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REVIEW OF POSTVACCINAL MYOCARDITIS BEFORE THE COVID-19 PANDEMIC

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INTRODUCTION

Myocarditis is an inflammation of the heart muscle (myocardium) that can occur as a result of infections, autoimmune diseases, reactions to drugs or vaccines. In the context of vaccines, an association with myocarditis has been documented in sporadic cases prior to the COVID-19 pandemic, but this phenomenon has taken on greater relevance since the emergence of SARS-CoV-2 mRNA vaccines. However, the occurrence of postvaccinal myocarditis is not a new phenomenon. Various vaccines, such as those developed against smallpox, rabies and other diseases, have been associated in some cases with this complication, although infrequently.

This paper aims to conduct a comprehensive review of the literature and databases on the incidence, characteristics and pathogenic mechanisms of postvaccinal myocarditis before the COVID-19 pandemic, in order to provide a historical perspective to better contextualize recent cases and improve the understanding of this phenomenon.

It is hoped that this study will provide a valuable historical review of postvaccinal myocarditis, which will serve as a basis for future research on vaccine safety. In addition, it will help contextualize current findings and strengthen communication strategies around vaccination and its adverse effects.

METHODS

STUDY DESIGN

This is a systematic review study. We will review the scientific literature published before December 2019 to identify studies, case reports, clinical trials, and reviews that mention the occurrence of myocarditis after vaccination.

SOURCES OF INFORMATION

- Scientific databases: PubMed, Scopus, Web of Science, Google Scholar, Cochrane Library.
- Reports and reports from international health agencies, such as the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC).

INCLUSION AND EXCLUSION CRITERIA

Scientific articles, systematic reviews and meta-analyses, clinical case reports, safety surveillance studies, health agency reports, documenting post-vaccinal myocarditis prior to the COVID-19 pandemic have been included.

Studies and series on myocarditis related exclusively to COVID-19 vaccines or non-vaccination etiologies have been excluded.

RESULTS AND DISCUSSION

To put these data in context, the annual incidence of myocarditis in the USA is 1-10 cases per 100,000 inhabitants.

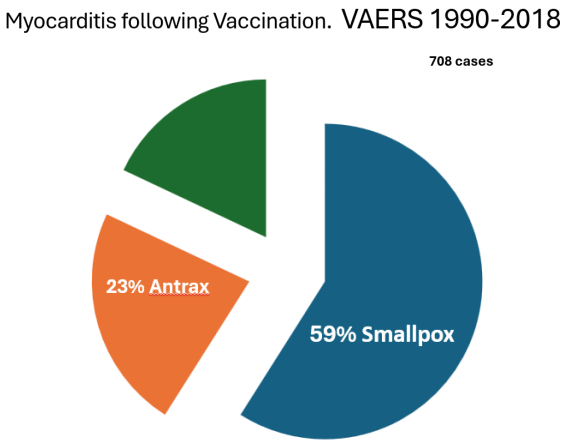
REVIEW OF MYOCARDITIS OF THE NOSRTEAMERICAN BASE VAERS BETWEEN 1990 AND 2018

NOTIFICATIONS

The results obtained in this analysis of postvaccination myocarditis reports provide detailed insight into the relationship between certain vaccines and the development of myocarditis in different population groups. With a total of 708 reports of myocarditis out of a total of 620,195 adverse event reports, 0.1% represents a small fraction, reinforcing that postvaccinal myocarditis is a rare adverse event. Nevertheless, the study of these cases is critical to understanding the risks and improving vaccination strategies.

DISTRIBUTION ACCORDING TO TYPE OF VACCINE

The predominance of ***smallpox*** vaccine, responsible for 59% of the cases of postvaccinal myocarditis, is consistent with what was already known about this vaccine, historically related to adverse cardiovascular events. In the case of ***anthrax*** (23% of cases), this relationship is less well documented, suggesting the need for further studies on the immunologic reactions induced by this particular vaccine.



DISTRIBUTION ACCORDING TO AGE

Age differentiation shows significant variations in the association of myocarditis with certain types of vaccines.

a) In children under 19 years of age, the highest incidence was observed with vaccines against *Haemophilus influenzae* type b (22.22%) and Hepatitis B (18.18%), which may reflect the high exposure of these groups to these vaccines due to childhood immunization schedules. However, it is important to note that although these vaccines are generally well tolerated, the possibility of myocarditis, although rare, should be monitored.

b) In the 19-49 years age group, smallpox remains the leading cause of myocarditis (79%). This is understandable given the historical use of this vaccine in adults, especially in military settings or in populations exposed to the risk of bioterrorism, highlighting the importance of vigilance in mass vaccination settings in young adults.

c) For persons over 50 years of age, myocarditis was mostly associated with inactivated influenza vaccine (31.36%) and, to a lesser extent, with herpes zoster vaccine (19.22%). The higher prevalence of these vaccines in this age group due to vaccination recommendations for older adults may explain this distribution. However, this underscores the need for careful risk-benefit assessment in older populations, who tend to be more susceptible to cardiac complications.

CHARACTERISTICS OF THE CASES

A relevant pattern that emerges from the analysis of this database is the predominance of myocarditis cases in males, who accounted for 79% of those affected. This gender bias is consistent with previous studies suggesting that men, particularly young men, have a greater susceptibility to develop myocarditis after vaccination, possibly due to differences in immune response or hormonal factors.

