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SARS-CoV-2 parental vaccination and risk of multisystem inflammatory syndrome in children: a single-center retrospective study

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Purpose: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) usually causes a mild disease in children and the most serious consequence is multisystem inflammatory syndrome in children (MIS-C). Currently, there are no data about the protective role of vaccination performed by parents on children regarding the development of MIS-C. The aim of our study is to establish whether parental vaccination is related to MIS-C and the protective value of SARS-CoV-2 vaccination performed by parents against the occurrence of MIS-C in their children.

Materials and Methods: Our retrospective single center study included 124 patients aged 1 month to 18 years admitted to emergency department from April 2020 to March 2022 for coronavirus disease 2019 disease.

Results: Parental vaccination was negatively correlated with the development of MIS-C: 4% of patients with both parents vaccinated developed MIS-C, while patients with no parent vaccinated to have developed MIS-C were 20%.

Conclusion: Parental vaccination could be an important factor influencing the course of the disease and reduces the probability that a child would develop MIS-C by 83% if both parents vaccinated.

Keywords: SARS-CoV-2 vaccination, Multisystem inflammatory syndrome in children, Pediatric COVID-19, SARS-CoV-2 infection

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the global pandemic of coronavirus disease, which originated in China in December 2019 and rapidly spread to various countries around the world [1,2]. The impact of this disease has been very significant [3] but studies have consistently shown that children present milder clinical pictures than individuals in other age groups [4-6]. In children, the most severe coronavirus disease 2019 (COVID-19)-related manifestation is the occurrence of a multisystem inflammatory syndrome having features partly overlapping with Kawasaki disease and toxic shock syndrome that has been called multisystem inflammatory syndrome in children (MIS-C) with a high mobility and a mortality rate of 2% [7,8].

In pediatrics, vaccination plays an important role in several ways: firstly, through the

immunization of the pregnant mother, then by vaccinating the child, and finally by guaranteeing herd immunity. In infants aged less than 6 months not eligible for vaccination, maternal vaccination with two doses of vaccine is associated with a reduced risk of hospitalization for COVID-19 due to transplacental transfer of antibodies against SARS-CoV-2 [9]. The messenger RNA (mRNA) vaccines are generally safe and effective in preventing severe diseases and hospitalization among children and adolescents [10]. Currently, there are no data in the literature regarding the protection conferred by parental vaccination on children against the development of MIS-C.

The aim of our study is to establish whether parental vaccination is related to MIS-C development and the protective value of SARS-CoV-2 vaccination performed by parents against the occurrence of MIS-C in their children.

Materials and Methods

We performed a retrospective single center cohort study from April 2020 to March 2022. This study is conformed to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement, all points on the checklist have been respected.

Sampling strategy

For the aim of our study, we used the database of the Laboratory of San Marco University Hospital of Catania and collected all positive molecular nasopharyngeal swab performed from April 2020 to March 2022 in patients between 0 days of life and 18 years age admitted to hospital due to COVID-19.

For everyone, we recorded any medical data available, and we collected the family history about the SARS-CoV-2 vaccination performed by the parents of each patient. Specifically, we divided the patients in relation to the vaccination performed by the parents into three categories: (1) patients who had both parents vaccinated, (2) patients who had only one parent vaccinated, and (3) patients who had no vaccinated parents. So, we investigated the correlation between parental vaccination and the occurrence of MIS-C and we study the protective value of SARS-CoV-2 vaccination performed by parents against the occurrence of MIS-C in their children.

This study was approved by the ethics committee of Comitato Etico Catania 1, Catania (protocol code 31/2022, on February 15, 2022). Authors acquired from each study participant written consent for participation and publication of data. The research was conducted in line with the Principles of the Declaration of Helsinki.

