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SPECIAL PAPER

Guidelines for immunization of children following multisystem inflammatory syndrome in children

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ABSTRACT

Multisystem inflammatory syndrome in children (MIS-C) is a late complication of SARS-CoV-2 infection, either symptomatic or asymptomatic. The underlying cause is immunological dysregulation, leading to severe inflammatory processes. Children with MIS-C require hospital treatment, the use of immunomodulating drugs, and often intensive care. COVID-19 vaccination is safe and highly effective in preventing not only severe COVID-19, but also MIS-C in adolescents. However, there are no explicit vaccination recommendations for children who underwent MIS-C. We present a summary of current knowledge on vaccinations against COVID-19 in the context of MIS-C. Moreover, we propose guidance concerning vaccinations for children following MIS-C.

KEY WORDS:

vaccines, COVID-19, SARS-CoV-2, PIMS-TS, BNT 162b2.

INTRODUCTION

Pediatric inflammatory multisystem syndrome (PIMS), also referred to as multisystem inflammatory syndrome in children (MIS-C) or in adults (MIS-A), is a complication of (even asymptomatic) SARS-CoV-2 infection occurring approximately 4 weeks after it [1–5].

The frequency of this complication is estimated at 1 : 3000 infected children in the USA [6] and 1 : 4000 in Denmark [7]. In Poland, as part of the National Registry of Inflammatory Diseases in Children (MultiOrgan Inflammatory Syndromes COVID Related – MOIS-CoR, study), more than 500 cases of MIS-C have been reported to date (data as of December 2021) [8], but it should be assumed that these data are underestimated due to the voluntary nature of the registry and the lack of reports from some Polish cities.

The median age of patients is 8 years, with adolescent boys having the highest risk of developing this complication [9]. As a result of the immune dysregulation evoked by SARS-CoV-2 infection, a severe multi-organ inflammatory state develops, mainly manifested by fever, abdominal, skin and mucosal involvement, myocardial damage and acute heart failure [9–14].

The occurrence of MIS-C is an urgent indication for hospitalization, due to the possible need for intensive treatment and the risk of death. According to data from the USA and the UK, at least half of the patients with MIS-C required intensive therapy and more than 20% required mechanical ventilation [10, 11, 15]. According

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to the Polish registry data, less than 10% of children with MIS-C required hospitalization in the intensive care unit and less than 5% required mechanical ventilation; single deaths were reported [9].

The treatment of MIS-C is mainly based on immunosuppressive therapy (high doses of intravenous immunoglobulins – IVIG) or corticosteroids, less commonly other immunomodulatory drugs and anticoagulant prophylaxis (acetylsalicylic acid – ASA, and sometimes heparin) [16, 17]. Most patients achieve a fairly rapid clinical improvement and the observed disorders usually subside within 2 weeks. Rare but permanent complications of MIS-C include coronary artery aneurysms [10, 11]. In Polish observations, coronary artery dilatation and aneurysms were found in less than 10% of patients [9]. The management of MIS-C is precisely described in the Polish recommendations for management of this disease [17].

COVID-19 VACCINATION EFFICIENCY IN CHILDREN

COVID-19 vaccination is by far the most effective method for prevention of SARS-CoV-2 infection. It has been proven to be highly effective in preventing infection of the current SARS-CoV-2 variants Alpha, Beta, Gamma and Delta (until the emergence of the Omicron variant), especially in preventing severe course, hospitalizations and deaths due to COVID-19 (which remains valid also in the context of the Omicron variant) [18]. Vaccination of children (≥ 5 years) and adolescents was considered advisable both in the assessment of the individual benefit-risk balance and from a public health perspective to reduce transmission [18]. The effectiveness of COVID-19 vaccination in preventing hospitalizations, the need for intensive care and deaths due to infection (delta variant) among adolescents is very high: 90–100% [19, 20].

In the USA, vaccination of adolescents aged 12–18 years has also been shown to be highly effective (91%) in preventing MIS-C. In an analysis of the effectiveness of vaccination with two doses of BNT 162b2 (BioNTech/Pfizer, Comirnaty) in preventing MIS-C, it was further found that no case of a child with PIMS requiring life-sustaining treatment occurred in the vaccinated group (such cases were observed in a concurrently evaluated group of unvaccinated children). These results indicate that not only is the risk of MIS-C significantly reduced in vaccinated children, but also post-vaccination immunity mitigates the course of MIS-C if it develops in a vaccinated child [21].

