⁹. The incubation period is estimated to be 1-14 days,

with a median of 5-6 days¹⁵. Virus can be detected in the upper respiratory tract 1-2 days before onset of symptoms and persists in the respiratory system for 7-12 days in moderate cases and up to two weeks in severe cases^{16,17}. Prolonged shedding of the virus has been observed in a few children with mild infections, up to 22 days in the respiratory tract and between two and four weeks in the faecal samples¹².

Our understanding of the pathogenesis and pathophysiology of COVID-19 is in the initial stages, and the studies are in progress^{18,19}. Angiotensin-converting enzyme 2 (ACE2) is identified as the main cellular entry receptor where the spike protein of the SARS-CoV-2 attaches and transmembrane protease serine 2 (TMPRSS2) acts as the co-receptor²⁰. In patients with severe diseases, elevated plasma levels of pro-inflammatory cytokines such as interleukin (IL)-6, IL-10, monocyte chemoattractant protein-1, macrophage inflammatory protein-1 α , tumour necrosis factor- α and granulocyte-colony stimulating factor are observed, and a cytokine storm is also proposed in severely affected patients^{18,19,21}. A hypercoagulable profile with elevated D-dimer and fibrinogen level is noted, and probable endothelial cell injury is also postulated^{19,21}. Notable pathological findings are consolidation in the lungs with serous fluid, fibrin exudate and formation of hyaline membrane. In addition, alveolar septum hyperaemia, oedema, mononuclear and lymphocyte infiltration and intravascular thrombosis are also observed²². Although most of the findings are from adults, limited data in a small number of children show increased levels of procalcitonin, C-reactive protein and D-dimer in those with moderate-to-severe disease^{23,24}.

COVID-19 in children

The global data showed that the proportion of children among the total number of COVID-19-affected patients was small and most children developed mild illness³⁻⁶. One study from China has reported that children aged below 10 yr have the same susceptibility as adults to get infected, but unlikely to develop severe disease²⁵. Another study from China²⁶ supports the concept that children are less susceptible to COVID-19 compared to adults. In this study, when the contact of people with known infections were traced and tested for the virus, for each affected child under the age of 15 yr, nearly three people were found to be infected between the ages of 20 and 64²⁶. The age group-wise distribution of cases and the differences

in fatality rate in the published large case series from different countries are summarized in Table I. A recent study from India reported the clinical features and epidemiological characteristics of 21 patients in New Delhi. All had mild illness except one who had lung consolidation and required oxygen inhalation²⁷. In this study, only one case was below 20 yr of age.

Clinical manifestations

Reports of paediatric infection are available from some affected global regions²⁸⁻³⁵, and two systematic reviews have been published based on the early data^{36,37}. Among the affected children, a spectrum of manifestations was seen with varying grades of severity (asymptomatic/mild/moderate/severe/critical illness) and a few deaths were also noted^{23,28}. Majority of the children develop only a mild illness, and present predominantly with fever and dry cough. Upper respiratory symptoms such as cold, nasal congestion and sore throat are less frequent. Severe cases manifest as dyspnoea and may rapidly worsen and develop acute respiratory distress syndrome (ARDS), shock, multi-organ failure and coagulopathy²⁸. GI symptoms such as nausea, vomiting and loose stools are also reported in some affected children^{11,12}.

In the largest published paediatric case series from China, young infants and those suffering from comorbid conditions were found to be vulnerable to the infection and affected severely²⁸. Among the age groups of <1, 1-5, 6-10, 11-15 and ≤ 16 yr, proportion of severe and critical cases were 10.6, 7.3, 4.2, 4.1 and 3.0 per cent, respectively. One child succumbed to the illness. A study on children hospitalized with COVID-19 in the paediatric intensive care units (ICUs) in the USA also reported pre-hospitalization comorbidities as an important factor in childhood COVID-19³¹. Chinese Experts' Consensus Statement categorizes high-risk group as (i) those children in contact with severe COVID-19 case, (ii) those with underlying congenital heart disease, pulmonary disease, chronic cardiac/renal disease, malnutrition, diabetes, immunodeficiency and hereditary metabolic diseases, (iii) those receiving long-term immunosuppressants, and (iv) infants under three months³⁸. Clinical characteristics of COVID-19 in children reported in various published studies are summarized in Table II.

Other clinical characteristics reported are the dermatological lesions, atypical presentation with neurological symptoms and the curious multi-system inflammatory syndrome, the Kawasaki disease.

Chilblain-like skin lesions of the extremities termed 'COVID toes' have been observed in children in Italy and Spain^{39,40} but need further confirmation. Presentation with neurological symptoms such as axial hypotonia, drowsiness and moaning sounds or both, without respiratory manifestations, has also been reported in a few infants. Their cerebrospinal fluid parameters were normal, and all had a favourable outcome⁴¹. Multi-system inflammatory syndrome in children, mimicking the Kawasaki disease has been reported from COVID-19-affected regions in Europe as well as the USA, which needs to be characterized^{42,43}. A link to COVID-19 is suspected but needs further research as reverse transcription-polymerase chain reaction (RT-PCR) test has been found to be negative in most of the cases⁴³.

COVID-19 case definitions

The WHO has published case definitions of COVID-19, and individual countries have been encouraged to develop their own definitions suitable to the country situation, stage of the epidemic and resources available⁴⁴. There are no separate criteria for children as of now but may be adapted from that of adults and modified as data emerge and as we come to know more about the disease in children. The Ministry of Health and Family Welfare (MoHFW), Government of India, has published guidelines for testing and treatment, being updated regularly as the scenario evolves and new scientific data emerge⁴⁵. As per this, "COVID-19 should be suspected in a patient with acute respiratory illness (fever and at least one sign/symptom of respiratory disease, *e.g.*, cough, shortness of breath), and a history of travel to or residence in a location reporting community transmission of COVID-19 disease during the 14 days prior to symptom onset; a patient with any acute respiratory illness and having been in contact with a confirmed or probable COVID-19 case in the last 14 days prior to symptom onset; or in a patient with severe acute respiratory illness (fever and at least one sign/symptom of respiratory disease, *e.g.*, cough, shortness of breath; and requiring hospitalization) and in the absence of an alternative diagnosis that fully explains the clinical presentation". A probable case is a suspect case for whom testing for the COVID-19 virus is inconclusive, or testing could not be performed for any reason⁴⁵.

