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REVIEW

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Immunogenicity of coronavirus disease 2019 vaccines in children: A review with ChatGPT

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Abstract

SARS-CoV-2 causes millions of infection cases and coronavirus disease 2019 (COVID-19)-related deaths worldwide. In addition to acute illnesses, children and adolescents suffer from post-infectious complications. Vaccination is a promising preventative treatment that can confer protection from these devastating outcomes. Utilizing ChatGPT, this review discusses the immunogenicity of mRNA and inactivated COVID-19 vaccines in children and adolescents. Rapid vaccine discovery during the COVID-19 pandemic led to the approval of the mRNA vaccines that stimulate potent antibody responses in pediatric population, and the younger age groups develop higher neutralizing and non-neutralizing antibody responses than those who are older. Natural infection induces weaker antibody responses than vaccination. Vaccine-induced humoral immunity decreases over time, as antibodies decline six months after the second dose. However, antibody avidity increases, which partly maintains neutralization and Fc-effector functions that provide more durable protection. Inactivated COVID-19 vaccines generate strong antibody responses in children and adolescents. They induce T cell responses against multiple structural protein antigens, although their neutralizing antibody responses appear weaker and wane more quickly than mRNA vaccines. Full-dose intradermal administration and heterologous prime-boost may improve the immunogenicity of inactivated vaccines. In children and adolescents, immune protection from the pre-Omicron variants of concern (VOCs) is maintained. Vaccination induces less antibody neutralization against the Omicron variant, but non-neutralizing antibodies and T cell responses persist. Hybrid immunity provides stronger immunogenicity against SARS-CoV-2 in the pediatric population. Future research must focus on long-term immunity, interaction with breakthrough reinfections, cross-reactivity against new VOCs, T cell immunogenicity and immunogenicity in young children.

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Keywords
ChatGPT, COVID-19, immunogenicity, pediatrics, vaccine

1 | INTRODUCTION

Toward the end of 2019, a newly described viral pathogen, SARS-CoV-2, that causes the highly transmissible coronavirus disease 2019 (COVID-19) began circulating around the world and led to over 760 million reported cases of infection and 6,890,000 associated deaths as of 31 March 2023.[1,2] The gastrointestinal and respiratory tracts are most commonly affected, although other organ systems can be involved.[3–5] While complications and deaths occur disproportionately in men and the elderly, the pediatric population has not been spared.[4–8] Children with chronic medical conditions and comorbidities, inborn errors of immunity (IEIs), or other immunocompromized states are the most susceptible.[4,9–13] As such devastation on human health spread globally at a rapid pace within the first few months, the World Health Organization (WHO) declared COVID-19 a pandemic on 11 March 2020.[14]

It was not long after that additional health complications specifically inflicting the pediatric population, such as multisystem inflammatory syndrome in children (MIS-C), characterized by myocardial damage and ventricular dysfunction, coronary dilation and aneurysms, cardiac arrhythmias, heart failure, coagulopathy, kidney injury, or even death due to post-infectious hyperinflammation, were reported.[15,16] Post-COVID-19 condition is another post-infectious health issue that can occur in children and adolescents, in addition to adults, that consists of long-term respiratory and neuropsychiatric manifestations.[17–20] Children and adolescents with post-COVID-19 condition experience functional impairment in daily activities.[17,18,20] Aside from the direct neuropsychiatric complications due to COVID-19, children and adolescents suffer from mental health issues related to societal restrictions, quarantines, and school closures implemented to control disease transmission.[21] These non-pharmacological measures interfere with educational opportunities, normal social interactions, and sport activities that are essential for the childhood development of psychological and physical well-being.[21,22] Therefore, effective vaccination and high immunization coverage are necessary to control the pandemic and mitigate its harmful effects on children.[19,23,24]

The recently developed mRNA-based, such as BNT162b2 (Pfizer-BioNTech, or INN-tozinameran, Comirnaty) and mRNA-1273 (Moderna, or INN-elasomeran, Spikevax), and inactivated whole-virus vaccines, such as CoronaVac (Sinovac, or PiCoVacc) and BBIBP-CorV (Sinopharm, or NVSI-06-07), have been evaluated and used in children and adolescents worldwide (Figure 1).[25–33] The mRNA vaccine is a novel platform, whereby the RNA transcript of the spike (S) gene of the SARS-CoV-2 is injected into the recipient, which is translated by the host into the S protein antigen to trigger an immune response.[34] On the other hand, inactivated vaccines are based on the more conventional method of introducing an inactivated form of the whole virion, which includes all the structural proteins, such as S, nucleocapsid (N) and membrane (M) proteins, and usually an adjuvant as well, into the host to stimulate the immune system.[25] Both vaccines induce adaptive immune memory in lymphocytes, known as T and B cells.[25,34] B cells are part of the humoral immune response and produces antibodies that can neutralize SARS-CoV-2 by inhibiting viral entry, bind and agglutinate the virus or tag infected cells for cellular cytotoxicity and eventual cell death (Figure 2).[25,34] T cells orchestrate the immune system for a coordinated antiviral response and cytotoxicity that results in apoptosis of infected cells (Figure 3).[25,34] Greater technical demands are implicated in the study of non-neutralizing antibodies and T cells than neutralizing antibodies, and therefore these aspects of the immune system are less well understood in COVID-19 vaccination.[25] Nonetheless, pediatric COVID-19 vaccination results in rapid recall of antigen-specific immunity upon encountering the virus that can prevent infections and transmission, reduce viral loads, and confer protection from severe disease.[23,24,35–37]