SAFETY OF COVID-19 VACCINATION IN CHILDREN

In Poland, the first mRNA vaccines for adults were approved for use in December 2020; from June 2021, mRNA vaccines were registered for the age group 12–17 years (initially the BNT1 62b2 vaccine – Comirnaty by Pfizer/BioNTech, and shortly thereafter the mRNA-1273 vaccine – Spikevax by Moderna), and from December 2021 for children aged 5–11 years (Comirnaty). To date, none of the vector (adenoviral) vaccines have been registered for children, so further analysis includes only the mRNA vaccines.

COVID-19 vaccination is safe and relatively well tolerated. The most common adverse reactions are local (pain, redness at the injection site) and general (fever, weakness, headache). Most of these are mild and of short duration, and vaccination tolerance among children and adolescents is better than among adults. Serious but very rare vaccine adverse reactions include anaphylactic reactions (5 : 1000,000 doses) [22–28].

A particularly worrying, although rare, reaction associated with mRNA vaccination, occurring mainly in adolescent boys and young men within a few days after the second dose of the vaccine, is myocarditis or pericarditis. Its nature has been described as mild; the frequency reported in the medical literature depends on the definition of myocarditis adopted and the population studied [26–29]. It is worth noting that, for the most part, these data are based on a very broad definition, without specifying the degree of diagnostic certainty of the diagnosis of myocarditis or pericarditis (ranging from a suspicion of myocarditis or pericarditis based mainly on symptoms to confirmed cases when symptoms coexist with laboratory findings indicative of myocardial damage, ECG abnormalities and changes in myocardial biopsy or magnetic resonance imaging) [29–31].

The increased risk of post-vaccination myocarditis or pericarditis (usually 3 days after the second dose) in practice occurs only in adolescent boys and young men [29, 30, 32, 33] and has been estimated at 12 per 1000,000 second doses of mRNA vaccines among those aged 12–39 years [29]. Importantly, SARS-CoV-2 infection alone increases the risk of myocarditis 16-fold [33], and in the group at highest risk of this complication (young men), it is 6-fold higher after SARS-CoV-2 infection than after vaccination [34]. The benefits of COVID-19 vaccination far outweigh the risks of possible adverse reactions, including myocarditis or pericarditis, as vividly illustrated by Bozkurt *et al.* [29].

VACCINATION AND RISK OF PEDIATRIC INFLAMMATORY MULTISYSTEM SYNDROME

Due to the unclear immunological pathomechanism of MIS-C, increased vigilance and specific surveillance of post-vaccination reactions for the occurrence of MIS-C symptoms after vaccination have been recommended. In an analysis of post-vaccination reactions among more than 10 million vaccinated people (over 11 million vaccine doses), including approximately 840,000 children and adolescents aged 12–17 years, mRNA vaccination was not found to be associated with a risk of MIS-C [24]. To date, only isolated cases of MIS-C/MIS-A temporally associated