Case definition criteria may require modification when community spread occurs, atypical or novel clinical presentations are noted, and when validated,

Table I. Age group-wise distribution of cases and fatality rate of coronavirus disease 2019

Study	Country	Total number of cases	Age group (yr)	Number of cases (%)	Deaths (%)	Case-fatality rate (%)
The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team ³	China	72,314 (confirmed cases - 44,672)	0-9	416 (0.9)	-	-
			10-19	549 (1.2)	1 (0.1)	0.2
			20-29	3619 (8.1)	7 (0.7)	0.2
			30-39	7600 (17.0)	18 (1.8)	0.2
			40-49	8571 (19.2)	38 (3.7)	0.4
			50-59	10,008 (22.4)	130 (12.7)	1.3
			60-69	8583 (19.2)	312 (30.5)	3.6
			70-79	3918 (8.8)	309 (30.2)	8.0
			≥80	1408 (3.2)	208 (20.3)	14.8
			Total	44,672	1023	2.3
Livingston and Bucher, 2020 ⁴	Italy	22,512	0-9	Number of cases not available in the range taken for comparison (age group mentioned as 0-18, 19-50, 51-70 and >70 yr)	0	0
			10-19		0	0
			20-29		0	0
			30-39		4 (0.2)	0.3
			40-49		10 (0.6)	0.4
			50-59		43 (2.6)	1.0
			60-69		139 (8.5)	3.5
			70-79		578 (35.6)	12.5
			80-89		694 (42.7)	19.7
			≥90		156 (9.6)	22.7
	Not reported		1 (0.06)	0.6		
Total		22,512	1625 (100)	7.2		
CDC COVID-19 Response Team, USA ⁵	USA	4,226 (confirmed cases - 2,449)	0-19	123 (5)	0	0
			20-44	705 (29)	9 (20)	0.1-0.2*
			45-54	429 (18)		0.5-0.8
			55-64	429 (18)		1.4-2.6
			65-74	409 (17)	20 (46)	2.7-4.9
			75-84	210 (9)		4.3-10.5
			≥85	144 (6)	15 (34)	10.4-27.3
			Total	2449	44	1.8-3.4
Korean Society of Infectious Diseases ⁶	South Korea	4,212	0-9	32 (1)	0	0
			10-19	169 (4)	0	0
			20-29	1235 (30)	0	0
			30-39	506 (12)	1 (4.5)	0.2
			40-49	633 (15)	1 (4.5)	0.2
			50-59	834 (20)	5 (22.7)	0.6
			60-69	530 (12)	6 (27.3)	1.1
			70-79	192 (5)	6 (27.3)	3.1
			≥80	81 (2)	3 (13.6)	3.7
			Total	4,212	22	0.5

*In lower and upper bound ranges

Table II. Clinical profile of coronavirus disease 2019 in children

Study	Country and period of the study	Number of cases	Clinical manifestations, n (%)	Severity, n (%) and other characteristics	Treatment, n (%)
Dong <i>et al</i> ²⁸	China (January 16 to February 8, 2020) Nation-wide case series	Total cases - 2,135 Confirmed cases - 728 Suspected cases - 1,407	Not mentioned	Mild 314 (43.1) Moderate 298 (40.9) Severe 18 (2.5) Critical 3 (0.4) Missing 1 (0.2) Death 1 (0.1) (Only confirmed cases included) Asymptomatic 94 (12.9)	Not mentioned
CDC COVID-19 Response Team USA ²⁹	USA (February 12 to April 2, 2020) Nation-wide case series	Total cases - 2,572 Data available for 291 cases only	Fever, cough, or shortness of breath 213 (73) Fever 163 (56) Cough 158 (54) Shortness of breath 39 (13) Myalgia 66 (23) Runny nose 21 (7.2) Sore throat 71 (24) Headache 81 (28) Nausea/vomiting 31 (11) Abdominal pain 17 (5.8) Diarrhoea 37 (13)	Among 345 paediatric cases with information on underlying conditions, 80 (23) had at least one underlying condition. The most common underlying conditions were chronic lung disease (including asthma) (40), cardiovascular disease (25) and immunosuppression (10). Three deaths were reported	Not mentioned
Lu <i>et al</i> ³⁰	China (January 28 to February 26, 2020) Wuhan Children's Hospital, Hubei	1,391 children with known contact with confirmed or suspected SARS-CoV-2 infection were evaluated and 171 were confirmed cases	Cough 83 (48.5) Pharyngeal erythema 79 (46.2) Fever 71 (41.5) Median duration of fever (range) days 3 (1-16) Diarrhoea 15 (8.8) Fatigue 13 (7.6) Rhinorrhoea 13 (7.6) Vomiting 11 (6.4) Nasal congestion 9 (5.3) Tachypnoea on admission 49 (28.7) Tachycardia on admission 72 (42.1) Oxygen saturation <92% during period of hospitalization 4 (2.3)	Upper respiratory tract infection 33 (19.3) Pneumonia 111 (64.9) Asymptomatic infection 27 (15.8) A 10-month old child with intussusception had multi-organ failure and died four weeks after admission	Three patients required intensive care support and invasive mechanical ventilation; all had coexisting conditions [hydronephrosis, leukaemia (for which the patient was receiving maintenance chemotherapy), and intussusception]

