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Pediatric Covid-19: Epidemiology and impact of pandemic on children

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Abstract

Covid-19 pandemic caused by the highly virulent virus, SARS-CoV-2 has caused innumerable infections and deaths in the world from December 2019 to date. Though the virus affects all age groups, data has shown that children are less prone to the virus. They also have a predominantly milder disease course though serious affliction and even deaths are reported in them.

However, this viral infection caused greater amount of other negative effects on the physical and mental well-being of children. The pandemic-induced increasing job losses and economic loss pushed more families below poverty line and nutrition, education, and health of their children would get compromised. Forced school closures disrupted student academics and might give rise to more child labor and child marriages in Asia. Children were at the receiving end and child abuses and assaults on them increased. Children's addiction to screens and its ill-consequences have also been observed during the lockdown. Childhood obesity increase has been noted and routine care of children, childhood vaccination and management of childhood illnesses have suffered. The movement restrictions led to sleep disorders and rise in mental issues in children. The effects are likely to continue long and prompt and adequate coordinated interventions from government and doctors are required to manage them. Newborns born to Covid-positive mothers need to have an in-depth study to know the impact of the disease on their lungs and nervous system.

Keywords: covid-19 pandemic, children, impact on child health, SARS-CoV-2.

INTRODUCTION

First reported in Wuhan, China in December 2019, the deadly respiratory virus, SARS-CoV-2 or Covid-19 engulfed the world as a pandemic forcing countries to impose lockdown on their citizens. This led to tremendous hardships for everyone with far-fetched physical, emotional, mental, and economic implications. Although, the disease affects all age groups, children have been found to be less vulnerable to the deadly virus [1-3]. However, the pandemic caused a lot of other adverse effects on children that might be long-lasting [4].

SARS-CoV-2: Microbiology and pathology

SARS-CoV-2 virus responsible for the ongoing pandemic is a type of coronavirus (CoV) and belongs to the family Coronaviridae and subfamily Coronavirinae. Its genus is beta-coronavirus that includes all species that cause severe acute respiratory syndrome (SARS) [5]. Only a few species in this genus infect humans directly. Most are enzootic and under certain circumstances and accidentally jump from animals to humans with lethal outcomes. SARS outbreak of 2003, the Middle East respiratory syndrome (MERS) outbreak in 2012 and the ongoing covid-19 pandemic are examples of such host-shifting life-threatening transmissions [6].

SARS-CoV-2 is an enveloped virus. It has a genome made of a positive-sense RNA that is single-stranded (+ssRNA) and 29.9 kB long. The genome of the new SARS-CoV-2 virus is 96 % similar to that of the bat SARS-like CoV strain named BatCov RaTG13 [7]. Its sequence bears 79.6% identity to SARS-CoV [8]. This genome is surrounded by a capsid made of nucleocapsid protein (structural protein N). There is another membrane around it containing 3 types of structural proteins; membrane protein M, envelope protein E, and spike protein S (S1 and S2) [9] [Figure 1]. S1 binds to host receptors called angiotensin-converting enzyme 2 (ACE2) and helps the virus to enter host cells. While S2 aids fusion of viral and host cell membranes. The virus also has 16 non-structural proteins (Nsps 1−16). The Nsps are functional proteins that help the virus gain entry into and replicate in host cells.

Nsp1- aids in processing and replication of the viral RNA

Nsp2 –helps modulate the survival signaling pathway of host cells.

Nsp3 –it slices the translated protein.

Nsp4 –contains the transmembrane domain 2 (TM2) that causes modification of the ER membranes.

Nsp5 –has a role in polyprotein formation during viral particles replication.

Nsp6 –it is presumed that it is a transmembrane domain.

Nsp7, Nsp8 - help to unite Nsp12 and template-primer RNA.

Nsp9 –it is probably an ssRNA-binding protein.

Nsp10 – it has a role in cap methylation of the viral mRNAs.

Nsp11 –it is an intrinsically disordered protein of small (13 aminoacids) size whose function is yet unknown.

Nsp12 –it has the RNA-dependent RNA polymerase (RdRp), a crucial element of coronavirus replication/transcription.

Nsp13 - it binds to ATP and its zinc-binding domain plays a part in viral replication and transcription.

Nsp14 - has immense capacity to proofread exoribonuclease domain.

Nsp15 - possesses Mn(2+)-dependent endoribonuclease activity.

