Coronavirus Disease 2019 (COVID-19) Vaccination for Children: Position Statement of Indian Academy of Pediatrics Advisory Committee on Vaccination and Immunization Practices

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Justification: Data generated after the first wave has revealed that some children with coronavirus 19 (COVID-19) can become seriously ill. Multi-inflammatory syndrome in children (MIS-C) and long COVID cause significant morbidity in children. Prolonged school closures and quarantine have played havoc with the psychosocial health of children. Many countries in the world have issued emergency use authorisation (EUA) of selected COVID-19 vaccines for use in children. In India, a Subject Expert Committee (SEC) has recommended the use of Covaxin (Bharat Biotech) for children from the ages of 2-18 years. The recommendation has been given to the Drugs Controller General of India (DCGI) for final approval. **Objective:** To provide an evidence-based document to guide the pediatricians on the recommendation to administer COVID vaccines to children, as and when they are available for use. **Process:** Formulation of key questions was done by the committee, followed by review of literature on epidemiology and burden of COVID-19 in children, review of the studies on COVID vaccines in children, and the IAP stand on COVID-19 vaccination in children. The available data was discussed in the ACVIP focused WhatsApp group followed by an online meeting on 24 October, 2021, wherein the document was discussed in detail and finalized. **Recommendations:** The IAP supports the Government of India's decision to extend the COVID-19 vaccination program to children between 2-18 years of age. Children with high-risk conditions may be immunized on a priority basis. The IAP and its members should be a partner with the Government of India, in the implementation of this program and the surveillance that is necessary following the roll-out.

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Children of all ages are susceptible to coronavirus disease 2019 (COVID-19). Almost 70% of SARS-CoV-2 infections in children are asymptomatic. When symptomatic, the symptoms are usually mild and critical illness and hospitalizations are extremely rare. Children account for ~1.5% of all COVID hospitalizations. Studies done in the initial stages of the pandemic suggested that children do not participate significantly in the chain of transmission [1]. According to the National Centre for Disease Control data as of 26/2/21, 3.9% of cases occurred in the 0-10 year age group and 7.99% in the 11-20 year age group [2]. The morbidity and mortality of COVID-19 in children are much lower than that seen in adults and the elderly [1]. Thus, the assessment of benefit vs risk of COVID vaccination in children is complex.

OBJECTIVES OF COVID VACCINATION IN CHILDREN

Reduction in Disease Incidence, Morbidity and Mortality

The surge in COVID-19 cases following the rapid spread of more transmissible variants has resulted in a steep increase

in the number of cases and hospitalization rates in children in many countries [3,4]. This may be amplified if more transmissible variants predominate in the coming months. This further underscores the need for COVID-19 vaccination in children.

In USA, during the peak of the Delta wave, the weekly hospitalization rate among children aged 0-4 years increased nearly 10 times. Nearly one third of adolescents aged 12-17 years hospitalized with COVID-19 during March 2020-April 2021 required intensive care, and 5% of those hospitalized required endotracheal intubation and mechanical ventilation [3]. The current surge of COVID-19 in UK, is being primarily driven by high levels of infection in school-age children, with more than a third of all recent cases being reported in those under 15 years of age [4]. In USA, during the period from June 20 to July 31, 2021, the hospitalization rate among unvaccinated adolescents (aged 12-17 years) was 10.1 times higher than that among fully vaccinated adolescents, underlining the utility of vaccines in reducing the morbidity and mortality associated with COVID 19 in adolescents [3].

Age distribution data from India revealed that children in the age group 0-10 years accounted for 3.28% of all cases, and individuals 11-20 years accounted for 8.03% of all cases in the first wave. Corresponding figures in the second wave were 3.05% and 8.57%, respectively [5]. Although the proportion remained almost similar in both waves, the second wave involved almost twice the number as in the first wave, with a consequent increase in the absolute numbers of children needing hospitalization and ICU care.

In a study conducted in Tamil Nadu and Andhra Pradesh, in the pediatric age group, the case fatality rate was highest in the 0-4 years age group [median (IQR) 0.16% (0, 0.36)], which was comparable to that observed in the 18-29 years age group but lower than that observed in the older age groups [6].

A systematic review and meta-analysis of severe COVID-19 infection and pediatric comorbidities concluded that children with comorbidities have a higher risk of severe COVID-19 and associated mortality than children without underlying disease [7]. Severe COVID-19 was present in 5.1% of children with comorbidities as compared to 0.2% in children without comorbidities. Children with comorbidities had higher risk of severe COVID-19 [RRR 1.79 (95% CI 1.27-2.51)] and COVID-19-associated mortality [RRR 2.81 (95% CI 1.31-6.02)] as compared to healthy children. Children with obesity had a relative risk ratio of 2.87 (95% CI 1.16-7.07) [8].