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Study	Country and period of the study	Number of cases	Clinical manifestations, n (%)	Severity, n (%) and other characteristics	Treatment, n (%)
Shekerdemian <i>et al</i> ³¹	USA (March 14 to April 10, 2020)	48 children admitted in paediatric intensive care unit (cross-sectional study)	Pre-existing comorbidities 40 (83) Respiratory symptoms 35 (73)	All were severe cases Two patients (4) died	18 (38) required invasive ventilation Extracorporeal membrane oxygenation was required for 1 patient (2) 28 patients (61) received targeted specific therapies The most common was hydroxychloroquine (alone or in combination) Azithromycin given in 8 children (alone in 1 case with hydroxychloroquine in 7 cases) Remdisivir used in 8 patients (alone in 2 and in combination in 6) Tocilizumab was used in 5 children (alone in 1 in combination with hydroxychloroquine in 1), in combination with hydroxychloroquine and azithromycin in 1, in combination with hydroxychloroquine and remdisivir in 1, and in combination with convalescent plasma in 1 patient Ventilation 4 (10)
Tagarro <i>et al</i> ³²	Spain (March 2-16, 2020) by 30 secondary and tertiary hospitals in Madrid, Spain	365 children were screened within the 30 hospitals, 41 confirmed cases	Respiratory tract infection 14 (34) Fever without a source 11 (27) Viral-like pneumonia 6 (15) Bronchiolitis 5 (12) Gastroenteritis or vomiting 2 (5) Bacterial-like pneumonia 2 (5) Asthma flare 1 (2) Co-infection with influenza B 2 (5)	Not mentioned 11 (27) had underlying co morbid conditions	
Qiu <i>et al</i> ²³	China (January 17 to March 1, 2020) Zhejiang	36 (retrospective case series)	Dry cough 7 (19) Dyspnoea or tachypnoea 1 (3) Pharyngeal congestion 1 (3) Sore throat 2 (6) Vomiting or diarrhoea 2 (6) Body temperature >37°C 13 (36) Headache 3 (8)	Mild 17 (47.2) Moderate 19 (52.8) Asymptomatic 10 (28)	Oxygen inhalation 6 (17) Interferon alpha 36 (100) Lopinavir-ritonavir 14 (39)

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Study	Country and period of the study	Number of cases	Clinical manifestations, n (%)	Severity, n (%) and other characteristics	Treatment, n (%)
Wang <i>et al</i> ³³	China (January 25 to February 21, 2020) 6 provinces (Shaanxi, Gansu, Ningxia, Hebei, Henan, and Shandong) of northern China	31 (retrospective case series)	Fever 20 (65) Cough 14 (45) Fatigue 3 (10) Diarrhoea 3 (10) Sore throat, runny nose, dizziness, headache, vomiting were rare	Mild 13 (42) Moderate 14 (45) Asymptomatic 4 (13)	29 cases (94), received antiviral treatment 10 cases, interferon alone 6 cases, antibacterial drugs 2 cases, intravenous gamma globulin 8 cases, traditional Chinese medicine
Zheng <i>et al</i> ³⁴	China (February 1-10, 2020) A cross-sectional multicentre study Carried out in 10 hospitals across Hubei province	25 (retrospective case series)	Fever 13 (52) Nasal congestion 2 (8) Cough 11 (44) Dyspnoea 2 (8) Abdominal pain 2 (8) Vomiting 2 (8) Diarrhoea 3 (12)	Upper respiratory infection 8 (32) Mild pneumonia 15 (60) Critical cases 2 (8) Co-infections: Influenza virus type B 2 (8) <i>Mycoplasma pneumoniae</i> 3 (12) Bacteria 1 (4)	Two cases received invasive mechanical ventilation and treated with immunoglobulin (2 g/kg), corticosteroid (2 mg/kg), antivirals (interferon, oseltamivir) and antibiotics (cefoperazone, sulbactam, meropenem, linezolid). One undergone continuous veno-venous haemodiafiltration and plasma exchange
Cai <i>et al</i> ³²	China (January 19 to February 3, 2020) Children's Hospital in Shanghai, Hainan, Hefei in Anhui province, and Qingdao in Shandong province	10 (prospective case series)	Fever 8 (80) Cough 6 (60) Sore throat 4 (40), Stuffy nose 3 (30) Sneezing and rhinorrhoea 2 (20) None of patients had diarrhoea or dyspnoea during the course of illness	High frequency (83.3%) of SARS-CoV-2 RNA detected in faeces in patients with mild disease and also prolonged virus RNA shedding in faeces for at least two weeks and even more than a month	All patients received symptomatic treatment and five patients with pneumonia received empirical antibiotic therapy
Sun <i>et al</i> ³⁵	China (January 24 to February 24, 2020) Wuhan Children's Hospital, Hubei	8 (severe or critically ill patients admitted in intensive care unit)	Polypnoea 8 (100) Fever 6 (75) Cough 6 (75) Expectoration 4 (50) Nausea 4 (50) Diarrhoea 3 (37.5) Fatigue/myalgia 1 (12.5) Headache 1 (12.5) Constipation 1 (12.5)	All severely/critically ill	Symptomatic and respiratory support, invasive mechanical ventilation (2 children) antiviral treatments (ribavirin, oseltamivir and interferon), antibiotic therapy, traditional Chinese medicine, intravenous glucocorticoid and immunoglobulin therapies were also used according to the patients' conditions

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

rapid test or serological diagnostic assays or imaging tools are used. In this regard, mild nature of the illness, extra-pulmonary manifestations and atypical features in children need attention. Diagnosis of infection in children was based on the clinical manifestations and history of exposure²⁸. If a child was exposed to a COVID-19 patient or lived in an epidemic area or community where COVID-19 cases were reported within the past two weeks, the child was defined as having high, medium or low-risk, respectively, based on the possibility of getting infected. A suspected case is defined when a child at high-risk has two of the following conditions: (i) fever or respiratory symptoms or GI symptoms such as vomiting, nausea and diarrhoea or fatigue, (ii) normal or decreased white blood cell count or elevated level of C-reactive protein, or (iii) abnormal chest X-ray findings. For children at medium or low-risk, similar diagnostic criteria were applied after excluding influenza and other common respiratory infections²⁸. Iranian guidelines recommend the following case definitions⁴⁶. A definite case is a child with history, signs and symptoms suggestive of COVID-19, along with abnormal chest CT findings and a positive RT-PCR test. A suspected case is a child with history, signs and symptoms along with abnormal chest CT scan (other causes for abnormal CT scan are ruled out) suggestive of COVID-19, with a negative PCR test. A rejected case is a child with negative RT-PCR test and abnormal chest CT scan due to causes other than COVID-19⁴⁶.