As the COVID-19 pandemic has such profound impact on young individuals, there has been an urgent need for discovery of more effective vaccines for the pediatric population. To achieve this, a thorough and deep understanding of the immune protection from COVID-19 vaccination is required for optimizing immunization strategies.[25] This review provides the most current, detailed, and comprehensive knowledge regarding the immune responses elicited against the SARS-CoV-2 by the aforementioned two major COVID-19 vaccine platforms in children and adolescents. The focus of this topic will be on mRNA and inactivated vaccines since there are limited to no published data on other COVID-19 vaccines in these young age groups. Immune responses against variants of concern (VOCs), some of which can be prone to vaccine escape, are described (Figure 4).[38] As almost all children have or soon will be infected with SARS-CoV-2, we present evidence available for hybrid immunity, which is the synergistic immune response between infection and vaccination.[39] The information from this review aims to be useful for public health policymaking, promoting safe

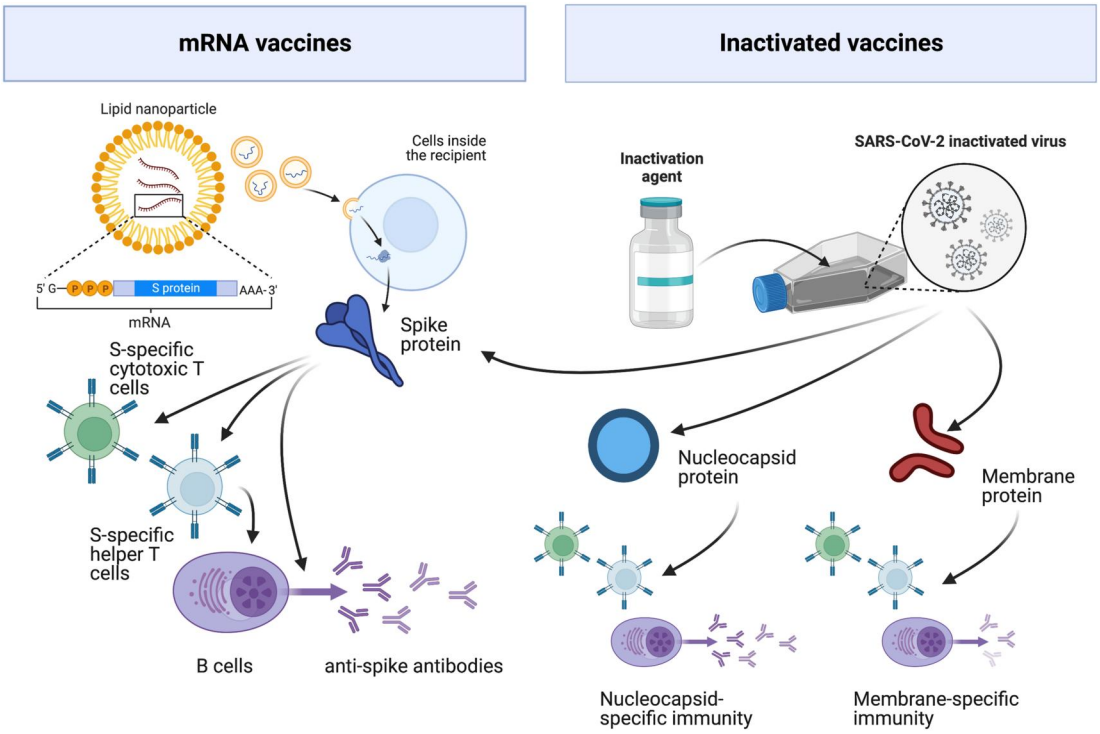

FIGURE 1 mRNA vaccines and inactivated vaccines. mRNA vaccines contain nucleoside-modified mRNA transcript encoding the spike (S) protein, enveloped in a lipid nanoparticle. The mRNA transcript is translated into S in cells of the recipient, which induces T and B cell responses. For the inactivated vaccines, the viruses are propagated in a cell line and inactivated. After injection into the recipient, the inactivated vaccine induces T and B cell responses against the nucleocapsid (N) and membrane (M) proteins, in addition to S. Created with biorender.com.

