Multisystemic inflammatory syndrome following COVID-19 mRNA vaccine in children: a national post-authorization pharmacovigilance study

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Key points:

Question. Is COVID-19 mRNA vaccine in 12-17-year-old children associated with subsequent multisystemic hyper-inflammatory syndrome?

Findings. The French national pharmacovigilance system identified 9 children with a hyper-inflammatory syndrome with multi-organ involvement following COVID-19 mRNA vaccination (reporting rate 1.1 [0.5; 2.1] per 1,000,000 doses), of which only three had evidence of previous SARS-CoV-2 infection. All cases fulfilled WHO definition for MIS-C, but clinical and immunological features, along with short-term outcomes, slightly differed from classical post SARS-CoV-2 MIS-C.

Meaning. Very rare cases of hyper-inflammatory syndrome can occur following COVID-19 mRNA vaccine in 12-17-year-old children. The very low rate of this entity, compared to classical post-SARS-CoV-2 MIS-C, supports the benefit of SARS-CoV-2 vaccination in children.

Abstract

Importance. Multisystem inflammatory syndrome in children (MIS-C) is the most severe life-threatening clinical entity associated with pediatric SARS-CoV-2 infection. Whether COVID-19 mRNA vaccine can induce this complication in children is unknown.

Objective. To assess the risk of hyper-inflammatory syndrome following COVID-19 mRNA vaccine in children.

Design, Setting, and Participants. Post-authorization national population-based surveillance using the French enhanced pharmacovigilance surveillance system for COVID-19 vaccines. All cases of suspected hyper-inflammatory syndrome following COVID-19 mRNA vaccine in 12–17-year-old children between June 15th, 2021 and January 1st, 2022, were reported. Each case was assessed for WHO MIS-C criteria. Causality assessment followed 2019 WHO recommendations.

Exposure. COVID-19 mRNA vaccine.

Main Outcome and Measures. The main outcome was the reporting rate of post-vaccine hyper-inflammatory syndrome per 1,000,000 COVID-19 mRNA vaccine doses in 12–17-year-old children. This reporting rate was compared to the MIS-C rate per 1,000,000 12–17-year-old children infected by SARS-CoV-2. Secondary outcomes included the comparison of clinical features between post-vaccine hyper-inflammatory syndrome and post SARS-CoV-2 MIS-C.

Results. From June 2021 to January 2022, 8,113,058 COVID-19 mRNA vaccine doses were administered to 4,079,234 12–17-year-old children. Among them, 9 presented a multisystemic hyper-inflammatory syndrome. All cases fulfilled MIS-C WHO criteria. Main clinical features included male predominance (8/9, 89%), cardiac involvement (8/9, 89%), digestive symptoms (7/9, 78%), coagulopathy (5/9, 54%), cytolytic hepatitis (4/9, 46%), and shock (3/9, 33%). 3/9 (33%) required intensive care unit transfer, and 2/9 (22%) hemodynamic support. All cases recovered. Only three cases had evidence of previous SARS-CoV-2 infection. The reporting rate was 1.1 (95%CI [0.5; 2.1]) per 1,000,000 doses injected. As a comparison, 113 MIS-C (95%CI [95; 135]) occurred per 1,000,000 12–17-year-old children infected by SARS-CoV-2. Clinical features (inflammatory parameters, cytopenia) slightly differed from post-SARS-CoV-2 MIS-C, along with short-term outcomes (less PICU transfer than MIS-C).

139 ***Conclusion and Relevance***. Very few cases of hyper-inflammatory syndromes with multi-
140 organ involvement occurred following COVID-19 mRNA vaccine in 12–17-year-old children.
141 The low reporting rate of this syndrome, compared to the rate of MIS-C among same age
142 children infected by SARS-CoV-2, supports the benefit of SARS-CoV-2 vaccination in children.
143 Further studies are required to explore specific pathways of this entity compared to post-
144 SARS-CoV-2 MIS-C.
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Background.

Multisystem inflammatory syndrome in children (MIS-C) is a novel clinical entity first described in April 2020.[1–5] Its association with SARS-CoV-2 infection has been documented, with a previous infection occurring 4 to 6 weeks before MIS-C onset.[4–6] The main clinical features of MIS-C are frequent acute cardiac dysfunction, shock, multi organ failure that often require pediatric intensive care unit transfer and hemodynamic support.[7] Thus, numerous studies showed that MIS-C is by far the most severe form associated with SARS-CoV-2 infection in children and the leading source of morbidity related to SARS-CoV-2 in this age group.[7,8]

The pathophysiology of this disease remains unknown, but previous investigations showed that MIS-C is characterized by a cytokine storm[9] associated with a superantigen-like activation of T cells with an expansion of Vβ21.3-expressing T cells which is not seen in toxic shock syndrome, Kawasaki disease or other COVID-19 features[10–13]. Notably, SARS-CoV2 spike harbors a motif located in the receptor binding domain the that is predicted *in silico* to interact with Vβ region in T cells. Whether antigenic exposure limited to the Spike protein can lead to similar dysregulated immune response remains unknown.

