Pharmacovigilance involves monitoring the safety of therapeutic products under real-world conditions after market authorization. In the case of immunization, pharmacovigilance includes the detection, evaluation, understanding, prevention, and communication of adverse events following immunization (AEFIs). Established surveillance systems and vigilance by healthcare professionals enabled the identification of safety signals for myocarditis/pericarditis associated with mRNA COVID-19 immunization. In this retrospective pharmacovigilance study, an international consortium of researchers used the Vaccine Adverse Events Reporting System (VAERS) to analyze reporting rates of myocarditis/pericarditis after the primary and up to three booster doses of mRNA COVID-19 vaccination (BNT162b2, Pfizer-BioNTech, and mRNA-1273, Moderna). The VAERS, the United States national passive surveillance system, receives reports from various stakeholders, including vaccine manufacturers, vaccine recipients, healthcare providers, and military personnel.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an enveloped, positive-sense, single-stranded RNA virus. Its genome encodes four structural proteins, namely the spike (S), envelope (E), nucleocapsid (N), and membrane (M) protein. The S protein is composed of subunits S1 and S2, separated by host cell proteases. A unique feature of the SARS-CoV-2 entry cascade is that the S1 subunit of the S protein can be shed from the surface of virions following engagement of the angiotensin-converting enzyme 2 (ACE2) receptor. Spontaneous shedding of the S1 subunit has been reported in the absence of host receptor binding. These data suggest that the S1 subunit of the S protein may interact with the host cells independently of the virion.

BNT162b2 (Pfizer-BioNTech) and mRNA 1273 (Moderna) vaccines were the first mRNA-based vaccines ever approved. In both vaccines, a mRNA sequence determines the structure and assembly of the immunogen, the SARS-CoV-2 S glycoprotein. The etiology of myocarditis/pericarditis associated with mRNA COVID-19 vaccination remains unknown. *Postmortem* heart histopathological examination demonstrated an inflammatory infiltrate, mostly of T lymphocytes and macrophages mixed with eosinophils, B lymphocytes, and plasma cells. Early hypotheses suggested that the SARS-CoV-2 S protein, which could be detectable in the blood, may induce cardiac-targeted autoantibodies through molecular mimicry. Other hypotheses are hypersensitivity myocarditis or autoimmune myocarditis driven by T-helper type 17 responses, but there is no evidence to support this pathology yet. Some arguments suggest that aberrant immune responses, both innate and adaptive, were triggered by the mRNA and/or lipid nanoparticles.

About the study

The authors conducted a retrospective pharmacovigilance study and analyzed reports of myocarditis/pericarditis in the VAERS from December 2020 to July 2022.

This study expanded previous analyses and included data from younger individuals, children 5 to 11 years old, approved for vaccination in the United States in November 2021, and children between 6 months and 4 years old, approved for vaccination in the United States in June 2022.

Results

During the study period, the analysis of VAERS data revealed 5154 reports of myocarditis/pericarditis after mRNA COVID-19 vaccination. The highest number of reports was for Pfizer/BioNTech vaccines, 3124 (60.6%), followed by Moderna with 1738 reports (33.7%) and Janssen with 204 reports (4%). In 24 reports (0.5%), the manufacturer name was missing.

Other vaccines had fewer reports of myocarditis/pericarditis, such as influenza vaccines (20 reports, 0.39%), varicella zoster vaccines (11 reports, 0.2%), smallpox vaccines (8 reports, 0.2%), meningococcal vaccines (7 reports, 0.1%), and pneumococcal vaccines (5 reports, 0.1%). The rest of the vaccines, such as human papillomavirus, anthrax, measles, mumps, rubella, varicella, rabies, hepatitis, Japanese encephalitis, typhoid, and yellow fever vaccines, had a total of 13 reports (0.3%).

The majority of cases (3485, 87%) diagnosed with myocarditis/pericarditis following mRNA COVID-19 vaccination were reported following the first or second doses. Importantly, the second dose of the mRNA COVID-19 vaccines showed the strongest signal. In contrast, the number of reported myocarditis/pericarditis cases for the booster doses was lower, with 495 (12%) cases reported after the third dose, and 23 (0.6%) cases following the fourth dose. The mean time to onset (TTO) for myocarditis/pericarditis was 5.9 days after vaccination.

The most frequently reported outcomes were hospitalization (2966, 34.6%), emergency room or clinic visits (2523, 29.4%), and doctor's office visits (1991, 23.2%).

Researchers also analyzed the other cardiac adverse events following immunization, such as chest pain, dyspnea, palpitations, and tachycardia. The mean time to onset (TTO) for palpitations was 5.6 days, for chest pain and tachycardia 6.9 and 7.2 days, and for dyspnea 9.3 days after immunization.

The analysis of age and gender differences in the VAERS reporting rates of myocarditis/pericarditis

The authors also analyzed age and gender differences in the VAERS reporting rates of myocarditis/pericarditis cases.

37.6% of cases that developed myocarditis/pericarditis following vaccination were under 25 years old. The highest percentages of reported cases were in the 18–24 years old group (20.6%) and 12–17 years old group (16.8%). The youngest age group of children between 6 months and 4 years old had 2 reported cases, whereas the group of children between 5 and

11 years old, had 21 reported cases.

This analysis also revealed significant gender differences in the reporting rates of myocarditis/pericarditis. The males comprised the majority of reported cases (66.1%), and females accounted for 31.6% of the reports, with missing data on gender in the remaining (2.29%) reports. The highest numbers of reported cases of myocarditis/pericarditis were in the groups of males aged 12–17 years (14.7%) and 18–24 years (17.1%). Females had a relatively low percentage of reported myocarditis/pericarditis cases across all age groups, with the highest percentage (5.6%) in the 31–40 and 41–50-year-old groups.

These differences were even more pronounced when the reporting rates of myocarditis/pericarditis cases were stratified by both age and gender. Specifically, 408 cases were reported in the 12–17-year-old age group, of which 363 (88.7%) were males and 45 (11.0%) were females. Similarly, 433 cases were reported in the 18–24-year-old age group, of which 367 (84.8%) were males and 66 (15.3%) were females.

Other cardiovascular symptoms, such as chest pain, dyspnea, palpitations, and tachycardia were found in both genders. For chest pain and dyspnea, safety signals were detected in adolescents and young adults after the second dose of the mRNA vaccine, with no significant differences between genders. For palpitations, safety signals were detected after the first dose among young adult males. In contrast, for tachycardia, safety signals were observed following the first dose in young girls under five years of age.

Conclusion

This analysis of VAERS reporting rates of myocarditis/pericarditis after mRNA vaccination demonstrated a higher reporting rate mainly after the second dose, particularly among young males. Females showed a similar pattern, with the strongest signal seen in young female teens after the second dose of the mRNA vaccine. Fewer cases were reported following booster doses, with no significant signals detected after the fourth or fifth dose. These data are in line with a recent PET/CT imaging study that investigated 18Fluorine-fluorodeoxyglucose (18F-FDG) uptake in asymptomatic individuals vaccinated with the mRNA COVID-19 vaccines, which has shown that myocardial 18F-FDG uptake was significantly higher in participants who underwent imaging up to 120 days after the second vaccination.
https://discovermednews.com/asymptomatic-vaccinated-participants-have-higher-myocardial-18f-fdg-uptake-than-unvaccinated-participants/

The authors emphasized that these results highlight the importance of continuous vaccine surveillance. Statistical signal detection provides an efficient way to investigate the potential risks and safety concerns within specific age groups, genders, time frames, and product types.

Further studies are needed to determine the clinical implications of these findings for public health decision-making, particularly in younger populations.

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