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Adverse effects of COVID-19 vaccine in the paediatric population: a focus on the cardiovascular system

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Review

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Abstract

The COVID-19 pandemic had an unprecedented impact on healthcare systems and exists globally. To control pandemic progression, COVID-19 vaccines were developed and licensed for use in the adult population in early 2021 and became available in paediatric cohorts several months later. Since then, several studies have reported adverse events and severe adverse events in the adult and paediatric cohorts. The question remains whether there exists a significant risk to paediatric COVID-19 vaccination. This study reviews the classification and presentation of severe adverse events and discusses relevant reports in the literature. An emphasis is put on cardiovascular severe adverse events and adverse events. This paper also provides current and future perspectives relative to the pandemic, its control, and the future of vaccine immunology.

Introduction

The pandemic: an overview

COVID-19, short for coronavirus disease 2019, is an infectious disease caused by a novel coronavirus known as SARS-CoV-2.[1] The virus is genetically similar to SARS-CoV and MERS, which both caused pandemics in 2002–2003 and 2012, respectively.[2,3] After emerging in Wuhan, China, in 2019, the virus spread rapidly leading to a global pandemic. The virus itself is made of a spike protein (S), a membrane protein (M), and an envelope protein (E). The spike protein permits viral entry into cells and is found on the surface of the virus, such that it is responsible for the characteristic crown-like appearance of the virus. The virus is an enveloped single-stranded RNA virus and uses the abundant membrane protein for viral assembly and the envelope protein for assembly and release. The virus also contains an N (Nucleocaspid) protein that encapsulates its genetic material.[4,5]

Because the virus is highly transmissible, and individuals can be asymptomatic carriers, containing the virus presented many challenges.[6] Closures and quarantine were in place internationally to varying degrees between 2020 and 2022, with unprecedented impacts on the healthcare and socio-economic sectors.[7] Studies showed that the pandemic limited access to healthcare leading to delays in disease diagnosis and scheduled intervention,[8] with a disproportionate impact on low-income households. The pandemic also highlighted racial disparities in both access to healthcare and education and livelihood,[9] with economic hardships such as unemployment most negatively impacting low-income service and hospitality workers.[10] Paediatric patients were particularly negatively impacted by these effects, with highly concerning increases in anxiety and depression being noted amongst young cohorts during the pandemic.[11]

Global vaccination efforts have allowed communities to shift out of quarantines and transition back into normal life, proving to be a highly effective form of COVID-19 prevention. Vaccines such as Pfizer/BioNTech (Comirnaty), AstraZeneca/AZD1222, Janssen/Ad26.COV 2.S, Sinopharm BIBP COVID-19 (Sinovac-CoronaVac) and more have permitted international travel, school re-opening, and a return of social life.[12] A summary of available adult and paediatric COVID-19 vaccines can be found in Tables 1 and 2. Though exact figures for global COVID-19 vaccine rates in the paediatric cohort are not available, they are highly suspected to comprise less than 5% of the total number of administered vaccine doses, which are 13,337,787,446 doses. Despite the overwhelming positive impact of vaccination on this transition, there remain several concerns about the efficacy and safety of these vaccines, particularly in the paediatric cohort. Vaccine hesitancy is highly attributed to the fear of severe adverse events, and since the beginning of vaccine administration, several reports and studies have been published highlighting the incidence, management, and impact of severe adverse events to COVID-19 in the paediatric cohort.[13]

Table 1. Adverse events reported by the Food and Drug Administration, Centers for Disease Control and Prevention, and World Health Organization relative to the five most popular modalities as of March 2023:*

