Review

Addressing immunization gaps in children with congenital heart disease - a narrative review

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Abstract

Vaccination programs have had a pivotal part in the successful reduction of global morbidity and mortality of infectious diseases. Despite their undeniable success, vaccination rates among children with congenital heart disease (CHD) remain suboptimal. This article aims to address the challenges surrounding immunization in CHD patients and provide guidance for immunization practices within this population.

Most experts advocate for adherence to standard immunization practices in CHD patients who are immunocompetent and in good health. Supplemental vaccinations against rotavirus, varicella, meningococcus, hepatitis A and influenza are recommended. RSV prophylaxis with palivizumab is advisable in patients with hemodynamically significant CHD during winter season. However, special considerations are warranted in specific situations, such as around cardiac surgery or in patients who are immunocompromised. Furthermore, adjustments to the vaccination schedule might be necessary for patients who require antithrombotic prophylaxis or blood transfusions. Lastly, special attention should be given to individuals at a high risk of decompensation after immunization, who might require close parental or medical monitoring for up to 72 hours post-vaccination.

Keywords: immunization, congenital heart defects, cardiac surgical procedures, vaccination

Introduction

Vaccines stand as one of the greatest public health success stories in modern times. World-wide vaccination initiatives have played a central role in reducing morbidity and mortality of infectious diseases, with an estimated 6 million deaths prevented each year [1]. It is estimated that global immunization programs have saved 386 million life years and prevented 96 million disability-adjusted life years, especially in children [1]. Moreover, the successful eradication of smallpox at the end of the 20th century demonstrated the effectiveness of well-coordinated immunization programs [1,2]. Despite the compelling evidence for the benefits of immunizations, vaccination rates remain unsatisfactory, especially within vulnerable populations [3].

Congenital heart disease (CHD) is the most prevalent congenital malformation, with an incidence of 6 cases per 1000 live births [4]. With the advancement of surgical techniques and management strategies, survival rates and quality of life of CHD patients have significantly improved in recent years. Better outcomes for CHD patients raise new questions about their long-term surveillance and treatment strategies, especially in primary care. Several studies have shown sub-optimal vaccination rates within this vulnerable population [5–7]. These findings are of particular importance considering that CHD patients are more susceptible to infections due to alterations of innate immunity and chronic inflammation [8]. Additionally, this particular group of patients faces a higher risk for adverse outcomes from infectious diseases compared to their healthy counterparts [9]. Multiple studies have sought to investigate the underlying

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reasons for the low immunization rates. Commonly encountered factors include frequent hospitalizations, recurrent infections that deferred immunizations, refusal of community centers to administer vaccines outside of hospital setting, as well as a lack of consensus on optimal vaccination practices [5,10].

In light of these observations, our article aims to clarify the underlying challenges of immunization in patients with CHD. By delineating recommended practices endorsed by responsible authorities, our goal is to provide clinicians with the guidance required to improve vaccination rates within this vulnerable population.

Recommended vaccines for children with CHD

The consensus among experts and authorities is that vaccination is safe in stable immunocompetent patients with CHD and can be administered according to the recommended schedule [11–13]. A study conducted in China has demonstrated a low incidence of adverse reactions in children with CHD who presented good health and normal heart function [14]. Therefore, it is essential to prioritize adherence to the recommended immunizations, considering the higher risk of adverse outcomes from infections in this group [9]. Key steps include reviewing the child's immunization records at each pediatric or family medicine scheduled visit and adhering to the vaccination schedule. In Romania, this includes vaccination against hepatitis B, tuberculosis, diphtheria, tetanus, pertussis, poliomyelitis, Haemophilus influenzae type B, pneumococcus, measles, mumps and rubella [15]. The national vaccination schedule can be consulted in table I. Prophylactic paracetamol can be prescribed after vaccinations, as fever might not be well tolerated in some CHD patients [12]. Fever-induced tachycardia can be particularly detrimental in certain types of CHD, as it may reduce effective ventricular filling time and exacerbate heart failure symptoms.

Besides the recommended vaccines from the national schedule, children with CHD should receive additional immunizations. Experts recommend that children with CHD are also immunized against varicella, meningococcus, hepatitis A and Rotavirus [11].

Table I. Romanian National Vaccination Schedule. Adapted from [15,16]. All vaccines are inactivated, except for the ones marked with *, which are live attenuated.

