COVID-19, should I worry about my child? Are they immune? A comprehensive overview.

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Abstract

The management protocols in children are mainly governed by symptoms severity and atypical cases. COVID-19 in pediatric group of patients can be asymptomatic. The aim to conduct the study was to assess the benefits and timely management of COVID19 when it is transmitted from the silent carriers like children. The two research questions below were determined.

- **Whether children are more dangerous than adults in spreading of infection?**
- **How long lasts viral shedding after recovery?**

We searched MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and Cochrane Database of Abstracts of Reviews of Effects, as well as foreign literature with English translations. Extra information and data have been collected from Google Scholar and American Society for Microbiology (ASM). No randomized controlled trial studies had been conducted in children with COVID-19 yet. Information on patients' age range, comorbidities, methods of treatment, and effects on mortality, morbidity were extracted. As a conclusion, this study shows that children are less susceptible to COVID- 19 disease than adults, also the symptoms are less sever than in adults and with regard to transmission, no evidence suggesting vertical transmission (intrauterine) except one case or through breastfeeding of COVID-19 virus. Finally, children are much immune than any other age group and this immunity is more resistant to COVID-19 as this is explained in details[1].

Keywords: Children, COVID-19, Asymptomatic, Kawasaki Disease.

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Introduction

A new virus was emerged in late December 2019 causing an epidemic infection in one of the biggest Chinese cities (Wuhan). The virus was diagnosed and named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is one amongst 7 viruses belongs to Coronaviridae and the disease was named as COVID-19 disease[2].

The epidemic of COVID-19 expanded to infect many countries; thus it was classified as a pandemic by the World Health Organization, which is abbreviated as "WHO" on the eleventh of March 2020. Up to this day (7 June 2021), COVID-19 hits 174,120,300 people across the globe with 3,745,561 deaths (data recorded on 7 June 2021) and the numbers are still increasing

The disease (COVID-19) in children in the beginning of the outbreak was thought to be "unexpected to happen in children" and the children would not contract the disease or at least less susceptible . This notion has been changed later on because evidences had shown involvement of children who demonstrated obvious clinical symptoms of COVID-19 disease. In this review, all medical findings would be added regarding COVID-19 infection in children.

Literature

COVID-19 in children, the corrected dogma and new concepts

The belief at the beginning of the COVID-19 disease was that it does not affect children, but later it became clear that children develop clinical symptoms as a result of contracting COVID-19 disease and that their infection is mostly without symptoms or very mild respiratory symptoms and heals quickly even without treatment. The previous reference indicates that the percentage of infected children (ranged from newborns to less than 18 years) did not exceed 2% of the total morbidity

rate in the world. The reference also added that severe infections of COVID-19 in children and deaths were very rare due to unknown causes. Simply the disease is mild and mostly without symptoms in children (asymptomatic). Based on the above data, the virus is not dangerous and mostly immune from the virus[3]. COVID-19 crisis caused a lot of problems to children, such as depriving them of going to school, playing with friends, and the annoying problem of "Stay at home" and their lack of embrace and kissing by their parents on the pretext of prevention and social distancing, which contradicts the nature of the child who loves affection, playing and many other social activities. It causes many social and psychological problems for any quarantined child.