Vaccine	Adverse event	Reported cases	Incidence rate per million doses**	Total number of administered doses worldwide
Pfizer/BioNTech (Comirnaty)[16]	Anaphylaxis	860 cases	2.6 cases	6.3 billion[17]
	Myocarditis and pericarditis	5,255 cases	15.8 cases	
	Guillain-Barré syndrome	1,172 cases	3.5 cases	
	Thrombosis with thrombocytopenia syndrome	116 cases	0.35 cases	
Moderna COVID-19 vaccine[16]	Anaphylaxis	18 cases	0.2 cases	1.4 billion[17]
	Myocarditis and pericarditis	2,213 cases	29.2 cases	
	Guillain–Barre syndrome	500 cases	5.5 cases	
Janssen/Ad26.COV 2.S[18]	Anaphylaxis	105 cases	12.4 cases	320 million[19]
	Thrombosis with thrombocytopenia syndrome	44 cases	5.7 cases	
AstraZeneca/AZD1222[20]	Anaphylaxis	1,143 cases	3.5 cases	890 million[21]
	Thrombosis with thrombocytopenia syndrome	1,326 cases	19.5 cases	
Sinopharm BIBP COVID-19 (Sinovac-CoronaVac)[21]	Anaphylaxis	Data not available	Data not available	2.8 billion[22]

*All incidence rates and totals were calculated based on data up until 3 March 2023.
**The incidence rates in the tables are calculated based on the reported cases in the cohort and the total number of doses administered in the USA, not the total number of doses administered worldwide. This is for the sake of consistency as most data were obtained from the Centers for Disease Control and Prevention and Food and Drug Administration that report exclusively on US severe adverse event.

Table 2. Adverse events of paediatric COVID-19 vaccination reported by the Food and Drug Administration, Centers for Disease Control and Prevention, and World Health Organization relative to the two most popular paediatric vaccine modalities as of March 2023.[24*]

Vaccine	Side effects[24]	Severe adverse event	Reported cases	Incidence rate per million doses**	Total administered doses worldwide
Pfizer/BioNTech (Comirnaty)[83]	• Pain at vaccine site • Swollen lymph nodes • Irritability/ crying • Sleepiness • Loss of appetite • Tiredness • Headache • Muscle or joint pain • Chills	Anaphylaxis	16 cases	7 cases	140 million
		Myocarditis and pericarditis	386 cases	172 cases	
		Febrile seizures	No official count	No official count, several reports of febrile illness after routine vaccination[42,84,85]	
Moderna COVID-19 vaccine[83]		Anaphylaxis	2 cases	17 cases	2 million
		Myocarditis and pericarditis	79 cases	214 cases	
		Febrile seizures	No official count	No official count, several reports of febrile illness after routine vaccination[42,84,85]	

*All incidence rates and totals were calculated based on data up until 3 March 2023.
**The incidence rates in the tables are calculated based on the reported cases in the cohort and the total number of doses administered in the USA, not the total number of doses administered worldwide. This is for the sake of consistency as most data were obtained from the Centers for Disease Control and Prevention and Food and Drug Administration that report exclusively on US severe adverse event.

Adverse event characterisation in adults

Though definitions of adverse events differ between studies and studied populations, it is generally accepted that adverse events are unsolicited events that are reported by subjects/patients or observed by healthcare professionals and negatively impact the prognosis or current quality of life of a patient. Severe adverse events have a personified negative influence.[14] An example of a severe adverse event following COVID-19 vaccination may be as extreme as a multisystem inflammatory syndrome.[15]

Because adults were vaccinated prior to paediatric vaccine authorisation, several adverse events have been described in an adult cohort. A review of the most common adverse events along with their incidence rates and management plans associated with the four most used COVID-19 vaccines can be found in Table 1.

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Table 1 contains data on the total reported number of administered doses and is not specific to a paediatric cohort, though the remainder of the review focuses exclusively on paediatrics.

Objective

The aim of this literature review is to summarise existing data on adverse events resultant of paediatric COVID-19 vaccination, as well as to present data on the safety of existing vaccine options. This review further summarises the outcomes of COVID-19 vaccination in paediatrics and comments on factors contributing to vaccine hesitancy. Lastly, this review highlights the impact of COVID-19 vaccination on the cardiovascular system of paediatric patients, with emphasis on cardiac-related severe adverse events and adverse events presenting in paediatric cardiac patients.

