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**ORIGINAL ARTICLE**

# Myocarditis and pericarditis in adolescents after first and second doses of mRNA COVID-19 vaccines

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**Aims** While some concerns about vaccination-related pericarditis and/or myocarditis have been raised, no published data are available on pericarditis and/or myocarditis with mRNA COVID-19 vaccines in the age group of adolescents, particularly 12–15 years. The objective of this study was to determine whether the risk of reporting pericarditis and/or myocarditis with mRNA COVID-19 vaccines varied according to dose of vaccination, age, sex, and type of pericarditis and/or myocarditis in adolescents between 12 and 17 years.

**Methods and results** We performed an observational study reviewing all reports of adolescents vaccinated with mRNA COVID-19 vaccines and recorded in VigiBase®, the World Health Organization global database of individual case safety reports. We included all reports registered between 1 January 2021 and 14 September 2021. Reporting odds ratios (RORs) with their 95% confidence interval (CI) were calculated to estimate the risk of reporting pericarditis and/or myocarditis. Among 4942 reports with mRNA COVID-19 vaccines in adolescents, we identified 242 pericarditis and/or myocarditis. Compared with the first dose of mRNA COVID-19 vaccines, the second dose was associated with an increased risk of reporting pericarditis and/or myocarditis (ROR 4.95; 95% CI 3.14, 7.89). The risk of reporting pericarditis and/or myocarditis was 10 times higher in boys than in girls and no difference between the two types of vaccines could be demonstrated.

**Conclusion** This investigation including only adolescent data suggests for the first time that the second dose of mRNA COVID-19 vaccines increases the risk of reporting myocarditis/pericarditis compared with the first dose particularly in boys without significant difference between tozinameran and elasomeran.



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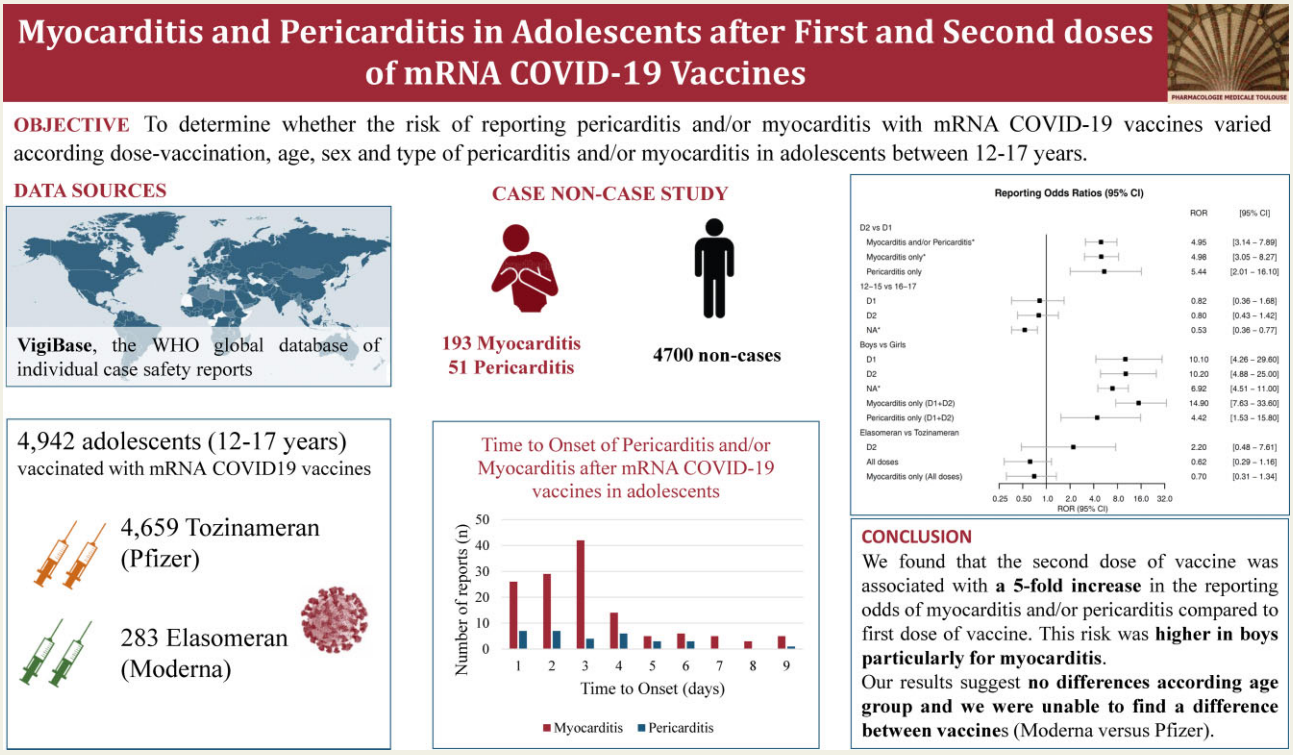
## Graphical Abstract




