

## COMMENTARY

# COVID-19 vaccination in pediatric cancer patients: A high priority

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Global COVID-19 burden continues to be on rise, affecting every facet of the health care system. The adult population has been severely affected during both waves of the pandemic including cancer patients and immunocompromised hosts who have shown higher susceptibility, morbidity, and mortality.<sup>1-3</sup>

The rate of SARS-CoV-2 infectivity in children has been low but there has been speculation that children will be more affected in future waves.<sup>4</sup> The second wave has done far more damage in countries like India with the severity of viral infection being much greater and the virus affecting more of the younger population. This trend has been observed across many countries.<sup>5,6</sup> A study reported a median of two COVID-19 pediatric cancer cases per institution from a total of 213 institutions across 79 countries, of which 24% of the institutions reported no cases in children.<sup>7</sup> The majority of the children presented with asymptomatic or mild form of infection,<sup>8</sup> but can be COVID-19 positive and can develop Kawasaki-like disease or multi-system inflammatory syndrome in children (MIS-C). Hospital stays and reported deaths are much less than in adults, who often suffer from lower respiratory infection.<sup>6,9,10</sup>

Why are children less affected by SARS-CoV-2? "Trained innate immunity" due to continuous exposure with infectious diseases in early childhood may be one of the reasons<sup>11</sup> apart from the age-related differences in immune response to virus, especially at the nasal mucosal site. Heightened innate immune responses due to frequent respiratory infections and recent immunization to other common infections like influenza, tuberculosis, and so forth are also unique to pediatric group.<sup>12</sup> It is known that S-protein of SARS-CoV-2 binds to host cell ACE2 surface receptor. As children express low levels of ACE2 receptors, they are less prone to infection.<sup>13</sup> Another reason could be increased number of lymphocytes especially NK cells providing immu-

nity against virus.<sup>14</sup> Cumulative innate immunity factors contribute to the differential severity of the disease in children.<sup>15</sup>

Yet, SARS-COV-2 infections in children with cancer show higher mortality and more complications. In one study, 17% of children with cancer were positive for SARS-CoV-2 and 25.5% among these were asymptomatic while 7.14% required mechanical ventilation and 25.5% were under oxygen supplementation with mortality 4%.<sup>16</sup> A systematic review showed that almost 10% of children with an underlying diagnosis of cancer developed severe disease and 32% needed oxygen support with a mortality rate of 5%. This indicates that children with cancer are vulnerable to serious effects of this virus.<sup>17</sup> A study conducted in our hospital's pediatric oncology unit revealed that 13.8% children needed oxygen therapy and an equal number needed admission to the intensive care unit.<sup>18</sup> One of the major complications that children develop after COVID-19 infection is MIS-C. It often develops 1-6 weeks postinfection and can present like Kawasaki disease.<sup>19,20</sup>

It is known that the immune status of children with malignancies is altered. Further, treatment with anticancer drugs weakens the immune system more. In fact, with the spread of SARS-CoV-2, cancer care in children has suffered collateral consequences in terms of decreased access to diagnosis and challenges in undertaking effective therapy. Meena et al. observed not only postponement of chemotherapy (123/169 patients) but also modification in the chemotherapeutic regimen (10/169). The authors noted several complications (pneumothorax, pleural effusion, pleural thickening, pulmonary arterial hypertension, bronchiolitis, bronchiolitis obliterans, diffuse alveolar hemorrhage, septic shock, and acute respiratory distress syndrome) among COVID-19 positive children with cancer.<sup>17</sup> A survey of 311 health care professionals at 213 institutions from 79 countries showed that 34% of centers reported increased abandonment, 72% decreased

**TABLE 1** Ongoing clinical trials among healthy children for COVID-19 vaccine<sup>27</sup>

Clinical trial number	Title	Responsible party/sponsor	Age group	Outcome measures	Phase
NCT04649151	A study to evaluate the safety, reactogenicity, and effectiveness of mRNA-1273 vaccine in adolescents 12 to <18 Years Old to Prevent COVID-19 (TeenCove)	Moderna	12 to <18 years	Adverse reactions, serum antibody levels, seroresponse rate	Phase 2
NCT04796896	A study to evaluate safety and effectiveness of mRNA-1273 COVID-19 vaccine in healthy children between 6 months of age and less than 12 years of age	Moderna	6 months to <12 years	Adverse reactions, serum antibody level, seroresponse rate	Phase 2
NCT04773067	A study to evaluate UB-612 COVID-19 vaccine in adolescent, younger and elderly adult volunteers	United Biomedical Inc., Asia	12–85 years	Antibody titer, seroconversion rate	Phase 2
NCT04611802	A study to evaluate the efficacy, immune response, and safety of a COVID-19 vaccine in adults $\geq 18$ years with a pediatric expansion in adolescents (12 to <18 years) at risk for SARS-CoV-2	Novavax	12 years and older	Reactogenicity, adverse events, antibodies to SARS-CoV-2 nucleoprotein	Phase 3
NCT04800133	COVID-19 vaccination in adolescents (COVA)	University of Hong Kong	11–100 years	Adverse reactions, binding antibody response, neutralizing antibody response, T-cell response	Phase 2
NCT04816643	Study to evaluate the safety, tolerability, and immunogenicity of an RNA vaccine candidate against COVID-19 in healthy children <12 years of age	Pfizer/BioNTech SE	6 months to 11 years	Adverse events	Phase 1
NCT04884685	Safety of an inactivated SARS-CoV-2 vaccine (CoronaVac) in children and adolescents	Sinovac Research and Development Co., Ltd.	3–17 years	Adverse reactions	Phase 2
NCT04917523	Immuno-bridging study of inactivated SARS-CoV-2 vaccine in healthy population aged 3–17 versus aged 18 years old and above (COVID-19)	China National Biotec Group Company Limited	3–17 years versus 18 years and above	Titer of neutralising antibody	Phase 3
NCT04918797	COVAXIN in a pediatric cohort (COVAXIN-Peds)	Bharat Biotech International Limited	2–18 years	Reactogenicity and immunogenicity	Phase 2 Phase 3