	Romanian National Vaccination Schedule						
Birth	**Calmette Guerrin vaccine***	Hepatitis B vaccination					
2 months			Hexavalent vaccine against diphtheria, tetanus, pertussis, poliomyelitis, Haemophilus influenzae type B and hepatitis B			Conjugated pneumococcal vaccine	
4 months			Hexavalent vaccine against diphtheria, tetanus, pertussis, poliomyelitis, Haemophilus influenzae type B and hepatitis B			Conjugated pneumococcal vaccine	
6 months							
11 months			Hexavalent vaccine against diphtheria, tetanus, pertussis, poliomyelitis, Haemophilus influenzae type B and hepatitis B			Conjugated pneumococcal vaccine	
12 months							**Measels-rubella-mumps vaccine***
5 years							**Measels-rubella-mumps vaccine***
5-6 years				Tetravalent vaccine against diphtheria, tetanus, pertussis, poliomyelitis			
14 years					Vaccine against diphtheria, tetanus and pertussis		

Special attention should be considered in the case of common respiratory viruses such as influenza and syncytial respiratory virus. Pediatric patients with lower respiratory tract infections and significantly hemodynamic cardiac disease have a restricted capacity to increase cardiac output and oxygenation delivery, consequently being at risk of respiratory failure and decompensation of the underlying heart disease [17,18]. Influenza infection carries a significantly higher risk of adverse outcomes and in-hospital mortality in children with cardiac disease [19]. Therefore, all patients with CHD over the age of 6 months are recommended to receive the influenza vaccination annually [11,19]. It is significant to highlight that live attenuated influenza vaccine should not be used in children with CHD, in order to prevent complications from potential live virus replication, especially when a viable alternative exists [11].

Respiratory syncytial virus accounts for most lower respiratory tract infections in infants, with 90% of all children being infected by the age of 2 years [18,20]. Children with cardiac abnormalities, especially those with pulmonary hypertension, are at greater risk of hospitalization and mortality from RSV infection. Several studies demonstrated that approximately 33% of hospitalized children with CHD and RSV infection require ICU admission, with 3.4% experiencing fatal complications related to the infection [18,21,22]. A large trial conducted in 2003 evidenced that monthly prophylaxis with palivizumab, a humanized murine monoclonal antibody against RSV, reduced RSV hospitalizations by 45% in children with hemodynamic significant cardiac abnormalities [22]. Subsequent studies have demonstrated the safety and efficacy of palivizumab in reducing morbidity and mortality in this group of patients [8,23]. Therefore, it is advisable that children under the age of 2 with clinically significant cyanotic or acyanotic congenital heart disease, requiring cardiac medication or corrective surgery, undergo monthly RSV prophylaxis with palivizumab during winter season (September – March). If the child contracts RSV infection, they should continue the administration of palivizumab throughout the season since acute infection in infants does not confer protective immunity [18].

In addition to the aforementioned recommendations, it is advised that close contacts of the patients, such as parents and siblings, receive appropriate immunizations in order to protect the child [24]. Moreover, special consideration should be taken into account in patients with scheduled cardiac surgery or immunocompromised children such as those with Di George or Asplenic Heterotaxy syndrome.

Special considerations – Cardiac Surgery

A significant proportion of patients diagnosed with CHD require corrective cardiac surgery. These interventions are scheduled at increasingly earlier ages, coinciding with the typical timing of routine immunizations. Consequently, clinicians face new challenges in ensuring that these patients adhere to their immunization schedule. Concerns about immunization before surgery include potential side effects from vaccines such as fever and rashes, which could add stress on patients during this period [13]. Moreover, these side effects might be incorrectly attributed to other causes, potentially leading to delays of the intervention. Therefore, it is recommended that vaccines should not be administered within a week of the scheduled surgical procedure [13]. A notable exception is the MRM vaccine, which should not be given within 2 to 4 weeks of the planned intervention, as side effects from this vaccine can arise up to 2 to 4 weeks after its administration [12,25]. Furthermore, the potential risk for thrombocytopenia after MRM vaccination also calls for precaution when considering this immunization before planned surgery [12,26]. Similar precautions should be considered with the varicella vaccine, which should not be administered within 4 to 6 weeks of the intervention for comparable reasons [12] .

