ASIAN PAEDIATRIC PULMONOLOGY SOCIETY

Paediatric COVID 2022 – the ways forward in Asia

(Highlights from the APPS COVID webinar on 15 June 2022)

Introduction

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A webinar on paediatric COVID was held on 15 June 2022 with 170 participants from 13 countries. The webinar was sponsored by an unrestricted grant from Sinovac. An online survey (Appendix 1) right after the presentation was also done with 87 participants from 12 countries allowing a broad representation from all over Asia. The results were as follows.

The majority, defined as >75% of respondents, supported vaccinating children less than 5 years old and pregnant women. Majority of respondents did not observe a higher mortality or more severe disease with the Omicron variant in the children infected with SARS-CoV-2 in their countries. Controversial issues with no majority agreement include lifting of all social restrictions after the population vaccination rate has reached a pre-defined level and healthy adults to take the 4th shot of COVID vaccine. Multisystem inflammatory syndrome in Children (MIS-C) as a complication of COVID requires further study as 37% reported a lower prevalence than that reported in the USA and the UK and 43% reported no data available.

COVID-19 pandemic: zero tolerance or to live with it

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Since the beginning of 2020, COVID-19 has infected more than 500 million people with more than 6 million deaths around the world. Before vaccines or anti-viral drugs have been developed, the global strategies have been directed in minimizing the number of infections by various public health measures including massive increase in testing, tracing of contacts, quarantine, border control, and varying degrees of social distancing. The most extreme form of reduction of contact between people was the use of lockdown. Because of a high percentage of asymptomatic infection and the existence of many natural reservoirs for the coronavirus, it is highly unlikely that we will be able to eliminate the virus from human in the near future. The strict measures used in many Asian countries such as China were associated with a very low number of infections and death compared to many countries in Europe and Americas. Such seemingly dichotomous approaches have been termed 'zero tolerance' and 'to live with the virus'. Countries in Europe and America put in enormous resources for development of vaccines and anti-viral treatments while the degrees of restrictions were very mild compared to the 'zero tolerance' approach as in China. If one examines the COVID-19 mortality around, it is obvious that the early adoption of 'to live with the virus' approach has resulted in dramatically high mortality but can allows for opening up the society earlier. Perhaps the example of Singapore provides an excellent example of 'zero tolerance' at the beginning. After reaching a high vaccine coverage, gradual opening was possible without excessive increase in mortality. COVID-19 will not be the last viral infection encountered by mankind. We must prepare for new and emerging infections to use the approach that minimizes morbidity and mortality with the least interference of normal life of the citizens. A coordinated fashion from restrictions to relaxation hopefully will achieve such goals.

Research progress of COVID-19 in children — from clinical features to immunology

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In early 2020 when COVID-19 just broke out, there were rather few pediatric cases and more than 60% of them were moderate cases. In the latest wave with the main circulating strain being the Omicron variant, over 90% were asymptomatic or mild cases which needed little or no medical intervention. Studies from other medical centers also show children to be less affected by COVID-19, with Omicron being significantly less pathogenic.

SARS-CoV-2 virus has complex strategies for infection, such as inhibiting the synthesis of host protein, modifying its RNA to evade pattern recognition receptors of the innate immunity to escape immunological surveillance and to bypass multiple innate immune activation pathways. Despite multiple mutations in the spike protein, ACE2 and TMPRSS2 are still the two most important receptors in the SARS-CoV-2 virus' entry to host cell.

On the one hand, the Omicron variant replicates significantly faster in the upper airway and bronchial epithelium compared with its predecessors. This accounts for the increased transmissibility of the Omicron variant. On the other hand, new evidence shows that children have significantly stronger local interferon production in the upper airway epithelium and higher T cell receptor repertoire diversity decreasing the contagiousness of Omicron.

According to current research on children and adult vaccinees, two doses of either ChAdOx1 or BNT162b2 vaccines offer limited protection against symptomatic COVID-19 infection caused by Omicron. A third booster shot in adults substantially raises the effectiveness against severe outcomes. Three-dose-vaccination may be the optimal plan for now. Vaccine effectiveness against BA.1 and BA.2 showed no statistical difference. With that said, data from children are still very limited and further investigations are needed urgently.