Two COVID-19 mRNA vaccines have been shown to be efficacious and well tolerated in adults, and have been introduced since December 2020.[14] Post-authorization studies confirmed their major impact on SARS-CoV-2 epidemics,[15] with very few serious adverse events reported to date.[16,17] In children, the immunogenicity, efficacy, as well as frequent adverse events have been assessed in trials involving thousands of 12-17-year-old children.[18] Based on these studies, the Food and Drug Administration (FDA) and European Medicines Agency (EMA) authorized formulations of BNT162b2 COVID-19 vaccine for ages 12-17-year. However, rare serious adverse events following immunization could not be detected by

these clinical trials. Especially, whether exposure to SARS-CoV-2 antigens due to mRNA vaccine can induce MIS-C is unknown.

Given the lower burden of SARS-CoV-2 related diseases in children compared to adults, elucidating the safety profile of mRNA vaccine, especially regarding MIS-C, is of critical interest to establish its benefit-risk balance in this population. In this context, monitoring post-vaccine MIS-C has been identified as a priority by the FDA, the EMA, and the French National Agency for Medicines and Health Products safety (ANSM).[19–21] Several cases reports of children with MIS-C following mRNA vaccine recently raised major concerns regarding this potential vaccine-related adverse event.[22–25]

Using a well-established national pharmacovigilance surveillance system coordinated by ANSM,[26,27] we aimed to evaluate the potential association of COVID-19 mRNA vaccine and subsequent hyper-inflammatory syndrome in children.

Methods.

Ethical review.

For the pharmacovigilance surveillance system, this study was performed according to the authorization from the National Commission on Informatics and Liberty (CNIL) n° 2014-302 for the national pharmacovigilance database done by ANSM. For the MIS-C following SARS-CoV-2 infection surveillance system, the study was approved by the INSERM ethics committee for evaluation (IRB00003888). A written information form validated by the ethics committee was given to all participants. Oral consent was obtained from study participants; no family members or participants refused to participate.

Study design and settings.

We conducted a post-authorization prospective national population-based surveillance using the well-established ANSM pharmacovigilance system.[26,27] This network is based on 31 regional pharmacovigilance centers, which cover all the French territory, and is coordinated by ANSM since 1973.[26] All ambulatory or hospital-based health practitioners throughout France or patient that observe a suspected adverse drug reaction (ADR) report the event to the regional center via a secure platform.[26] Reporting of all ADRs, independently of the seriousness or expectedness, is compulsory for health practitioners. All reports undergo a pharmacological, clinical and biological assessment process by a trained assessor of the Regional Center. Cases are then registered in the national computerized pharmacovigilance database, centralized at ANSM, to allow anonymized case reviewing at a national level by ANSM and experts in the field, drug causality assessment, and to recommend specific measures if required.[27] The detailed methodology of this French pharmacovigilance system has been previously published.[26,27]

As part of the national COVID-19 vaccination campaign, ANSM had put in place a specific reinforced surveillance system to provide real-time monitoring of COVID-19 vaccines ADRs at a national level.[21,28] This is part of the risk management plan coordinated by the European Medicines Agency (EMA). The objectives are to carry out a continuous assessment of the safety of vaccines COVID-19 vaccines in order to confirm their safety or to quickly take the relevant measures, and to allow the Health Ministry to adapt the vaccination strategy, if necessary. For each marketed COVID-19 vaccine, two to five regional pharmacovigilance centers have been designated to gather and assess on a daily basis all adverse drug reactions reported following immunization. An expert of the organ involved is solicited to analyze the reported cases every week, to identify atypical and/or serious patterns leading to potential safety signals.[21] Then a weekly meeting involving ANSM and all regional pharmacovigilance centers is organized to discuss the expert pharmacovigilance reports, potential safety signals, and new data from the literature, in order to confirm or not safety signals.[21,28] A complete report including the synopsis of these meeting are published by ANSM every two weeks.[21,28] If a national safety signal is validated, appropriate measures are issued in relation with European Medicine Agency to prevent or reduce the likelihood of the risk occurring in vaccinated people. The detailed methodology of this specific COVID-19 vaccine monitoring is available elsewhere.[21,28]