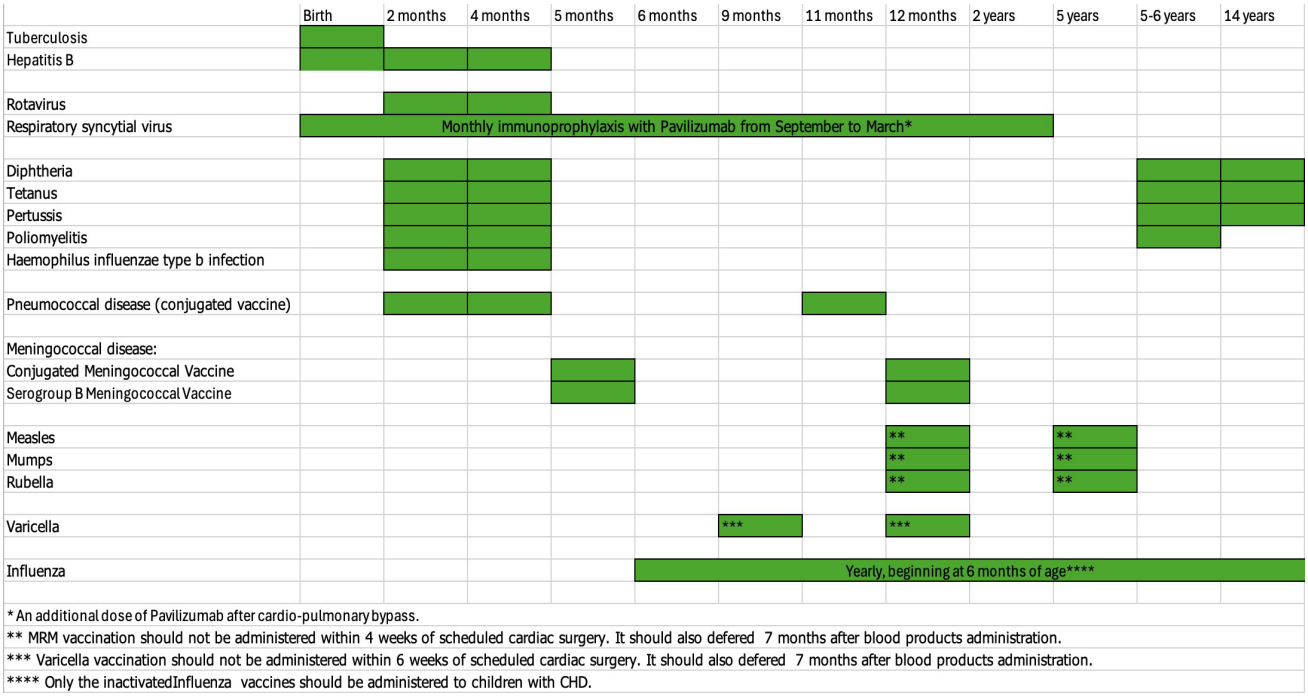
After cardiac operation, the administration of immunizations requires careful consideration due to the complex nature of the procedures involved. Surgery requires hospital admission, employment of cardiopulmonary bypass and administration of blood products, all contributing to the inherent risks of infections and subsequent organ sequelae [12]. Concerns arise regarding the potential for vaccine side effects to mask or complicate post-surgical issues [12]. Consequently, it is recommended that inactivated vaccines be delayed for 4 to 6 weeks after surgery [13]. Moreover, cardiopulmonary bypass requires blood transfusions, which can exert important immunomodulatory effects [12]. Since blood products can diminish the immune response to live attenuated vaccines, it is advisable to defer the administration of such vaccines for up to 7 months after the intervention [12,13]. This restriction does not apply to Rotavirus immunization, because of its oral route of administration and minimal interaction with circulation antibodies [13]. A list of live attenuated vaccines frequently used in Romania is provided in table II. Additionally, cardiopulmonary bypass is known to diminish serum palivizumab concentrations under the protective level. Therefore, it is recommended to administer an additional dose of palivizumab after the procedure [22].

A proposed immunization schedule for children with CHD that require corrective surgery can be found in table III.

Table II. List of live attenuated vaccines found in Romania. Adapted from [11,15].