Methods

A literature search was conducted on PubMed under the COVID-19 vaccination MeSH term. "COVID-19 vaccination" and "cardiovascular" as well as their synonyms were used as keywords. The search was restricted to adverse events and patients aged 0–18 years (paediatric). The search revealed 251 articles between the end of 2020 and the beginning of 2023. A concurrent search was done on ClinicalTrials.gov to obtain data on ongoing and future trials relevant to the subject. Post-title abstract screening where inclusion criteria was a clearly stated objective to the paper and discussion of both COVID-19 vaccination in paediatric patients and adverse events, 112 articles were relevant. Papers were only referenced if written in English and published by an official public health authority (Centers for Disease Control and Prevention, World Health Organization, etc.) or in peer-reviewed journals. A diversity of works was discussed, ranging from case reports to large-scale clinical trials.

Results

mRNA vaccines

Though the focus of this review is severe adverse events, it is important to first consider side effects and adverse events of paediatric COVID-19 vaccination. Side effects tend to be routine, mild, temporary, and similar to those observed as a consequence of any routine vaccination (tetanus, Measles Mumps Rubella, etc.). Unsolicited adverse events tend to have an unclear connection to vaccine immunology and include symptoms of vertigo, arthralgias, skin or eye irritation, musculoskeletal pain, and more.[23] In a cohort of 6-month to 3-year-old children, the most common side effects are pain at vaccination site, swelling of lymph nodes, irritability/crying, sleepiness, and loss of appetite.[24] Pain at vaccination site is expected, as the vaccines are intramuscular, and other side effects such as lymph node swelling and loss of appetite are indicative of vaccine immunogenicity. Several studies report that amongst immunocompromised patients such as oncology patients, vaccine immunogenicity and thus routine side effect incidence rates are low.[25,26]

The KidCOVE trial conducted across 79 centres in the USA and Canada revealed valuable data on the safety and immunogenicity of mRNA-1273 COVID-19 vaccine in children aged 6 months to 5 years. The study found that solicited local and systemic vaccine side effects presented at a low grade and appeared an average of 2 days after injection, persisting for an average of 2–3 additional days. Side effects were most common after the second vaccination and occurred at a higher rate in the experimental compared with the placebo group. Researchers also found that unsolicited adverse events reported an average of 28 days post-vaccination occurred at similar rates between experimental and placebo groups. Severe adverse events were also similar amongst the two study groups, with only eight severe adverse events reported in infants aged 6–23 months and 0 in children aged 2–5 years. Of the eight children experiencing severe adverse events, one experienced a fever and febrile seizure with concurrent maculopapular rash developing 2 days after the first dose administration, suggesting an incidental concomitant viral infection. Symptoms eventually resolved, and the second dose was administered with no complications. Post-vaccine COVID-19 antibody titres were similar to figures reported in similar studies of older children, adolescents, and adults.[27] Another study cited the incidence of maculopapular rash in 43 participants across three observational studies, 49% of whom received the BNT162b2 vaccine and 51% of whom received the mRNA-1273 vaccine.[28] All but one resolved within 2–3 days, with one persisting for 1 month. Several other studies reported similar results amongst this age group.[29] Limited information is available on adverse events of other vaccine modalities, owing to their limited of use in young cohorts.

Results are similar in older paediatric age groups. A study by Kasif et al. found that amongst the 3,732 adolescents that were randomised in a 2:1 ratio into experimental and placebo groups, only mild, non-remarkable local or systemic adverse events occurred in both groups. No incidence of death, multisystem inflammatory syndrome in children, myocarditis, or pericarditis were observed. Researchers also noted that the incidence of unsolicited adverse events was similar in participants 12–15 years of age and 16–17 years of age, indicating homogeneous findings.[30] In an ongoing, placebo-controlled, observer-blinded, multinational, pivotal efficacy trial of 44.165 participants aged 16 and above, the incidence of life-threatening adverse events was 0.1% in both placebo and experimental groups, and the incidence of severe adverse events was also the same (0.3%) amongst both study groups.[31] A visual summary of the most common side effects and severe adverse events of these vaccine modalities can be found in Figure 1.