Vaccines targeting specific variants and new medications to treat COVID-19 infections are being developed. With all the hard work being put into fighting against COVID-19, we hope to see an end to the COVID pandemic in the near future.

COVID vaccination — filling the gap

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Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has been causing a global pandemic since late 2019 when it was first discovered in China. Worldwide there has been 544 million cumulative cases confirmed with the infection and 6.4 million deaths reported. The reported incidence in children is lower than in adults accounting for about 5% of total cases. SARS-CoV-2 is believed to be milder in children with many being either asymptomatic or having mild disease presenting like the common cold.

However, some of these children do require admission to hospital and some need intensive care. From a prospective observational cohort of children admitted for SARS-CoV-2 infection in the United Kingdom, infants were most likely to be admitted, and children 10-14 years old as well as neonates were most likely to require intensive care. The main reason for intensive care admissions for these 10-14year old children were for multi-system inflammatory syndrome. This newly described syndrome referred to as multisystem inflammatory syndrome in children (MIS-C) has been observed occurring shortly after COVID-19 infection. This condition can be severe but relatively uncommon, with an estimated incidence of 2 per 100,000 children less than 21 years old. Complications that can arise from MIS-C include myocardial dysfunction, shock and respiratory failure. Another complication following COVID infection is Long COVID or Post-COVID-19 Syndrome. Long COVID is defined as persistence of symptoms after COVID-19 infection. The prevalence of symptoms is about 35% in patients treated for mild COVID-19 but is around 87% among cohorts of hospitalized patients.

Mortality from COVID-19 infection do occur in children even though they account for only about 0.4% of total deaths. The highest mortality occurred in neonates and infants. This was due to infection in the pregnant women which led to an increased perinatal morbidity and mortality in the neonate, especially if the neonate became infected as well at birth. These neonates had an increased risk of admission into the neonatal intensive care and increased perinatal morbidity including bronchopulmonary dysplasia, hypoxic-ischemic encephalopathy, sepsis, intraventricular haemorrhage and necrotizing enterocolitis.

New variants have emerged over the two years of the pandemic. From the original strain, there has been several waves of infections with the alpha, beta, delta and omicron variants. With each variant, the transmissibility has changed with the later variants being more transmissible with higher secondary attack rates. This has an impact on infection rates to children as with higher household secondary attack rates, more children are being infected. However, the severity of the disease also varies and it has been demonstrated that the Omicron variant though being more transmissible, did not lead to an increase in intensive care admissions or the need for mechanical ventilation.

Several vaccines have been developed against the SARS-CoV-2 virus, the most effective vaccines being the mRNA vaccines. For children, the main vaccine approved for use from 5 years and older has been the Pfizer BNT162b2. Several studies have shown the efficacy of vaccination in reducing infection rates in the vaccinated individual as well as household secondary attack rates. A pooled meta-analysis on SARS-CoV-2 vaccines demonstrated a vaccine efficacy of 92.7% against COVID19 infection after 2 doses. However, with each new variant, the efficacy of the vaccine has decreased but vaccination was still effective in protecting against

severe disease and hospitalizations in children and adolescents even through the delta-predominant period. It has been demonstrated that immunity wanes with time whether from natural infection or with vaccination. Immunity is improved with a booster dose of the vaccine and has been demonstrated to be effective against the omicron variant.

There has been a lot of concerns with the use of the mRNA vaccines and especially the reports of myocarditis after the 2nd dose in adolescent males. It was found that though there was an increased risk of myocarditis in adolescent males after the 2nd dose of the mRNA vaccine, estimated 4.3 myocarditis cases per million doses of vaccine, having COVID-19 infection had a much higher incidence of myocarditis with an estimated 450 per million cases. Thus vaccination actually reduced the risk of myocarditis by reducing infection risk. Vaccination after COVID infection also reduced the odds of Long COVID developing by 12.8% after the first dose and 8.8% after the 2nd dose.

To protect the neonates who cannot be vaccinated, it has been demonstrated that maternal vaccination during pregnancy is effective in reducing hospitalizations in infants <6 months old from COVID infection, and especially when given during late pregnancy. Maternal antibodies were also found in maternal breastmilk in vaccinated mothers. Antibody levels were higher in vaccinated pregnant women compared to those who had natural infection from COVID-19. Maternal vaccination can be given at any time during pregnancy and has not been shown to increase the risk of congenital foetal anomalies.