Laboratory diagnosis

Laboratory tests are required for confirming a suspected case as there are no clinical characteristics that are specific to COVID-19. At present, this is based on the molecular detection of SARS-CoV-2 genetic material in clinical specimens and needs to be carried out in a laboratory with at least biosafety level-2 or equivalent facilities⁴⁷.

Real-time reverse transcription-polymerase chain reaction (RT-PCR) test

Nasopharyngeal or throat swabs are the preferred specimens, and viral nucleic acid amplification test (NAAT) employing real-time RT-PCR is performed. Different assays target different areas of the viral genome - open reading frame (*orf*) 1a and 1b, RNA-dependent RNA polymerase (*RdRp*), envelope (*E*), nucleocapsid (*N*) or spike (*S*) protein genes⁴⁷. A sample is considered positive if any of the target genes are amplified from an area with known SARS-

CoV-2 circulation, while in geographic regions with no known virus circulation, minimum two different gene targets should be positive or one positive NAAT for *Betacoronavirus* and whole- or partial-genome sequencing of the virus⁴⁷. Another nucleic acid assay for the detection of SARS-CoV-2 under development is reverse-transcription loop-mediated isothermal amplification (LAMP)⁴⁸. This is a rapid and cost-effective assay as it requires only heating and visual inspection. This test is shown to be effective in detecting SARS-CoV-2 viral RNA and may be used as an alternative tool for RT-PCR, however, needs validation for clinical application.

Serological assays

Although real-time RT-PCR is the gold standard for SARS-CoV-2 diagnosis at present, usefulness of serological assays needs exploration, especially in resource-limited settings. A preliminary study on 82 confirmed and 58 probable cases of COVID-19 in adults showed appearance of specific IgM antibodies on day five with a positivity rate of 85.4 per cent and IgG antibodies on day 14 with a positivity rate of 77.9 per cent⁴⁹. IgM and IgG serological tests are available in ELISA and also as a rapid test format. Serological tests are not very useful for diagnosis in early phase of the illness as antibodies take time to develop⁵⁰. However, serological tests are recommended for epidemiologic research and disease surveillance. These are especially useful in retrospective identification of asymptomatic cases, and to identify and monitor individuals recovered from COVID-19 infection whose antibodies may serve to treat patients through convalescent plasma therapy. Utility of serological assays, alone or in combination with RT-PCR, needs to be explored in children as they may present late to healthcare facilities because of the milder nature of the disease.

Other laboratory findings

In COVID-19 patients, abnormalities are noted in routine laboratory tests as well, which may be helpful in clinical assessment and prognostication. In general, leucopenia, lymphopaenia and thrombocytopaenia are noted in both adults and children^{51,52}. Increased blood levels of lactate dehydrogenase, procalcitonin and D-dimer are seen in severe disease^{23,51}. In a study of 36 COVID-19-affected children²³, increased creatine kinase MB (31%), lymphocytopenia (31%), leucopenia (19%) and increased procalcitonin levels (17%) were the typical findings observed.

Variables significantly associated with severe disease were increased levels of D-dimer, procalcitonin and creatine kinase MB and decreased lymphocytes²³. D-dimer levels may be useful to estimate the severity of COVID-19^{23,53}. Increased procalcitonin values may lead to about five-fold increased risk of severe disease. Elevated levels of hepatic enzymes such as alanine aminotransferase and aspartate aminotransferase are seen, especially in severe cases of COVID-19 in adults, but not in children^{23,51}.

Imaging findings

Imaging tools such as X-ray, CT scan and ultrasonography are valuable for diagnostic support as well as for assessment of progression of disease and follow up.

Chest X-ray and CT scan

The most commonly reported X-ray and CT findings of COVID-19 are lung consolidation and ground-glass opacities^{23,54}. COVID-19 and other viral pneumonias generally show pulmonary opacities in more than one lobe, whereas community-acquired bacterial pneumonia is usually unilateral and involves a single lobe. Bilateral multifocal air-space disease with lower lung distribution on X-ray can be an important clue to COVID-19 pneumonia^{23,54}. Peripheral lung involvement is reported as a unique and to some extent a specific feature of COVID-19 pneumonia⁵⁴. Pleural effusions, cavitation in the lungs and pneumothorax are rare.

Chest X-ray is less sensitive in detecting COVID-19 pulmonary disease in comparison to CT scan. However, chest X-ray minimizes the risk of cross-infection, which usually occurs post-CT scan if decontamination is not done properly. X-ray, especially portable, offers several advantages in resource-limited settings. Role of X-ray for diagnosing COVID-19 where RT-PCR facilities are not available needs to be explored⁵⁴.

In a study of 36 children, 19 (53%) cases showed ground-glass opacities in the lung in CT scan, suggesting pneumonia²³. Mixed ground-glass opacity and consolidation lesions (36%), consolidations (32%) and ground-glass opacities (14%) were the major CT findings observed in 22 paediatric cases⁵⁵. Peripheral distribution (45%) of pulmonary lesions was predominant, and majority of the lesions were multilobar (68%). Another study (20 children) reported elevated procalcitonin levels and consolidation with surrounding halo sign in the chest CT scan as characteristic features in children²⁴.

Ultrasonogram

A study on 10 children affected with COVID-19 indicated the application of ultrasonography of lungs in detecting COVID-19 pneumonia⁵⁶. Described findings include vertical artefacts (70%), pleural irregularities (60%), areas of white lung (10%) and sub-pleural consolidations (10%). Bed-side ultrasound offers several practical advantages such as ease of operation and decontamination and lowering the radiation exposure of the patients, and hence, its usefulness needs further exploration⁵⁷.