Etiology, nomenclature and the origin of the virus

During the last week of December 2019, a viral disease hit Wuhan city in China and caused epidemic wave of a disease characterized by respiratory symptoms. The virus was named as 2019-nCov which is one of 7 corona viruses belongs to Coronaviridae family. The virus was renamed later by World Health Organization (WHO) to become "severe acute respiratory syndrome coronavirus 2" (abbreviated as SARS-CoV-2). The disease named as COVID-19 which is an acronym that means (CO= corona, VI= virus, D= disease, and 19= 2019, which is the year disease appeared). SARS-CoV-2 is the causative agent of COVID-19 disease, which is a positive sense single strand RNA virus surrounded by an envelope and not segmented. The diameter of SARS-CoV-2 is 65–125 nm in length, containing crown-like spikes on the external surface. SARS-CoV-2 belongs to β-coronavirus to which SARS-CoV viruses (the causative agent of Severe Acute Respiratory Syndrome "SARS") and MERS-CoV viruses (the causative agent of Middle-East Respiratory Syndrome "MERS") previously emerged as 2 major epidemics characterized by respiratory symptoms in China and the Kingdom of Saudi Arabia during 2004 and 2012 respectively[4]. There were many theories about the evolution of SARS-CoV-2 virus. Genome sequencing of the virus revealed presence of about 96.2% identity with CovRaTG13 bats virus. Later and further molecular studies discovered that the virus was developed in pangolin (ants eater animal) where the similarity reached 91.02% with Pangolin-CoV virus, and up to 99.83–99.92% identity was found between SARS-CoV-2 and Pangolin-CoV virus in Malayan pangolin. Therefore, the most accepted theory is now that SARS-CoV-2 originated and developed in pangolin, but not bats.

Clinical symptoms

Normal and regular symptoms: In general, COVID-19 clinical signs tend to be milder and less severe in children than any other age group. In China, 2143 children were examined and identified as COVID-19 positive (laboratory diagnostics), it was found that 34.1% of them were asymptomatic. Clinical symptoms of COVID-19 in children are mainly respiratory signs which includes fever, coughing, pharyngeal erythema, sore throat, intermittent sneezing, muscles' pain and exhaustion. Some children suffered from wheezing. There were some more clinical symptoms related to the digestive system which hit by the virus which includes diarrhoea, vomiting, tiredness and exhaustion, rhinorrhoea and emissions. In a study reviewed by Zimmermann and colleagues documented that most children were asymptomatic or expressed mild respiratory symptoms for those tested positive for COVID-19. The study mentioned that there was only 2% children tested positive for COVID-19 in a population of 72,314 children (aged less than 19 years) surveyed. The study divided the infected children into 3 categories. The first, second and third categories included 20 kids in Zhejiang (China), 34 kids in Shenzhen (China), and 9 kids in diverse cities in China respectively. In the first category, the main symptoms included no fever, mild or moderate fever, rhinitis, coughing, exhaustion, headache, diarrhea and commonly in advanced cases there were dyspnea, cyanosis, and poor feeding. In the second category, 26% of children who had underlying issues were asymptomatic, or developed mild respiratory signs, whereas the most common 2 signs noticed were fever and cough (50% and 38%) respectively. The last (third) category reported only 4 feverish kid out of 9 and only one asymptomatic infant. No deaths were recorded in the above study and generally the majority of children were recovered after 7-14 days post-infection[5]. Severe clinical symptoms in COVID-19 positive children were recorded in China which includes difficult breathing (dyspnoea), cyanosis, decreased oxygen saturations of less than 92%, tachypnoea, respiratory failure occasionally accompanied by acute respiratory distress syndrome (ARDS), rarely shock and symptoms of multi-organ failure (for example, encephalopathy, cardiac failure, abnormal coagulation and acute renal failure).

In a study in China, the severity of clinical symptoms in children contracting COVID-19 positive was recorded in infants (less than 1 year old) as 10.6%, babies (aged between 1-5 years) as 7.3%, children of 6-10 years as (4.2%), children aged 11-15 years (4.1%) and finally teenagers of 16-17 years (3%). It was noticed that 50% of the severe cases COVID-19 positive children were infants (less than one year of age), whereas it was shown exceptional very severe symptoms in a case study on a 55-day old newborn. More examples of children expressed severe clinical symptoms with COVID-19 positive were shown in a study in Wuhan (China), where 3 children required intensive care (these children suffered from underlying issues). One of above-mentioned children had developed bilateral hydronephrosis with urolithiasis. The second child was on chemotherapy to treat leukaemia, while the third child suffered from intussusception[6].

