RESEARCH LETTER

Multisystem Inflammatory Syndrome in Children by COVID-19 Vaccination Status of Adolescents in France

COVID-19 mRNA vaccine immunogenicity and effectiveness are well established in adolescents.[1] However, the effect of vaccination on multisystem inflammatory syndrome in children (MIS-C),[2] a severe complication associated with SARS-CoV-2,[3] has not yet been described. Summer 2021 in France was marked by both a fourth wave of COVID-19 cases due to the Delta variant, with a peak in August 2021, and by the recommendation of the French Public Health Agency to vaccinate children 12 years and older. We estimated the risk of MIS-C among adolescents by COVID-19 vaccination status during September 2021 and October 2021.

Methods | All pediatric patients diagnosed with MIS-C according to World Health Organization criteria and admitted to one of the 41 French pediatric intensive care units (PICUs) between September 1, 2021, to October 31, 2021, were included in this study. In addition, all patients with MIS-C who were not admitted to a PICU and mandatorily reported to the French Public Health Agency[4] during this period were included.

Data regarding age, sex, admission to a PICU, and vaccination status of patients 12 to 18 years (hereafter referred to as *adolescents*) were recorded.

To account for the increasing number of adolescents vaccinated over time, including during the period in which MIS-C cases were measured, hazard ratios (HRs) of unvaccinated vs vaccinated adolescents with at least 1 dose of vaccine were estimated using Cox proportional hazards model. Given the delays between vaccine injection and immune response and between SARS-CoV-2 infection and MIS-C onset, 3 sensitivity analyses were performed in which adolescents were considered vaccinated at least 14, at least 28, and at least 42 days after the first vaccine dose. The delay of more than 42 days covers the 28 days between the first and second injection and 2 additional weeks to achieve full immunity. Data describing vaccination status per day are available from https://solidarites-sante.gouv.fr/grands-dossiers/vaccin-covid-19/article/le-tableau-de-bord-de-la-vaccination.

All statistical analyses were performed with Stata, version 16.1 (StataCorp), and 2-sided $P < .05$ was considered statistically significant.

This study was approved as a medical registry assessment without a requirement for patient consent by the French Advisory Committee on Information Processing in Health Research.

Results | On June 15, 2021, the beginning of the adolescent COVID-19 vaccination campaign, 2.2% of the 4 989 013 adolescents in France were vaccinated with at least 1 dose and 0.2% were fully vaccinated. On October 31, 2021, vaccination rates reached 76.7% of adolescents having received at least 1 dose and 72.8% being fully vaccinated. Vaccines used were BNT162b2 (Pfizer-BioNTech; >95%), mRNA-1273 (Moderna; <5%), and other COVID-19 vaccines (<1%).

From September 1, 2021, to October 31, 2021, a total of 107 children with MIS-C were hospitalized in France and, among them, 33 (31%) were adolescents eligible for vaccination. Adolescents with MIS-C were a median (IQR) age of 13.7 (12.5-14.9) years, 27 (81%) were male, and 29 (88%) were admitted to a PICU. Among them, 0 had been fully vaccinated, 7 had received 1 dose with a median (IQR) time between vaccine injection and MIS-C onset of 25 (17-37) days, and 26 had not been vaccinated. The HR for MIS-C was 0.09 (95% CI, 0.04-0.21;

Table. Multisystem Inflammatory Syndrome in Children (MIS-C) Risk by COVID-19 Vaccination Status of Adolescents

COVID-19 vaccination status[a]	No. of patients with MIS-C (N = 33)	Hazard ratio (95% CI)[b]	*P* value
Unvaccinated	26	1 [Reference]	<.001
One dose	7	0.09 (0.04-0.21)	
Sensitivity analysis: fully vaccinated ≥14 d after first dose[c]			
Unvaccinated	28	1 [Reference]	<.001
One dose	5	0.07 (0.03-0.18)	
Sensitivity analysis: fully vaccinated ≥28 d after first dose[c]			
Unvaccinated	31	1 [Reference]	<.001
One dose	2	0.03 (0.01-0.12)	
Sensitivity analysis: fully vaccinated ≥42 d after first dose[c]			
Unvaccinated	31	1 [Reference]	<.001
One dose	2	0.04 (0.01-0.16)	

[a] More than 95% of vaccinated adolescents received BNT162b2 (Pfizer-BioNTech), <5% received mRNA-1273 (Moderna), and <1% received other COVID-19 vaccines.

[b] Cox proportional hazards regression models were used to calculate hazard ratios, with the number of adolescents vaccinated with at least 1 dose as the exposure and MIS-C as the outcome.

[c] Given the delays between vaccine injection and immune response, and between SARS-CoV-2 infection and MIS-C onset, 3 sensitivity analyses were performed in which adolescents were considered vaccinated at least 14, at least 28, and at least 42 days after the first vaccine dose.

$P < .001$) after the first vaccine dose compared with unvaccinated adolescents. Sensitivity analyses showed similar results (**Table**).

Discussion | Most adolescents with MIS-C for whom vaccination was indicated in France had not been vaccinated. These results suggest that COVID-19 mRNA vaccination was associated with a lower incidence of MIS-C in adolescents. The median of 25 days between single vaccine injection and MIS-C onset compared with a mean 28-day delay between SARS-CoV-2 infection and MIS-C onset[4] suggests that, in most cases, SARS-CoV-2 infection occurred before or shortly after the vaccine injection, when immune response was incomplete. The absence of MIS-C cases in fully vaccinated children prevented calculation of an HR for this group, but suggests that 2 doses are warranted for efficient protection. The study had limitations, including the low number of patients, use of national data to calculate HR without considering regional variations, and inability to control for individual risks of MIS-C, such as sex, race and ethnicity, and comorbidities.[5]

The association between mRNA vaccination with MIS-C in younger children should be evaluated as vaccines are approved for use in children aged 5 to 11 years. Close monitoring is required given the alert on myocarditis occurring in adolescents after COVID-19 mRNA vaccine.[6]

Michael Levy, MD, PhD
Morgan Recher, MD, PhD
Hervé Hubert, MD, PhD
Etienne Javouhey, MD, PhD
Olivier Fléchelles, MD, PhD
Stéphane Leteurtre, MD, PhD
François Angoulvant, MD, PhD

Author Affiliations: Pediatric Intensive Care Unit, Hôpital Universitaire Robert-Debré, Paris, France (Levy); ULR 2694 - METRICS, Université de Lille, Lille, France (Recher, Hubert, Leteurtre); Pediatric Intensive Care Unit, Hôpital Femme Mère Enfant, Lyon, France (Javouhey); Pediatric Intensive Care Unit, Centre Hospitalier Universitaire de Martinique, Fort-de-France, France (Fléchelles); Department of General Pediatrics, Pediatric Infectious Disease and Internal Medicine, Hôpital Universitaire Robert-Debré, Paris, France (Angoulvant).

Corresponding Author: Michael Levy, MD, PhD, Pediatric Intensive Care Unit, Hôpital Universitaire Robert-Debré, Assistance Publique–Hôpitaux de Paris, 48 boulevard Sérurier, 75019 Paris, France (michael.levy@aphp.fr).

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