Inclusion and exclusion criteria

The inclusion criteria of our study were: (1) a positive molecular swab for SARS-CoV-2 performed before hospital admission to the pediatric department, (2) children who had not yet received vaccination for SARS-CoV-2, and (3) parents who had completed the vaccination cycle with two doses of vaccine (Pfizer, New York, NY, USA). The exclusion criteria of our study were: (1) no complete clinical information, (2) no available family history of vaccination, and (3) parents who had not completed the vaccination cycle and had received only one dose of vaccine (Pfizer).

Laboratory analysis of swab

Our laboratory uses the "Xpert Xpress SARS-CoV-2 test" developed by Cepheid (Sunnyvale, CA, USA), which is a real-time reverse transcription-polymerase chain reaction test for qualitative detection of nucleic acid from the SARS-CoV-2 in upper respiratory samples [11]. The analysis was made using primers and probes in relation to 110,206 SARS-CoV-2 sequences available at the date of October 21, 2020, in the GISAID gene database (https://gisaid.org/) for only two genetic targets of the virus, E and N2 [11].

Statistical analysis

Statistical analysis was conducted using R ver. 4.3.0 (The R Foundation for Statistical Computing, Vienna, Austria). Chi-square test was used to compare each vaccination possibility with the presence/absence of MIS-C in the patients. The test was considered significative with a $p<0.05$. Moreover, odds ratio was calculated for each analysis. The analysis results have been plotted using ggplot2 [12] and ggstatsplot [13].

Endpoints

The primary endpoint, also referred to as the true endpoint, was to determine whether there was an association between parental vaccination status (one parent vaccinated, both parents vaccinated, no parent vaccinated) and the occurrence of MIS-C. As a secondary endpoint, also defined as a surrogate endpoint, we studied the protective value of SARS-CoV-2 vaccination by parents (one parent vaccinated, both parents vaccinated, no parent vaccinated), expressed as a reduction in the odds of their children having MIS-C.

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Results

Cohort characterization

During the study period, 5,165 pediatric molecular swabs were performed by our microbiology laboratory. Of these, 612 (12%) were positive and 4,553 (88%) were negative for COVID-19. Clinical hospitalization data was available for 249 positive pediatric patients (40.7% of total positive swabs), and of these, only 124 (49.8%) fully met the criteria for inclusion in the study (Fig. 1).

Finally, the cohort of our study consists of 124 subjects selected based on a positive molecular nasopharyngeal swab for SARS-CoV-2, with complete clinical data and family history regarding parental vaccination. Of the patients, 49% (n=61) were male and 51% (n=63) were female. The age ranged from 3 days to 15 years, with an average age of 4.42 years.

Parental vaccination and occurrence of MIS-C

According to our endpoints, we divided the patients in relation to the vaccination performed by the parents into three categories: (1) patients who had both parents vaccinated (n=74 subjects), (2) patients who had only one parent vaccinated (n=25 subjects), and (3) patients who had no vaccinated parents (n=25 subjects). In our cohort multisystemic inflammatory syndrome occurred in 10 patients (8.1%) and no patients died for this reason.

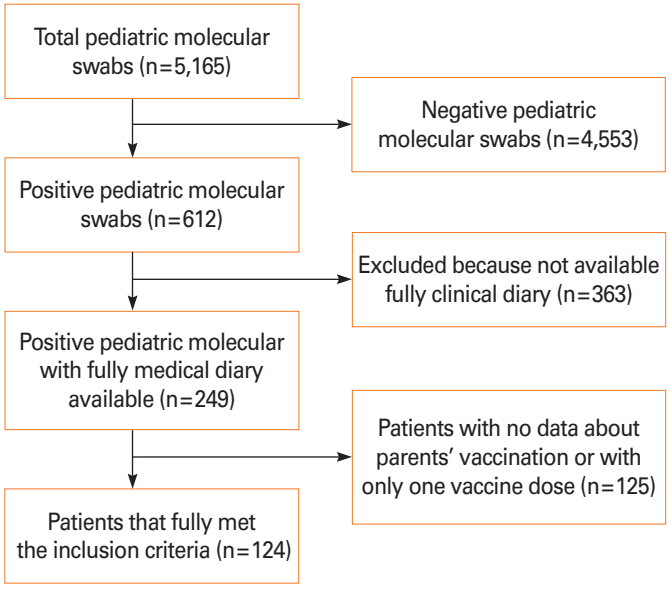

Fig. 1. Patients included in the study.