Nsp16 - is actually a 2'-O-ribose methyltransferase.

Some Nsps also suppress host defences [10].

The viral Main protease (Mpro or 3-chymotrypsin-like protease or 3CLpro) plays a pivotal role in viral replication as well as its transcription. There is another enzyme called papain-like protease (PLpro) which processes the polyproteins produced from the viral RNA [9].

Similar to adults, the respiratory system is the main route of infection in children. This transmission is direct (via respiratory droplets or through viral particles suspended in an aerosol form) or indirect through fomites and other contaminated surfaces. Feces and urine of patients contain viral particles and can be potential sources of infection [11]. Children are usually secondarily infected from adult family members. But the infection risk is lesser compared to that in the older members in the family (16.8% vs. 28.3% respectively) [12]. Some studies have shown that chances of infection in children increase with age, but both genders are equally affected [13].

SARS-CoV-2 infects via ACE2 [Figure 2]. Since these receptors are heavily expressed in the placenta, it is likely that pregnant women with corona infection might transmit the virus to their fetus. But vertical transmission from mother to fetus has not yet been proven satisfactorily in case of covid-19. However, the rising cases of neonatal covid-19 infection point to a high likelihood of perinatal transmission of this virus. Long term detailed studies on larger number of deliveries along with cord blood or amniotic fluid viral testing are needed to confirm it and also to evaluate the effect of the infection on fetal/neonatal lungs and nervous system [14]. Virus or antibodies testing in breast milk samples have yielded variable results. However, WHO and UNICEF recommend continuing breastfeeding even with covid-19 infection in mother. But the breastfeeding mother should wear a face mask and adhere to adequate hygiene measures during breastfeeding. If donor milk is used to feed the baby, it should be pasteurized by Holder method (62.5°C for 30 min) prior to giving the baby. This step will kill the virus. [15].

Statistics of Covid-19 in children

Global data on childhood morbidity and mortality due to coronavirus disease 2019 is available but has its limitations. The reason is that all countries have not provided the data and some countries have provided incomplete data as regards age and gender. According to Max Planck Institute for Demographic Research (MPIDR), 18 percent of cases of covid cases worldwide were in children less than 20 years of age. And these children constitute 33.2% of world population [16]. In the USA, more than 12.3 million children tested positive for the virus until now. 19% of total cases of Covid-19 in the USA until now comprise children. The infection rate in children has been 16397 positives per 100000 children [17]. But during the first few months of the pandemic, children less than 18 years formed only 1.7% of all cases in the USA [18]. After the Omicron variant arrived, children comprised 26.2% of the cases of covid. Thus, the pediatric cases numbers were relatively less during the first two years of the pandemic. But with time, a gross shift was noted in age-group affliction. Covid-19 cases in over 60 years declined and those in 0 to 19 years and 20 to 39 years doubled [19]. This was due to lifting of restrictions, increased mobility, non-essential work, and social gatherings especially in the young. And with the onset of 2022 and Omicron variant with higher transmissibility more children (over 4.5 million) tested positive for Covid-19 in the USA since 1 January 2022 until now [17]. But fortunately, these cases in children were still of the mild type. WHO reports that children under the age of 5 years represented 1.8% of global covid-19 cases and 0.1% of global deaths. Whereas, children 5 to 14 years of age were 6.3 % of the global cases and 0.1% of global deaths. And 15 to 24 years age-group young people were 14.5% of global cases and 0.4% of global fatalities [20].

A meta-analytic study on the severity of SARS-CoV-2 infection in children < 20 years of age revealed that 15 to 42% of the infections in them were asymptomatic [21]. A mid-2020 systematic review of literature showed that 66% pediatric covid cases were mild to moderate in severity [22]. And a serological survey study proved that half of the children with seroprevalence positivity to covid reported no symptoms at all [23].

When we talk of hospitalization of covid cases in children in the

USA, only 0.1%-1.5% of pediatric covid-19 cases required hospitalization. And of the total hospitalized patients, children occupied only 1.5%-4.6% of the beds [17]. Children less than 2 years of age and those in 12-17 age group had a higher admission rate. One in 3 hospitalized children needed ICU care [24]. However, an Italian study showed higher hospitalization rate in children (57.7%) and in Greece, this figure was 26.1% during the first wave [25, 26]. The intensive care need varied in different studies and ranged from 0 to 18% [23].