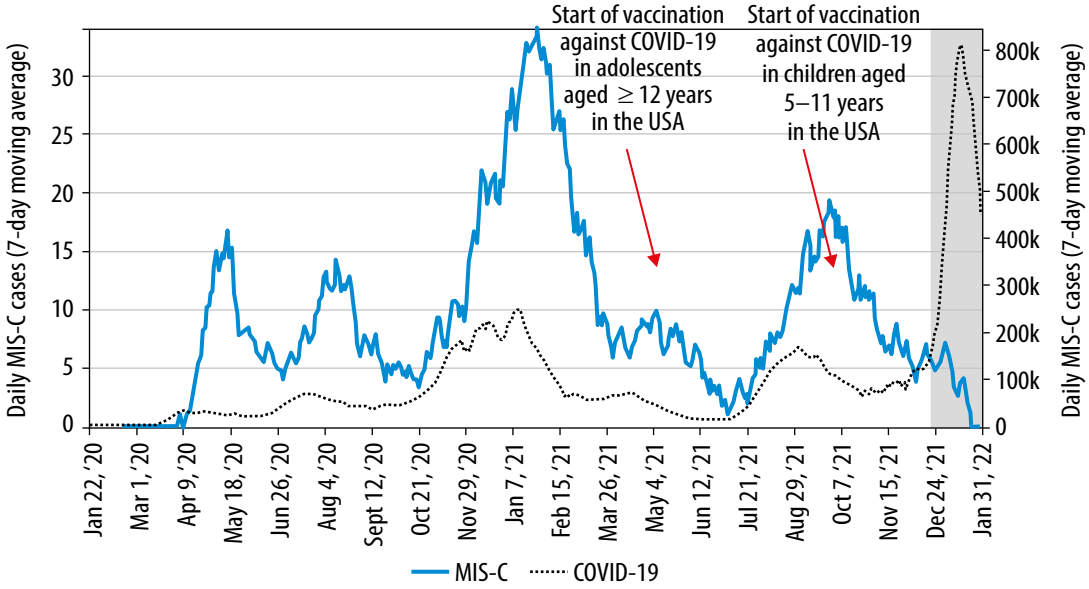

FIGURE 1. American data showing successive multisystem inflammatory syndrome in children waves following COVID-19 waves
MIS-C – multisystem inflammatory syndrome in children

with vaccination have been recorded worldwide, usually among adults and adolescents. In some of these cases, vaccination was preceded by SARS-CoV-2 infection within a short period of time (by about one month), and it is not possible to say clearly whether vaccination influenced the onset or course of MIS-C/MIS-A [35–39].

In the USA, where most cases of MIS-C have been reported to date, there is close epidemiological scrutiny of COVID-19 and MIS-C incidence as well as of vaccination rates among children. According to Payne *et al.*, approximately 1 in 3000 SARS-CoV-2 infected children in the USA developed MIS-C [6]. According to US data, by February 2022, approximately 25.5 million children (8,727,846 aged 5–11 years and 16,738,906 aged 12–17 years) had already received at least one dose of COVID-19 vaccine [39].

Figure 1 presents the American data showing successive MIS-C waves following COVID-19 waves [40]. The arrows indicate the introduction of universal vaccinations against COVID-19 in successive age groups (12–17 and 5–11 years old). As can be seen in the figure, vaccinating about 25.5 million children was not associated with an increased incidence of MIS-C.

Recommendation 1.

Current data are sufficient to conclude that, for the population of children aged 5–18 years, vaccination against COVID-19 is an effective method of prevention of MIS-C and not a risk factor for the development of this complication.

Vaccination of children after MIS-C

COVID-19 vaccination

MIS-C was not considered a contraindication to COVID-19 vaccination in any of the recommendations published thus far [41–45]. However, data on the optimal vaccination strategy for children who have had MIS-C remain limited.

The need for vaccination

Natural SARS-CoV-2 infection does not guarantee long-term immunity, and post-infection protection may be inadequate and transient, especially for Omicron variant infections. Post-infection vaccination (hybrid immunity) reduces the risk of reinfection and severe COVID-19 in case of reinfection [46–48]. At present, there is no need for a specific interval between infection and vaccination, and local recommendations are based on vaccine supply management rather than on concerns about adverse effects. In Poland, an interval of one month after infection is currently recommended, which corresponds to the proven effective (in terms of immunogenicity) interval between two doses of the same vaccine [41].

Recommendation 2.

An interval of one month should be preserved between SARS-CoV-2 infection and vaccination against SARS-CoV-2.

Humoral immunity of children with pediatric inflammatory multisystem syndrome

Children who have had MIS-C tend to have higher levels of specific antibodies to SARS-CoV-2 spike antigens than children who have not had this complication from SARS-CoV-2 infection [49, 50]. Treatment of the disease is mainly based on immunomodulatory drugs, which may impair the response to vaccination for some time. Occasionally, a relapse of MIS-C symptoms has been observed (shortly after the end of steroid therapy, usually after about 4 weeks – data from the MOIS-CoR Registry). There are also diagnostically ambiguous sit-

uations in which MIS-C should be differentiated from rheumatological diseases. Taking into account these reasons, it seems reasonable to maintain a 3-month interval before COVID-19 vaccination after MIS-C, during which time the child usually recovers from MIS-C, no longer requires immunomodulatory treatment, and at the same time continues to be effectively protected by the natural immunity acquired after SARS-CoV-2 infection complicated by MIS-C.