<u>Cases review to assess WHO criteria for MIS-C and vaccine causality.</u>

All pediatric cases of inflammatory syndrome, fever > 3 days, shock, or acute organ dysfunction without any obvious cause, occurring any time after COVID-19 mRNA vaccine injection in children under 18 years of age in France from June 15th, 2021, to January 1st, 2022, were eligible. Following 2019 WHO guidelines for causality assessment of an adverse

event following immunization,[29] each case was reviewed by a multidisciplinary committee, with experts in pediatric immunization, pediatric infectious diseases, pediatric rheumatology, immunology and internal medicine, pediatric intensive care, pediatric cardiology, and experts pharmacologists from pharmacovigilance centers. All these experts were involved in MIS-C surveillance and management in France as part of the French MIS-C consortium, and developed specific expertise in this field.[5,30,31] Medical records were obtained for all cases to accurately assess if cases fulfilled WHO criteria for MIS-C. Cases were included after reviewing if they fulfilled WHO MIS-C criteria, with a delay between the last vaccine administration and disease onset < 2 months, based on available data from the literature regarding the delay between SARS-CoV-2 infection and MIS-C onset.[4–6] An important part of the vaccine causality assessment relied on identifying other potential causes for the event.[29] For hyper-inflammatory syndrome, extensive investigation of previous exposure to SARS-CoV-2 over the past two months was critical, and relied on investigating history of documented infection, and performing nasopharyngeal SARS-CoV-2 Polymerase chain reaction (PCR) and anti-Nucleocapsid (anti-N) serology.[32]

National immunization program.

BNT162b2 COVID-19 mRNA vaccine have been introduced for 12-17-year-old children on June 15th, 2021 in France.[33] It has been followed by mRNA-1273 approval for same age children on July, 27th, 2021.[33] A higher risk of myocarditis or pericarditis has been suggested following mRNA-1273 compared to BNT162b2 in adults younger than 30 years old.[34] This has led French authorities to prioritize BNT162b2 for 12-17-year-old children immunization. Thus, by January 1st, 2022, the large majority of vaccinated 12-17-year-old children received BNT162b2 (>95%).[31]

Outcome measure.

The main outcome was the national reporting rate of hyper-inflammatory syndrome following COVID-19 mRNA vaccine per 1,000,000 doses in 12-17-year-old children in France. To calculate national reporting rate, we used as a denominator the total number of COVID-19 mRNA vaccine dose administered in 12-17-year-old children over the study period (available at https://solidarites-sante.gouv.fr/grands-dossiers/vaccin-covid-19/article/le-tableau-de-bord-de-la-vaccination). We also estimated in the same age-group, in the same population, the rate of post-SARS-CoV-2 MIS-C cases per 1,000,000 infections in 12-17-year-old children in France for comparison.

Secondary outcomes were the reporting rate of hyper-inflammatory syndrome following first and second injections of COVID-19 mRNA vaccine in 12-17-year-old children in France, reporting rate by sex, and comparison of clinical features of hyper-inflammatory syndrome following COVID-19 mRNA vaccine versus post-SARS-CoV-2 MIS-C cases.

MIS-C following SARS-CoV-2 infection surveillance system.

To estimate the rate of post-SARS-CoV-2 MIS-C cases per 1,000,000 infections in 12-17-year-old children in France, we used data from the French COVID-19 Pediatric Inflammation Consortium, coordinated by Public health France.[5,30,31] As previously published, since April 2020, all suspected MIS-C cases in France were mandatorily reported to Public health France. Each suspected case was then assessed following WHO criteria for MIS-C.[5,30,31] Furthermore, Public health France also conducted seroprevalence studies that allowed estimating the proportion of 12-17-year-old old children infected by SARS-CoV-2 since the beginning of the pandemic.[35] Thus, to estimate the rate of post-SARS-CoV-2 MIS-C

cases per 1,000,000 infections, we used as a numerator the number of confirmed 12-17-year-old MIS-C cases reported to Public health France since the start of the pandemic, and as a denominator the estimated number of 12-17-year-old French children infected by SARS-CoV-2 since the start of the pandemic. To avoid any bias in MIS-C rate estimation due to vaccine implementation,[31] we restricted this analysis to the pre-vaccine period, i.e. from the start of the pandemic to June 15th, 2021.