In a multi-centric study done in five major institutions across India, 44% of 402 children had some underlying comorbidity, malignancy (leukemia and other malignancy) followed by cardiac disease was the most common underlying comorbidity. In this study, children with underlying disease had an odds ratio of 8.85 (6.07-12.91) for moderate-severe disease [9].In a study done from a dedicated COVID-19 hospital in India, 30 out of 100 admitted children had underlying comorbidities, 60% had severe disease, and the presence of underlying comorbidities and the number of comorbidities were significant predictors of severity of the disease [9].

A review of cases till December, 2020, revealed that 91.5% of COVID-19 deaths were reported from low- and middle-income countries (LMICs), and 83.5% of reported pediatric Covid-19 cases from all included countries were from LMICs. The pediatric deaths/1,000,000 children, case fatality rate (CFR) and ICU admission/1,000,000 children were significantly higher in LMICs than in high-income countries [10]. This data underscores the greater need for vaccination of children in LMICs, for the prevention of COVID-19.

Prevention of Complications

Multi-Inflammatory syndrome in children (MIS-C) first reported in April, 2020, is generally reported during the weeks following a peak in COVID-19 disease. MIS-C may need hospitalization and ICU care in addition to expensive medications [11]. The burden of MIS-C in our country has previously been documented [12-14]. By preventing SARS-CoV-2 disease, COVID-19 vaccines may prevent MIS-C.

Some patients who have recovered from COVID-19 may experience persisting symptoms after the resolution of acute disease [15], the so-called long COVID. Estimates in the literature range from 0-27% [16, 17]; however, similar literature regarding long COVID-19 in children is not available from India. Similar to MIS-C, COVID-19 vaccines may prevent long COVID; although, currently there is no data available to support this statement. A report of three children with subacute neuropsychiatric impairment following COVID-19 and the detection of intrathecal anti–SARS-CoV-2 antibodies also raises the spectre of direct involvement of the central nervous system by the SARS-CoV-2 virus [18].

Reduction of Transmission

School-age children and adolescents can efficiently transmit SARS-CoV-2 to household members, which may lead to hospitalization of adults who are secondarily infected [19]. Recent data suggest that adolescents contribute significantly to household transmission, and rates of transmission by this age group (11-18 years) may be higher than that in adults [20] The highest probability of transmission, given exposure, in an Indian study was shown to be within case-contact pairs of similar age, and

this association was strongest among children aged 0 to 14 years and among adults aged ≥65 years [6].With reopening of schools, outbreaks have been reported from all over the world. High attack rates of 44% have been reported at a youth camp in Georgia, USA suggesting that SARS-CoV-2 can transmit readily in young populations [21].

Vaccination of children may reduce transmission. Some of the COVID vaccines in use have been shown to reduce infection and thus transmission. However, during the Delta surge, vaccinated and unvaccinated individuals had similar viral loads in the nasopharynx [22].

Prevention of psychosocial issues due to prolonged school closure: The COVID-19 pandemic has resulted in drastic changes in the lives of children and adolescents. Restrictive measures, such as nationwide lockdown, school closures, online lectures, and quarantines, have resulted in significant adverse psychological effects on children, and adolescents [23-25]. COVID-19 associated obesity has become a real issue [26]. Children are losing out on their development and learning opportunities, including nutritional deficiencies and delayed immuni-zations. Vaccination and other measures to reduce community transmission may help to avert some of these indirect effects of the pandemic. Although vaccinations and school reopening are not linked, parents will be more confident about sending their vaccinated children to school.

Herd immunity: Herd immunity against COVID-19, either through vaccinations or natural infection, is the logical way to terminate the pandemic. Initially, a population immunity of 65-70% was estimated as the threshold for herd immunity [27]. However, ongoing vaccine hesitancy and the circulation of more transmissible variants have raised the bar for achieving herd immunity. The goal of attaining herd immunity can never be achieved if children, who constitute 20-35% of the population, are excluded from the vaccination process. If unprotected, children could act as reservoirs of infection and may contribute to the rise of variants in the future.

Potential risks of vaccinating children: Myocarditis has been recognized as a rare complication of mRNA vaccines against COVID-19, especially in young adult and older adolescent males [28]. Of the 8.9 million U.S. adolescents aged 12-17 years, who had received Pfizer-BioNTech vaccine, up to July 16, 2021, there were 9246 adverse events reported, of which 9.3% were serious adverse events, including myocarditis (4.3%). It should be noted that most of these cases were mild and resolved spontaneously. The risk, if any, in the younger age groups is unknown.