Interestingly, a recent systematic review found that the frequency of events/manifestations following vaccination decreased with subsequent dosing in attenuated, viral vector and protein subunit vaccines. Adverse events (43.7% of which were cutaneous manifestations) decreased in frequency from 52 post-first dose to two after the booster dose. Additionally, almost 90% of cutaneous manifestations were of known etiology, treatable, and resolved in less than 10 days, suggesting that even in the case of adverse events safety is not significantly compromised.[32]

Other vaccines

A double-blind phase 1/2 clinical trial conducted in China revealed that amongst children aged 3–17 years old, the Sinovac vaccine showed a 26% rate of side effects (injection site pain, fever, fatigue) for one dose and 63% for a double dose. Pneumonia was the only severe adverse event recorded and affected one participant, with researchers considering it unrelated to vaccination.[33] Pneumonia is more correlated with exaggerated COVID-19 infection rather than COVID-19 vaccination.[34] Humoral responses were high in both

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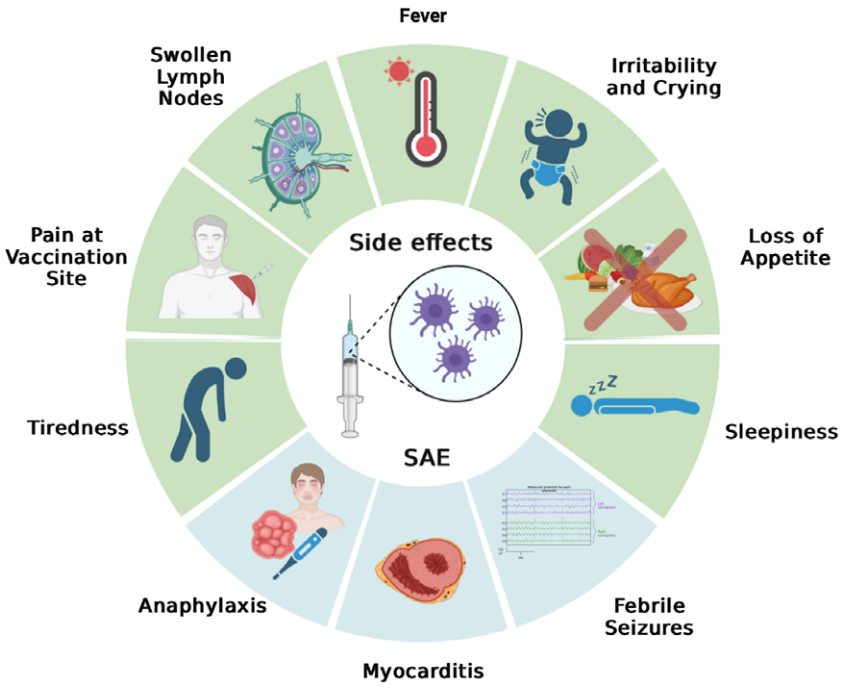

Figure 1. A visual summary of side effects and severe adverse events observed post-paediatric COVID-19 vaccination.[24] ****This figure was developed using Biorender software.*

single- and double-dose cohorts with seroconversion being 100% in both cohorts with 95% confidence intervals of 87.2–100% and 86.8–100%, respectively.[33]

Further data on Sinovac are comparative, as the vaccine has not yet been authorised for use in paediatric cohorts.[35] Thus, reports of severe adverse events for this vaccine are limited. A study of 39 children and adults with inborn errors of immunity revealed no severe adverse event with both mRNA and Sinovac vaccines, though results suggested that three doses of each vaccine must be given to reach optimal immunogenicity comparable with that observed in non-immunocompromised persons.[36]

Limited data is available on the AZD122 vaccine. A study including more than 300 participants between the ages of 6 and 17 revealed a safety profile comparable with that observed in all other vaccine modalities. Notably, fewer adverse events (severe, unsolicited and otherwise) were observed after the second rather than the first dose of the vaccine, irrespective of the timing between the doses.[37]