The recommendation of a 3-month interval should be seen as conditional, and in individual situations early vaccination should be considered. Examples of situations when early vaccination should be considered after MIS-C:

- if low levels of antibodies are found in the acute phase of the disease. In some publications, it is suggested that values > 54 international units (IU)/ml or 150 binding antibody units (BAU) should significantly reduce the risk of severe reinfection [51, 52]. However, although the level of antibodies correlates positively with protection against COVID-19 infection, a correlate of immunity, i.e. a specific antibody concentration as evidence of protection, guaranteeing protection against infection sustained over time, has not yet been determined. The absence of specific anti-SARS-CoV-2 antibodies may indicate a lack of immunity. If no anti-SARS-CoV-2 antibodies are detected in the acute phase of MIS-C, it is advisable to repeat the test after one month and, in the case of persistently negative or low levels of antibodies, to qualify the child for vaccination in less than 3 months;
- if the child's living conditions involve a high risk of reinfection or if the child is planning to participate in activities that increase the risk of reinfection (e.g. nursing home residents, children living in boarding schools, attending indoor sports or choir classes, planning to go to summer camps, etc.);
- in case of residence in an endemic area of new virus variants with an increased risk of reinfection or development of complications;
- in children with coexisting chronic disease, prone to severe COVID-19 – immediate vaccination should be considered irrespective of the recommended 3-month interval, especially in children who may not have developed protection after SARS-CoV-2 infection (complicated by MIS-C), e.g. with chronic disease with concomitant immunosuppression.

When choosing the optimal vaccination strategy after MIS-C, particular attention should be paid to the acceptance of vaccination by both the child's parents and the patient himself. The sense of fear of vaccination and the fear of reoccurrence of MIS-C after vaccination are often almost equal to the sense of need for this vaccination in families of children who have experienced MIS-C (preliminary data, in progress by the authors). In discussing the optimal strategy to protect the child from reinfection with SARS-CoV-2, it is worth citing the argument of the high efficacy of vaccination in the prevention of MIS-C [21].

Due to the relatively short duration of observation to date and the high degree of protection against infection with alpha, beta, gamma and delta variants of SARS-CoV-2 after MIS-C, it has not yet been possible to assess the risk associated with reinfection; also, no cases of reinfection with second MIS-C in the same child due to subsequent SARS-CoV-2 infection have been described. In Poland, the first cases of reinfection with SARS-CoV-2 wof children with a history of MIS-C are currently observed (probably due to the gradually decreasing level of antibodies and the appearance of a new variant – Omicron). To date, there is a lack of publications describing the safety profile of COVID-19 vaccination in children who have undergone MIS-C. However, it is worth noting that MIS-C is nowhere treated as a contraindication to vaccination and to date there have been no reported re-occurrences of vaccine-associated MIS-C. The Department of Pediatric Infectious Diseases, Wroclaw Medical University (Poland) is conducting a study to evaluate the safety profile of the BNT 162b2 vaccine (Pfizer, Comirnaty) in children with a history of MIS-C, and the observations to date (so far limited) indicate vaccine safety comparable to a control group of children who did not develop MIS-C after SARS-CoV-2 infection.

Recommendation 3.

After MIS-C, we recommend a 3-month interval before COVID-19 vaccine administration. The recommended interval is conditional and earlier administration of COVID-19 vaccination should be considered in situations such as: lack of or low levels of anti-SARS-CoV-2 antibodies, presence of chronic diseases predisposing to a severe course of COVID-19, living in conditions associated with a high risk of reinfection, and living in or traveling to an area endemic with new variants of the virus.

Other vaccinations after MIS-C

A history of MIS-C alone does not usually play a significant role in scheduling immunizations other than against SARS-CoV-2. However, an individualized approach to the immunization program may be necessary due to the treatment being administered (as discussed below). In the treatment of MIS-C, immunomodulatory and antiplatelet drugs, and possibly anticoagulant prophylaxis, are of primary importance [17].