Clinical management

Supportive treatment

The mainstay of clinical management is supportive. Children with mild-to-moderate illness may be managed with symptomatic treatment at home, with strict adherence to infection control measures by the family. However, the consideration for home management versus health centre/hospital may vary from region to region, based on the stage of the epidemic and the availability of resources^{38,46,58,59}. As per the Indian guidelines, the cases need to be clinically categorized as very mild/mild, moderate or severe and accordingly admitted to (i) COVID care centre, (ii) dedicated COVID health centre, or (iii) dedicated COVID hospital, respectively. However, very mild/pre-symptomatic/asymptomatic children having the requisite facility at his/her residence for self-isolation will have the option for home management^{58,59}. Control of body temperature and maintenance of humidity of airways are recommended as the important considerations in symptomatic management in the updated Chinese guidelines³⁸. Care should be taken not to use mask in young children because of the risk of suffocation. Parents should be clearly explained about the danger signs and instructed to take the child to health facility immediately, if any adverse events occur.

Children with moderate-to-severe illness are better managed in a designated COVID-19 health centre or hospital. Respiratory support varying from oxygen therapy to mechanical ventilation might be required. Children on non-invasive ventilation for two hours without improvement, or unable to tolerate non-invasive mechanical ventilation, with excessive airway secretions, severe cough or haemodynamic compromise, need to be put on invasive mechanical ventilation³⁸. Low-tidal volume lung protective ventilation strategy is preferred to reduce ventilator-associated lung

injury. Prone position ventilation, lung recruitment or extracorporeal membrane oxygenation (ECMO) may be considered³⁸. Some consensus guidelines recommend short-course steroid therapy for moderate and severe cases^{38,45}. Standard protocols need to be followed for the management of sepsis and shock. Hypercoagulable states may necessitate the use of anticoagulants. Bacterial infections need to be taken care of by appropriate use of antibiotics. Management of co-infections with other respiratory viral pathogens such as influenza with oseltamivir is also important³⁸. Nutrition and fluid management need to be done carefully.

Specific treatment

As of now, there is no specific therapy approved for COVID-19. Clinical trials are in progress in adults, and similar studies need to be carried out in children also. Generally, use of an experimental therapy outside a clinical trial setting is not recommended. Antiviral treatment is likely to be beneficial in the first phase of the illness. Immunomodulatory treatment may only be indicated if there is a clear evidence of hyperinflammation, or in the second phase of the illness, as there is limited evidence currently. However, compassionate off-label treatment may be given on a case-to-case basis. There are anecdotal reports of off-label treatment with various agents such as antivirals, immunomodulatory agents, immunoglobulins and even convalescent plasma therapy (Table II).

In one case series, 36 children were given interferon α by aerosolization twice a day and 14 of them additionally received lopinavir-ritonavir syrup. Since it was an observational study without any control arm and all the children were of mild-to-moderate severity illness, it was not possible to infer the effect of the antiviral medication²³. In a recent study on children admitted in the ICU with COVID-19, various antivirals and immunomodulatory drugs such as chloroquine, azithromycin, remdesivir, tocilizumab and convalescent plasma therapy have been tried³¹.

Consensus treatment guidelines

There are consensus treatment guidelines and position statements published by the various government bodies as well as professional societies of some countries^{38,45,46,60,61}. A summary of the salient features of different consensus treatment guidelines for children with COVID-19 published from China, Iran, the UK and India is provided in Table III.

Differences in recommendations by various bodies are noted as the guidelines need to suit the country situation and are based primarily on anecdotal reports and preliminary experiences with COVID-19 in addition to lessons learnt from SARS and MERS epidemics. It is also to be pointed out that some guidelines are developed during the early phase of the pandemic, based on knowledge and experience at that point of time. Hence, recommendations in some of the guidelines may not hold merit in the current situation and require updating. Despite limitations, these guidelines are useful in triaging and optimizing utilization of resources and provision of standard and scientific treatment. Treating physicians may evaluate the situation on a case-to-case basis and take appropriate decisions.

COVID-19 in pregnant women and neonates: Specific concerns

Although pregnant women were found to be infected with COVID-19, no increased risk of severity was seen unlike that observed during the H1N1 influenza pandemic. In the largest series of 147 infected pregnant women from China, eight per cent developed severe and one per cent developed critical illness; however, the details are not available⁹. In another series of 116 cases, 6.9 per cent had severe illness; fever (50.9%) and cough (28.4%) were the most common symptoms. Interestingly, 23.3 per cent patients presented without symptoms; 86 per cent of women underwent caesarean delivery. Among the 100 neonates tested, 86 were found to be negative for SARS-CoV-2. The data suggested that infection with SARS-CoV-2 during pregnancy was not associated with higher risk of spontaneous abortion/preterm birth¹³. Clinical features, severity, pregnancy outcome, treatment and neonatal infection in different published case series are summarized in Table IV. Separate delivery rooms as well as surgical theatres are necessary for COVID-19-suspected or -confirmed mothers. Neonatal resuscitation corners need to be located at least two meters away from the delivery table. Unless for obstetric indications, vaginal delivery is preferred⁶¹.

Neonates may acquire infection from the infected mother or from the infected healthcare worker. Reported clinical manifestations include fever, lethargy and respiratory distress. In general, new-born develops mild illness and has good prognosis. Currently, there is a lack of evidence to suggest intrauterine or

Table III. Consensus treatment guidelines for children with coronavirus disease 2019