Statistical correlations

To investigate a possible association between parental vaccination (one parent vaccinated, both parents vaccinated, no parent vaccinated) and the occurrence of MIS-C in their children we saw, an association statistically significant between parents that was not vaccinated and the insurgence of MIS-C (p-value=0.041). In this group, in fact, MIS-C was noted in 20% of cases. Instead, MIS-C was detected in only 4% of the patients with both of parents vaccinated and in 8% of the cases with only one patient vaccinated against SARS-CoV-2 (Fig. 2).

In the following correlation plot, we depict the association between parents' vaccination and MIS-C (Fig. 3A), as well as their contribution to this association (Fig. 3B). In Fig. 3A, we observe the test residuals, which represent the difference between the observed and expected values. The larger residual, so the larger contributing cell, is the one with a positive association between the presence of MIS-C and no vaccinated parent followed by a negative association between the presence of MIS-C and both vaccinated parents. In Fig. 3B instead, we can see which variables contribute the most to the chi-square results. The contribution is calculated using the formula contribution=r^2/χ^2, where r is the residual and χ^2 is the result of the chi-square test. The cells that contribute the most to our results are those with no vaccinated parent and the presence of MIS-C, accounting for approximately 68% of the contribution.

According to the secondary endpoint to establish the protective value of SARS-CoV-2 parental vaccination against the insurgence of MIS-C in their children we assessed the odds

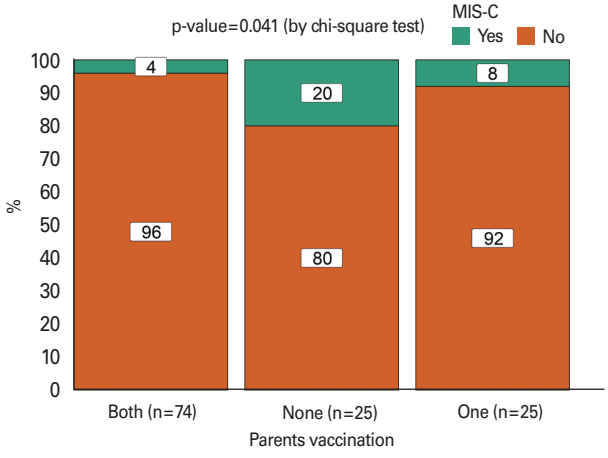

Fig. 2. Parents vaccination: both (n=74), none (n=25), and one (n=25). p-value=0.041 (by chi-square test). MIS-C, multisystem inflammatory syndrome in children.