Complications, unexpected symptoms and deaths: COVID-19 infection in children has been described as mild disease in children and mostly not fatal (see above). However, one of most dangerous complications happened to the children infected with COVID-19 is that getting infected with. The mixed infection (coinfection) of COVID-19 and Kawasaki disease happened in European and North American children. The infection of children with Coronavirus in conjunction with Kawasaki disease caused very severe injuries (which is uncommon) that necessitated the entry of children to the ICU

and caused high numbers of deaths. The cause of death was diagnosed as a result of toxic shock-like syndrome and multisystem inflammatory syndrome in children (MIS-C) as reported by. Kawasaki Disease (KD) is a non-infectious viral disease that affects the blood vessels, especially the coronary artery. The disease is limited to children under 5 years of age in the Winter and Spring, and usually causes mild injuries in children that are recovering without taking any treatment. It is believed that children of Asian descent in Europe and America are most at risk of contracting this disease. The causes of the disease are still unknown, but some epidemiological and clinical characteristics support that it may be of infectious origin.

Transmission, susceptibility of children to infection and viral shedding

The virus SARS-CoV-2 is transmitted through several routes to infect human beings. Person to person spread route is most accepted route and the most common way. SARS-CoV-2 virus can infect all age groups, adults, children, infants, babies, newborns and toddlers. However, the total percentage of infected children by COVID-19 is less than 2% of total population as an average in the world. The reason for this low percentage belongs to the fact that kids are mostly asymptomatic or mild symptoms were seen which make them not diagnosed well. There was around only 1% of Lab-confirmed children (aged less than 9 years) tested positive to SARS-CoV-2 in South Korea, while it was 5.2% positive COVID-19 cases in children aged between 10 and 19 years old. Studies in Iceland revealed quite a very few positive children with COVID-19 aged less than 10 years out of the total population. Also, there were no positive COVID-19 children (374 child) aged less than 10 years in Italy where 2.4% of Italians tested positive to COVID-19 at all age groups[2]. In Guangzhou and Wuhan, the two big cities in China, and in Japan respectively noted that children are not or less susceptible to COVID-19 infection even when mixing with COVID-19 positive people in spite of the fact that children were susceptible as equal as adults. In the United States of America, there were 150,000 children under 18 years (1.7% out of total children in the US) tested positive to COVID-19, while the percentage of children is 22% out of the total population in USA.

Viral shedding of SARS-CoV-2 in children was studied by Yu-Han and colleagues who studied 3 children tested positive for COVID-19 in Qingdao(China) and followed up the cases after about a month after recovery from infection. The findings of the above study revealed presence of the virus alive in the stool samples after more than a month in the assayed children (after the clearance of clinical symptoms). In addition, the virus was undetected after about 3 weeks in the throat swabs of 2 kids[5]. Study conducted in China by Pengcheng et al. looked up for the viral shedding of SARS-CoV-2 of nine children who were tested positive for COVID-19. Follow up continued up to 6 weeks after resolution of symptoms. The findings confirmed presence of SARS-CoV-2 virus in nasopharyngeal swabs (9/9, 100%), faecal specimens (8/9, 89%), and oropharyngeal swabs (3/9, 33%) but absence of virus in both serum and urine samples. The average duration of viral shedding in nasopharyngeal, oropharyngeal swabs, and stools was 13, 4, and 43 days respectively, and only viral shedding from stools after discharge lasted up to 46 days. Moreover, when Xu et al. reviewed SARS-CoV-2 virus in children concluded that the viral shedding is longer in feces than in upper respiratory tract.

Prevalence, morbidity and mortality rates

COVID-19 infects all age groups (including children). However, children contracts COVID-19 less severe than adults. More than 90% of infected children expressed asymptomatic, mild to approximately moderate clinical symptoms. Studies in China showed that approximately 2% children diagnosed COVID-19 positive of 44,672 total surveyed children where about less than 1% of these children aged less than 10 years old. In Italy, only 1.2% children diagnosed COVID-19 positive of 22,512 total assayed children, where zero mortality rate was noted. In the United States of America, the morbidity of children with COVID-19 was higher which hit up to 5% of the total 170,000 children surveyed.