Country	Consensus guidelines/position statement - salient features
China	
Updated diagnosis, treatment and prevention of COVID-19 in children: experts, consensus statement, second edition ³⁸	<p>Supportive treatment</p> <p>Control of body temperature with antipyretics and expectorant drugs to avoid respiratory tract obstruction.</p> <p>For hypoxia, effective oxygen therapy with nasal catheter, mask oxygen. Nasal high-flow oxygen therapy, and non-invasive or invasive mechanical ventilation as appropriate.</p> <p>Prone position and lung protective ventilation strategy is preferred. ECMO may be tried in refractory cases.</p> <p>Glucocorticoids in severe cases 3-5 days for ARDS.</p> <p>Increased D-dimer and at high-risk of thrombosis - low molecular weight heparin and anticoagulants may be initiated.</p> <p>Oseltamivir and other anti-influenza agents for co-infection with influenza and others.</p> <p>Specific treatment</p> <p>IFN-alpha spray/nebulization; plasma exchange, immunoglobulin or convalescent plasma on case-to-case basis. Traditional Chinese medicine may also be given.</p> <p>Updated guidelines do not recommend lopinavir/ritonavir, ribavirin or chloroquine phosphate in paediatric patients.</p>
Iran	
An Algorithmic Approach to Diagnosis and Treatment of Coronavirus Disease 2019 (COVID-19) in Children: Iranian Expert's Consensus Statement ⁴⁶	<p>Supportive treatment</p> <p>Supportive therapy with antipyretics, fluids and electrolytes replacement, analgesia and ventilation as per requirement.</p> <p>Specific treatment</p> <p>ICU-admitted patients: Treatment for patients who were admitted in ICU included combined antiviral agents and immunomodulators [oseltamivir + hydroxychloroquine + kaletra (lopinavir + ritonavir)] ribavirin and if necessary, antibiotics according to the patient's situation.</p> <p>Moderate to severe pneumonia: Treatment for these patients included combined antiviral agents and immunomodulators [oseltamivir + hydroxychloroquine + kaletra (lopinavir + ritonavir)], and if necessary antibiotics according to the patient's situation.</p> <p>Mild pneumonia with risk factor: Treatment for these patients included combined antiviral agents and immunomodulators (oseltamivir + hydroxychloroquine), and if necessary antibiotics according to the patient's situation.</p> <p>Mild pneumonia without risk factor: These patients should be placed in a watchful waiting programme and followed. Treatment in these groups is optional and related to physician's decision according to the situation. It may include oseltamivir-hydroxychloroquine, and if necessary, antibiotics.</p>
UK and Ireland	
British Paediatric Allergy immunity and infection group Position Statement: Management of novel coronavirus (SARS-CoV-2) infection in paediatric patients in the UK and Ireland ⁶⁰	<p>Mild to moderate disease: Supportive care only.</p> <p>Severe disease (mild - moderate ARDS): Supportive care, treatment with antivirals may be considered. Treatment with immunomodulatory therapy if evidence of hyperinflammation (raised CRP, ferritin, IL6, sCD25).</p> <p>Critical disease (severe ARDS or septic shock or altered consciousness or multi-organ failure): Supportive care treatment with antivirals. Treatment with immunomodulatory therapy may be considered if evidence of hyperinflammation (raised CRP, ferritin, IL6, sCD25).</p> <p>Antiviral therapy: Lopinavir, ritonavir + ribavirin or chloroquine or remdesivir.</p> <p>Immune modulation therapy: Tocilizumab and anakinra.</p>

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Country	Consensus guidelines/position statement - salient features
India	<p>Supportive treatment</p> <p>Mild cases: Antipyretics/analgesics/antitussives/appropriate hydration and adequate nutrition. Moderate cases: Antipyretics/analgesics/antitussives/appropriate hydration and adequate nutrition. Oxygen support (target SpO₂ 92-96%), prophylactic anticoagulation, corticosteroids (methyl prednisolone/dexamethasone), Close monitoring for worsening. Severe cases: Supportive therapy to continue as in moderate cases. On failure of standard oxygen therapy, consider HFNO/non-invasive mechanical ventilation or mechanical ventilation. Lung protective ventilation - prone position, low tidal volume, lower inspiratory pressures, higher PEEP. Management of septic shock, bacterial infection Anticoagulation</p> <p>Specific treatment (investigational therapy/repurposed or off-label therapy)</p> <p>Mild cases with risk factors and in moderate cases - Consider hydroxychloroquine (dose 400 mg BD - for 1 day followed by 200 mg BD for 4 days) in patients above 12 yr. These drugs should be administered under close medical supervision, with monitoring for side effects including QTc interval. In severe cases hydroxychloroquine is to be avoided. In selected moderate cases with worsening and severe cases, remdesivir (children above 12 yr), convalescent plasma or tocilizumab may be considered.</p> <p>ARDS, acute respiratory distress syndrome; ICU, intensive care unit; ECMO, extracorporeal membrane oxygenation; CRP, C-reactive protein; SpO₂, oxygen saturation; HFNO, high-flow nasal cannula oxygenation; PEEP, positive end-expiratory pressure</p>

transplacental transmission of SARS-CoV-2^{13,63,67}. Possibilities of intrauterine vertical transmission was investigated in a small group of pregnant women (n=6) in samples such as amniotic fluid, cord blood, breast milk and neonatal throat swab. All the samples were found to be negative for SARS-CoV-2, suggesting that vertical transmission was unlikely⁶³. However, reports of increased IgM levels detected in the blood sample of three neonates born to mothers affected by COVID-19 are of concern; the RT-PCR tests carried out from the samples from these neonates were negative and the issue of vertical infection remained unresolved^{14,68}. Future studies in pregnant women should carefully address such paradoxes.

The Italian Society of Neonatology suggests that under strict practices of infection control, breastfeeding is advisable by COVID-19-positive mothers. However, neonates need to be managed separately if mothers are too sick to care for them⁶⁹. The Federation of Obstetric and Gynecological Societies of India, National Neonatology Forum of India, and Indian Academy of Pediatrics have issued guidelines for perinatal-neonatal management of COVID-19, which suggest direct breastfeeding⁶¹. Mother should wear mask and wash hands frequently including before breastfeeding. If breastfeeding is not feasible due to maternal or neonatal condition, expressed breast milk may be considered. Recently, RNA of SARS-CoV-2

has been detected in breast milk from an infected mother⁷⁰. Hence, there is a need to exercise caution and wait for further research.

Prognosis and long-term effects

Individuals who recover from the illness generally do well. However, this is a new disease, and hence, the long-term effects of COVID-19 in the affected individuals are unknown. A few observations during the previous SARS epidemic are noteworthy in this context. A study reported mild reduction in exercise tolerance and muscle weakness for a variable period of 3-6 months in children recovered from SARS⁷¹. Further, diffuse thinning as well as shedding of hairs was noted in some children. However, lung functions and psychological status were normal⁷¹. In affected adults, pulmonary fibrosis was reported in some individuals after recovery⁷². In a study on 25 individuals recovered from SARS infection, metabolic disruptions such as increase in phosphatidylinositol and lysophosphatidylinositol levels were observed 12 years later. It was not clear whether this was the effect of the viral infection or due to high-dose methyl prednisolone received for treatment⁷³. Although there is a lack of evidence of vertical transmission in the current scenario, but evaluation of children born to women who were COVID-19 affected during early phase of pregnancy may be advisable to know the teratogenic effect, if any.