This surveillance system also collected clinico-biological and short term outcome data of MIS-C cases that fulfilled WHO criteria.[5,30,31] Thus, to compare the clinical presentation of hyper-inflammatory syndrome following COVID-19 mRNA vaccine to post-SARS-CoV-2 MIS-C cases in the same population, we included all unvaccinated 12-17-year-old MIS-C cases fulfilling WHO criteria with available clinical files as same-age and same-population comparator group.

Statistical analysis.

We describe patient characteristics with numbers (percentages) for categorical variables and median (interquartile range [IQR]) for quantitative variables. We compared clinical and biological characteristics using non-parametric Fisher's exact test for categorical variables and Mann-Whitney U test for quantitative variables. A two-sided p-value <0.05 was considered statistically significant. Reporting rate of hyper-inflammatory syndrome was expressed as cases per 1,000,000 vaccine injections with 95% CIs. All statistical analyses involved using R v3.6.1 (http://www.R-project.org).

Results.

From June 15th, 2021 to January 1st, 2022, 8,113,058 COVID-19 mRNA vaccine doses were administered to 4,079,234 12-17-year-old children in France (including 4,079,234 first injections, 3,905,636 second injections, and 128,188 third injections). Over this period, 2,028 adverse drug reactions related to COVID-19 mRNA vaccine have been reported to the pharmacovigilance centers in 12-17-year-old children. Among them, 9 cases of hyper-inflammatory syndrome were reported. All cases fulfilled WHO criteria for MIS-C (Table 1). All cases involved BNT162b2 vaccine (5 cases following the first injection, 4 following the second injection). The delay between last injection and disease onset ranged from 2 days to 42 days.

Investigation of previous SARS-CoV-2 infection.

All 9 cases had complete data for history of documented infection, nasopharyngeal SARS-CoV-2 PCR, and anti-N serology. In one case, a previous infection 7 months before disease onset was reported, but was too far apart to be considered as linked to the disease. All children had negative SARS-CoV-2 PCR, and three children had a positive anti-N serology (Table 1). Based on all information available, the mRNA vaccine causality was considered consistent in 4 cases, and indeterminate in 5 cases (details Table 1 and Appendix 1).

National reporting rate of hyper-inflammatory syndrome following mRNA vaccine

Considering all 9 cases of hyper-inflammatory syndrome, a national reporting rate of 1.1 (95% CI [0.5; 2.1]) per 1,000,000 mRNA vaccine doses administered in 12-17-year-old children was observed. Excluding cases for which evidence of previous SARS-CoV-2 infection has been found, the reporting rate was reduced to 0.7 (95% CI [0.3; 1.6]) per 1,000,000

mRNA vaccine doses administered. This reporting rate varied from 1.2 (95% CI [0.4; 2.9]) following the first mRNA vaccine injection to 1.0 (95% CI [0.3; 2.6]) after the second mRNA vaccine injection (Table 2). The reporting rate was significantly higher for males compared to females (1.9 [0.8; 3.8] versus 0.3 [0.0; 1.4] per 1,000,000 doses, respectively, p=0.039).

As a comparator, 130 post-SARS-CoV-2 MIS-C cases occurred in 12-17-year-old children, for 1,148,299 same-age children infected by SARS-CoV-2, leading to a MIS-C rate of 113.3 [94.7; 134.6] per 1,000,000 12-17-year-old infected children (Table 2).

Clinical features of hyper-inflammatory syndrome following COVID-19 mRNA vaccine compared to post-SARS-CoV-2 MIS-C cases

The detailed clinical presentation of children with hyper-inflammatory syndrome following COVID-19 mRNA vaccine is provided Table 1. Median age was 12.5 years (IQR [12.0; 13.5]), 8/9 (89%) children were male and 3/8 had comorbidities (one type 1 diabetes, one osteochondritis with overweight, and one leukemia in remission). The most frequent clinical features were cardiac involvement (8/9, 89%, including 7 elevated cardiac enzymes, 4 pericarditis, 3 acute left ventricular ejection fraction decrease ≤ 55%, 1 transient coronary dilation and 1 myocarditis), gastrointestinal symptoms (7/9, 78%), coagulopathy (5/9, 56%), mucocutaneous involvement (5/9, 56%), cytolytic hepatitis (4/9, 44%) and shock (3/9, 33%). Macrophage activation syndrome was identified in one case. For comparison, among 199 children with post-SARS-CoV-2 MIS-C, 108 (54%) were male (p=0.081), and cardiac involvement was found in 63% (p=0.16, Table 3).

