

should validate whether extending vaccine dosing intervals leads to more sustained vaccine protection.

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1. Centers for Disease Control and Prevention (CDC). COVID-19. Accessed August 11, 2021. <https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html>

2. Voysey M, Costa Clemens SA, Madhi SA, et al; Oxford COVID Vaccine Trial Group. Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. *Lancet*. 2021;397(10277):881-891. doi:10.1016/S0140-6736(21)00432-3

3. Wahl M, Hermodsson S, Iwarson S. Hepatitis B vaccination with short dose intervals—a possible alternative for post-exposure prophylaxis? *Infection*. 1988; 16(4):229-232. doi:10.1007/BF01650758

4. Romero-Brufau S, Chopra A, Ryu AJ, et al. Public health impact of delaying second dose of BNT162b2 or mRNA-1273 covid-19 vaccine: simulation agent based modeling study. *BMJ*. 2021;373(May):n1087. doi:10.1136/bmj.n1087

5. Moghadas SM, Vilches TN, Zhang K, et al. Evaluation of COVID-19 vaccination strategies with a delayed second dose. *PLoS Biol*. 2021;19(4):e3001211. doi:10.1371/journal.pbio.3001211

6. Khoury DS, Cromer D, Reynaldi A, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. *Nat Med*. 2021;27(7):1205-1211. doi:10.1038/s41591-021-01377-8

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 aged 12 years or 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 1 of the 41 French pediatric intensive care units (PICUs) between September 1, 2021, and 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 Agency⁴ during this period were included.

Data regarding age, sex, admission to a PICU, and vaccination status of patients aged 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 a 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 a 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

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 \geq14 d after first dose^c			
Unvaccinated	28	1 [Reference]	<.001
One dose	5	0.07 (0.03-0.18)	
Sensitivity analysis: fully vaccinated \geq28 d after first dose^c			
Unvaccinated	31	1 [Reference]	<.001
One dose	2	0.03 (0.01-0.12)	
Sensitivity analysis: fully vaccinated \geq42 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), less than 5% received mRNA-1273 (Moderna), and less than 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.

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 age of 13.7 (IQR, 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 time between vaccine injection and MIS-C onset of 25 (IQR, 17-37) days, and 26 had not been vaccinated. The HR for MIS-C was 0.09 (95% CI, 0.04-0.21; $P < .001$) 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 onset⁴ 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 HRs 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 ap-

proved 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

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1. French RW Jr, Klein NP, Kitchin N, et al; C4591001 Clinical Trial Group. Safety, immunogenicity, and efficacy of the BNT162b2 Covid-19 vaccine in adolescents. *N Engl J Med*. 2021;385(3):239-250. doi:10.1056/NEJMoa2107456
2. Feldstein LR, Rose EB, Horwitz SM, et al; Overcoming COVID-19 Investigators; CDC COVID-19 Response Team. Multisystem inflammatory syndrome in US children and adolescents. *N Engl J Med*. 2020;383(4):334-346. doi:10.1056/NEJMoa2021680
3. Whittaker E, Bamford A, Kenny J, et al; PIMS-TS Study Group and EUCLIDS and PERFORM Consortia. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. *JAMA*. 2020;324(3):259-269. doi:10.1001/jama.2020.10369
4. Belot A, Antona D, Renolleau S, et al. SARS-CoV-2-related paediatric inflammatory multisystem syndrome, an epidemiological study, France, 1 March to 17 May 2020. *Euro Surveill*. 2020;25(22):2001010. doi:10.2807/1560-7917.ES.2020.25.22.2001010
5. Dhar D, Dey T, Samim MM, et al. Systemic inflammatory syndrome in COVID-19-SISCoV study: systematic review and meta-analysis. *Pediatr Res*. Published online May 18, 2021. doi:10.1038/s41390-021-01545-z
6. Diaz GA, Parsons GT, Gering SK, Meier AR, Hutchinson IV, Robicsek A. Myocarditis and pericarditis after vaccination for COVID-19. *JAMA*. 2021;326(12):1210-1212. doi:10.1001/jama.2021.13443

COMMENT & RESPONSE

Effect of Fractional Carbon Dioxide Laser vs Sham Treatment on Vaginal Symptom Severity in Postmenopausal Women

To the Editor A recently published double-blind randomized clinical trial¹ found that fractional carbon dioxide laser did not significantly improve vaginal symptoms associated with menopause compared with sham treatment. The Editorial² associated with this study appealed for a pause on the use of vaginal laser treatment. However, we are concerned that vaginal mucosa wetness may have affected the results of this trial. Because the energy of fractional carbon dioxide laser can be easily absorbed by water, the area of the body being treated with this technology must be completely dry to ensure full effect of treatment.³ In this study, 4% lignocaine topical anesthetic cream was applied to the vaginal introitus for 20 minutes to reduce tactile difference or pain perception in both groups. It is unclear whether there was any residual moisture on the vaginal wall because this information was not reported in the study. Moreover, vaginal mucosa wetness is an important baseline variable that should be measured and reported before insertion of the vaginal probe to exclude the effect of vaginal mucosa surface wetness in the 2 groups on treatment results.

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1. Li FG, Maheux-Lacroix S, Deans R, et al. Effect of fractional carbon dioxide laser vs sham treatment on symptom severity in women with postmenopausal vaginal symptoms: a randomized clinical trial. *JAMA*. 2021;326(14):1381-1389. doi:10.1001/jama.2021.14892
2. Adelman M, Nygaard IE. Time for a "pause" on the use of vaginal laser. *JAMA*. 2021;326(14):1378-1380. doi:10.1001/jama.2021.14809
3. Filippini M, Del Duca E, Negosanti F, et al. Fractional CO₂ laser: from skin rejuvenation to vulvo-vaginal reshaping. *Photomed Laser Surg*. 2017;35(3):171-175. doi:10.1089/pho.2016.4173

To the Editor I have several questions about the study¹ investigating the effect of fractional carbon dioxide laser vs sham treatment on symptom severity in women with postmenopausal vaginal symptoms. First, I would like to know whether this study's treatment protocol included a 90° probe introital treatment in addition to the straight probe vaginal treatment. In clinical practice, this additional introital therapy substantially enhances the treatment effect of the carbon dioxide laser therapy. Second, in relation to the histological evaluation of the vaginal tissue before and after treatment, do the authors have an explanation for the change in vaginal histology in the sham group to premenopausal status in 3 of the 24 patients? Third, did patients with recurrent vulvovaginal candidiasis receive antifungal medication prior to treatment with the fractional carbon dioxide laser? Fourth, were women with vulvodinia excluded from this trial? In clinical practice, patients with untreated vulvovaginal candidiasis and/or vulvodinia typically do not have improvement in their vaginal symptoms with laser therapy unless these underlying conditions are addressed and managed.

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1. Li FG, Maheux-Lacroix S, Deans R, et al. Effect of fractional carbon dioxide laser vs sham treatment on symptom severity in women with postmenopausal vaginal symptoms: a randomized clinical trial. *JAMA*. 2021;326(14):1381-1389. doi:10.1001/jama.2021.14892

To the Editor We have several concerns about the recent study by Li et al.¹ First, specific groups of women who were not the focus of this trial may benefit from fractional carbon dioxide laser treatment. As mentioned by the authors, this study¹ was not powered to examine the efficacy of vaginal laser treatment on patients with breast cancer. Women receiving endocrine therapy for breast cancer typically have more severe vaginal symptoms associated with menopause and more vaginal atrophy² and theoretically could derive a larger relative benefit from laser treatment.^{3,4}