Mortality rates (deaths) are less common or very rare (0.01%) in children infected with COVID-19 when compared with adults. In China, a study was performed on 44,672 individuals (mixed children and adults) diagnosed as COVID-19 positive showed 2.2% case fatality rate, while no deaths were recorded in kids at age of 10 to 11 months. In addition, one male child (boy) aged 14 years was recorded dead, but the author was not sure whether he was diagnosed as COVID-19 positive or not. No deaths were recorded neither in the case study in China to the 10 month infant suffered from intussusception and multi-organ failure, nor in the American children surveyed for COVID-19 infection in the United States of America[1].

COVID-19 outcomes

The prognosis of children infected with COVID-19 is rarely worse and deaths were rarely reported. In a study on 171 children examined as COVID-19 positive showed that only 12.9% of cases were admitted to the hospital whereas the rest all were discharged. Another study on 398 children in China revealed that the vast majority of the infected kids were cured after 7 to 14 days post-infection.

Methodology

Diagnosis

Blood parameters: The laboratory diagnostic parameters for COVID-19 in children is rare. In adults, COVID-19 positive patients showed anemia, elevation in inflammatory indicators such as ESR*, CRP*, PCT* (see abbreviations below the paragraph) and occasionally hyperglycemia. A study on children positive for COVID-19 to detect some clinical parameters is performed by Henry and colleagues who surveyed 66 kid tested positive for COVID-19 and claimed that 69% of kids had normal WBCs count, but neutrophilia was

recorded (4.6%) and neutropenia (6%). There was lymphocytopenia noted in 2 kids only (3%). An increase in both CRP and PCT was recorded in 13.6% and 10.6% respectively. Another review research explained that lymphocytopenia was noticed (3.5%). The main specimens collected for COVID-19 suspected children includes nasal, pharyngeal or nasopharyngeal swabs or blood samples (less accurate) to detect the RNA of the virus by Real Time-Polymerase Chain Reaction (RT-PCR) method. There laboratory picture of both COVID-19 and Influenza looked the same. This was explained in a Chinese research performed on 366 child (less than 16 years old of age), who were admitted to the hospital because of the respiratory symptoms in the beginning of the outbreak. The majority of these kids were not attributed to COVID-19 but these cases were tested as influenza A or B viral infection[3].

Chest CT Scan: One of most precise clinical method to detect COVID-19 is CT Scan which has specificity of up to 97% in a study done on 1014 adult individuals (COVID-19 with clinical symptoms) both genders in Wuhan. The main finding of using this method represented by presence of ground-glass opacity reported in about 33% of total cases (171 child), as well as localized or bilateral patchy shadowing which was reported in 18.7% and 12.3% of cases respectively. Moreover, this method was successfully used to diagnose pneumonia in 64.9% of the total kids assayed. Another study used CT Scan was performed on 5 kids recorded that 3 of them showed patchy ground-glass opacities, which is in line with the results of Liu and colleagues who tested 40 kids with CT Scan method and discovered that 80% of cases revealed abnormal pictures such as halo signs along with ground-glass opacities noticed in 60% of affected kids.

Treatment

From an extensive search through the literature, it seems there is no specific treatment for children contracting COVID-19 disease. Many published papers referred to supportive treatment which includes oxygen supply, broad spectrum antibacterial for secondary bacterial infection. However, some researchers except Cai and colleagues recommended the use of antiviral therapy especially for severe cases. Anyway, the efficiency of antiviral drugs to cure COVID-19 infection in children is still not investigated (Table 1).