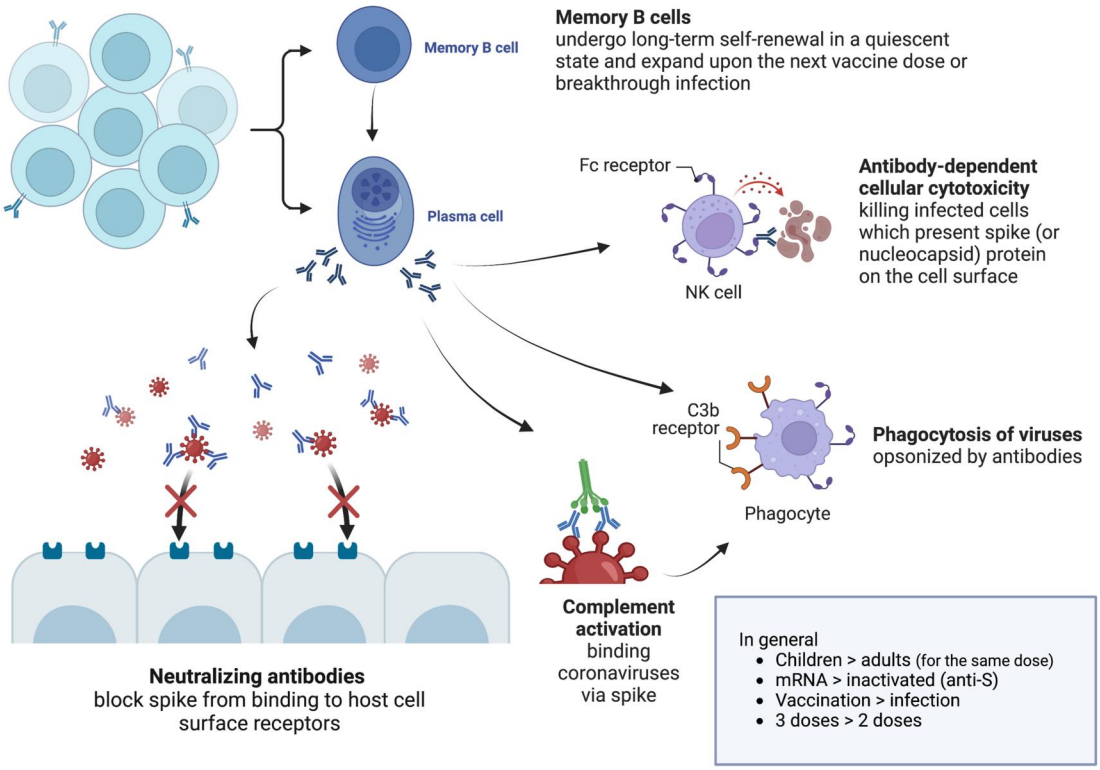

FIGURE 2 Antibody and B cell responses. B cells differentiate into memory B cells and plasma cells. Plasma cells secrete different isotypes of antibodies that have a variety of functions, including neutralization, complement activation, phagocytosis of viruses and antibody-dependent cellular cytotoxicity. Created with biorender.com.

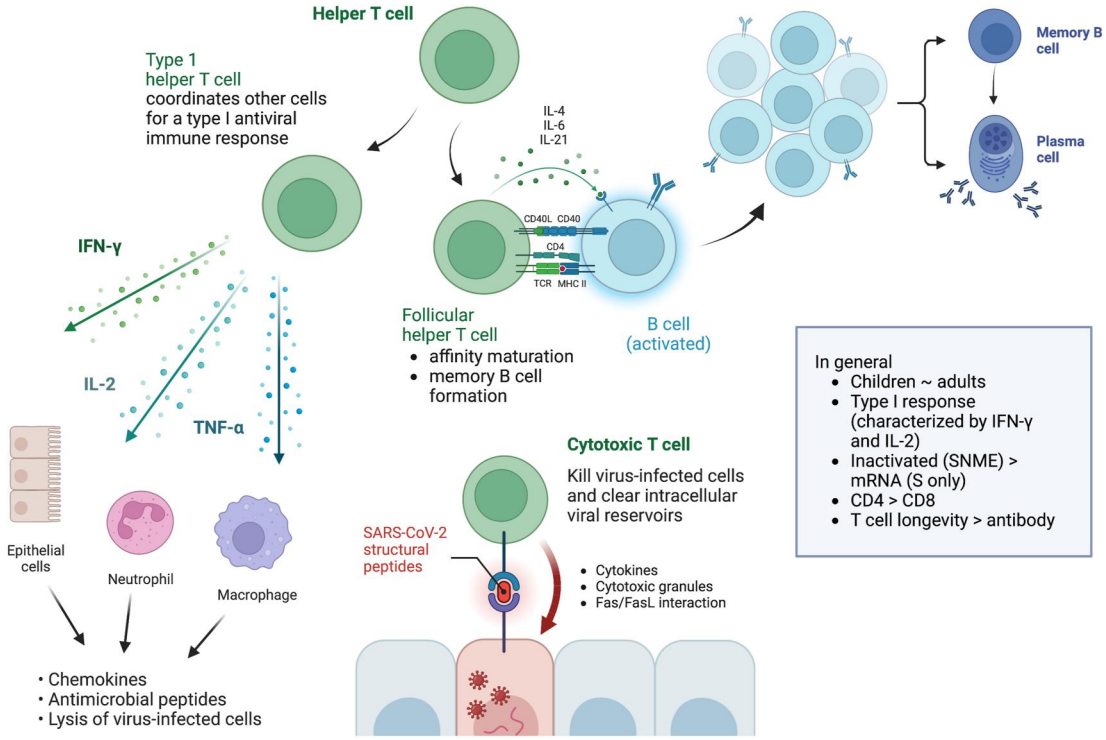

FIGURE 3 T cell responses. Helper T cells differentiate into type 1 helper T cells, which orchestrate an antiviral response, and follicular helper T cells, which stimulate B cells to undergo affinity maturation and memory B cell formation. Cytotoxic T cells kill infected cells that present SARS-CoV-2 structural peptides on their cell surfaces. Created with biorender.com.