So is COVID vaccination safe for children? Several reports on safety have been published which have shown that the mRNA vaccines are safe and well tolerated. Majority of children report mild symptoms with only about 2.3% being considered more serious adverse events such as raised troponin levels and chest pain. Myocarditis was extremely rare in children outside of the adolescent age.

The SARS-CoV-2 pandemic has had an impact on children besides that of the infection. The pandemic has affected those in the lower socioeconomic strata much more as it had caused a disruption in health services and other childhood vaccinations. Deaths in the family, unemployment and food insecurity all have an impact on the child and their mental health. Several studies looking at the prevalence rate of depression and anxiety have shown a doubling form pre-pandemic years during the pandemic. Increased suicide rates have been reported especially in adolescents during the pandemic in many States in the USA. With the relaxation of the COVID social distancing rules in many countries, co-infections with other respiratory viruses are likely to occur. This may increase the risk of severe disease when co-infections occur.

In summary, vaccination in children can reduce the risk of COVID infection and its complications. To protect neonates, maternal vaccination is advocated. COVID vaccination is generally safe and well tolerated. The risk of myocarditis from vaccination is small compared to myocarditis form COVID infection itself.

COVID-19 in children: therapeutic options

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The evidence base for therapeutics for COVID-19 is evolving. Multiple therapeutic agents have been tried for varying severity of illness since the pandemic started. In the beginning of the pandemic, drugs were chosen by pharmacologic properties, in-situ evaluations and efficacy of molecules in other similar viruses. Symptomatic COVID-19 in children is less common, less severe and majority are asymptomatic or mildly symptomatic. Less than 1% required PICU care. Severe illness in children occurs in those with co-morbidities. Majority of RCTs included patients above 18 years of age. Drug therapies were extrapolated from experience in patients above 18 years of age.

Evidence for therapy for COVID-19 are inadequate as most RCTs enrolled patients >18 years of age. Drugs (Hydroxychloroquine, ritonavir-lopinavir, ivermectin) were found to be of no benefit in adult patients and may not be considered in children. Drugs found to be of benefit in adults may be considered after checking for potential side effects in children due to differences in the pharmacokinetics.

As children are less likely to develop severe illness, clear evidence of safety and efficacy in children need to be decided for by individual cases. Children with mild disease but are at risk of severe disease, may use the following drugs:

1. Nirmatrelvir-ritonavir: Children >12 years and >40 Kg: 300 mg nirmatrelvir plus 100 mg ritonavir PO BID x 5 days. Initiate as soon as possible after COVID-19 diagnosis and within 5 days of symptom onset. Children <12 years: safety/ efficacy/ doses not yet established.
2. Remdesivir: Initiate as soon as possible after diagnosis of symptomatic COVID-19 has been made and within 7 days of symptom onset. Weight ≥40 kg: 200 mg IV on Day 1, then 100 mg IV on Days 2-3 (ie, 3 consecutive days). Weight 3-40 kg: 5 mg/kg IV on Day 1, then 2.5 mg/kg IV on Days 2-3.
3. Sotrovimab: Administer as soon as possible (not later than 7 days) after onset of symptoms. ≥12 years and weight ≥40 kg: 500 mg as a single IV infusion.
4. Casirivimab-imdevimab Administer as soon as possible (not later than 10 days) after positive results. Make sure that the variant is likely to be responsive (Delta). Dose ≥12 years and weight ≥40 kg: 600 mg of casirivimab and 600 mg of imdevimab together as a single intravenous infusion.

Children having Severe/critical disease should be considered for the following treatment.

1. Dexamethasone in those who require high-flow oxygen, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). Not routinely recommended for children who require only low levels of oxygen support (i.e., via a nasal cannula only).