Some biological parameters differed between post-vaccine hyper-inflammatory syndrome and post-SARS-CoV-2 MIS-C, including inflammatory parameters (median CRP level 186 [97; 250] vs 271 [187; 354], respectively, p=0.031), and blood cell count (median hemoglobin

12.3 [11.6; 13.6] vs 11.0 [10.1; 11.0], respectively, p=0.022, Table 3). Of note, 2/9 (22%) children with post-vaccine hyper-inflammatory syndrome had a transient hypereosinophilia (compared to 9/199 (5%) in post-SARS-CoV-2 MIS-C). These two children were explored for TRBV11-2/Vb21.3 expansion, none of them had an expansion of this repertory, while it was present in 75% of post-SARS-CoV-2 MIS-C patients[11].

Specific therapy and short-term outcomes.

Short term outcomes seemed also less severe for post-vaccine hyper-inflammatory syndrome, with a lower rate of PICU transfer (3/9, 33%), compared to 143/199 (72%) for post-SARS-CoV-2 MIS-C (p=0.022, Table 3). Six children were treated by an association of intravenous immunoglobulins plus methylprednisolone, of whom one received a subsequent 10mg/kg/day methylprednisolone pulse. Two children received methylprednisolone alone, and one did not receive specific immunomodulator agent. All children fully recovered at the time of discharge. Median length of hospital stay was 7 days (IQR [7; 9]).

Discussion.

To our knowledge, this is the first post-authorization population-based pharmacovigilance study assessing the risk of hyper-inflammatory syndrome following COVID-19 mRNA vaccine in 12-17-year-old children. We found that this entity was observed with an reporting rate of 1.1 (95% CI [0.5; 2.1]) per 1,000,000 doses in this population. In most cases, no evidence of previous SARS-CoV-2 infection was observed, suggesting a link between this entity and COVID-19 mRNA vaccine. This rare serious adverse event should be put in balance with the rate of post-SARS-CoV-2 MIS-C in the same age group in the same population, which was 100-fold higher. A recent study highlighted that COVID-19 mRNA vaccine may significantly reduce the incidence of post-SARS-CoV-2 MIS-C (Hazard Ratio 0.09 (95% CI, 0.04-0.21)).[31] Taken together, these findings suggest that the benefit-risk balance of COVID-19 mRNA vaccine is largely in favor of the vaccination in this age group, in a context of active circulation of SARS-CoV-2.

An important issue is to delineate the clinical spectrum of this entity, which may have overlap with several other diseases. First, cases of myocarditis have been reported following COVID-19 mRNA vaccines, especially in young men.[36,37] These cases mainly occurred after the second dose of vaccine, few days after the injection, and were rapidly resolutive in most cases.[36,37] The higher rate of hyper-inflammatory syndrome following COVID-19 mRNA vaccine in males, and the rate of cardiac involvement (8/9 cases) suggest similitudes with this entity. However, myocarditis were classically afebrile, with low inflammatory parameters, and were a mono-organ involvement.[37] These major clinical differences may allow distinguishing these two entities. Second, all cases of hyper-inflammatory syndrome following COVID-19 mRNA vaccine fulfilled WHO definition for MIS-C. Indeed, the prolonged hyper-inflammatory state, the multi-organ involvement and the severity of the disease are

388 principal features of these two entities,[7] indicating at least a major overlap. However, if
389 statistical comparison between these two diseases was limited by the low number of cases,
390 our findings suggest that post-SARS-CoV-2 MIS-C may have still higher inflammatory
391 parameters, and more cytopenia. This may be in line with the significantly lower rate of PICU
392 transfer (33% vs 72%) for hyper-inflammatory syndrome following COVID-19 mRNA vaccine
393 cases, which might reflect a less severe immune storm and disease course. Notably, a 4-
394 week delay has been observed in the context of MIS-C following SARS-CoV-2 infection[38–40].
395 Here, the delay from first antigen exposure to hyper-inflammatory syndrome occurred
396 within a week in 3 patients and after 4-12 weeks in the 6 others. In the cases with early
397 reaction, a hypereosinophilia was seen in 2 patients, a feature not seen in classical MIS-C.
398 This observation might reflect immunoallergic reaction distinct from the superantigenic like
399 features of MIS-C. Expansion of Vb21.3 expressing T cells is a hallmark of the MIS-C and can
400 be easily assessed by flowcytometry.[11] By contrast, the two children with post-vaccination
401 hyper-inflammatory syndrome had no expansion of this T cell subset. Taken together, these
402 clinical and immunological divergences may imply distinct underlying pathways and further
403 studies are required to expand this finding. Third, a recent study coordinated by the CDC
404 reported cases of multisystem inflammatory system in adults (MIS-A) in USA, in vaccinated
405 and unvaccinated adults.[32] Twenty cases were identified, of whom seven were vaccinated.
406 However, all of them had a documented previous exposure to SARS-CoV-2, questioning the
407 direct causal role of mRNA vaccines in these manifestations, and diverging with the pediatric
408 syndrome reported here, with only 2/9 patients presenting a seropositivity to N antigen. The
409 issue of delineating these different entities underline the need to extensively investigate
410 cases of hyper-inflammatory syndromes following mRNA vaccines, especially by performing
411 anti-S and anti-N serology, along with exploration for TRBV11-2/Vb21.3 expansion.