**Keywords** Myocarditis • Pericarditis • Tozinameran • Elasomeran • Pharmacovigilance • mRNA COVID-19 vaccines

# Introduction

While mRNA COVID-19 vaccines like tozinameran (Pfizer-BioNTech BNT162b2) and elasomeran (Moderna mRNA-1273) have shown a high level of efficacy and effectiveness in real life, some concerns about vaccination-related pericarditis and/or myocarditis have been raised.[1,2] After the initial signals from Israel, the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) alerted on the risk of pericarditis and/or myocarditis with mRNA COVID-19 vaccines.[2,3] In August 2021, the US Centers for Disease Control and Prevention (CDC) published data suggesting a higher rate of vaccination-related myocarditis in young men, but no stratification was made on the adolescent age group.[4] Recently, two observational studies from Israel estimated the incidence of myocarditis to be around 0.64 and 1.42 per 100 000 persons after the first dose of tozinameran and 3.83 per 100 000 after the second dose.[5,6] The risk difference between the first and second doses of tozinameran was evaluated to be 1.76 per 100 000 persons, with a great difference among boys between 16 and 19 years of age.[6] To date, no data have been published on young adolescents between 12 and 15 years of age. In addition, a recent update from Canada (Ontario) and from European Nordic countries suggests that elasomeran has higher rates of post-vaccination myocarditis than tozinameran in all male age groups.[7,8] Considering these cardiac risks, different vaccination policies have been decided in particular among adolescents. While the USA and several European countries (such as France) recommend two doses of mRNA COVID-19 vaccines, the UK recommends one dose to low-risk adolescents against COVID-19.[9] The European Nordic countries (Norway, Denmark, Sweden, and Finland) decided recently to limit vaccination with elasomeran in adolescent and/or young adults (<30 years).[10]

Since most of the data came from drug agency communications, mostly from the USA and Israel, there is an urgent need to provide additional data on pericarditis and/or myocarditis with mRNA COVID-19 vaccines in the age group of adolescents, particularly those between 12 and 15 years of age. It is also necessary to have more information on the risk of pericarditis and/or myocarditis between the two mRNA COVID-19 vaccines in this young population Thus, the objective of this study was to determine whether the risk of reporting pericarditis and/or myocarditis with mRNA COVID-19 vaccines varies according to dose of vaccination, age, sex, and type of pericarditis and/or myocarditis in adolescents between 12 and 17 years of age.

# Methods

We performed a pharmacovigilance analysis reviewing all reports with mRNA COVID-19 vaccines recorded in VigiBase®, the World Health Organization (WHO) global database of individual case safety reports (ICSRs). VigiBase includes more than 25 million reports forwarded to the WHO Uppsala Monitoring Center (UMC) by national

**Table 1 Characteristics of pericarditis and/or myocarditis reports with mRNA COVID-19 vaccines in adolescents, in VigiBase**

| | Myocarditis[a] | Pericarditis[a] |
|---|---|---|
| *n* (%) | 193 | 51 |
| Age (mean, SD/median) | 15.9 (1.3)/16 | 15.6 (1.5)/16 |
| *Age* | | |
| [12–15] | 50 (25.9) | 19 (37.3) |
| [16–17] | 143 (74.1) | 32 (62.7) |
| *Sex* | | |
| Men | 172 (89.1) | 35 (68.6) |
| Women | 21 (10.9) | 16 (31.4) |
| *Country* | | |
| Germany | 57 (29.5) | 2 (3.9) |
| France | 28 (14.5) | 13 (25.5) |
| Spain | 16 (8.3) | 2 (3.9) |
| Austria | 15 (7.8) | 0 |
| Italy | 15 (7.8) | 10 (19.6) |
| Denmark | 12 (6.2) | 4 (7.8) |
| Hungary | 9 (4.7) | 1 (2.0) |
| UK | 8 (4.2) | 2 (3.9) |
| Others | 33 (17.1) | 17 (33.3) |
| Reported by physician | 121 (62.7) | 31 (60.8) |
| High completeness[b] | 178 (92.2) | 41 (80.4) |
| *Event-related dose number*[c] | | |
| D1 | 31 (16.1) | 6 (11.8) |
| D2 | 58 (30.1) | 10 (19.6) |
| NA | 104 (53.9) | 35 (68.6) |
| *mRNA vaccine* | | |
| Tozinameran | 185 (95.9) | 50 (98.0) |
| Elasomeran | 8 (4.1) | 1 (2.0) |
| Serious (yes) | 190 (98.5) | 41 (80.4) |
| Hospitalization | 172 (89.1) | 21 (41.2) |
| *Co-reported event* | | |
| Chest pain | 50 (25.9) | 13 (25.5) |
| Pyrexia | 22 (11.4) | 6 (11.8) |
| Headache | 13 (6.7) | 1 (2.0) |
| Time to onset (days), median[d] | 3 d | 4 d |