An experimental recombinant adenovirus type-5 (Ad5)–vectored COVID-19 vaccine developed in China was also assessed for adverse events in participants more than 6 years old. Results indicate the same adverse events noted for routine vaccination and other COVID-19 vaccines summarised above, with no severe or life-threatening reactions. Two other experimental vaccines (WIBP-CorV and BBV-152) are also in development with very similar safety profiles.[38,39] Interestingly, fewer adverse events were reported following boost vaccination than following primary vaccination.[40] Another experimental vaccine in development is the ZyCoV-D vaccine being researched in India. Khobragade et al. found that much like all other vaccines, mild side effects were observed at higher rates in experimental compared with control groups of participants aged 12 and older. However, researchers also noted that two deaths were observed in the experimental group, though causes of death were not attributed to vaccine side effects. Two doses of ZyCoV-D were also found to be 100% efficacious at preventing severe cases of COVID-19.[41] Two doses of the tetanus toxoid COVID-19 vaccine FINLAY-FR-2 followed by one dose of FINLAY-FR-1A in children revealed extremely promising results. No severe adverse events were noted, and the vaccines mounted a humeral response similar to that of natural infection. Adverse events that were observed were unremarkable and solicited.[42]

Vaccine combinations have also been under study. Viral vector (AstraZeneca) and attenuated (Sinopharm) vaccines were tested in combination with Postovac protein subunits by Larjiani et al. Results show that combined vaccination carries a 4.2% increased risk of adverse events compared with isolated Postovac vaccination during an 18-month follow-up period. However, results show a low number of adverse events after the 18-month period in all experimental and control groups, suggesting favourable safety profiles.[43]

Severe adverse event 1: Anaphylaxis

As is the case with other novel vaccines and drugs, the risk of anaphylaxis is of interest. A nationwide observational study in the adult population found that there were 66 incidences of anaphylaxis out of 61,414,803 administered doses of various COVID-19 vaccines, corresponding to an incidence of 1.07 per 1,000,000, with most (86%) being female.[44] One prospective cohort study conducted in 2021 suggested a higher incidence, with nine patients out of 403 (2.2%) experiencing severe anaphylactic reactions after the administration of either the Pfizer or AstraZeneca vaccines. Having a prior history of anaphylaxis did not appear to be a risk factor, as 1.5% of enrolled patients with a prior history of anaphylactic reactions experienced a reaction with a COVID vaccine, while 3% of enrolled patients with no prior history experienced a reaction.[45] This contrasts with the findings of a case series in which 15 out of 22 (68%) patients who were enrolled after suffering an anaphylactic reaction to a COVID-19 vaccine were found to have a prior history of such reactions. The basophil activation test was positive to PEG in the 11 patients who agreed to further testing, though PEG IgE was negative, suggesting a

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non-IgE-mediated aetiology.[46] A review published in the *Italian Journal of Pediatrics* points out that though the risk of post-COVID-19 vaccine anaphylaxis in children is low, high-risk children, including those with prior history of anaphylaxis or reactions to other vaccines, should consult with their paediatrician before receiving a dose.[47]

Severe adverse event 2: multisystem inflammatory syndrome in children

Multisystem inflammatory syndrome in children is a rare side effect of COVID-19 exposure, including vaccination. A 2022 study used the Vaccine Adverse Event Reporting System to determine the incidence of post-vaccination multisystem inflammatory syndrome in children in patients aged 12–20 years. It was found that 21 individuals out 21,335,331 were diagnosed with multisystem inflammatory syndrome in children, corresponding to a reporting rate of 1 in 1,000,000.[48] There have also been two published case reports discussing the hospital course of three paediatric patients who developed multisystem inflammatory syndrome in children shortly after vaccination, all of whom made uneventful recoveries.[49] The evidence in the current literature suggests that though multisystem inflammatory syndrome in children can occur post-vaccination, such events are much more common following organic COVID-19 infection, with vaccination even having a protective effect in some cases.[50]