Vaccine-induced thrombotic thrombocytopenic purpura (VITT) is a rare but potentially life-threatening adverse effect following adeno-vectored COVID vaccines administered to those >18 years [29]. As this vaccine has not been administered below 18 years of age, the risk, if any, in the younger age groups is unknown.

There is also a theoretical risk of COVID-19 vaccines triggering systemic, dysregulated inflammatory response (MIS-C). Post-vaccination surveillance data, with the mRNA vaccines, has not detected any case of MIS-C following vaccination.

VACCINES AVAILABLE FOR PEDIATRIC POPULATION

Internationally, only the Pfizer and the Moderna vaccines have received emergency use authorization (EUA) for use in children between 12 and 17 years of age. The Pfizer vaccine has received EUA for use in children 5-11 years. In India, ZyCov-D (Zydus Healthcare) has received EUA in the age group 12-17 years, while Covaxin (Bharat Biotech Ltd) has received EUA for 2-18 years.

BNT162b2 (Pfizer) Vaccine

In the 12-15-year-old cohort, the geometric mean titer (GMT) of the serum-neutralizing antibodies one month after BNT162b2 dose 2 was higher as compared to the 16 to 25-year- old cohort. This established the non-inferiority and a greater response in adolescents than in young adults [30]. The vaccine efficacy (VE) was 100% (78.1 to 100) in the efficacy trial, with 16 cases in the placebo group and none in the vaccine group [30].

EUA was granted by the USFDA, on May 10, 2020, for use in children 12-15 years of age. This vaccine is now in use in children 12-15 years in European countries, Israel, UK, Dubai, UAE, Singapore, Japan, Philippines, Canada, and Chile. Of the 8.9 million doses of the vaccine administered to adolescents 12-17 years (as of July 16, 2021), serious adverse effects were noticed in 9.3% children. Among the serious adverse effects, myocarditis accounted for 40.3% [24]. The overall rate of myocarditis was 4.3% [31]. Trials for children 6 months to 11 years of age, are ongoing. Children ages 5 to 11 years will receive two-doses of 10 µg each while children less than age 5 years will receive a 3 µg dose.

The SARS-CoV-2–neutralizing antibody GMT in the 5-11 years was 1197.6 (95% CI, 1106.1, 1296.6), as compared to the 16-25 years cohort [1146.5 (95% CI: 1045.5, 1257.2)], proving non-inferiority in the 5-11 years cohort. The reactogenicity and adverse effects profile was similar to that observed in the 16-25 years age group [32]. On 29 October, 2021, EUA was granted by the USFDA for use in children 5-11 years.

mRNA-1273 vaccine (Moderna vaccine)

Adolescents aged 12-17 year received two doses of 100 µg /dose of Moderna vaccines, at 0-28 days. The GMTs of

neutralizing antibodies was 1401.7 (1276.3 to 1539.4) compared to levels of 1301.3 (1177.0 to 1438.8) in young adults, establishing non-inferiority [33]. The VE against COVID-19, 14 days after second dose, in the per protocol cohort was 100% (28.9 to NE: not estimated). On 4 September 2021, this vaccine was granted EUA by the USFDA, for adolescent 12-17 years.The phase 2/3 study (KidCove), is being done in three age cohorts, 6-12 years, 2-6 years and 6 months to 2 years, in two parts. Part 1 is a dose-escalation study. In Part 2, participants will receive two intramuscular injections of mRNA-1273, on 0-28 days, at the dose selected from Part 1. This study involves 13275 participants enrolled from 79 centres across USA [34].

Gam-COVID-Vac (Sputnik)

This vaccine is being studied in 12-17 years in two stages, in stage 1 (Phase I-II) 100 volunteers will be included in two dosing groups and in stage 2 (Phase III) 3000 volunteers will be divided in two age groups, 12-14 years and 15-17 years. Recruitment is ongoing in this trial [35].

Covaxin in Children

A Phase II/III, open-label study was conducted in healthy volunteers in three age groups, 2-6 years, 6-12 years and 12-18 years, with 175 subjects in each group. Each participant was administered two doses of Covaxin (6 μg/0.5 mL) on 0-28 days [36]. Based on data provided by the company to the Special Expert Committee, the vaccine was granted EUA by the Government of India, on October 12, 2021 for use in children 2-17 years. So far, no data is available in the public domain and Drugs Controller General of India (DCGI) approval is still pending.

ZyCov-D

This vaccine has been granted EUA for use in children 12-17 years. The phase 3 efficacy trial done in 28000 subjects included 1400 subjects between 12-17 years of age. No severe side effects related to the vaccine were seen in the 12-18 years age group. The overall vaccine efficacy has been reported as 66.6% [37]. The company has received approval for phase 3 studies in children 2-17 years [38].