D1, first dose; D2, second dose; NA, information relative to the dose not available; SD, standard deviation.
[a]Of the 242 reports mentioning pericarditis and/or myocarditis, 2 had both events (pericarditis and myocarditis).
[b]The Uppsala Center (manager of VigiBase) has developed a notification completeness score (VigiGrade). It is calculated by assigning penalties according to the availability of information and its clinical relevance. Here, high completeness was defined by a completeness score ≥0.6.
[c]Event-related dose number means the dose at which the event occurred (D1 for dose 1, D2 for dose 2, and NA when no information was found on the dose number).
[d]Based on 45 cases' data for pericarditis and 173 cases' data for myocarditis.

pharmacovigilance systems from over 148 countries. The Medical Dictionary for Regulatory Activities (MedDRA®) is used to code each adverse drug reaction. According to the clinical research French law, review from an ethics committee is not required for such observational studies. As all data from VigiBase® were deidentified, patient informed consent was not necessary.

We included all reports registered between 1 January 2021 and 14 September 2021, with age and sex known. All adolescents (12–17 years) who received mRNA COVID-19 vaccines were included. As the reports from the USA did not include dose information (first or second dose), we have excluded these data from the study. All reports were reviewed by authors (D.F., C.F., P.D.P.), including one clinical cardiologist (D.F.), and were classified in reports related to first dose (D1), second dose (D2), or non-available information (NA). Performing disproportionality analyses, we compared the cases of pericarditis and/or myocarditis in patients exposed to the second dose of mRNA COVID-19 vaccines with those reported in patients exposed to the first dose of mRNA COVID-19 vaccines. Reporting odds ratios (RORs) with their 95% confidence intervals (CIs) were calculated to estimate the risk of reporting pericarditis and/or myocarditis. ROR is a ratio similar in concept to the odds ratio in case control studies and corresponds to the exposure odds among reported cases of pericarditis or myocarditis over the exposure odds among reported non-cases. Cases were reports containing any terms including the terminology 'non-infectious pericarditis' or 'non-infectious myocarditis' found in the MedDRA dictionary. Non-cases were all other reports recorded in VigiBase® during the same period of interest for our population. Logistic regression models were performed for the disproportionality analysis to take into account the potential confounders including the following variables: age, sex, type of reporter (physician or other), completeness of individual case safety reports (high or low), and number of coreported drugs when the headcount allowed it. As secondary objectives, we also evaluated the risk of reporting pericarditis and/or myocarditis according to age group (12–15 vs. 16–17 years), sex, and type of mRNA COVID-19 vaccine (elasomeran vs. tozinameran). Sensitivity analyses were performed, including only physician reports.

## Results

In total, we analysed 4942 reports with mRNA COVID-19 vaccines in adolescents aged 12–17 years old (tozinameran = 4659; elasomeran = 283). We identified 242 pericarditis and/or myocarditis (49 pericarditis only, 191 myocarditis only, 2 myopericaditis), and 233 were reported with tozinameran and 9 with elasomeran (*Table 1*). Among these cases, patients were mostly boys (205, 85%), with a mean age of 15.8 ± 1.4 years. Most of the reports were serious (229, 95%), including 191 (79%) leading to hospitalization. The evolution was fatal in only one case. Reports of pericarditis and/or myocarditis came mostly from Germany (59; 24%), followed by France (40, 17%) and Italy (24; 10%), and from physicians in 150 cases (62%). The most frequent coreported symptoms were chest pain, pyrexia, or dyspnoea. The time of onset was 4 days for D1 and 3 days for D2 (3 days for NA) (*Figure 1*).