As regards fatality, world data reveals that female children < 20 years with covid deaths were 17% of the total female deaths (35% of female population are children <20 years). And male children < 20 years constituted 18% of covid deaths in male population of the world (37% of global male population are less than 20 years). Thus deaths were lesser in children overall but more male children succumbed to the viral disease than female children [16]. Only 0.00 to 0.01% of American children with positive covid reports died. And of all the deaths due to covid in the USA, only 0.00 to 0.23% were children [17]. Only 1 state reported a case fatality rate of 2% in children [27]. First year of pandemic data from Brazil revealed that mortality rate was 7.6% of children hospitalized for covid-19. The toll was more in children less than two years and between 12 to 19 years, in children of indigenous ethnicity, in those from Northeast and North regions of Brazil, and in children with comorbidities. Access to health care and poverty played a role in this type of statistics [28]. Studies have shown that severe cases of coronavirus disease 2019 in children had worse outcomes in poor countries compared to the affluent nations. [29]. This is attributed to differential health care quality, biological factors, and social factors.

Schools were closed as soon as the pandemic struck the world. But later analysis of data from Europe, the UK, and Israel revealed that school closures did not have a major impact on the incidence or outcome of covid in children. School reopening was not associated with any increased surge in pediatric cases in school-going children. The preventive measures adopted with school reopening were more important determinants [23].

Likely reasons for lesser propensity of children to Covid-19 disease, hospitalizations, and death

Early variants of covid-19 affected lesser number of children. They caused no or milder symptoms in them and fewer deaths. It has been unclear why children have less severe symptoms and mortality with covid-19 infection compared to adults.

Some attribute the lesser number of reported cases in children to under-testing in children. There was a concern that the asymptomatic children might act as a reservoir of the infection and spread the virus in the community [20]. But WHO analyzed all the available data and reached the conclusion that most children are symptomatic though mildly and are not silent spreaders of the virus [20, 30]. Thus, spread to and from children is scarce. But another study in children showed that half of seropositive children had no complaints [23].

The biological reasons for mildness of covid infection in children are under investigation. But various explanations have been provided by experts in the field. The general hypothesis is that a child's less mature and less functioning immune system could be a plausible reason [1, 31]. It is also believed that children experience infection with other milder forms of seasonal coronavirus every winter. This confers them with immunity that offered them cross-reactive protection even during this coronavirus pandemic. But in adults this immunity is waning and leads to antibody dependent enhancement (ADE) and hence severe disease [32].

It is also thought that co-morbidities such as hypertension, diabetes, or chronic lung disease that is common in adult population but lesser in children is responsible for the less severe disease in the latter group. It is also speculated that angiotensin-converting enzyme-2 (ACE2) receptors that viruses bind to before entering host cells are less mature and less functional in children [33]. Hence, children get less frequent and less severe infection. The study of Bunyavanich et al also showed that children had less ACE2 expression in their nasal epithelium [34]. However, previous animal studies have shown that ACE2 in lower respiratory tract helps decrease severe lung injury due to its anti-inflammatory, anti-vasoconstricting, and anti-fibrotic action [35]. Hence its paucity in the lower respiratory tract of children would in fact lead to more severe disease. Therefore, this receptor-based explanation seems invalid and controversial needing more investigation.

Other scientists feel that children are usually infected from an adult family member. Hence their infection is from second or third generation of the virus which may have reduced pathogenicity [36]. There are some who feel that the innate immunity of children is stronger and this explains the diminished propensity to get covid-19 [37]. They have higher lymphocytes predominantly of NK cell types. Besides, their frequent viral infections and administration of live, attenuated childhood vaccines in them enhances this immunity [38, 39]. The concomitant presence of other viruses in the respiratory mucosa of children could probably be providing competition to covid-19 and lessen its uptake [40].

Though less susceptible, children do get severely ill with the virus and some also die. The main factors found to determine the severity, prognosis and outcomes in children are ethnicity, nutritional status, lifestyle, comorbid conditions including obesity, and therapy used [41].

Clinical differences of coronavirus affliction in children

There are some stark differences noted in the clinical manifestations of covid-19 disease in children and adults. Besides less chances of infection, children also have a milder course of the disease, lesser need for hospitalization, and lesser fatalities [3].

Most studies have shown that majority of children infected with the virus were asymptomatic or presented only with mild symptoms. Other studies revealed that children might get infected without shedding the virus or seroconverting [42].