Other severe adverse events

There are a few reports of autoimmune and/or neurological disease following COVID-19 vaccination in paediatric patients, including cases of Guillain–Barre syndrome and thrombotic thrombocytopenic purpura. A case report published in the *British Journal of Clinical Pharmacology* details the case of a 13-year-old female that presented with bilateral weakness and was subsequently diagnosed with Guillain–Barre syndrome. The patient had received the COVID-19 vaccine 3 days ago.[51] Another case report discussed similar findings in a 14-year-old male 1 month after COVID-19 vaccination. Both cases were treated with multiple sessions of Intravenous immunoglobulins (IVIG) followed by gradual complete resolution.[52] As is the case with multisystem inflammatory syndrome in children, it appears that Guillain–Barre syndrome is much more common after COVID-19 infection than after vaccination.[53] As for thrombotic thrombocytopenic purpura, there are two published papers that discussed cases in paediatric patients following COVID-19 vaccination. The first describes the cases of two females, 15 and 19 years old, who developed thrombotic thrombocytopenic purpura following Pfizer COVID-19 vaccination.[54] The second paper discussed the case of a 14-year-old female who also developed thrombotic thrombocytopenic purpura after the first dose of COVID-19 vaccination.[55] All patients were treated with plasma exchange, methyl prednisone, and immunosuppressants and subsequently improved.[56]

Cardiac severe adverse events

Several peer-reviewed articles report incidence of myocarditis following mRNA COVID-19 vaccination in a paediatric cohort.[57–62] In the case of Snapiri et al,[63] myocarditis was transient, and there was no data on prior COVID-19 infection or receival of a second dose of the BNT162b2 vaccine.[64] The majority of reported cases of myocarditis post mRNA vaccination have been reported in adolescents and young adults between the ages of 12 and 24 after receiving a second dose of the vaccine. Conditions have been reported to be mild and transient in most cases, with only minimal treatment required and complete recovery within a few days.[65] A typical presentation for a case is a 17-year-old previously healthy male presenting with chest pain and having fulfilled multisystem inflammatory syndrome in children criteria post-BNT162b2 vaccination.[66,67] Diagnosis is myocarditis with a reduced ejection fraction up to 20%. Many patients do not satisfy the multisystem inflammatory syndrome in children criteria and present with myocarditis or myopericarditis nonetheless.[68] Treatment entails admission to the ICU for around 6 days for high-flow oxygen therapy, norepinephrine infusion, steroids, intravenous immunoglobulins, and antibiotics. Several cases are self-resolving or require a simple course of nonsteroidal anti-inflammatory drugs.[69] Discharge is typically 10 days post-admission with a normalization of ejection fraction on MRI at 62%. Follow-up 8 days post-discharge typically reveals an asymptomatic patient with residual fatigue of no obvious clinical consequence.[70]

Furthermore, a study published in *Nature* found that 1,615 (0.004%) of 38,615,491 patients presented with myocarditis after receiving a COVID-19 vaccine shot. Of these patients, 359 (22.2%) tested positive for COVID-19, 287 (80%) of whom tested positive for COVID-19 prior to vaccination. Authors further report an association between 1–7 and 1–238 days post-COVID-19 vaccination and the incidence of myocarditis, particularly following the second dose.[71] It is worth mentioning that this is true for a sample population aged 12 and over and is therefore not necessarily characteristic of vaccinated paediatric patients. Further studies are needed to properly characterise myocarditis post-COVID-19 vaccination in paediatric patients.