To date, almost 90% of children with MIS-C in Poland have received high-dose IVIG (2.0 g/kg) in their treatment; in addition, almost 70% of patients have also received glucocorticosteroids (GCS), usually in an immunosuppressive dose. Almost 90% of children received treatment with ASA [9]. Individual patients have also received blood products (red blood cell or platelet concentrate) in the course of treatment.

TABLE 1. Recommended intervals between administration of antibody-containing products and measles- or varicella-containing vaccine

Product	Dose (mg IgG/kg) and route of administration	Recommended interval [months]
Blood transfusion		
Red blood cells, washed	10 ml/kg *i.v.* (negligible IgG content)	–
Red blood cells, adenine-saline added	10 ml/kg (10) *i.v.*	3
Packed red blood cells (hematocrit 65%)	10 ml/kg (60) *i.v.*	6
Whole blood (hematocrit 35–50%)	10 ml/kg (80–100) *i.v.*	6
Plasma/platelet products	10 ml/kg (160) *i.v.*	7
IVIG		
300–400 mg/kg *i.v.*		8
1000 mg/kg *i.v.*		10
2 g/kg *i.v.*		11

IgG – immunoglobulin G, IVIG – intravenous immunoglobulin, mg IgG/kg – milligrams of immunoglobulin G per kilogram of body weight, i.v. – intravenous
Based on: ACIP. ACIP Timing and spacing guidelines for immunization. CDC. Available from: https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/timing.html (lastly accessed: 1 February 2022).

History of treatment with intravenous immunoglobulin or other blood products

After high-dose IVIG (2.0 g/kg body weight or 100.0 g for children > 50 kg), live attenuated measles, mumps, rubella and chickenpox vaccines should be deferred for at least 11 months. This is based on the persistence of (passively) acquired antibodies and the expected lack of efficacy of these vaccines. It should be made clear that this recommendation does not apply to inactivated vaccines. In addition, the contraindication to live vaccines is temporary and a relative contraindication. In epidemiological emergencies (e.g. outbreaks of chickenpox or measles in the child's environment), vaccination should be considered, taking into account the possible lack of efficacy, while maintaining a good safety profile for such an intervention that does not differ from the general population. Chickenpox prophylaxis may be necessary especially in children receiving ASA (due to the theoretical risk of Reye's syndrome in case of infection) [53, 54]. Similar rules for the implementation of live vaccination apply to the use of other blood products. In the case of other blood products, however, the deferral period for live attenuated vaccines is less than 11 months (depending on the type of product, usually 3–6 months) (Table 1). The primary consideration in setting up a vaccination schedule after MIS-C will therefore be the use of IVIG – if given, the use of other blood products will have no additional impact on vaccination recommendations.

Recommendation 4.

Treatment with IVIG (2.0 g/kg body weight or 100.0 g for children > 50 kg) is a temporary contraindication for live attenuated vaccines against measles (in Poland a combined vaccine is used: measles, mumps, rubella) and chickenpox. The minimal interval guaranteeing effectiveness of these vaccines after such treatment is 11 months.

Glucocorticosteroid treatment

Treatment of children with MIS-C with immunosuppressive doses of GCS is usually short-term (for several days); in some cases the dose of GCS is gradually reduced over the following 2–4 weeks. An equivalent dose of ≥ 2.0 mg/kg body weight in children ≤ 10 kg or ≥ 20.0 mg prednisone per day (for those > 10 kg) for at least ≥ 14 consecutive days should be considered an immunosuppressive dose in the context of immunization planning [54]. A very small proportion of children with MIS-C meet this criterion. However, if such treatment is given, this is a temporary contraindication to the use of all live attenuated vaccines due to possible serious adverse effects. Administration of live vaccines is possible at least one month after the end of GCS immunosuppressive therapy [54].

Immunosuppressive treatment with GCS is not a contraindication for the administration of inactivated vaccines. However, it is important to note that the efficacy of inactivated vaccines given during immunosuppression is limited [54]. Given the anticipated short duration of treatment of MIS-C with GCS and the fact that most children with MIS-C are of school age when mandatory vaccinations are booster doses (e.g. against diphtheria, tetanus, pertussis), in most cases it is advisable to schedule immunizations for the period after completion of immunosuppressive treatment. This decision should be made on the basis of current epidemiological indications and the vaccinations already carried out in the child.