Some initial reports showed that infants get more serious disease with covid compared to older children. But this claim has been refuted [17, 43, 44]. However, a prospective multicentric UK study did reveal that risk of hospitalization was more in infants and in 10 to 14 years old children [45]. It was assumed that immunosuppression in children due to any cause could predispose them to getting covid infection in a more severe nature. But some small-scale studies revealed this not to be the case. It found no increased risk even in children with cancer or compromised immune system [46, 47].

But as the pandemic progressed, severe and life-threatening clinical features of the disease in pediatric patients emerged. These included an enormous inflammatory response in multiple organs of the body called multisystem inflammatory syndrome in children or MIS-C in short [48, 49]. It is called paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) in Europe [50]. These children had a hyper-inflammatory response with fever and affecting heart, skin, gastrointestinal tract, and mucous membrane after 4 to 6 weeks of covid infection. It simulated Kawasaki disease, its shock syndrome, and toxic shock syndrome and has markedly elevated C-reactive protein, d-dimer, IL-6, and fibrinogen levels [51]. They have either RT-PCR for covid-19 positive or covid antibodies positive or both.

Most symptomatic children with covid disease have fever, cough, sore throat, and running nose [52, 53]. They may also have headache, vomiting, loose motions, myalgia, and fatiguability. Skin rash, tachycardia, and tachypnoea are also noted. Older children have more chances of respiratory distress compared to infants (44 vs 7% respectively) [27].

Children infected with the virus are less likely to complain of loss of smell (anosmia) or loss of taste (ageusia). Neurological complications such as seizures in children due to the virus are rare and mostly seen in severe cases. Occasionally, these children get acute disseminated encephalomyelitis, acute transverse myelitis, respiratory failure needing ventilatory support and oxygen, ocular symptoms, acute renal failure or multi-organ system failure [23]. Likely risk factors for severe disease were obesity, underlying chronic lung disease like bronchial asthma, and immunosuppression due to any cause [14]. But data on asthma or immunosuppression and covid-19 severity gave conflicting results [14]. A Brazilian pediatric study found that covid severity had a bimodal presentation; more severe cases were seen in less than 30 days old and in adolescents. Their study also showed that underlying chronic conditions especially neurological condition worsened the severity of covid-19 [54].

Turkish pediatricians found lymphopenia in 13.5% of their infected children [55]. Co-existent infections such as influenza type A and B, Mycoplasma pneumoniae, and/or respiratory syncytial virus (RSV) were seen in 47.1% of covid-infected children in China but in Latin America only 3.4% of children had simultaneous other viral infections. These dual infections did not necessarily increase risk of ICU admission or ventilation requirement [14].

Besides MIS-C, children could potentially also have prolonged clinical symptoms (long covid-19, post covid condition, post-acute sequelae of SARS-CoV-2 infection) similar to those in adults. But data on it is limited. The long-term implications of the viral infection on the respiratory system and development of children would be clear on follow ups. Also, clinical characteristics of the disease in children and adolescents inflicted with newer variants of the virus are under investigation.

Covid-19 pandemic and its effects on children

Children do not form the face of the pandemic. But increasingly they are getting infected. Children also could turn out to be the greatest and prolonged victims of this global infectious crisis. The consequences on them are not only direct but indirect as well due to socioeconomic impacts as well negative effect on their learning due to imposed mitigation measures [56]. The impact is bound to be widespread but may not be equal. More damage might be observed in poorer countries and in more disadvantaged and more vulnerable sections of all countries [56].

Job losses occurred due to the pandemic and unemployment showed a steep rise. Many families lost their sources of income. It is estimated that over 60 million more children might fall below poverty line compared to that in 2019. An additional 100 million more children might have to forego their access to education, health care, housing, adequate food, water, and sanitation. This effect would be more in sub-Saharan Africa and South Asia and in those with no insurance support [56]. On the other hand, in the developed world such as the USA, where money was not much of an issue, increasing obesity was a matter of concern in children. Due to lockdown the diet and lifestyle of people including children changed drastically. Families purchased more of non-perishable foods and highly processed food items that could fatten. Snack foods and dessert intake increased and exercise lessened. Depression led to overeating. All this added to the current childhood obesity epidemic in these countries [57].