Live attenuated vaccines
- Calmette Guerrin vaccine;
- Measles-rubella-mumps vaccine;
- Varicella vaccine;
- Rotavirus vaccine;
- Live attenuated influenza vaccine (intranasal);
- Oral Polio Vaccine

Table III. Proposed Proposed Vaccination Schedule for children with CHD in need of corrective cardiac surgery. Adapted from [15,16,27]. This schedule does not apply for children with CHD and asplenia or immunodeficiency.



Special considerations – Di George syndrome

Di George syndrome is a genetic defect commonly caused by 22q11.2 microdeletions. It is characterized by the triad: hypocalcemia caused by hypopituitarism, immunodeficiency and congenital heart defects [11,28]. Among the observed cardiac anomalies are conotruncal malformations such as conoventricular ventricular septal defect (VSD), truncus arteriosus, tetralogy of Fallot, pulmonary atresia with VSD or interrupted aortic arch [28,29]. Immunodeficiency is present in approximately 75% of patients and results from hypoplasia of the thymus and impaired T-cell production [28,30]. The coexistence of severe cardiac disease, which often requires corrective surgery, and immunodeficiency, which increases the risk for infections and their adverse outcomes, prompts inquiry about the correct immunization practices in individuals with 22q11.2 deletions. Live attenuated vaccines are a concern in this group, due to potential vaccine-related disease [31]. Therefore, this type of vaccine should only be administered after consultation with an immunologist [11,13]. Furthermore, it is recommended that these patients receive additional doses of pneumococcal vaccines, as well as annual influenza immunization [31]. In settings of cardiac surgery, blood products should be irradiated and CMV negative in order to prevent transfusion-associated graft-versus-host disease. These measures also aim to reduce lung injury, particularly in surgical cases requiring cardiopulmonary bypass [32].

Special considerations – Heterotaxy syndrome

Heterotaxy syndrome is a complex lateralization abnormality of the thoracoabdominal viscera, caused by aberrant embryological development [33]. It determines an atypical symmetry of the internal organs located in the thorax and abdomen, including the atria of the heart [34]. In left heterotaxic syndrome, the right organs are a mirrored image of the left viscera, leading to complex congenital cardiac malformations where both atria are morphologically left atria, bilateral bilobed lungs, midline liver and multiple spleens [33,34]. Right isomerism is defined as the condition where opposite organs on the right-to-left axis of the body are mirrored images of the right structures [33]. It determines severe cardiac defects such as discordant atrioventricular and ventricular-arterial connections, common atria or univentricular heart, bilateral trilobed lungs, midline liver and hyposplenia or absent spleen [33,34]. Hypo – and asplenia cause derangements of the immune system, primarily attributed to the depletion of IgM memory B cells and impaired phagocytosis [35,36]. It increases the risk of infections, especially with encapsulated bacteria such as Neisseria meningitidis, Streptococcus pneumoniae and Hemophilus Influenzae type B [11,36]. All children with right isomerism and hypo-/asplenia should receive age-appropriate immunization as per routine guidelines [34,36]. Special considerations should be given to vaccines targeting encapsulated bacteria. Immunizations against Meningococcus, Pneumococcus and Hemophilus

Influenzae type B are recommended for these individuals, with additional boosters required to maintain long-term immunity. Additionally, annual influenza vaccination is advised [36]. It is important to emphasize that no vaccines, including live attenuated ones, are contraindicated in these patients [13].

Special considerations – drugs and blood products

Children with heart disease often require medication, whether for a short or extended period, in order to maintain their health. Following corrective cardiac surgery, patients may require antithrombotic prophylaxis with anticoagulants and/or salicylates [37]. Due to the association between natural varicella infection, aspirin and Reye syndrome, the CDC and vaccine producers recommend avoiding aspirin use for six weeks following varicella immunization [13,38–40]. While no reported cases have linked the vaccine to Reye syndrome, avoidance of aspirin is advised as a precaution [13,39]. In children on long-term salicylate therapy, clinicians must carefully assess the potential risk of Reye syndrome against the known risks of thrombosis or varicella disease before administering the vaccine or deciding to interrupt aspirin therapy [13]. The same precautions should be considered for influenza vaccination. However, since an inactivated vaccine is available for administration, live inactivated vaccines are contraindicated in this group of patients [41]. Regarding anticoagulation therapy, intramuscular vaccine administration may be associated with a theoretically higher risk of bruising, hematoma, and bleeding. Therefore, subcutaneous administration has been regarded as a potential option to mitigate these complications. However, it's important to note that in addition to the potential diminished immunological effect associated with subcutaneous administration, this route has not been proven to be safer than the intramuscular route [42]. As a result, the decision to use either route should be individualized taking into account the patient's past history of bleeding, clinical data, renal, hepatic and coagulation parameters [43].