Table IV. Clinical profile of coronavirus disease 2019 in pregnant women and neonates

Study	Country	Number of pregnant women	Clinical features, n (%)	Delivery and pregnancy outcome, n (%)	Treatment, n (%)	Neonatal infection/ outcome
WHO-China-Joint-Mission ⁹	China (as of February 20, 2020)	147 (64 confirmed)	Severe disease (8) Critical (1)	N/A	N/A	N/A
Yan <i>et al</i> ¹³	China (January 20 to March 24, 2020)	116 (retrospective case series) (65 confirmed)	Characteristics of 116 cases: Fever 59 (50.9) Cough 33 (28.4) Fatigue 15 (12.9) Shortness of breath 9 (7.8) Sore throat 10 (8.6) Myalgia 6 (5.2) Dyspnoea 3 (2.6) Diarrhoea 1 (0.9) No symptoms 27 (23.3) Severe cases 8 (6.9)	Caesarean delivery - 85 (85.9) Vaginal delivery - 14 (14.1) One of eight patients (12.5) who presented in the first- and early-second-trimester had a missed spontaneous abortion The rate of spontaneous preterm birth before 37 wk was 6.1% (6/99) Twenty one of 99 patients (21.2) who had delivered, had preterm birth, including six with preterm premature rupture of membranes One neonatal death due to asphyxia	Following treatment was given to 8 severe cases Antibiotic therapy 109 (94.0) Antiviral therapy 63 (54.3) Use of corticosteroid 37 (31.9) ICU admission 8 (6.9) Non-invasive ventilation 6 (5.2) Invasive mechanical ventilation 2 (1.7) ECMO 1 (0.9) Plasmapheresis 1 (0.9) Arbidol/oseltamivir/ aciclovir/ribavirin/interferon alone or in combination	14 neonates tested positive out of 100 Ten neonates had paired amniotic fluid and cord blood samples that were tested negative for SARS-CoV-2
Zeng <i>et al</i> ⁶²	China (January to February 2020) Wuhan Children's Hospital	33 (cohort study)	Fever on admission 8 (24) Cough 30 (33) Postpartum fever 5 (15) Pneumonia 33 (100) Premature rupture of membranes 3 (9)	26 (79) delivered by caesarean section	N/A	All three (3/33) infected neonates recovered One had respiratory distress

Contd...

Study	Country	Number of pregnant women	Clinical features, n (%)	Delivery and pregnancy outcome, n (%)	Treatment, n (%)	Neonatal infection/ outcome
Chen <i>et al</i> ⁶³	China (January 20-31, 2020) Zhongnan Hospital, Wuhan	9 (retrospective case series)	Fever on admission 7 (78) Post-partum fever 6 (67) Myalgia 3 (33) Malaise 2 (22) Cough 4 (44) Dyspnoea 1 (11) Sore throat 2 (22) Diarrhoea 1 (11) Foetal distress noted in two cases	All were in third trimester and delivered by caesarean section	Oxygen support (nasal cannula) 9 (100) Antiviral therapy 6 (67) Antibiotic therapy 9 (100)	Nine neonates SARS-CoV-2 negative SARS-CoV-2 negative in amniotic fluid, cord blood, neonatal throat swab, and breast milk in 6 patients
Zhu <i>et al</i> ⁶⁴	China (January 20 to February 5, 2020) Five hospitals in Hubei	9 (retrospective case series)	Fever 9 (100) Cough 4 (44) Intrauterine foetal distress 6 (67) Premature rupture of membranes 3 (33)	Caesarean delivery - 7 (77.8) Vaginal delivery - 2 (22.2)	Postpartum antiretroviral therapy (oral oseltamivir) is given for 4 mothers	RT-PCR for all neonates was negative. However, intrauterine foetal distress present in 6 cases One neonate died
Wu <i>et al</i> ⁶⁵	China (January 23 to February 10, 2020) Maternal and Child Health Hospital of Hubei Province, Wuhan	8 (retrospective case series)	Post-partum fever 2 (33) All women asymptomatic before delivery but became symptomatic post-partum	All were in third trimester Caesarean delivery - 6 (75) Vaginal delivery - 2 (25)	All patients received empirical antibiotic treatment and supportive care	N/A
Yu <i>et al</i> ⁶⁶	China (January 1 to February 8, 2020) Tongji Hospital, Wuhan	7 (retrospective case series)	Fever 6 (86) Cough 1 (14) Shortness of breath 1 (14) Diarrhoea 1 (14) Pneumonia 6 (86) H1N1 infection 2 (28)	Caesarean delivery - 7 (100)	All patients received oxygen therapy Antiviral treatment (oseltamivir and ganciclovir) Antibiotic treatment (cephalosporins, quinolones, and macrolides), interferon and arbidol tablets Traditional Chinese medicines (granules and Lianhuaqingwen capsules) were also given Methylprednisolone was given to 5 patients (71) after caesarean section	One infant was positive 36 h after birth

Contd...

Study	Country	Number of pregnant women	Clinical features, n (%)	Delivery and pregnancy outcome, n (%)	Treatment, n (%)	Neonatal infection/outcome
Zeng <i>et al</i> ¹⁴	China (February 16 to March 6, 2020) Zhongnan Hospital, Wuhan	6 (retrospective case series)	All 6 mothers had mild clinical manifestations	All were in third trimester Caesarean delivery - 6 (100) 5 mothers had elevated IgG	N/A	RT-PCR negative in all neonates. However, SARS-CoV-1 specific IgM detected in 2 neonates
N/A, not available; RT-PCR, reverse transcription-polymerase chain reaction						

Quarantine, hospital admission and stigma associated with the disease have negative psychosocial effect on the affected individual. At the same time, school closure, lack of play activities and home confinement during the lockdown period seem to have negatively affected the uninfected children. A study from China reported 22.6 per cent of students having depressive symptoms and 18.9 per cent symptoms of anxiety during the lockdown period⁷⁴. Apart from the direct effects on the health due to the virus infection, there are many other ways through which children are affected. The most notable are the immediate socio-economic impact of the measures taken to mitigate the pandemic and the long-term effects of delay in the implementation of the sustainable development goals⁷⁵.