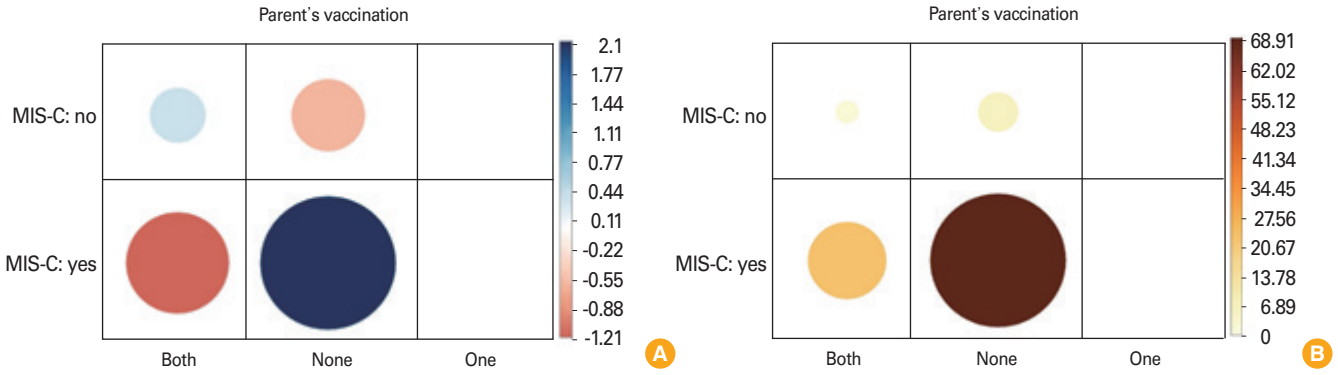

Fig. 3. (A, B) Parent's vaccination. MIS-C: no. MIS-C: yes. MIS-C, multisystem inflammatory syndrome in children.

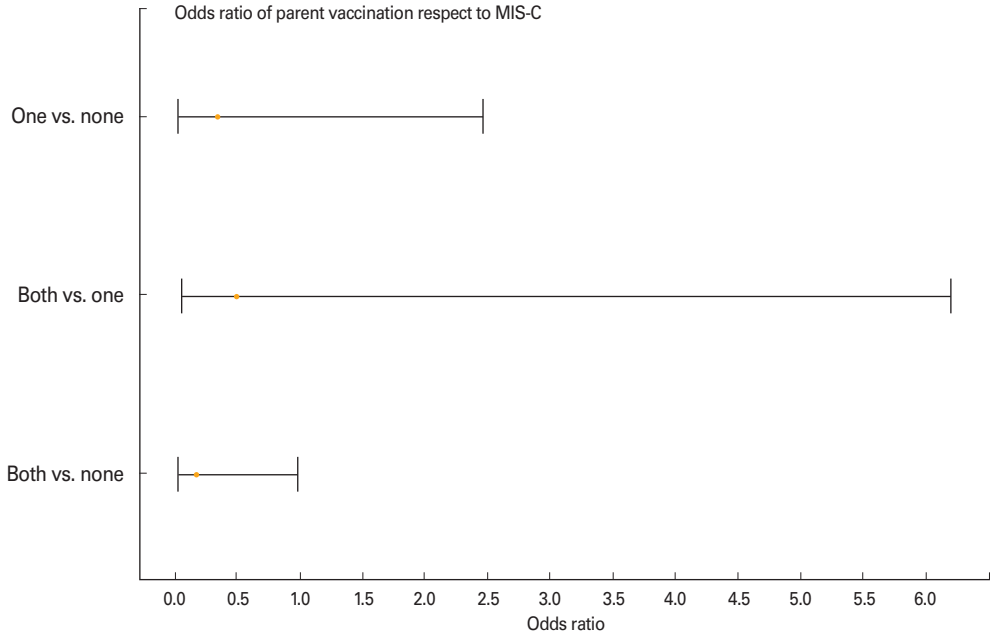

Fig. 4. Odds ratio of parent vaccination respect to multisystem inflammatory syndrome in children (MIS-C). One vs. none. Both vs. one. Both vs. none.

ratio by comparing each category of patients (i.e., one parent vaccinated, both parents vaccinated, and no parent vaccinated) (Fig. 4). (1) Both parents vaccinated versus no parents vaccinated (odds ratio, 0.17): In these patients, we saw an 83.1% reduction in the odds of having MIS-C (p-value=0.023). (2) One parent vaccinated versus no parents vaccinated (odds ratio, 0.35): In this case, we found a 65% reduction in the odds of having MIS-C but it was not significant in our sample (p-value=0.42). (3) Both parents vaccinated versus one parent vaccinated (odds ratio, 0.49): These patients had a reduction of 51% in the probability of having MIS-C but this finding was not significant in our sample (p-value=0.6).