Covovax

Covovax, a subunit vaccine developed by Novavax received DCGI approval for phase 3 studies in children [39]. A total of 920 eligible children of ≥2 years of age will be enrolled in this study. The schedule is two doses on days 0-22.

Corbevax

Corbevax, an adjuvanted subunit vaccine by Biological E Limited, had received permission from the DCGI to conduct Phase 2 and 3 clinical trials on children aged 5-18 years [40].

J & J Vaccine

Johnson and Johnson has applied to the Indian drug regulator to conduct a study of its COVID-19 vaccine in adolescents aged 12-17 years [41].

IAP-ACVIP RECOMMENDATIONS

1. The IAP supports the Government of India's decision to extend the COVID-19 vaccination program to children between 2-18 years of age. Children with high-risk conditions should be immunized on a priority basis, as follows:
   - *i*) high-risk population in age group 2-18 years
   - *ii*) children aged 2-18 years living with high-risk individuals
   - *iii*) all population below 18 years of age (in an age de-escalation manner)

Although the Fourth All-India sero-survey showed a positivity of 57.2% in the 6-9 years age group and 61.6% in the 10-17 years age group [43], it should be noted that antibodies and efficacy decline with time. Studies done with the mRNA vaccines have shown that unvaccinated individuals are more than twice as likely to be reinfected with COVID-19 than those who were fully vaccinated after initially contracting the virus. Moreover, the antibody responses were superior in adults hospitalized with COVID-19-like illness, who had prior vaccination with a mRNA vaccine compared to those with prior natural infection [44,45].

The IAP strongly recommends that its members should be made a part of the process of vaccinating children, either by vaccinating in their clinics or as a part of the government initiative.

2. Pediatricians are well acquainted with cold chain, vaccine administration skills, AEFI (adverse events following immunity) recognition and management, and biomedical waste disposal. They also have the infrastructure to maintain the rigorous protocols for vaccination, as put forth by the regulatory authorities. Their rapport with children and their parents will provide the most reassuring situation for vaccinating the children in the clinics and can lessen vaccine hesitancy and vaccine refusal.

Local and district branches of IAP can be involved in the process to disseminate information, education and communication (IEC) activities via print media, social media, radio and television in local languages. This may be important for better acceptance by the parents of COVID-19 vaccines for children.

Pediatricians and parents have to be convinced about

the safety and efficacy of COVID-19 vaccines in children. Study data has to be provided to the pediatricians and parents before embarking on any COVID-19 vaccination programs for children.

3. The IAP supports a school-based vaccination program, as this is the quickest way to achieve maximum immunization coverage. However, this should not be made mandatory, and the parents should be offered a choice of administering the vaccine to their children, in the schools or in the clinics of their pediatricians.
4. School-based centers should have a medical personnel trained to handle emergencies, nursing and administrative staff, emergency medications and equipment, tie-up with the closest hospital for emergency care, and immediate availability of transport to the referral hospitals.
5. The IAP recommends administering currently available COVID-19 vaccines and other scheduled childhood vaccines, either simultaneously or at any interval between them.
6. The IAP recommends the setting up of an active and passive surveillance mechanism for adverse effects of COVID-19 vaccines. This should include surveillance for any link between COVID-19 vaccines and MIS-C, and other adverse effects observed during long-term follow-up. IAP should be a part of this surveillance mechanism. Children have striking differences in their immunological responses to vaccines as compared to adults. Younger children have a more active immune response that may translate into heightened immunological responses and probably reactogenicity. The link, if any, between dysregulated immune responses e.g., MIS-C and vaccination, should be thoroughly studied in the post-marketing surveillance.
7. In children with acute illnesses, the vaccination may be postponed till clinical recovery.
8. Immunodeficiencies due to drugs or diseases are not contraindications for the COVID-19 vaccines to be rolled out for children. The COVID-19 vaccines approved for children are inactivated vaccines.
9. Studies should be initiated to determine the duration of protection and efficacy against variants. This data will be necessary for booster dose recommendations.
10. The government should prioritize research for safer and more effective COVID-19 vaccines for children.

CONCLUSION

India has the largest childhood immunization program in the world, with a well-established and time-tested vaccination network, including cold chain networks. These can be utilized for the COVID-19 vaccination program. India has sufficient manufacturing capability for the vaccine (more than 2.4 billion doses annually), including surgical disposables such as vials, stoppers, syringes, gauze, and alcohol swabs and adequate storage and transportation of the vaccines. Real-time remote temperature monitoring of 29,000 cold-chain points exists through COVID Vaccine Intelligence Network (Co-WIN) vaccine delivery and E-VIN [42].