Table 1: *Recommended treatment for COVID-19 in children.*

Breathing and airway	**Other support**	**Infectious disease**	**Experimental treatment Not yet supported by the literature.**
Oxygen supply	Caloric intake (for a review of nutritional interventions	Antibiotics when there are bacterial superinfections	Interferon-alpha
Inhalations	Water and electrolyte supply/ balance		Lopinavir/litonavir
Keeping respiratory tract unobstructed	Anti-pyretic if high fever		Interleukin-6 inhibitors
Regular re-examination of airways			Arbidol, oseltamivir, ribavirin and other anti-influenza drugs
Non-invasive/ invasive respiratory support/ mechanical ventilation including ECMO			Glucocorticoids
Fluid resuscitation, vasoactive drugs			Immunoglobulin
			Traditional Chinese medicine

Management

Discharging recovered children from hospital can be made based on three criteria if meets satisfaction. Normal body temperature for at least 3 days; improvement of the respiratory system and finally a clue of negative COVID-19 tests. There is not yet any evidence available with regards to essential faecal-oral route transmission and one of the most important steps prevent the spread of the disease is by hindering transmission of the disease.

Closure of nurseries and primary schools made children much upset and influenced their psychological, mental and physical health which includes longer screen time, bad uncomfortable sleep, unhealthy food intake that caused obesity and disturbances of cardiorespiratory fitness as reviewed by Wang and colleagues. Away from COVID-19, a study revealed that children quarantine and isolation measurements due to whatever reason (medical, health-related issue or dilemma ... etc) might put these children at risk of post-traumatic stress illness (information and data collected based on screening, focus groups as well as interviews from 398 families), reviewed by Sprang and Silman[6].

Are children immune?

This question is part of the title of this review article which needs attention. It is a fact that COVID-19 clinical symptoms tend to be mainly milder and less severe in children than any other age group. But why?

There are many reasons and theories to interpret this phenomenon which include the following items:

- Children and adults' immune systems are not the same in terms of anatomical, physiological and functional characteristics which results in different responding styles to multiple microbes and viruses.
- Added to above item, there are additional differences between children age groups, i.e. neonates, infants, kids, young and preschool children, as well as teens do not have the same immune system, therefore each responds in a

different manner to any invasive pathogen. In addition, the immune system develops, changes and progress dramatically through different age groups starting from infants, neonates and babies to children and this is the theory of evolution.

- Maternal immunity thought to play a very important role in supporting and boosting the immune system of newborns and infants. Maternal immunity represented by presence antibodies' titers against different microbes and viruses including SARS-CoV-2 virus.
- Qualitative diverse response to COVID-19 has been reported in children more than that in adults. Also, children commonly hold viruses in the mucosal layer of respiratory system (lungs and upper and lower pathways), therefore these viruses may act against SARS-CoV-2 virus through a competitive defense mechanism. Therefore, this agrees with the published data that support the idea of presence a connection between viral load and SARS-CoV-2 virus severity.
- One of the most accepted theories to interpret why children are immune and contract mild COVID-19 disease is that the angiotensin-converting enzyme (ACE) 2 receptor is less or not mature in children by comparison with adults. This ACE 2 receptor is essential for viral attachment and it is expressed less or not in the lung and intestines, but not in the immune cells[1].
- ACE inhibitor medications or ACE blockers cause higher rates of ACE2 expression. Both medicines were considered very commonly used for adults to treat hypertension and this is very rare in children.
- In general, children are less susceptible to severe acute respiratory distress syndrome (ARDS), impaired heart malfunction and decease which are quite common in adults.
- Administration of MMR vaccine (Measles, Mumps, and Rubella), and/or BCG vaccine (Bacille Calmette-Guérin) might give children relative protection against COVID-19 disease and this is one of the controversial theories which still needs an evidence.
- Children do not smoke, thus fresh functional lung and upper respiratory pathways are stronger and much resistant to SARS-CoV-2 virus or any other respiratory viruses in contrast to adults who smoke.
- Children may have immunity acquired from the four corona viruses (HCCoV-229E, HCCoV-OC43, HCCoV-NL63, HCCoV–HKU1) that infect humans with simple cold (cross immunity). The immunity they acquired from light viruses gives them immunity against harmful SARS-CoV-2[2].
- Presence of SARS-CoV-2 neutralizing antibodies elicited by prior exposure to common cold coronaviruses. Up to 60% of healthy children /teenagers showed some cross reactivity relative to about 6% of adults.
- Children are new to vaccinations and these vaccinations may give them active immunity during childhood.
- Measles vaccine gives immunity to the first SARS virus in experimental animals.
- Children are more able to produce t2 immune cells in abundance and it may be the reason to protect them from SARS-CoV-2.