surgical rates, 60% blood shortages, 57% chemotherapy modifications, and 28% interruption in radiotherapy services.<sup>7</sup> Not only low- and middle-income countries, but also the most advanced pediatric oncology centers in the world reported deaths, high incidence of oxygen therapy, delays in chemotherapy (54%), and postponements in surgery (46%) and stem cell transplant (30%).<sup>16,21</sup> The coming months to years may see an increase in relapse of childhood cancers secondary to interruptions in timely therapy.

Can the delays in treatment be prevented? Can treatment interruptions or hospitalizations due to COVID-19 be avoided? Can the severity of illness be mitigated? The answer to many of these questions lies in vaccination of this vulnerable population.

The vaccination program in adult population across the globe clearly shows reduced risk to SARS-CoV-2 infection and protection from severity. There is as low as 0.04% positivity rate after receiving both doses of Covaxin, 0.02% positivity after a single dose of Cov-

ishield, and 0.03% positivity after the second dose.<sup>22</sup> Post vaccination, the reinfection rates of COVID-19 among adults have decreased. A multicenter study by Hall et al. showed an 84% lower risk of COVID-19 reinfection post vaccination.<sup>23</sup>

In fact, COVID-19 vaccination in adult cancer patients has also shown promising results. Studies have reported that the vaccine is well tolerated even in patients undergoing chemotherapy 15 days prior to vaccination or immune checkpoint inhibitor therapy. No severe side effects were observed in these patients and there was no alteration in their therapeutic regimens. The SARS-CoV-2 positivity rate was also decreased in these patients. However, it is worth noting that a longer time span between the two doses of vaccine showed poor seroconversion in cancer patients.<sup>24–26</sup> Hence, we can look forward to carry out rigorous clinical trials in order to address pediatric cancer patients. Direct application of the results of COVID vaccine trials done in the adult cancer population on pediatric cancer patients would be

inappropriate. This is because of the differences in biology and types of cancers, with hematological malignancies being more common in children. The immune response generated in these patients is very different from those with solid tumors.<sup>24</sup>

Recently, similar efforts of conducting COVID-19 vaccination clinical trials in children have been initiated although in smaller proportion than adults. The primary outcomes are safety, efficacy, immunogenicity, and reactogenicity among healthy children across the globe, detailed in Table 1.

Pfizer is conducting a Phase II clinical trial (NCT04895982) to evaluate the safety, tolerability, and immunogenicity of mRNA-based COVID-19 vaccine in immunocompromised patients with non-small cell lung cancer (>18 years) and solid organ transplant and stem cell transplant (2–18 years). However, the selection criteria of children aged 2–18 years are not very clear. Therefore, as vaccination programs in adult cancer patients are fruitful, we can move ahead and consider the pediatric cancer population for COVID-19 vaccination trials.

In summary, although children experience less morbidity and mortality with COVID-19 infection, pediatric cancer patients appear to be more susceptible to infection, with higher mortality and complications owing to their immunocompromised status. To date, there is only a single clinical trial addressing the pediatric immunocompromised host, and this leaves vaccine development and research in a primitive state for patients who need it the most. It becomes essential to take necessary steps to design appropriate clinical studies encompassing the pediatric cancer population to determine outcomes that clearly define vaccine dosage regimens, efficacy, and postvaccination effects. Until the vaccine becomes available to pediatric cancer patients, COVID-appropriate behavior and the vaccination of their caregivers should be given a priority. Childhood cancer is curable. The augmented efforts to vaccinate children with cancer can preserve their excellent outcomes and help build a better future. Protecting the immunocompromised children will definitely decrease the health care burden and save lives.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## AUTHOR CONTRIBUTIONS

The manuscript was written through contribution of all authors. All authors have given approval to the final version of the manuscript. Yashika Charla and Manas Kalra equally contributed toward drafting the manuscript. Manas Kalra also edited and proofread the manuscript. Neha Chopra contributed to advising and editing the manuscript. Sangeeta Choudhury conceptualized, guided, framed, and edited the manuscript.

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