Recommendation 5.

Treatment of MIS-C with corticosteroids (GCS) does not contraindicate the administration of inactivated vaccines, but their limited efficacy when administered during immunosuppression should be considered.

Treatment with GCS at immunosuppressive doses (≥ 2.0 mg/kg body weight in children ≤ 10 kg or

≥ 20.0 mg prednisone per day for those > 10 kg for at least ≥ 14 consecutive days) is a temporary contraindication to the use of live attenuated vaccines. Administration of live vaccines is possible at least one month after completion of GCS immunosuppressive therapy.

Acetylsalicylic acid treatment

All children with MIS-C who do not have a contraindication for that should receive antiplatelet prophylaxis for at least 6–8 weeks, until cardiac follow-up and exclusion of coronary artery lesions (or longer if required). The most commonly used antiplatelet drug is ASA [17]. Taking ASA at an anti-inflammatory dose (> 30 mg/kg) in children may be associated with Reye's syndrome, especially if influenza or chickenpox virus infection occurs. Although a similar risk has not yet been confirmed to be associated with the anti-aggregation dose of ASA (3–5 mg/kg, max 75 mg/day), given the theoretical risk of such a complication, these children should be particularly protected against influenza and chickenpox. This can be achieved through two strategies – vaccination of the children themselves (unless they have contraindications) and a cocoon strategy – vaccination of non-immunized persons in the child's environment against these diseases [55–57].

Prolonged bleeding at the injection site may occur in children using ASA. Patients should be informed about this and be aware of the mild nature of the complication. Appropriate vaccination technique is advisable: use the thinnest needle available (usually 25–27 G), and apply pressure to the injection site for ≥ 2 minutes (without rubbing or palpation) after injection [58].

Recommendation 6.

Acetylsalicylic acid treatment is not a contraindication to vaccination. Due to the risk of Reye's syndrome, influenza vaccination with inactivated or attenuated vaccine is recommended if there are no contraindications (use of GCS).

Cardiac complications as an indication for extended infectious disease prophylaxis

In the acute phase of MIS-C, a number of cardiac abnormalities are found, most notably acute heart failure, valvular regurgitation, coronary artery dilatation and aneurysms, or cardiac arrhythmias. Most of these are transient in nature. In case of persistent cardiac problems such as coronary artery aneurysms, arrhythmias, valvular defects or impaired systolic function of ventricles, it is worthwhile to cover the patient with additional prophylaxis, especially concerning influenza and pneumococcal infections. Detailed recommendations for vaccination of patients with heart disease are discussed in a separate article [55].

Recommendation 7.

Pneumococcal vaccination and annual influenza vaccination should be recommended in children after MIS-C due to cardiac complications.

Intervals between COVID-19 vaccination and other vaccines

Studies are underway to assess the safety and immunogenicity of the concomitant administration of COVID-19 with other vaccines. Coadministration of COVID-19 with other vaccines is in accordance with the general immunization guidelines, however. Extensive studies on the concomitant administration of commonly used "live" attenuated and inactivated vaccines have shown that immunogenicity and the frequency of adverse events are similar to those observed when they are administered separately [59].

Recommendation 8.

COVID-19 vaccines may be administered concomitantly with other vaccines, only at a separate site, and may be administered at any time before or after administration of other vaccines.

CONCLUSIONS

Vaccination of children and adolescents against COVID-19 is effective in preventing both the severe course of COVID-19 and the occurrence of MIS-C – the SARS-CoV-2 infection complication. COVID-19 vaccination reduces the risk of MIS-C both in the general population and among patients who have experienced this complication after SARS-CoV-2 infection. Children who have had MIS-C should be vaccinated against COVID-19 as reinfection with SARS-CoV-2 is likely and its course in this patient group remains unpredictable. The optimal interval we suggest following MIS-C to COVID-19 vaccination is 3 months. The individual vaccination schedule may need to be modified due to the history of MIS-C treatment. The dose of IVIG administered, the duration of administration of GCS (for live attenuated vaccines) and the use of ASA (as an indication for additional prophylactic measures for protection against influenza and chickenpox) are most relevant.

DISCLOSURE

The authors declare no conflict of interest.

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