412 Because this hyper-inflammatory syndrome following COVID-19 mRNA vaccine was
413 severe with acute multi-organ dysfunction, therapeutic aspects are of major interest. In this
414 cohort, most children were treated by an association of immunoglobulins plus
415 methylprednisolone, following MIS-C therapeutic protocols.[30] Only one child treated with
416 this combination required a therapeutic escalation, and received a methylprednisolone pulse
417 (10mg/kg/day). All children fully recovered. If sample size precludes any definitive
418 conclusion, these findings suggest that the association of immunoglobulins plus
419 methylprednisolone may be a suitable approach while awaiting more evidence regarding
420 these treatments.
421
422 Several limitations should be discussed. First the causality of COVID-19 mRNA
423 vaccines assessment was mainly based on investigation for previous SARS-CoV-2 infection.
424 However, pauci or asymptomatic infections are frequent in children, and may not have been
425 documented. Furthermore, false negatives can be observed for anti-Nucleocapsid serology.[41]
426 Thus, we cannot exclude that some of the cases reported here could be related to
427 undiagnosed SARS-CoV-2 infections. Second, because this entity has not been previously
428 described in healthy populations, we could not have a control population to estimate the
429 expected incidence of this disease in unvaccinated children, which would help in elucidating
430 the vaccine causality.[16] Third, we cannot rule out under reporting of adverse drug events in
431 our population, which may have biased the estimated rate of hyper-inflammatory syndrome.
432 However, following the implementation of COVID-19 mRNA vaccine, a major effort has been
433 made by all pharmacovigilance centers to publicize that the reporting of any suspected
434 adverse drug reaction following these vaccines was mandatory.[26] The impressive number of
435 suspected adverse drug reaction reports (>80,000 between January 2021 and January 2022

in France) suggest that underreporting may have been very rare, especially for serious adverse drug reactions.[26] Fourth, given the very low proportion of 12-17-year-old children vaccinated by mRNA-1273 (<5%), we could not conduct subgroup analysis to compare the risk of hyper-inflammatory syndromes according to COVID-19 mRNA vaccine type. Further studies are required to explore if this risk differ between BNT162b2 and mRNA-1273. Fifth, because mRNA vaccines were only recommended to 12-17-year-old children in France until December 2021, we could not explore the risk of hyper-inflammatory syndrome in younger children.

Conclusion.

In this study, we identified cases of hyper-inflammatory syndrome following COVID-19 mRNA vaccines in 12-17-year-old children in France. This syndrome was very rare, and its reporting rate, in comparison with the rate of MIS-C following SARS-CoV-2 infection in the same age-group, largely supports the vaccination in a context of an important circulation of SARS-CoV-2. This syndrome shared many clinical features with post-SARS-CoV-2 MIS-C, but some clinical, immunological and short-term outcomes divergences call for further studies to explore its specific pathway.

Author Contributions:

NO, HB, FA, and AB made substantial contributions to the conception or design of the work. NO and AB drafted the manuscript. NO, HB, CLeb, CLev, EJ, BBM, CO, SR, VH, IKP, ND, LDP, XI, CGLG, FA and AB were involved in the acquisition, analysis, or interpretation of data. All authors provided critical revision of the manuscript for important intellectual content. NO and HB had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Table 1. Characteristics of children with hyper inflammatory syndrome following COVID-19 mRNA in France.