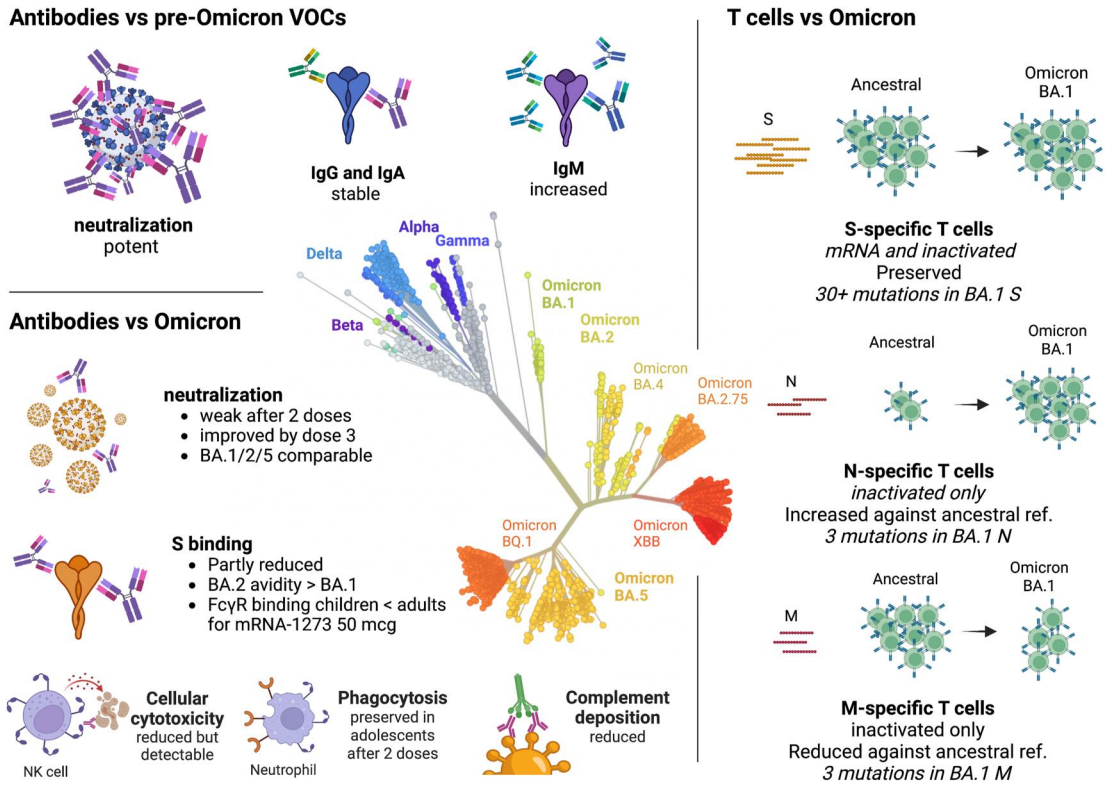

FIGURE 4 Cross-reactivity toward variants of concern. Pre-Omicron variants of concern (VOCs), such as Alpha, Beta, Gamma, and Delta remain susceptible to neutralization and binding by IgG, IgA, and IgM. For Omicron, antibody responses are reduced by variable degrees. T cell responses to spike (S), nucleocapsid (N), and membrane (M) proteins are preserved, increased, and reduced when compared to ancestral reference pool (ref). Created with nextstrain.org and biorender.com.

school environment, and ensuring children's best future outcomes for living with COVID-19 long term,[40,41] now that the WHO has declared COVID-19 no longer a public health emergency of international concern.[42]

2 | IMMUNE RESPONSES TO mRNA-BASED VACCINES

The mRNA vaccines, specifically BNT162b2 and mRNA-1273, induce robust antibody responses in children and adolescents.[26–31] In pivotal trials, investigators compared neutralization titers in the pediatric age group of interest to an older age group for which clinical efficacy had been demonstrated previously.[26–31] This is known as the immunobridging approach and is based on the correlation between neutralization and efficacy against infection.[43,44] Consistently, neutralizing antibody titers were non-inferior in the various pediatric age groups tested, and the point estimates of the geometric mean ratios (GMR) for neutralization in most trials exceeded 1.0 when compared to the older-aged standard group, suggesting neutralizing antibody responses increased with younger age.[26–31] After two doses of BNT162b2 in adolescents aged 12–15 years, the GMR of neutralization titers was 1.76 (95% confidence interval, CI 1.47–2.10) compared to participants aged 16–25 years who received two doses of BNT162b2.[26] Two separate studies reported higher neutralizing antibody responses in children aged 6–11 years who received two doses of 50 μg mRNA-1273 (GMR 1.2, 95% CI 1.1–1.4) and in children aged 6–23 months who received two doses of 25 μg mRNA-1273 (GMR 1.3, 95% CI 1.1–1.5) when compared to young adults aged 18–25 years who received two doses of the 100 μg dose formulation.[30,31] These results suggested mRNA vaccines are more efficacious in children than in adults.

A similar pattern was observed when both non-neutralizing and neutralizing antibody responses were comprehensively profiled further in investigator-initiated studies. Our group compared an array of antibody responses to two doses of 30 μg BNT162b2 in adolescents aged 11–18 years against adults and found superior S IgG, surrogate virus neutralization test inhibition (sVNT), 90% plaque reduction neutralization test titers (PRNT), S IgG avidity, and S IgG FcγRIIIa-binding responses in adolescents.[35] This suggests antibody responses in vaccinated adolescents had high neutralization capacity and could bind S more strongly, which is likely to facilitate Fc effector cells such as natural killer (NK) cells and phagocytes for stronger Fc-dependent responses. In another study, there were higher S IgG1 titers, S IgG FcγRIIIa-binding, antibody-dependent complement deposition, and antibody-dependent neutrophil phagocytosis in children aged 5–11 years who received 100 μg mRNA-1273 compared to adults, providing functional proof that antibodies in vaccinated children could trigger stronger responses from Fc effector cells that can aid viral clearance on top of neutralization.[45] Taken together, these studies reveal adolescents and children mount more robust neutralizing and non-neutralizing antibody responses than older individuals. The superior immunogenicity of younger individuals could be due to the naivety of the adaptive immune system and smaller body volume or surface area in children and adolescents, and therefore they receive higher vaccine dosages per body volumes surface areas.