Cardiac surgery and other associated conditions or complications of CHD require blood product transfusion. These blood products frequently contain antibodies against numerous pathogens, gained either by natural infection or immunization. These antibodies can interfere with the natural response of the immune system to live vaccines, leading to a diminished response [12,44]. The same principle applies to Intravenous Immunoglobulin. (IVIG), a product commonly utilized in the treatment of Kawasaki disease [12,44]. Table IV contains the necessary interval between receipt of blood products or IVIG and subsequent administration of live vaccines in order to amount to an adequate immune response. Clinicians are recommended to consult it to facilitate appropriate scheduling of immunizations in these patients.

CHD patients at risk for decompensation after immunization

While most children with CHD tolerate immunizations without any complications, some patients are at a higher risk of decompensation after vaccinations. Individuals with previous adverse reactions to immunizations, shunt-dependent lesions, univentricular defects or Norwood corrections, as well as premature or low-birth-weight infants, might be particularly susceptible to decompensation post-immunizations [45]. It's important to emphasize that these conditions are not a contraindication to vaccination. However, physicians should exercise caution with these individuals. Clinical reviews are necessary before administration and if deemed safe, immunizations can be administered in an outpatient setting. Parents must be instructed to monitor for general deterioration, respiratory distress, or cyanosis for up to 72 hours post-immunization and seek medical assistance if these symptoms arise. Hospital admission and monitoring can be considered in special circumstances in some particularly high-risk infants, such as those with univentricular hearts, especially those with Norwood correction. Antipyretic prophylaxis with paracetamol should be administered, especially in high-risk individuals [45].

Table IV. Necessary interval between receipt of blood products and subsequent administration of MRM or Varicella vaccine. Adapted from [12] and [44].

Blood product	Interval between receipt of blood products and subsequent administration of MRM or Varicella vaccine
Washed Red Blood Cells	0
Reconstituted Red Blood Cells	3
Packed Red Blood Cells	5
Whole Blood	6
Fresh Frozen Plasma	7
Platelets	7
Intravenous Immunoglobulin (IVIG – 2g/kg)	11

Discussion

Ensuring that children with congenital heart disease (CHD) receive appropriate immunizations is essential for safeguarding their health and well-being. Alongside adhering to the national vaccination schedule, it's essential to provide additional immunizations such as varicella, meningococcus, hepatitis A, rotavirus and influenza vaccination in stable immunocompetent children with CHD [11–13,19]. Furthermore, these children might benefit from immunoprophylaxis against RSV with palivizumab in the cold season [18]. However, caution is advised in patients who require corrective cardiac surgery. It is recommended that vaccines are not administered in the period right before the planned intervention. Following the procedure, immunization should be delayed for 4-6 weeks for inactivated vaccines and 7 months for live ones [12,13].

Patients with CHD and compromised immunity require meticulous planning for their immunization schedule. For instance, patients with Di George syndrome live vaccines should only be administered after consultation with an immunologist [11,13]. Similarly, patients with anatomic or functional asplenia, such as those with Right Heterotaxy syndrome, have special requirements regarding vaccination, especially against encapsulated bacteria. Besides the required immunizations from the national schedule, these individuals must be vaccinated against Meningococcus, Pneumococcus, Hemophilus influenzae type B, and influenza, with the potential need for additional boosters [34,36]. Special immunization considerations are warranted for patients undergoing antithrombotic prophylaxis, especially for those with salicylate therapy [13,38–40]. If transfusions are administered, immunization with live vaccines should be deferred according to the required interval depending on the specific blood product administered [12,44].

Conclusion

In light of the reported benefits of vaccination in children with CHD, we advocate for comprehensive education on immunization practices, as well as emphasizing the importance of collaborative efforts among pediatric cardiologists, pediatricians, primary care physicians and immunologists. Such endeavors are central to improving immunization rates and ensuring the well-being of children with CHD.

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