School closure forced learning to go online. 1 in 3 children had no access to technology for it. Online remote learning has its own pitfalls and even those children with internet and gadget availability found it difficult to comprehend the online teaching. This was due to skill gaps among the teachers, no proper parental support and inherent limitations of online teaching. In poor nations, the temporary academic loss could see a significant rise in child labor and child marriages [56]. This might be a permanent end to further schooling of these children. There is a likelihood that 10 million girls might become child brides. Some might even be sold for money to old or rich people [56]. School closures negatively affected children physically, in their social interactions, well-being, and mental status [58, 59]. As previously stated, the stagnant lifestyle potentially could worsen the already present childhood obesity epidemic of most countries [60]. More and more children got hooked onto and became addicts of internet and online games [61].

Though children health was less affected directly, the health systems were strained due to the pandemic. Hence, only life-threatening medical and surgical care was provided in hospitals and most doctors were diverted to covid care units. Hence,

immunization services in children and antenatal care of pregnant women suffered. There is a fear that this disruption in routine care of children and pregnant mothers might show up later on as rise in childhood diseases or neonatal issues. The pandemic could regress the progress made over the decades in curbing preventable child deaths. HIV disease treatment was pushed to the back due to covid-19. New HIV cases could double and pediatric deaths would rise tremendously [62].

UNICEF has also stated that child abuses in various forms could heighten due to the tensions in household due to income loss and social isolation [63]. New cases of violence on children might erupt. And those already facing it at home might have it more frequently and in more severity.

Adolescents suffered on their mental health and behaviors. Children from lower socioeconomic strata of society and those with previous mental health issues were more susceptible to the ill-effects of lockdown, school closures, and inaccessible routine psychological care during the pandemic [64]. More than half of the children in Spain had sleep disturbances. Most parents questioned felt that their kids were sadder and more irritable and anxious. 41% of the parents questioned felt that their child has gained weight. But this Spanish survey also showed that children overall coped well with the situation. They showed high resilience and adaptation capability [65]. A Saudi Arabian similar study noted almost alike findings. It also showed that punishment threats or screaming at children or beating them only tended to increase negative feelings and behaviors in them. Children of divorced parents had more mental issues than those with non-divorced parents [66]. Almost similar findings came out of an Israeli study conducted on Arabic children. 45% of the studied children expressed fears that they never had experienced prior to the pandemic [67].

Long term effects on children who were born to mothers infected during pregnancy remains largely unknown yet [23].

Covid-19 Vaccination and children

The review would not be complete without a mention on covid-19 vaccines in children. Covid-19 vaccine trials in children above 12 years have yielded good and safe outcomes. CDC states that children above 12 years should get mRNA vaccines. This will disrupt the transmission chain from these silent infections and help control the pandemic. Also, this measure would increase herd immunity and protect the children as well [68]. In some nations, even children as small as 5 years of age are now being given the vaccine for their own protection as well as of the community.

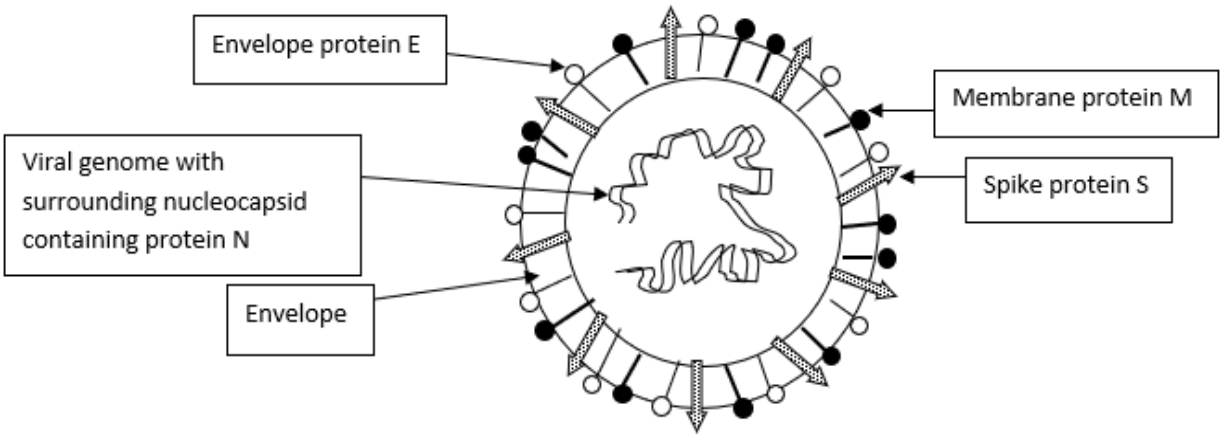

Figure 1: Structure of SARS-CoV-2 (Schematic)