Prevention of COVID-19: Distinct facets in children, caregivers and community

Until an effective vaccine is available, containment and mitigation strategies largely depend on non-pharmacological public health measures which include physical distancing, personal hygiene, frequent hand washing with sanitizers or soap and water, mass masking, cleaning of floors and surfaces and drastic measures such as countrywide lockdown. Isolation of the infected, tracing the contacts, quarantine of the exposed individuals and protection of the vulnerable groups from exposure are crucial.

Special precautions should be taken for the high-risk groups, such as young infants, those suffering from comorbid conditions and those on immunosuppressive therapy. Specific measures need to be taken to limit exposure in the schools and day-care centres, once these reopen. All routine vaccinations in the universal immunization programme should be given without delay⁷⁶. Quarantining exposed children is a difficult task; home quarantine with a caregiver in a separate room may be suitable. Mother-to-child transmission is a special scenario; the need of strict adherence to infection prevention and control measures during delivery is important as described earlier.

Second aspect is the protection of the elderly and vulnerable from an infected child at home. It is speculated that aerosols may be generated while crying and screaming in young children⁷⁷. In addition to prolonged viral shedding by respiratory route, virus shedding is also reported in the faeces of children^{11,12}. Therefore, caregivers and healthcare workers are encouraged to wear personal protective equipment at homes or hospitals while handling the infected children.

Third aspect of concern is the risk to community from children with asymptomatic or mild infection, especially during re-opening of schools and day-care centres. Asymptomatic carriers with prolonged viral shedding in the respiratory and faecal samples pose risk to the contacts. Several case series have reported relatively high proportion of asymptomatic cases varying from 13 to 16 per cent (Table II). However, during COVID-19 contact tracing, the China/WHO Joint Commission did not find any transmission event occurring from a child to an adult⁹. In this scenario, studies are warranted to assess the extent of asymptomatic infection in children and their role as links in transmission chain in the community. Serosurveys would be useful for this purpose. It is also important to mention that strict implementation of non-pharmacological measures may be difficult in young children.

Why COVID-19-affected children manifest only mild illness?

Variable severity of viral infection in different age groups is not a new phenomenon. With their immature immune system, in general, children are severely affected by respiratory viruses such as the influenza and respiratory syncytial virus in comparison to adults^{78,79}. However, on the contrary, relative sparing of children and the mild nature of COVID-19 in them have perplexed the epidemiologists, clinicians and scientists alike. Currently, there are no clear answers to this; there are only theories and hypotheses that are summarized below:

Angiotensin-converting enzyme 2 (ACE2) and renin angiotensin system (RAS)

A biologically plausible explanation is that the cellular expression of entry receptor ACE2 and the binding between the receptor and the spike protein of the virus may be different in children from that in adults. Studies are needed to find the difference in renin angiotensin system (RAS) pathophysiology in children and adults and its possible role in determining the differential outcomes of COVID-19. Dysregulation of RAS is known in comorbid conditions such as hypertension, cardiac diseases and diabetes⁸⁰. Abnormalities in RAS were noted in SARS and MERS virus infection also⁸¹.

Differences in immune system of adults versus children

The difference in immune systems of children and adults also needs special attention while considering

this issue. Immune system in children is not fully developed. There is a possibility that children are not mounting an intense inflammatory response, and hence, the host-mediated damage is limited^{19,82}. On the other hand, adults may be at risk of severe disease due to their different immune response characterized by excessive inflammation^{83,84}.

Role of childhood vaccinations

Children receive several doses of different vaccines as part of the universal immunization programme, and whether the resulting immune stimulation has any role in protection from COVID-19 needs to be elucidated. Cross-protection by antibodies generated following measles vaccination and cell-mediated immune response generated by BCG vaccination also need evaluation⁸⁵.

Role of other human coronaviruses and other infections in children

Children frequently suffer from mild infections by the respiratory and GI viruses. It needs to be seen whether pre-existing antibodies against human coronavirus infections causing common cold or other respiratory virus infections or GI infections confer cross-protection against COVID-19⁷.

Role of co-infections

During H1N1 pandemic, bacterial co-infection with *Streptococcus pneumoniae* was common which caused considerable morbidity⁸⁶. Data on co-infections with bacterial pathogens are not yet available for COVID-19 patients. One group of researchers put forward a hypothesis that co-infection with pathogens such as *Bordetella* due to waning of vaccine-mediated immunity in adults could be a possible reason for the severity in COVID-19⁸⁵.

Knowledge gaps and research priorities

Despite the global spread, epidemiology and clinical patterns of COVID-19 in children remain largely unclear, and emerging data indicate significant differences from adults. There is a need for systematic research to address the knowledge gaps. Future COVID-19 studies in children should focus on the extra-pulmonary and atypical clinical features, risk factors for severe illness, markers of severity, role of imaging, optimal supportive care and trials with newer therapies - antivirals and immunomodulatory drugs. Another area that needs attention is developing case definitions and testing strategies specific to children, as the initial strategy may not be suitable when community

transmission occurs. From an epidemiological point of view, high proportion of asymptomatic infection in children and their role in disease transmission needs to be elucidated. Drug prophylaxis in exposed children and child-centric issues in quarantining need to be addressed. The psychosocial effects of closure of schools, lack of play activities and home confinement during lockdown need attention of researchers.

Conclusion

COVID-19 in children poses challenges different from adults. Although the numbers of infected children and the severity of illness are expected to be low, healthcare professionals need to be prepared to face the situation. At present, it is uncertain how long the pandemic may continue and what would be the long-term effects. However, far-reaching socio-economic, political and environmental effects are likely, and the post-COVID-19 pandemic world is not going to be the same. The impacts of COVID-19 in children may go far beyond health including psychosocial, economical and educational and others that are beyond the scope of this article. It would be interesting to observe how children, whether infected or uninfected, grow up in the post-COVID-19 pandemic world.

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