There had been questions as to whether infection by SARS-CoV-2 would elicit better protective immunity than vaccination. Subsequently, several studies showed natural infection induces weaker antibody responses than vaccination alone.[45,46] Post-vaccine S IgG, pseudovirus neutralization, and antibody-dependent NK cell-mediated cytotoxicity endpoint titers were significantly higher after two doses of BNT162b2 than infection or MIS-C.[46] Furthermore, there were more robust binding and neutralizing antibody titers and Fc-dependent effector responses in children vaccinated with two doses of either 50 or 100 μg mRNA-1273 than in infected children.[45]

Another important question was the durability of vaccine-induced immunity. Adolescents who received two doses of BNT162b2 experienced a significant drop in IgG responses against S and S-receptor-binding domain (RBD) six months after two doses that are comparable to levels elicited after one dose only.[47] Neutralizing titers, antibody-dependent cellular phagocytosis and antibody-dependent neutrophil phagocytosis also decreased significantly at six months, although they remained detectable in most adolescents. Our group observed similar findings that there was minor but significant decline in S IgG, sVNT, PRNTs, and S IgG FcγRIIIa-binding responses five months after dose 2.[36] Neutralization responses, including sVNT, 50% PRNTs, and 90% PRNTs, were maintained at moderate levels. This may be explained by a large and significant increase in avidity five months after dose 2 compared to onr month after dose 2. This implies an establishment of long-lasting spike antibody responses, which could partly preserve neutralization and Fc receptor-dependent responses despite a loss of binding antibody titers, offering durable protection from more severe forms of disease.

Compared to antibody responses, much less is known about cellular immunity generated by mRNA vaccines in children. Using the intracellular cytokine staining assay on flow cytometry, our group found two doses of BNT162b2 significantly induced S-specific IFN-γ^+ $CD4^+$, IL-2^+ $CD4^+$, and IFN-γ + $CD8^+$ T cell responses in adolescents

compared to pre-vaccination.[35] Approximately 80%–90% adolescents mounted detectable S-specific IFN-γ^+ and IL-2^+ $CD4^+$ T cell responses and approximately 40%–60% adolescents mounted detectable S-specific IFN-γ^+ and IL-2^+ $CD8^+$ T cell responses after two doses of BNT162b2. These responses were non-inferior or comparable to adults. In this same cohort, T cell responses were maintained over five months after two doses, and IL-2^+ and IFN-γ^+ $CD8^+$ T cell were significantly boosted by a third dose, and there were no significant differences between the responses in adults and adolescents after the third dose.[36] In children aged 5–11 years who received BNT162b2, two doses induced S-specific memory B cells and IFN-γ^+ T cells.[48] As T and B cell responses are long-lasting and memory B cells can undergo affinity maturation, these studies provide the basis for the partial preservation of vaccine protection over time.

Fractional dosing of mRNA vaccines has been explored as an alternative approach to optimize immune responses in adolescents, especially because of the rare but concerning risk of myocarditis in adolescents who receive mRNA vaccines.[49–52] In adolescents, aged 12–18 years who were randomized into six arms for primary series administration and received either two doses of BNT162b2 at 30/30 μg, 30/20 μg, or 20/20 μg dosage with three or six weeks in between, S-RBD IgG and S-specific T cell responses were all comparable in the fractional dosing arms (30/20 μg and 20/20 μg) compared to the conventional dosing arm (30/30 μg).[53] A fractional booster dose of BNT162b2 consisting of 10 and 15 μg induced higher S-RBD IgG levels, with no significant difference between the 10 and 15 μg arms. This study suggests lower dosages of mRNA vaccines for adolescents can be considered in the future. Whether fractional dosing is associated with lower incidences of myocarditis needs to be confirmed.

3 | IMMUNE RESPONSES TO INACTIVATED VIRUS VACCINES

Inactivated COVID-19 vaccines also demonstrated robust antibody responses in pivotal trials.[32,33,54–59] The notable similarity between the inactivated and mRNA vaccines is that immune responses to both appeared to be age-dependent. Higher S-RBD IgG titers in adolescents aged 12–17 years who received two doses of BBIBP-CorV were observed compared to healthy young adults aged 18–30 years (GMR 2.79, 95% CI 2.25–3.46).[54] Children aged 2–18 years who received two doses of BBV152 also had higher PRNTs compared to adults (GMR 1.76, 95% CI 1.32–2.33).[58] A major difference between inactivated and mRNA vaccines is that inactivated vaccines can induce immune responses against N and M, while the mRNA vaccines cannot.[35,37] Our group found non-inferior and superior N IgG and N-CTD IgG, along with S IgG, sVNT, and S IgG avidity, in adolescents aged 11–17 years who received two doses of CoronaVac compared to adults.[35] The same cohort had non-inferior and superior 50% PRNTs, S IgG avidity, N IgG, and N-CTD IgG after three doses.[37] Younger children had higher antibody responses. After two doses of CoronaVac, children aged 3–11 years mounted significantly higher neutralization titers than adolescents aged 12–17 years.[59] Children aged 3–5 years who received three doses of WIBP-CorV had the highest neutralization titers compared to children aged 6–12 years and 13–17 years.[55] These studies suggest children and adolescents who received inactivated vaccines develop superior clinical protection than adults.

Very few studies evaluated the durability of antibody responses to inactivated vaccines in children. Our group studied the waning of antibody responses at least two months after two doses of CoronaVac in adolescents aged 11–17 years and found marked reductions in S-RBD IgG and sVNT, with a large proportion of adolescents losing neutralization capacity.[37] In another study, the neutralizing antibody titers in children aged 3–17 years who received CoronaVac also significantly waned at 10–12 months after dose 2, and many had undetectable neutralization titers.[56] Taken together, there appears to be a more rapid waning of neutralization responses following inactivated vaccines relative to mRNA vaccines.