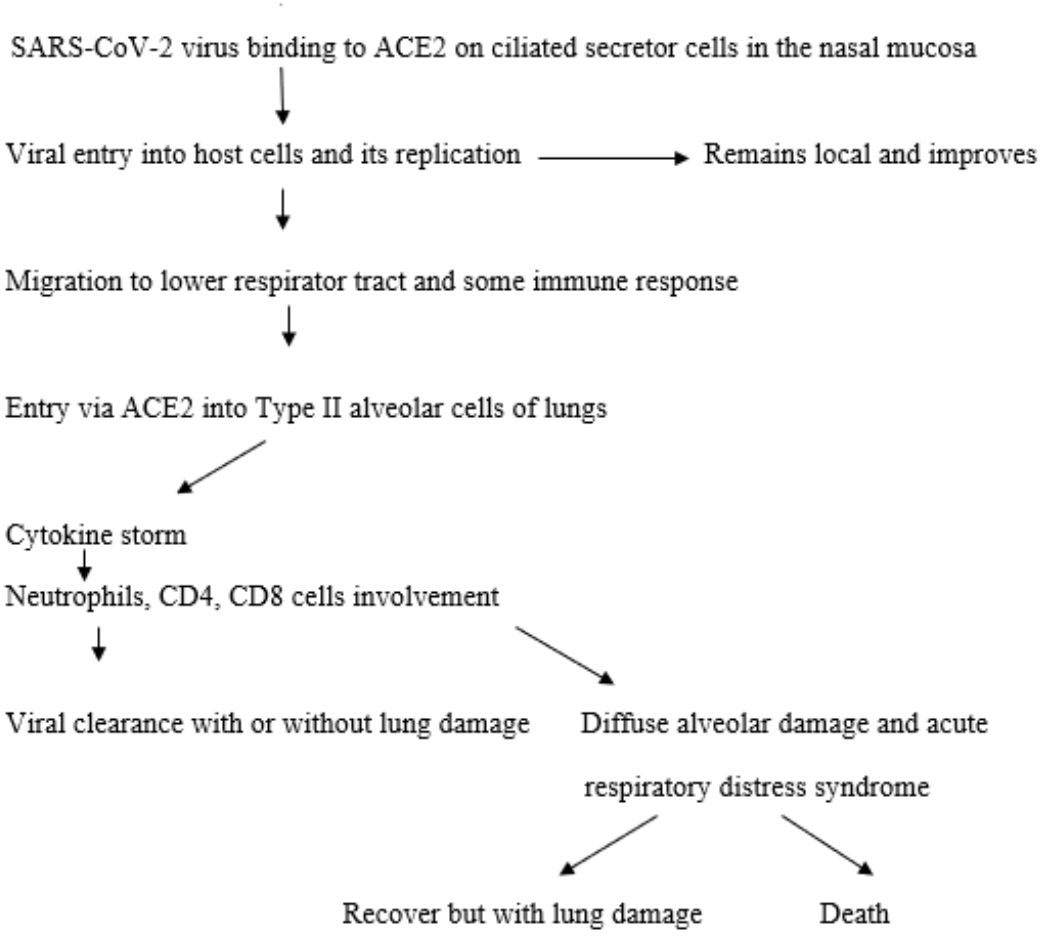

Figure 2: Mechanism of action of the SARS-CoV-2 and the possible disease course

CONCLUSION

Children do get infected with the covid-19 virus and the risk depends on biological, social factors and measures taken in the community to curtail the infection. But most children get secondarily infected and are either asymptomatic or have mild disease with less likelihood for hospital admission. Death rate is also less in them. But the impact of the pandemic on them is enormous. They suffer on several fronts and the effects might last long.

It is recommended that parents should hold frank talks with children about the pandemic and allay their fears. Government should increase efforts to handle the various problems in children in the long run. Detailed studies on perinatal transmission of covid and effect on newborn child should be undertaken. Covid vaccine safety in children should be stressed and they should be brought into the gamut of vaccine coverage.

Conflict of interest

There is no conflict of interest of any kind in preparation of this manuscript.

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