Discussion

Many studies have shown that COVID-19 vaccines effectively prevent SARS-CoV-2 infections, especially in susceptible people like healthcare workers. So, effective and safe vaccines are essential for controlling the COVID-19 pandemic [14]. However, vaccine performance is affected by the constant acquisition of viral mutations and the existence of a highly variable receptor-binding motif in the spike protein [15].

Zheng et al. [16] performed a meta-analysis of existing literature to evaluate the effectiveness of vaccines against SARS-CoV-2. A total of 51 studies were included in this meta-analysis. Among individuals who received complete vaccination against the infection, the Pfizer-BioNTech vaccine demon-

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strated an observed efficacy of 91.2%, while the Moderna vaccine (Moderna Inc., Cambridge, MA, USA) showed an efficacy of 98.1%. Based on the findings of this meta-analysis, the results indicated a vaccine efficacy of 97.2% in preventing hospitalization, 97.4% in preventing ICU admission or severe illness, and 99.0% in preventing COVID-19-related deaths.

Liu et al. [17] conducted another meta-analysis to assess the effectiveness of vaccines against SARS-CoV-2. A total of 32 studies on vaccine efficacy were analyzed. The findings revealed that administering two doses of the vaccine resulted in an effectiveness of 85% in preventing SARS-CoV-2 infections. Additionally, the vaccines were found to be 97% effective in preventing symptomatic cases of COVID-19, 93% effective in preventing hospital admissions, 96% effective in preventing ICU admissions, and 95% effective in preventing COVID-19-related deaths.

While currently approved COVID-19 vaccines were safe in clinical trials, the resulting adverse reactions are numerous, including fever, headache, fatigue, injection site pain, and nausea. Although the incidence of these complications is low, the relationship between vaccines and these diseases needs to be explored [18]. Of interest, the first vaccination against SARS-CoV-2 was made in Italy on 27 December 2020 with a massive distribution to the population starting from 31 December 2020 [19].

Since the onset of the COVID-19 pandemic, it has become apparent that children infected with SARS-CoV-2 remain mostly asymptomatic or mildly symptomatic. The true prevalence of asymptomatic SARS-CoV-2 infection is most likely underestimated, as asymptomatic children are tested less frequently. Serological surveys indicate that half of the children who test positive for SARS-CoV-2 report no symptoms. In general, children with COVID-19 are at lower risk of hospitalization and life-threatening complications [7].

The results of the COVID-19 vaccine studies indicate very good efficacy and tolerability in children [20]. The Advisory Committee on Immunization Practices recommends the Pfizer-BioNTech COVID-19 vaccine for children aged 5–11 years for the prevention of COVID-19 [21].

In a systematic review conducted by Tian et al. [22], it was found that RNA vaccines exhibited efficacy of over 90% following the administration of the second dose during clinical trials involving individuals aged 5–17 years.

Ali et al. [23] assessed the safety, immune response, and effectiveness of the mRNA-1273 vaccine (Moderna) in a group of 3,732 adolescents aged 12 to 17 years. The findings revealed a vaccine efficacy of 93% following the second dose, with an optimal serological response observed in 98.8% of the participants. Therefore, there is a strong case for vaccinating children to reduce the possible long-term effects of the infection and decrease transmission. However, questions remain about what role vaccination plays in long-term complications.

A challenge of this pandemic has been the emergence of MIS-C, a rare postinfectious hyperinflammatory disorder associated with SARS-CoV-2 infection. This syndrome is characterized by overwhelming systemic inflammation, fever, hypotension, and cardiac dysfunction and presents overlapping features with Kawasaki disease, macrophage activation syndrome, and toxic shock syndrome [24].