The vaccination capacity in India has been established with record immunizations of 7-10 million adults in a day. In a span of nine months, India has immunized over a billion individuals with at least one dose of the COVID-19 vaccine. It becomes more important during a pandemic that scarce resources are used efficiently, balancing the principles of equity and justice. The decision to vaccinate healthy children would depend on the availability of one or more suitable vaccines in the quantities enough to immunize the vulnerable population in our country.

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NEWS IN BRIEF

Effect of mixing the vaccines against Covid-19

Vaccines trigger the immune response by imitating an infection, leading to the generation of the memory T-cells and B-cells. This antibody response gets enhanced with the second dose and boosters leading to the generation of antibody levels which will be protective against future infections.But does this response appear / persist, if the type of vaccine has been changed for the second dose?

In a recently published paper by Com-COV-2 Study Group - a multicentre survey network of nine institutions in the UK, researchers studied the effect of mixing of different COVID-19 vaccines on the antibody response. In this study, 1072 participants were studied where the participants were inoculated with a dose of the Pfizer- BioNTech mRNA (BNT162b2), Moderna mRNA (mRNA-1273), Astra Zeneca (chimpanzee non-replicating adenovirus (ChAdOx1 nCoV-19), or Novavax Matrix M-adjuvanted recombinant S protein (NVX-CoV2373) vaccine after an initial dose of Astra Zeneca or Pfizer. Higher levels of binding and neutralizing antibodies were seen with the second dose of Moderna vaccine after a first dose of Astra Zeneca or Pfizer compared to two doses of either Pfizer or Astra Zeneca.

Findings of the present study, provide the data to support the mix and match of COVID-19 vaccines in primary immunization schedules. This will provides the much needed flexibility required to vaccinate the large unvaccinated population in low income countries.

With the emergence of new variant Omicron, it is the need of hour to vaccinate as many people as possible (*BMJ 07 December, 2021*)

Finally something against childhood dental caries

Exact burden of dental caries in India is not known due to poor awareness among the general public about its long term impact on health affecting the growth, early childhood development, learning and limited published literature. A recent meta-analysis estimated that the approxi-mately 52% of children aged 3-18 years have caries in India.

In the absence of a validated risk determining tool, prevention and screening are the best modalities. Recently, United States Preventive Services Task Force (USPSTF) has recommended that the primary care physicians must prescribe oral fluoride supplements to all asymptomatic children aged 6 months to 5 years, living in areas having lesser than 0.6 ppm fluoride levels (fluoride deficient areas). Use of fluoride varnish containing 5% sodium fluoride is also recommended to all childrenaged 6 months to 5 years after the eruption of primary teeth. These recommendations are beyond the routine dental evaluation and referral to the dental health professionals.

More Indian data is needed before recommendations in Indian context are produced to reduce the potentially preventable burden of dental caries in Indian children.
(*JAMA 07 December, 2021*)

Microfluidics: Future of treatment of Neonatal Jaundice

Neonatal jaundice is the most common morbidity in the first week of life after birth. Almost 60% of term and 80% of preterm babies develop jaundice. Approximately 5-8% of these babies require one or another modality to lower the serum bilirubin levels, in order to prevent neurological damage. Beyond particular levels or in the presence of features suggestive of bilirubin encephalopathy, double volume exchange transfusion (DVET) rapidly lowers the bilirubin levels but in VLBW/ELBW babies it can cause hemodynamic instability.

Researchers at Oregon State University College of Engineering has led to a promising potential therapy for the treatment of neonatal jaundice using microfluidics. Microfluidics is the branch of science which study the behavior of fluids, as they travel through or are confined in microminiaturized devices equipped with channels and chambers. The team has found a simpler and safer alternative to DVET, by treating the patient's blood by circulating it through an external device known as a microfluidic photoreactor. The basic principle is same as that of phototherapy but using the microfluidics helps in lowering the bilirubin at faster rates. Preclinical studies in Gunn rats, using high-intensity light at 470 nm for 4 hours demonstrates a significant reduction in the bilirubin levels without causing an appreciable DNA damage. The rates of bilirubin reduction were similar to those observed with exchange transfusion and on a similar time scale. Mathematical prediction model for the human newborn, suggested that this newer modality will outperform the exchange transfusion at the clinical scale.

Use of microfluidics is a potential promising approach for the treatment of neonatal jaundice, especially in the VLBW/ ELBW, babies without the use of donor blood.
(*Biomicrofluidics 24 November, 2021*)

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