Lessons extracted from this extensive review

The lessons can be summarized by the following points:

- COVID-19 causes mild disease in children (compared to adults), which is mostly asymptomatic, undiagnosed or even miss-diagnosed. This was supported by Li and colleagues who found that 86% of Chinese children were not properly diagnosed or not documented and these children were the risky source of transmission to the aged and immunocompromised people. Children are the "invisible" or "hidden" carriers of COVID-19 disease[4].
- The reason why children are more resistant to COVID-19 than adults might be attributed to the immaturity (or less maturity) of angiotensin-converting enzyme (ACE) to which SARS-CoV-2 S protein binds, and that the immune system of children undergoes considerable alterations while growing from neonates to adults. Therefore, children are immunologically much protected and immune against COVID-19.
- Clinically, prevalence of COVID-19 disease in children was recorded in low rates, only 2% positive cases in China, 1.2% of positive cases in Italy, and 5% positive cases in USA.
- There is no comorbidities of COVID-19 disease in children and the morbidity rates are very rare mainly linked to other serious diseases such as leukemia.
- Inflammatory markers in COVID-19 positive children are extremely low. However, elevated levels of procalcitonin were attributed to a few severe infection with COVID-19 in children as well as increased interleukin-6 (IL-6). Interestingly, it is important to report that antiviral drugs such as chloroquine and remdesivir works as IL-6 inhibitors.
- Lymphocytopenia is as low as 3.5% in children positive to COVID-19 in a study done on 171 kids [unlike adults which reached 83.2% in a study done on 1099 adults][5].
- Children do not smoke at all. Their lungs are fully functional and healthy, and this reason may interpret the low incidence of COVID-19 in children [unlike adults who smoke. Risk factors of smoking was reviewed by Vardavas and Nikitara who explained how the smokers developed doubled much severe clinical symptoms than non smokers].
- SARS-CoV-2 virus does not transmit from the mother to the baby which means no intrauterine route of transmission, no vertical transmission except one case report as well as the virus does not transmit through milk from breast feeders to their babies. All these findings were recorded in a review study on 9 pregnant women tested positive to COVID-19.
- A cohort study of 120 neonates born to mothers positive for SARS-CoV-2 at the time of delivery found no cases of virus transmission, even after 2 weeks of breastfeeding and skin to skin contact with appropriate hygiene precautions.

- To prevent your neonates from contracting COVID-19, Chinese neonatologists, pediatricians and obstetricians outlined the steps you should follow to prevent your newborns and babies from being infected by COVID-19.

Conclusion

It could be concluded that children are less susceptible to COVID-19 disease than adults. Also, symptoms of COVID-19 disease are less severe in children than in adult population. In addition, very severe disease of COVID-19 infection in children may result from coincidence of Kawasaki diseases and SARS-CoV-2 in the same child host. With regards to transmission, no evidence suggesting vertical transmission (intrauterine) except one case report or through breast milk of SARS-CoV-2 virus. Children are the dangerous silent transmitters of COVID-19 infection among families especially elderly members. Although most of children with positive COVID-19 test are asymptomatic or mildly symptomatic, but still studies recorded some of them as severely infected mainly those who had some other health issues. Health care providers should be aware of other corona linked diseases such as Kawasaki disease which was recorded in some children. Collecting data from healthy and COVID-19 recovered children may support the literature in establishing new and evidence-based guidelines regarding approach and management of these patients as well as the epidemiological status about the nature of immune response resulted from the vast majority of children both infected and exposed. Social distancing between children is very difficult to be maintained because of their growing social behavior and tendency to play around with their friends and family members most of the time. We, the authors of this paper, declare that this review article has been written and revised by the authors and the data collected from all the publications in the field of pediatrics with regards to COVID-19 (a huge work).

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