However, inactivated vaccines contain all the structural proteins in the SARS-CoV-2 virion, which may elicit multiprotein T cell responses. An activation-induced marker expression assay revealed two doses of CoronaVac induced $OX40^+$ $CD137^+$ $CD4^+$ T cells against S, N, and M in children aged 3–17 years.[59] The responses against S between children aged 3–11 and adolescents aged 12–17 were similar. Two doses of CoronaVac induced SNM-specific IFN-γ^+ $CD4^+$, IL-2^+ $CD4^+$ and IL-2^+ $CD8^+$ T cells in the study performed by our group.[35] In addition, there were comparable or non-inferior SNM- specific IFN-γ^+ and IL-2^+ $CD4^+$ and $CD8^+$ T cells between adolescents and adults. In this cohort, SNM-specific T cell responses did not wane two months after two doses of CoronaVac in adolescents, and the responses in adolescents after three doses remained non-inferior or comparable compared to adults.[37] These studies support the notion that inactivated vaccines elicit robust T cell responses against multiple structural protein antigens in SARS-CoV-2, which has implication on sustained protection from VOCs with various mutations in S, which will be further elaborated in the following section.

Although inactivated vaccines, such as CoronaVac, appeared to have lower efficacies against infection than

mRNA vaccines in adults, few head-to-head immunogenicity trials on an mRNA vaccine versus an inactivated vaccine are available. According to our unique study, adolescents aged 11–17 years who received two doses of BNT162b2 had higher antibody responses, including S IgG, S-RBD IgG, sVNT, 90% and 50% PRNTs, S IgG avidity, and S IgG FcγRIIIa-binding antibodies.[35] In contrast, S-specific IFN-γ^+ $CD4^+$, IFN-γ^+ $CD8^+$ and IL-2^+ $CD8^+$ T cell responses were comparable between the two vaccines in the same study, where N and M-specific T cell responses were also detected after CoronaVac but not BNT162b2. This implies there are differences in the durability and cross-variant protection to symptomatic and severe disease between mRNA and inactivated vaccines.

Several teams investigated ways to improve the immunogenicity of inactivated vaccines. The heterologous prime-boost approach, by boosting children who received one dose of inactivated vaccines with an mRNA vaccine, has been studied.[60] Although there was no control group that received two doses of inactivated vaccines, adolescents who received 2-dose primary series of CoronaVac-BNT162b2 had high sVNT against the Delta variant that persisted at five months after the second dose. Using another approach, our group explored whether full-dose intradermal vaccination could result in superior immunogenicity, based on the rationale that fractional-dose intradermal administration of vaccines against other viruses could elicit comparable immunogenicity to the intramuscular injection route.[61] Interestingly, comparing the immunogenicity of adolescents who received three intradermal versus intramuscular doses of CoronaVac, we found superior S-RBD IgG, sVNT, 90% and 50% PRNTs, S IgG avidity, and S IgG FcγRIIIa-binding responses, which demonstrated intradermal vaccination can elicit comprehensively more robust humoral responses against SARS-CoV-2 in this age group. In terms of T cell responses, M-specific IL-2^+CD4^+, IFN-γ^+CD8^+, and IL-2^+CD8^+ T cells were superior. Future research can further explore the intradermal route of administration with the full dose of inactivated vaccines in enhancing the immunogenicity for other age groups and against other infectious pathogens.

4 | CROSS-VARIANT REACTIVITY

VOCs poses a challenge to the protection conferred by the COVID-19 vaccines that received early approval for use, as VOCs contain mutations that may cause immune escape (Figure 4).[38] Subsequently, mRNA vaccines were shown to elicit robust antibody responses against many SARS-CoV-2 VOCs in children and adolescents. A study that assessed the VOC-specific humoral responses including binding titers of several immunoglobulin isotypes and FcγR-binding after two doses of BNT162b2 found children and adolescents maintained binding IgA and IgG against all four pre-Omicron VOCs tested (Alpha, Beta, Gamma, and Delta).[62] IgM binding against pre-Omicron VOCs was unexpectedly enhanced in children and adolescents compared to the ancestral strain, which was not observed in adults. For adolescents who received two doses of BNT162b2, IgG titers, and neutralization against Beta, Gamma, and Delta against VOCs seemed similar to adults, though the two age groups were not statistically compared.[63] After a third dose of BNT162b2, adolescents had very high neutralizing capacity, with a median of 100% inhibition on sVNT, which was 82.9% pre-booster.[64] These results suggest that protection from pre-Omicron VOCs is likely preserved.

The Omicron variant is much more of a concern as it contains many mutations in S. Indeed, using various pseudovirus and sVNT assays, several studies demonstrated large reductions in neutralization against Omicron BA.1 in children and adolescents vaccinated with two doses of BNT162b2.[48,62–64] On the other hand, our group employed an authentic SARS-CoV-2 PRNT assay, and there was preservation of neutralization against Omicron BA.1, with 24 of 25 adolescents who maintained seroconversion against BA.1 at six months after two doses of BNT162b2.[36] For mRNA-1273, 100% of the children and adolescents who received two inoculations of age-appropriate dosages had sufficient neutralization titers against the BA.1 pseudovirus.[65] After adolescents received a third dose of BNT162b2, they had high sVNT against BA.1, which were significantly boosted compared to pre-booster.[64] Our group further studied Omicron BA.1, BA.2, and BA.5 neutralization using PRNT in adolescents after a third dose of BNT162b2, and these adolescents had similar moderate levels of neutralization against the three subvariants.[36] These findings suggest similar, partly preserved efficacy against the three Omicron subvariants.