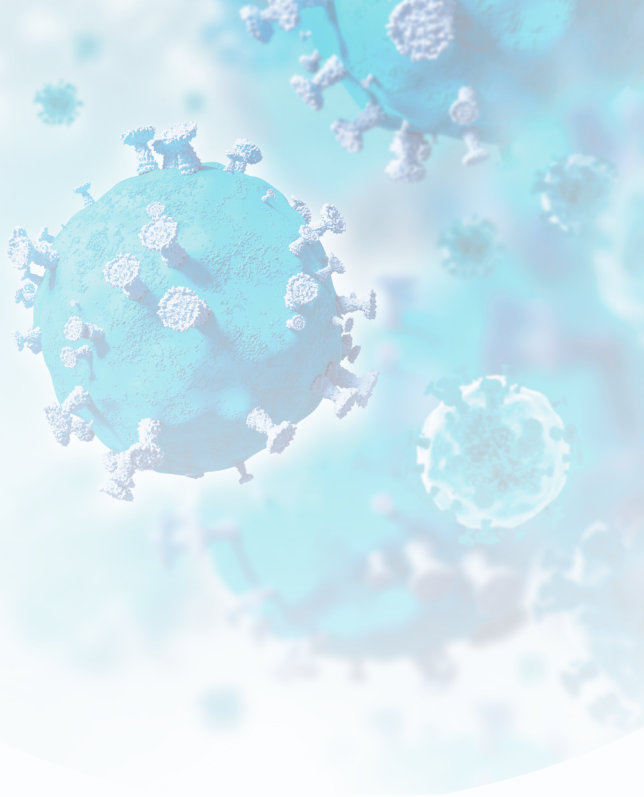
   Safety and efficacy dexamethasone in severe COVID-19 in immunocompromised children has not been evaluated. It may be harmful and therefore should be considered only on a case-by-case basis.

Dose of dexamethasone: 0.15 mg/kg/dose (maximum dose 6 mg) once daily for up to 10 days. If dexamethasone is not available, alternative glucocorticoids such as prednisone, methylprednisolone, or hydrocortisone can be considered.

2. Anti- IL 6 drugs: Tocilizumab may be used in hypoxic respiratory failure. The dose for weight <30 Kg: 12 mg/kg IV infusion single dose and weight >30 Kg: 8 mg/kg IV infusion single dose.

   Sarilumab doses have not been established for children.

Therapy under development:
A combination monoclonal antibody (Tixagevimab–cilgavimab) for treatment of patients hospitalised with COVID-19 has shown that it does not change the outcome of time to sustained recovery but was safe and mortality was lower. No study on children below 18 years and may have to wait for more trials.



Conclusion

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COVID-19 is the most recent global pandemic that the world has encountered which has resulted not only in great losses of lives around the world but has disrupted the lives of many. It highlights the need to be prepared for future pandemics and the approaches that each country takes has a profound impact on the lives of their citizens. It is also the first time that vaccines have been developed so quickly that it can be used during an ongoing pandemic. This advance in technology has saved the lives of many and has had a major role in allowing for a faster return to 'normalcy' in many countries. However, this pandemic also highlighted the fact that vaccine hesitancy and mistrust in new technologies exist which has hampered the impact of vaccination on the disease. A better understanding of the pathophysiology of the infection has allowed for a more scientific approach to management. Most of the currently available anti-viral drugs have been used and tested only in adolescents and adults. For severe disease in younger children, dexamethasone and anti-IL 6 drugs such as Tocilizumab may be used. Paediatricians and respiratory paediatric pulmonologists remain in the forefront for managing these children with COVID-19 infection.

Appendix 1

1. **Will you vaccinate pregnant women?**
   Yes: 61 (84%) No: 12

2. **Will you vaccinate children less than 5 years old?**
   Yes: 65 (84%) No: 12

3. **Would you recommend healthy adults to take the 4th shot of COVID vaccine?**
   Yes: 38 (66%) No: 20

4. **Do you observe a higher mortality or more severe disease with Omicron variant in the children infected with SARS-CoV2 in your country?**
   Yes: 6 (9%) No: 60

5. **Do you support lifting all social restriction after the population vaccination rate has reached a pre-defined level?**
   Yes: 46 (67%) No: 23

6. **Are you using therapeutic agents for children with COVID?**
   Yes: 33 (46%) No: 38

7. **If you are using therapeutic agents for children with COVID, please identify them.**
   Systemic steroid: 32
   Ramdesevir: 12
   Nirmatrelvir-ritonavir: 4
   IL 6 blocker: 2
   Monoclonal antibodies: 2
   Others: 10

8. **What is the prevalence of MISC in your countries?**
   Same as that reported from the US/UK: 9 (18%)
   More than that reported from the US/UK: 1 (2%)
   Less than that reported from the US/UK: 18 (37%)
   No data: 21 (43%)
   Do not know: 19