Another important finding is that 72% of myocarditis cases occurred in the first 14 days post-vaccination, suggesting a critical window of time in which clinicians should be alert for symptoms of myocarditis in vaccinated patients. This knowledge may guide health care professionals to follow up more closely during the first two weeks post-vaccination, especially in persons receiving vaccines with a higher association with this adverse effect.

Finally, the fact that 69% of myocarditis cases were considered severe underscores the importance of early and appropriate management. Although the incidence of postvaccinal myocarditis is low, the severity of the cases warrants close surveillance

and prompt medical evaluation to prevent major complications such as heart failure or arrhythmias.

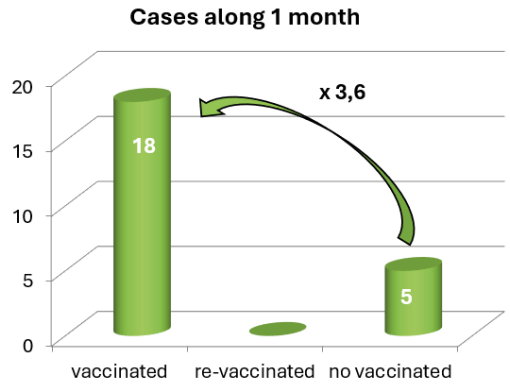
REVIEW ON MYOCARDITIS AFTER SMALLPOX VACCINATION IN THE UNITED STATES ARMY

The results of the smallpox vaccination campaign in American soldiers provide important evidence on the association between this vaccine and the occurrence of myopericarditis. In an analysis involving 230,734 soldiers vaccinated in a one-month period, 18 cases of myopericarditis were reported, highlighting a significant rate of myopericarditis compared to the unvaccinated population.

INCIDENCE AND COMPARISON WITH THE UNVACCINATED POPULATION

One of the most relevant findings is that the rate of myopericarditis was 3.6 times higher in the vaccinated compared to the unvaccinated. This suggests a clear association between smallpox vaccination and the development of this cardiovascular condition. Although the overall incidence was low (1 case per 12,819 vaccinees), the magnitude of the increased risk is of concern. Primary vaccination (first contact with the vaccine) appears to play a key role in susceptibility to this adverse effect, highlighting the need for closer monitoring of first-time vaccinated patients, particularly in populations with at-risk characteristics.

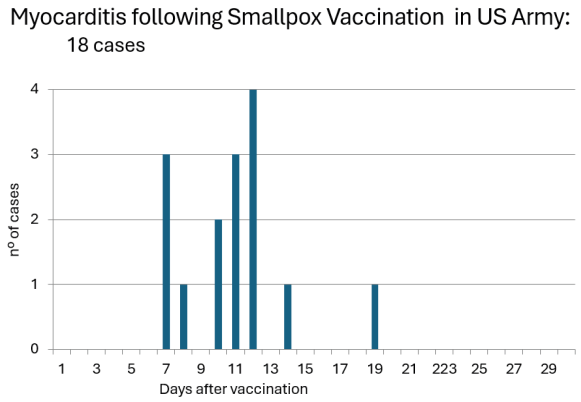
Myocarditis following Smallpox Vaccination in US Army (Dec 2002 to March 2003)



CLINICAL PATTERNS: AGE, SEX AND LATENCY

The study revealed a uniform clinical pattern in the reported cases: all affected were young, white males, aged 21-33 years, with a mean age of 26.5 years. This bias toward young men is consistent with previous observations in other vaccines, such as COVID-19 mRNA vaccines, which may be related to differences in immune response between sexes and age groups. This pattern suggests that young men may be a particular risk group for the development of postvaccinal myopericarditis, and should be considered a population for increased surveillance following smallpox vaccination.

As for the latency period, the average onset of myopericarditis was 7 to 19 days after vaccination. This time window is congruent with the vaccine-induced immune response, which tends to develop in the first 2 weeks. This is also consistent with other studies in which most cases of postvaccinal myocarditis occur within the first two weeks after immunization. This latency interval is critical, as it can help clinicians identify and treat patients with compatible symptoms, such as chest pain or shortness of breath, early, thus preventing progression to more serious complications.



CLINICAL RECOMMENDATIONS

The fact that the study concludes that myopericarditis should be considered an expected adverse event following smallpox vaccination reinforces the importance of including this diagnosis in routine post-vaccination evaluations. Given the temporal pattern of onset (between 4 and 30 days post-vaccination), clinicians are advised to maintain high clinical suspicion in patients presenting with chest pain in this time interval. The recommendation of alertness for this diagnosis is key to improving early management and prevention of associated complications.

CONCLUSIONS

These results provide critical information on the characteristics of postvaccinal myocarditis before the COVID-19 pandemic, showing that, although rare, this condition can be severe and varies according to vaccine type and age group.

The results of this review highlight that, although myocarditis is a rare event, it has a significant incidence among smallpox vaccinees, especially in young men. The average latency in the first few days post-vaccination and the predominance in young males offer important clues for post-vaccination monitoring and early intervention that should be considered when designing surveillance and follow-up policies. In addition, this analysis provides important historical context that can be used to compare with current cases related to COVID-19 vaccines, thus contributing to a better understanding of postvaccine myocarditis in general.

ETHICAL RESPONSIBILITIES

Protection of humans and animals. The authors declare that no experiments on humans or animals have been performed for this research.

Confidentiality of data. The authors declare that no patient data appear in this article.

Conflict of interest: the researchers declare that they have no conflicts of interest.

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