Case	1	2	3	4	5	6	7	8	9
Sex	Male	Male	Male	Male	Male	Male	Female	Male	Male
Comorbidity	No	No	No	No	Type 1 diabetes	Osteochondritis	Leukemia	No	No
Overweight	No	No	No	No	No	Yes	No	No	No
Number of COVID-19 mRNA injection	2	1	1	2	1	1	1	2	2
COVID-19 mRNA vaccine	BNT162b2	BNT162b2	BNT162b2	BNT162b2	BNT162b2	BNT162b2	BNT162b2	BNT162b2	BNT162b2
Delay from COVID-19 mRNA last injection to symptoms onset	26 days (50 days from first injection)	6 days	6 days	2 days (24 days from first injection)	4 days	20 days	19 days	42 days (72 days from first injection)	7 days (28 days from first injection)
MIS-C WHO criteria	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Details of MIS-C WHO criteria	Fever > 3 days, mucocutaneous involvement, Cardiac involvement, Elevated markers of inflammation, No other obvious microbial cause	Fever > 3 days, Shock, Cardiac involvement, Coagulopathy, Acute gastrointestinal symptoms, Elevated markers of inflammation, No other obvious microbial cause	Fever > 3 days, mucocutaneous involvement, Shock, Cardiac involvement, Coagulopathy, Acute gastrointestinal symptoms, Elevated markers of inflammation, No other obvious microbial cause	Fever > 3 days, Cardiac involvement, Coagulopathy, Acute gastrointestinal symptoms, Elevated markers of inflammation, No other obvious microbial cause	Fever > 3 days, mucocutaneous involvement, Shock, Cardiac involvement, Acute gastrointestinal symptoms, Elevated markers of inflammation, No other obvious microbial cause	Fever > 3 days, mucocutaneous involvement, Cardiac involvement, Elevated markers of inflammation, No other obvious microbial cause	Fever > 3 days, Coagulopathy, Acute gastrointestinal symptoms, Elevated markers of inflammation, No other obvious microbial cause	Fever > 3 days, Coagulopathy, Cardiac involvement, Acute gastrointestinal symptoms, Elevated markers of inflammation, No other obvious microbial cause	Fever > 3 days, mucocutaneous involvement, Cardiac involvement, Acute gastrointestinal symptoms, Elevated markers of inflammation, No other obvious microbial cause
Other manifestations	Lymphopenia, Cervical lymphadenopathy	Acute renal failure, proteinuria, Cytolytic hepatitis, Neurological involvement, Polyserositis, Hypereosinophilia.	Lymphopenia, Coronary dilation.	Acute renal failure, Cytolytic hepatitis, Pyelitis, Ileo-colitis.	Cervical lymphadenopathy, Hypereosinophilia, Acute generalized exanthematous pustulosis.	Lymphopenia.	Macrophage activation syndrome, Cytolytic hepatitis.	Lymphopenia, Cervical lymphadenopathy Cytolytic hepatitis.	Lymphopenia, Ileitis.
Biological features									
CRP, mg/L	250	300	257	228	70	97	49	167	186
Ferritinemia	527	195	600	Not performed	309	9185	25 020	430	Not performed

(µg/L)									
Hemoglobin (g/dL)	12.6	11.6	10.6	14.6	NA	NA	15.6	12.3	11.5
Leucocytes (/mm3)	16 500	11 130	16 600	4 050	NA	12 800	1 250	10 000	8 690
Neutrophils (/mm3)	15 500	4 340	13 000	Not performed	NA	9 700	1 040	9 400	7 600
Lymphocytes (/mm3)	520	3 560	900	Not performed	NA	890	100	920	540
Eosinophils (/mm3)	20	2 000	310	Not performed	1 170	NA	0	220	10
Platelets (/mm3)	225 000	472 000	278 000	321 000	204 000	350 000	27 000	230 000	113 000
SARS-CoV-2 infection documentation									
Past history of SARS-CoV-2 infection	No	No	No	No	Yes (documented SARS-CoV-2 infection 7 months before)	No	No	No	No
Nasopharyngeal SARS-CoV-2 PCR	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
SARS-CoV-2 antibody	Anti-Spike: positive Anti-N: negative	Anti-Spike: positive Anti-N: negative	Anti-Spike: positive Anti-N: positive	Anti-Spike: positive Anti-N: positive	Anti-Spike: positive Anti-N: negative	Anti-Spike: positive Anti-N: negative	Anti-Spike: negative Anti-N: negative	Anti-Spike: positive Anti-N: limit of significance*	Anti-Spike: positive Anti-N: positive
Specific therapy	IVIG+ steroids	None	IVIG+ steroids	IVIG+ steroids	IVIG+ steroids followed by steroid pulse	IVIG+ steroids	Steroids	IVIG+ steroids	Steroid pulse
PICU transfer	Yes	Yes	No	No	Yes	No	No	No	No
LVEF ≤ 55%	Yes (55%)	NON	No	Yes (40%)	Yes	No	No	No	Yes (40%)
Hemodynamic support	No	Yes	No	No	Yes	No	No	No	No
Outcome	Favorable	Favorable	Favorable	Favorable	Favorable	Favorable	Favorable	Favorable	Favorable
Causality of COVID-19 mRNA (WHO AEFI classification)	A1	A1	B2	B2	A1	A1	B1	B1	B2

*: antibody titer: 1.2 (Norms of the laboratory: positive: ≥ 1.68, negative: <0.49, limit: 0.49 ≤ x < 1.68).