A study published in the *Pediatric Infectious Diseases Journal* describes a time association between adolescents aged 16–18 receiving the COVID-19 BNT162b2 vaccine and the incidence of peri-myocarditis. In six of the seven patients, symptoms proceeded the second dose, while the seventh patient showed symptoms following the first dose. The sample case displays several cardiac and laboratory findings indicating myocarditis and pericarditis, the hallmark of which is more than a 22-fold increase in troponin levels. Upon treatment with ibuprofen (dose not mentioned) and hospitalisation in the paediatric ICU, the patient recovered in 6 days and left the paediatric ICU with normal troponin levels.[63] Interestingly, patients presenting with concurrent GI symptoms were subjected to more intensive care but also recovered well.[72]

The exact mechanism through which COVID-19 vaccines may trigger myocarditis and troponinemia are unknown. Suspected mechanisms include molecular mimicry between SARS-Cov-2 and self-antigens and dysregulated activation of the immune system. Several earlier studies found that myocarditis is amongst the main cardiovascular manifestations of paediatric COVID-19 infection, triggered primarily by an overwhelming immune response manifested by an elevation in the level of inflammatory markers such as IL6, C-reactive protein, and pro-calcitonin. Authors of the paper mentioned previously suggested potential inoculation with COVID-19 during the study period to explain the incidence of myocarditis, though this is not confirmed.[73]

It is postulated that free-floating spike protein from vaccination may interact with ACE-2 receptors resulting in degradation and consequently hypertension. Thus, COVID-19 vaccination may lead to cardiac discomfort that does not manifest as myocarditis. This is especially true in young adult (aged 18–26) and adult populations compared with teenage populations (aged 12–17). Myocarditis is known to have a slight increased propensity to occur

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in teenagers. Likewise, myocarditis following COVID-19 vaccination is observed in paediatric populations more so than adult ones, though the incidence of cardiac symptoms post-vaccination does not follow this trend.[74]

Paediatric patients with significant comorbidities such as CHD may be at greater risk of severe adverse events with COVID-19 and possibly even following vaccination. There is very limited data on the incidence of severe adverse events following COVID-19 vaccination in paediatric patients with CHD, though some studies on adults exist. A 2022 report described the case of a 63-year-old woman with a ventricular septal defect who suffered a transient episode of ventricular tachycardia following administration of an adenoviral COVID-19 vaccine.[75] Another study, conducted in an Italian tertiary care centre, found that 0 out of 208 adult CHD patients suffered major adverse events from the vaccine, and the number of minor adverse events was no different from the control group.[76] There is no available evidence to suggest that COVID-19 vaccination is more dangerous in CHD patients than others. In fact, the risk of complication following organic COVID-19 infection far outweighs the risks of vaccination in these patients. A retrospective review using the Vizient Clinical Database found that children with CHD had a 4.75 times higher risk of mortality from COVID-19.[77] Another study described the hospital course of 9 children with CHD that were admitted for COVID-19. Two of the patients, both of whom had hypoplastic left heart syndrome and aortic stenosis, died.[78] Other studies are more ambivalent as to whether COVID-19 infection is more dangerous in CHD patients, with the consensus being that patients in poor physiologic states may indeed have worse outcomes.[79–82] This points to the importance of vaccination to protect from COVID-19 in these vulnerable patients.

Discussion

Weighing the evidence

Generally, in a case series report given the current state of knowledge, the rare outcome of transient myocarditis and pericarditis should not significantly alter vaccine recommendation.[72,86,87] The Centers for Disease Control and Prevention reported an incidence of approximately 12.6 cases of myocarditis per million doses.[73] The Advisory Committee on Immunization Practices concluded that the benefits of COVID-19 vaccination in an adolescent population outweigh the potential risk of myocarditis, thus recommending mRNA vaccination.[88] In addition, a 2022 systematic review found that the risk of myocarditis from organic COVID-19 infection was seven-fold attributable to vaccination.[89] This means that any risk of vaccine-related myocarditis is offset by that of organic infection, especially given the widespread nature of the virus. This is especially relevant in CHD patients, who are at an increased risk for fibrotic cardiomyopathy and lasting cardiac dysfunction after episodes of myocarditis.[77] These patients are particularly in need of prompt vaccination to prevent these COVID-19 infection complications.