Feldstein et al. [25] reported on 186 patients defined as having MIS-C in surveillance data collected from pediatric health centers in 26 states. Most patients were male, with major symptoms including gastrointestinal (92%), cardiovascular (80%), mucocutaneous (74%), and respiratory (70%). Eighty percent of patients received care in the intensive care unit, with 20% requiring mechanical ventilation, and three patients receiving extracorporeal membrane oxygenation. Coronary aneurysms were found in 8% of patients, and 40% of patients presented with Kawasaki-like disease. Most patients were treated with intravenous immunoglobulin (77%), systemic glucocorticoids (49%), and interleukin-1 receptor antagonist (IL-1Ra) or interleukin-6 (IL-6) inhibitor (20%). The mortality rate was approximately 2%.

The exact pathophysiology of MIS-C remains unknown. However, post-infectious immune dysregulation, particularly involving the innate immune system, is implicated, given that many patients improve drastically with immunomodulatory agents. A “cytokine storm” plays an important role, with activation of the IL-1β pathway and elevation in levels of proinflammatory cytokines such as IL-6, IL-8, IL-18, tumor necrosis factor-α, and interferon-γ having been reported in patients. This leads to the multi-organ involvement noted in MIS-C patients, with cardiac injury in particular [26].

Due to the commonly observed overlapping features between MIS-C and Kawasaki disease, patients with MIS-C are currently treated empirically based on Kawasaki disease treatment protocols [27]. Of interest, the exact definition of MIS-C remains debated, with minimal differences between what is reported by the Centers for Disease Control and Prevention [28] and the World Health Organization [29].

Currently, there are no studies in the literature on the protective value of parental vaccination against SARS-CoV-2 and

the development of MIS-C complications in their children. In our sample, we found that only 4% of patients who had both parents vaccinated developed MIS-C. In contrast, 20% of patients whose parents were not vaccinated developed MIS-C. Interestingly, in the group of patients with only one vaccinated parent, MIS-C was found in only 8% of cases (p-value=0.041). From the association study, we derived that the cell contributing most to our results is the one without a vaccinated parent and with the presence of MIS-C, with approximately 68% contribution.

Regarding the protective role of SARS-CoV-2 parental vaccination, if both parents were vaccinated compared to children with no parents vaccinated, we observed an 83.1% reduction in the odds of having MIS-C (p-value=0.023).

If only one parent was vaccinated compared to patients with no vaccinated parents, we observed a 65% reduction in the likelihood of developing MIS-C (p-value=0.42). This suggests that vaccination of only one parent might be associated with a reduced risk of MIS-C, but this association was not statistically significant in our study.

When comparing patients with both parents vaccinated to those with only one parent vaccinated, results showed a 51% reduction in the likelihood of developing MIS-C (p-value=0.6). Thus, we were unable to statistically confirm a significant difference in MIS-C risk between patients with both parents vaccinated and those with only one parent vaccinated, but the tendency towards protection of children may be clear. These results, albeit from a small sample, demonstrate the importance of vaccination against SARS-CoV-2 not only directly but also indirectly by protecting all individuals who encounter vaccinated persons, especially children, thereby avoiding MIS-C, which represents one of the most important causes of intensive care unit admission in pediatric patients.

Limits of the study

Our study was performed on a small cohort of patients through a retrospective analysis, including patients in the neonatal age (range, 0–28 days). Another limitation of the study is the lack of stratification of the patients in relation to risk factors for developing MIS-C and the date when subjects were enrolled.

Conclusions

Parental vaccination was negatively correlated with the occurrence of MIS-C in our sample. In fact, only 4% of patients with both parents vaccinated developed MIS-C, while the rate was 20% in patients with no parent vaccinated. Furthermore, our study showed an 83% reduction in the likelihood of a child developing MIS-C when both parents were vaccinated. These results underline the importance of promoting vaccination among parents as a preventive measure to safeguard children's health, emphasizing the importance of parental vaccination not only for the health of the individual but also for the well-being of their children. Vaccination provides direct protection to vaccinated individuals and indirectly protects vulnerable populations, such as children not yet eligible for vaccination or those with compromised immune systems. These findings reinforce the importance of widespread vaccination campaigns to protect both individuals and their children, ultimately contributing to the control of the COVID-19 pandemic.

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