Compared with the first dose of mRNA COVID-19 vaccines, the second dose was associated with an increased risk of reporting pericarditis and/or myocarditis (ROR 4.95; 95% CI 3.14, 7.89) (*Figure 2*). The ROR remained significant when analysis was limited to myocarditis only (ROR 4.98; 95% CI 3.05, 8.27) or pericarditis only (ROR 5.44; 95% CI 2.01, 16.10). No differences were found when we compared age groups (12–15 vs. 16–17 years) whatever the dose (except for the analyses with NA). The risk of reporting pericarditis and/or myocarditis was 10 times higher in boys than in

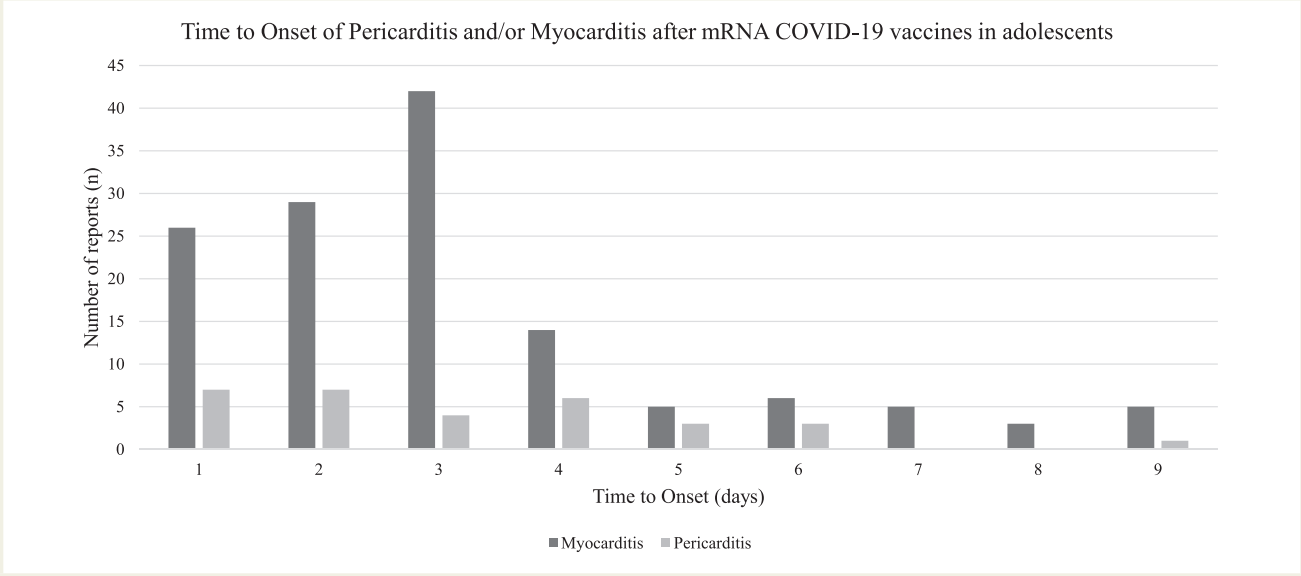



**Figure 1** Time to onset of pericarditis and/or myocarditis after mRNA COVID-19 vaccines in adolescents (days).

girls at both the first dose (ROR 10.1; 95% CI 4.26, 29.6) and second dose (ROR 10.2; 95% CI 4.88, 25.0). No difference between the two types of vaccines could be demonstrated (D2; ROR 2.20; 95% CI 0.48, 7.61). Consistent results were observed in sensitivity analyses restricting data to reports made by physicians.

# Discussion

This study evaluated more than 4900 adverse effects of mRNA COVID-19 vaccines in adolescents mainly reported by European countries. We found that the second dose of vaccine was associated with a five-fold increase in the reporting odds of myocarditis and/or pericarditis compared with first dose of vaccine. This risk was higher in boys particularly for myocarditis. Our results suggest no differences according to age group or type of vaccine. As the US pharmacovigilance data did not include dose information (dose 1 or dose 2), we were unable to analyse the reports. This lack of information is a potential limitation of our study on the transferability of the results to the US vaccination context and may have limited the statistical power of our study, particularly when comparing the two vaccines. However, to our knowledge, this is the first investigation based on non-US data that provides additional data on vaccine safety in adolescents. Such pharmacovigilance analyses could be subject to reporting bias, but our results add new information to relatively young adolescents (12–15 years), the difference between age group and type of mRNA COVID-19 vaccine, and corroborate the higher risk of the second dose, particularly in boys.[5,6,11] While randomized clinical trials show that mRNA COVID-19 vaccines represent an effective method of preventing infection, our finding should be integrated as a component of the vaccine strategy to limit the impact of cardiac adverse effects, in balance with the exceptionally severe form of COVID-19 in adolescents. Our study calls for corroboration in large real-world studies and evaluation of long-term consequences of this vaccine-associated pericarditis/myocarditis.