The risk of anaphylaxis with COVID-19 vaccines is low and is comparable with the risk of other vaccines.[90] Still, patients with a history of anaphylaxis should consult with their paediatrician before receiving a dose.[47] Other rare complications such as Guillain–Barre syndrome and multisystem inflammatory syndrome in children appear to occur at higher rates with organic COVID-19 infection compared with vaccination. This means that COVID-19 vaccination is protective against these complications.[50,53,91] Therefore, the benefit of vaccination, especially in vulnerable patients, outweighs the risk. Thrombotic thrombocytopenic purpura appears to be exceedingly rare post-COVID-19 vaccine, with only two published case reports documenting its occurrence, with all patients making uneventful recoveries.[54,55]

Patients with congenital heart disease are a vulnerable population, and COVID-19 infection may place them at an increased risk of death compared with other patients.[77,78] This is especially true in patients in poor physiologic states.[79–82] However, vaccination against COVID-19 does not appear to place them at any increased risk of harm.[76] Current evidence therefore suggests that the benefit acquired from protection against COVID-19 and its complications outweighs the risk of side effects in these patients.

Vaccine hesitancy

Recently, social media has also been used to track and collect data on vaccine attitudes and efforts. Cuschieri et al. conducted a cross-sectional study in Malta to understand vaccine willingness, hesitancy, and unwillingness amongst adult social media users through an online questionnaire advertised linked on social media. Results indicate that amongst this cohort, vaccine hesitancy is low, though vaccine unwillingness is high, particularly with regard to receiving one or potentially more booster shots in the future. Fear of severe adverse events was the main reason participants cited for vaccine unwillingness.[92] Several similar studies cite similar results.[93–96] Social media use has also been used as both a demographic marker and a marker of social and emotional well-being of participants in surveys and questionnaires regarding the pandemic, with results indicating that the majority of surveyed individuals obtained public health information from social media regarding the pandemic and that social media use was positively correlated with vaccine hesitancy.[97]

Though over 90% of teenagers utilise social media,[98] studies concerning vaccine hesitancy specifically targeting a paediatric cohort through social media have not been reported. This is probably due in part to the ethical dilemmas surrounding the use of social media to influence individuals under the age of 18[99] and in part to physician- and health personnel-related hesitancy towards social media use. A study by Hou et al. reported a significant knowledge gap between physicians and the social media. Authors reported fear of litigation, lack of understanding, time, and fear of unprofessionalism as barriers to social media use amongst healthcare workers.[100] During the pandemic, social media became a major source of unregulated public health information,[101] underscoring the importance of demographically appropriate interventions to promote knowledge and combat vaccine hesitancy.[102,103]

Furthermore, while a very large number of randomised controlled trials have been conducted to assess self-reported COVID-19 vaccine symptoms in adults,[104] similar studies in a paediatric cohort remain unfound. There are also significant gaps in the literature when it comes to COVID-19 vaccination in not only CHD patients but the paediatric cohort as a whole. Specific COVID-19 vaccine rates in children are not well reported or well characterised. There is a lack of published studies reporting post-vaccination adverse events in paediatric CHD patients and very few in adults with CHD. More large-scale studies should be done to evaluate the risk of myocarditis and other vaccine-associated cardiac complications in CHD patients. Even though current evidence points towards the benefit of COVID-19 vaccination

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outweighing the risk, cardiac complications of vaccination appear to be underreported in this patient population.

Conclusion

The most relevant severe adverse events following paediatric COVID-19 vaccination include anaphylaxis, multisystem inflammatory syndrome in children, and cardiac events (myocarditis and pericarditis). However, the reported incidence of these vaccine-related complications is extremely low and appears not to be significant. Thus, vaccination benefits may outweigh potential risks. The most widely studied paediatric vaccines are the mRNA vaccines that have high efficacy rates and favourable safety profiles suggesting possible slight superiority to other vaccine modalities though further studies are needed to support conclusions. Needless to say, it is important to treat complicated cases in a case-by-case manner, as vaccines have not yet been studied in all paediatric disease states. For example, cardiac complications in CHD patients are underreported and represent a gap in the literature. Further studies are needed to rationalise vaccine hesitancy such that it may be promptly addressed.

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