Despite the dramatic loss of neutralization, by and large, binding and FcR-dependent antibody responses were maintained. Adolescents and children who were vaccinated with BNT162b2 had reduced yet detectable Fc-mediated antibody effector functions against BA.1, although this was lower in children receiving the 10 μg dose.[62] Antibody-dependent complement deposition was dramatically reduced, while antibody-dependent neutrophil phagocytosis was preserved in adolescents six months after two doses of BNT162b2.[47] Children who received the 50 μg dose of mRNA-1273 had a greater loss of Fcγ receptor binding against BA.1 S than adults, which was possibly due to a lower dosage of vaccine received.[45] As BA.1 contains more mutations than BA.2, S IgG

avidity is expected to be reduced more against BA.1. This postulation was confirmed by our study of adolescents who received three doses of BNT162b2.[36] In addition to binding antibody responses, T cell responses, which are cross-reactive, are likely preserved against Omicron S. Indeed, our group showed persistently detectable S-specific IFN-γ^+ and IL-2^+ $CD4^+$ and $CD8^+$ responses in adolescents who received three doses of BNT162b2, a similar observation for adults.[36] Therefore, the observation from real-life effectiveness studies that there is residual clinical protection by mRNA vaccines against Omicron is likely due to the preservation of binding antibody and T cell responses.

Inactivated vaccines that target the ancestral SARS-CoV-2 also elicit antibody responses against VOCs in children and adolescents. Initially, significant reductions in neutralizing antibody titers against Omicron BA.1 after two doses of CoronaVac had been observed.[59] The drop was more significant in adolescents aged 12–17 than children aged 3–11, which again suggests an age-dependent immune response.[59] However, despite such significant reduction in neutralization titers, neutralization was achieved in a large proportion (86.2%) of adolescents who received three doses of CoronaVac.[37]

In terms of T cell immunity against the Omicron variant after inactivated vaccination, our group found cellular immunogenicity outcomes against the Omicron BA.1 variant mutation pools for S, N, and M were stable, increased, and halved compared to the ancestral virus, respectively, in adolescents who received three doses of CoronaVac.[37] Our study detected no difference in S-specific T cell responses between the ancestral and BA.1 mutated sequences, which aligns with studies on mRNA vaccines. For N, the increases in T cell responses were likely due to mutations in BA.1 N (31_33delERS, 203_204delRGinsKR) that were situated at the edges of the immunodominant regions, which could have enhanced T cell responses.[66] These variable changes in T cell responses to BA.1-associated mutations in different SARS-CoV-2 proteins support the notion that T cells do not exert selection pressure against the virus.[67] Overall, T cell responses against the ancestral SARS-CoV-2 were conserved against Omicron BA.1, and this is likely to be the case for other subvariants as well.

5 | HYBRID IMMUNITY

Hybrid immunity, or immunity that is developed after both vaccination and infection, became an important topic in understanding immune responses against SARS-CoV-2 as more children became infected before or after vaccination. Two months after the second dose of BNT162b2, children aged 5–11 years old with a prior history of COVID-19 had higher S-RBD IgG and neutralization titers than those without prior infection.[68] This superior antibody response by hybrid immunity was also observed five months after vaccination, as waning of S-RBD IgG titers was observed in those vaccinated without prior infection. Interestingly, at five months, neutralizing antibody titers was even increased for children with hybrid immunity. This suggests affinity maturation continued two months after vaccination. Another cohort of children aged 5–11 years who had detectable S-specific memory B cells at baseline, an indicator of prior infection, and received BNT162b2 demonstrated superior neutralization capacity against Omicron compared to those without detectable S-specific memory B cells at baseline.[48] Evidently, past infection enhances vaccine immunogenicity in children who receive mRNA vaccines.

In unvaccinated children, infected with the ancestral, Delta or Omicron variants and children with at least one dose of vaccine and a breakthrough Omicron infection, children who were both vaccinated and infected had higher neutralizing capacity against the ancestral variant than children who were unvaccinated but infected with the ancestral, Delta, or Omicron variants.[69] This confirms the concept that hybrid immunity generates more potent antibody responses than infection alone. Amongst children who were infected with the Omicron variant, vaccinated children also had a significantly higher neutralization response against Omicron than unvaccinated children. Overall, vaccination with the ancestral strain does not impair infection-induced immunity against VOCs.

Unvaccinated children who become infected with SARS-CoV-2 are more likely to develop MIS-C. mRNA vaccines have been offered to some children who had a history of MIS-C. In two separate studies, S IgG titers in these MIS-C patients were successfully boosted by two doses of mRNA vaccine.[70,71] These results demonstrate that hybrid immunity can be achieved by mRNA vaccine in this population.

6 | CONCLUSION

In children and adolescents, the mRNA vaccines induce strong antibody, B, and T cell immune responses. The inactivated virus vaccines elicit moderate humoral immunity but potent cellular immunogenicity. Both vaccine types provide cross-variant reactivity and protection from Omicron. Children have robust hybrid immunity, including those with MIS-C. Although currently available research data have provided valuable insight into the immunogenicity of mRNA and inactivated virus vaccines in the pediatric population, significant knowledge gaps

remain. These include the long-term durability of immune responses, optimal dosing strategies, cross-reactivity, and protection from emerging variants with and without hybrid immunity. Additionally, immune responses to other vaccine platforms, such as viral vector, protein subunit, and inhaled vaccines, in the younger age groups warrant further investigation. Addressing these knowledge gaps will provide essential information for refining current vaccination strategies and discovery of novel vaccines for the pediatric population.[25,34] These efforts will be crucial for supporting the control of infections and disease complications around the world.[40]