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## Author contributions

All the authors conceived and designed the study. F.M. and C.F. acquired the data and did the statistical analyses. All the authors analysed and interpreted the data. D.F. wrote the manuscript, and all the authors critically revised the manuscript. F.M. supervised the study and is the guarantor. All the authors approved the final version of the manuscript and are accountable for its accuracy.

**Conflict of interest:** None disclosed.

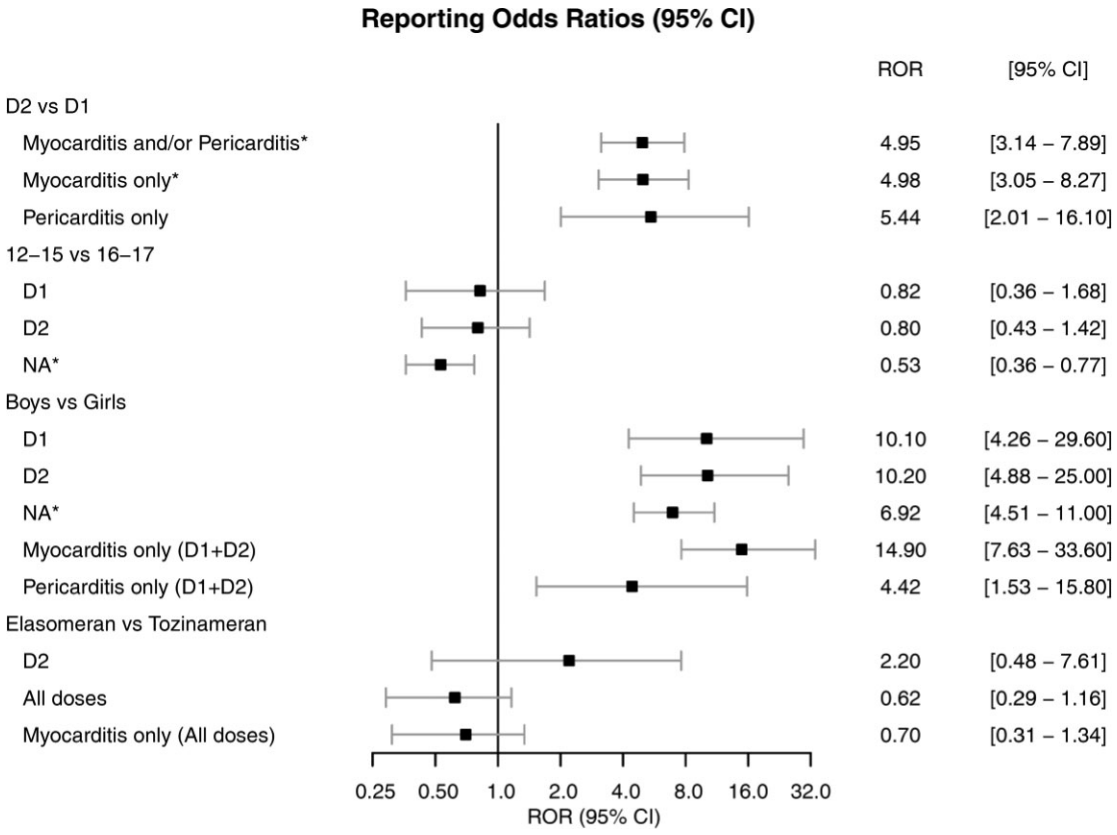


**Figure 2** Reporting odds ratios for the association between reports of non-infectious myocarditis and/or non-infectious pericarditis and the use of tozinameran and elasomeran†. CI, confidence interval; ROR, reporting odds ratio; D1, first dose; D2, second dose; NA, information relative to the dose not available. †We used the case non-case method, which is similar to case-control studies but adapted for pharmacovigilance studies. We used reporting odds ratios (RORs) and their 95% confidence interval (95% CI) to calculate disproportionality. ROR is a ratio similar in concept to the odds ratio in case-control studies and corresponds to the exposure odds among reported cases of myocarditis/pericarditis over the exposure odds among reported non-cases. Cases were reports containing any terms including the terminology 'non-infectious pericarditis' or 'non-infectious myocarditis' found in the MedDRA (Medical Dictionary for Regulatory Activities) dictionary. Non-cases were all other reports recorded in VigiBase® during the same period of interest for our population. The logistic regression model performed for the disproportionality analysis was adjusted for five variables: age, sex, type of reporter (physician or other), completeness of individual case safety reports (high or low), and number of coreported drugs (none, one or two, or more than two) when the headcount allowed it.

## Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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