Abbreviations: PCR: polymerase chain reaction. Anti-N: anti nucleocapsid. NA: missing data.

Table 2: Rate of hyper-inflammatory syndrome following COVID-19 mRNA vaccine compared to MIS-C post SARS-CoV-2 infection in 12-17-year-old children in France.

A) Reporting rate of hyper-inflammatory syndrome following COVID-19 mRNA vaccine in 12-17-year-old children

	Number of injected doses	Number of hyper-inflammatory syndrome	Reporting rate per 1,000,000 doses
Overall vaccination	8,113,058	9	1.1 [0.5; 2.1]
Excluding cases for which evidence of previous SARS-CoV-2 infection has been found	8,113,058	6	0.7 [0.3; 1.6]
First COVID-19 mRNA injection	4,079,234	5	1.2 [0.4; 2.9]
Second COVID-19 mRNA injection	3,905,636	4	1.0 [0.3; 2.6]
Vaccination by sex			
Males	4,126,275	8	1.9 [0.8; 3.8]
Females	3,986,783	1	0.3 [0.0; 1.4]

B) Rate of MIS-C following SARS-CoV-2 infection in 12-17-year-old children

	Estimated number of infected children	Number of MIS-C	Rate per 1,000,000 of infections
	1,147,150	130	113.3 [94.7; 134.6]
MIS-C by sex			
Males	587,086	74	126.0 [99.0; 158.2]
Females	560,064	56	100.0 [75.5; 129.8]

Abbreviations: MIS-C: multisystem inflammatory syndrome in children.

Table 3: Comparison of clinic-biological features of hyper-inflammatory syndrome following COVID-19 mRNA vaccine and MIS-C post SARS-CoV-2 infection in France.

	Hyper-inflammatory syndrome following COVID-19 mRNA vaccine (N=9)	MIS-C post SARS-CoV-2 infection (N=199)	P value
Clinical characteristics			
Sex ratio (F/M)	0.13	0.84	0.081
Age	12.5 [12.0; 13.5]	8.7 [4.8; 12.1]	
Organ involvement following MIS-C WHO definition			
Mucocutaneous involvement	5 (56%)	159 (80%)	0.097
Shock	3 (33%)	100 (50%)	0.318
Cardiac involvement	8 (89%)	125 (63%)	0.161
Including LVEF ≤ 55%	3 (33%)	52 (26%)	0.701
Coagulopathy	5 (56%)	82 (41%)	0.496
Digestive symptoms	7 (78%)	178 (89%)	0.261
Other organ involvement			
Cytolytic hepatitis	4 (44%)	36 (18%)	0.071
Lymphadenopathy	3 (33%)	39 (20%)	0.390
Renal failure	2 (22%)	31 (16%)	0.637
Neurological involvement	1 (13%)	65 (33%)	0.278
Biological features			
Maximal CRP, mg/L	186.0 [97.0; 250.0]	271.0 [187.2; 353.5]	**0.031**
Ferritinemia, (µg/L)	527.0 [369.5; 4892.5]	390.0 [206.0; 748.5]	0.228
Hemoglobin, g/dL	12.3 [11.6; 13.6]	11.0 [10.1; 11.0]	**0.022**
Leucocytes, /mm3	10 560 [7 530; 13 720]	9 945 [7 000; 14.155]	0.768
Neutrophils, /mm3	9 400 [5 970; 11 350]	8 090 [5 245; 12 065]	0.940
Lymphocytes, /mm3	890 [530; 910]	1 000 [690; 1 805]	0.217
Eosinophils, /mm3	220 [15; 740]	100 [5; 220]	0.463
Platelets, /mm3	230 000 [204 000; 321 000]	186 000 [142 000; 277 500]	0.336
Short term outcomes			
PICU transfer	3 (33%)	143 (72%)	**0.022**
Hemodynamic support	2 (22%)	86 (43%)	0.307
Hospital length of stay	7.0 [7.0; 9.0]	8.0 [6.0; 12.0]	0.960

Categorical variables are described with numbers (percentages) and quantitative variables are described with median (IQR). Abbreviations: MIS-C: multisystem inflammatory syndrome in children.