Future research will need to focus on long-term immunity. Data on longer term longitudinal studies on vaccine efficacies with extended follow-up of existing cohorts would be beneficial, and these will be needed to elucidate how breakthrough reinfections with various new Omicron subvariants or VOCs interact with pre-existing vaccine-derived or hybrid immunity. Currently, there is insufficient evidence on the waning of immunity and data on the kinetics of hybrid immunity in the pediatric population, which poses a challenge for recommendations on seasonal booster immunization. It is noteworthy that for children and adolescents, additional COVID-19 boosters are not prioritized by the WHO as they are likely of the least public health benefit in this age group due to the low case fatality rate, except for those with significant comorbidities (e.g., diabetes and heart disease) or immunocompromizing conditions (e.g., people living with HIV and transplant recipients).[72] Furthermore, assessment of T cell immunogenicity using a new generation of laboratory methods, such as the mass cytometry by time-of-flight (CyTOF), that can be more reflective of the polyfunctional nature of the cellular adaptive immunity must be explored.[73,74] Whether immunogenicity of the vaccines varies between younger children and older adolescents, who have different weights, body surface areas, pubertal status, and immune maturation, needs to be delineated. More studies are required to investigate whether different dosing schedules, including extended intervals between doses, heterologous prime-boost, and intradermal administration, can improve immune responses while reducing the risks of myocarditis and pericarditis.[49–52,75] Erosolized inhaled vaccines induce a mucosal immune response, and boosting with these vaccines theoretically aborts infections and prevents transmission.[76–80] Such studies performed particularly in children and adolescents to prevent the spread of SARS-CoV-2 or development of post-COVID-19 condition are required.[17,19,80] There are minimal data on optimal immunization for those with immunocompromized conditions and comorbidities, which are absolutely necessary for protecting these vulnerable, high-risk patients.[81–84] As primary vaccination rates have peaked with satisfactory coverage in most geographical regions by this time, newer generations of polyvalent vaccines must be thoroughly investigated in the future, especially in unvaccinated infants who have not been exposed to the virus on which there is currently minimal research.[1,49–52,85] This will be essential to inform policymakers on their decision to incorporate COVID-19 vaccines in national immunization programs.

7 | REVIEWING WITH ChatGPT

COVID-19 vaccine research has been evolving rapidly. When ChatGPT gained popularity in early 2023, reaching 100 million users in February 2023, the authors considered whether ChatGPT could be a useful tool in scientific literature review. We postulated the use of the advanced multimodal, large language model that could potentially speed up parts of the review process, such as developing an outline, designing the search strategy and Boolean query, screening the literature, writing summaries, and drafting portions of the paper. However, the authors came to realize that reports of the large language model's capabilities may have been exaggerated. We included the interaction log with ChatGPT-4 in the Supplementary Information S1 of the review and found that while ChatGPT-4 was a fluent chatbot that could give pertinent responses, major limitations existed in different steps of the review process. ChatGPT provided an outline of the review based on a given title, although it did not include all the proposed parts that were relevant. As an example, ChatGPT-4 suggested the authors include information for Ad26.COV2.S despite the lack of trial data published for this vaccine. We requested ChatGPT-4 to come up with the Boolean PubMed query based on the review outline, and the initial query it proposed was not correctly phrased, which returned fewer than 20 results. At the time of writing, ChatGPT-4 did not have Internet access and only had information up to 2021, so the authors needed to manually perform the search. We pasted abstracts derived from PubMed search onto ChatGPT-4, but there was a character limit on ChatGPT-4 that required several queries for ChatGPT-4 to evaluate all the abstracts returned from the PubMed search. ChatGPT-4 also determined the relevance of PubMed search results based on the abstracts of the papers in a manner that appeared to be random, often ruling out appropriate immunogenicity papers. Additionally, it included non-pertinent safety papers despite clear instructions. It failed to extract and summarize information from an abstract correctly. At times, ChatGPT-4 made up what was reported in a paper when asked to write a paragraph on T

cell responses based on several papers on a particular vaccine platform, some of which only reported antibody results. As a result, the ChatGPT-only version of this review article (in Supplementary Information S2) was completely rewritten, which was vastly different from the final version.

While ChatGPT-4 did not accelerate the review process, we agree with Professor Adriano Aguzzi (Twitter @AdrianoAguzzi) that ChatGPT is comparable to an enzyme.[86] ChatGPT was able to draft a summary for most steps in the review process, which reduced the planning workload for the authors. ChatGPT is a general-purpose AI tool, designed merely to help with common tasks and not scientific writing or medical tasks.[87] We foresee that within a few years, it is possible newer large language models, with Internet access and trained for specialist medical and scientific writing, would be useful.

AUTHOR CONTRIBUTIONS

Yu Lung Lau and Wenwei Tu conceptualized and supervised the review. Daniel Leung instructed and interacted with ChatGPT to develop an outline, search strategy, filter and assess the literature and generate the first draft (Supp. File 1; Supp. File 2). Daniel Leung and Jaime Rosa Duque rewrote the entire manuscript. All human authors then revised, reviewed and approved the submission of the final manuscript.

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CONFLICT OF INTEREST STATEMENT

D. Leung received conference sponsorship from CSL Behring and Merck Sharp & Dohme in 2022 and 2023, while J.S. Rosa Duque received a conference sponsorship from Merck Sharp & Dohme in 2023. Y.L. Lau chairs the Scientific Committee on Vaccine Preventable Diseases of the HK Government. The authors declare no conflicts of interest pertinent to this review. W.W. Tu is the Deputy Editor-in-Chief of *Pediatric Discovery*. To minimize bias, he was excluded from all editorial decision-making related to the acceptance of this article for publication.

DATA AVAILABILITY STATEMENT

The records of interactions and drafts with ChatGPT are included as Supplementary Information (Supp. File 1; Supp. File 2). Deidentified data from our studies as discussed in the review can be shared with scientific investigators who submit a justifiable inquiry to lauylung@hku.hk.

ETHICS STATEMENT

Not applicable.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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