Elsevier has created a Monkeypox Information Center in response to the declared public health emergency of international concern, with free information in English on the monkeypox virus. The Monkeypox Information Center is hosted on Elsevier Connect, the company's public news and information website.

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Correspondence

Precautions and recommendations towards possible cardiac manifestations of monkeypox vaccination

Dear Editor,

Monkeypox (MPX) was declared as a public health emergency of international concern (PHEIC) by the World Health Organization (WHO) on July 23, 2022 [1]. MPX has infected over 35706 confirmed cases across 88 countries worldwide [2]. Monkeypox virus (MPXV), a zoonotic Orthopoxvirus, is a double-stranded DNA virus [3]. Although MPXV was first isolated in monkeys, more common reservoirs include squirrels, dormice, and Gambian pouched rats [4]. Of the two main clades of MPX, the West Africa clade is associated with less severe disease compared with the Central African Clade [5]. Recently, there are suggestions of sexual transmission of MPX, (mainly among certain groups of homosexual, bisexual, and men who have sex with men (MSM)). However, direct contact with body fluids, sores, and fomites has generally been considered to be the mode of human-to-human transmission of the disease [6]. MPX is characterized by fever, rash, and lymphadenopathy [7]. MPX is generally self-limiting with minor outbreaks being controlled using smallpox vaccines, vaccinia immunoglobulin, and antiviral agents such as tecovirimat, Brincidofovir, and cidofovir [6]. Smallpox vaccination shows 85% protection against MPX [8].

The re-emergence of MPX has resulted in renewed interest on the potential use of smallpox vaccines to combat the current MPX multi-country outbreak affecting non-endemic countries. The modified vaccinia virus Ankara and the ACAM2000 vaccines are used in specific circumstances in response to the MPX outbreak [6].

Myocarditis may occur in several viral infections. However, it is a rare occurrence in young individuals [9]. Myocarditis following ACAM2000 is 3.6-fold among the vaccinated compared to the unvaccinated USA military personnel [10]. In this cohort, definite vaccinia myocarditis occurred in 1 in 10000 vaccinated individuals, usually 8–14 days after receiving the smallpox vaccine [11]. Other rare cardiac-related side effects include dilated cardiomyopathy (DCM) and cardiac ischemia [12]. Of note, DCM and cardiac ischemia have been reported with smallpox vaccines. However, it is still unclear which of them cause these adverse events, calling for more research in this area. Additionally, adverse events should be monitored, and caution with those with compromised heart patients should be considered [13].

Both myocarditis and pericarditis occur up to 6 weeks after vaccination [12]. Myocarditis presents with chest pain, dyspnea, palpitations, cardiac enzymes, and electrocardiographic (ECG) abnormalities [12]. Similarly, pericarditis presents with chest pain that worsens on lying down and relieves on sitting up, pleuritic chest pain, and ECG abnormalities [12]. The criteria for diagnosis of dilated cardiac myopathy include ventricular dilatation and impaired contraction leading to cardiac muscle dysfunction in a patient without a prior history of DCM or other cardiac diseases before vaccination [12].

Smallpox vaccines can generally be classified into four generations [3]. The first-generation vaccines such as Dryvax, produced by crude methods, are no longer used [3]. Second-generation vaccines such as ACAM2000 have been developed from effective seed viruses from the first-generation vaccines grown in tissue cultures [3]. Since the second-generation vaccines have similar cardiac complications to the first-generation vaccines, third and fourth-generation vaccines were developed [3]. The third-generation vaccines tested in various human trials include Modified Vaccinia Ankara (MVA) (e.g., INVAMUNE also known as JYNNEOS™) and Lister Strain Vaccinia derivative (LC16m8) [3]. See Table 1.

INVAMUNE, given in two doses four weeks apart, is suitable for people requiring vaccination but who have contraindications to second-generation vaccines such as laboratory personnel exposed to orthopox viruses and medical personnel caring for victims of smallpox or related orthopox viruses [3]. Although progressive vaccinia may occur in immunocompromised patients that receive prior smallpox vaccines, MVA has shown promise even in patients who are human immunodeficiency virus (HIV) positive [3].

Both first-generation vaccines (e.g., Dryvax) and second-generation vaccines (e.g., ACAM2000) have been associated with myopericarditis [3]. For instance, a patient who developed primary myocarditis has been described after receiving ACAM2000 clonal Vero cell culture vaccinia virus (New York City Board of Health strain) [9]. Myocarditis is reported to occur in 7.8 per 100,000 vaccinated persons in the United States army [10]. Based on the description of the Finnish cohort, severe chest pain signals the start of vaccinia myocarditis [10]. ECG features and cardiac enzyme elevation may be similar to features of acute myocardial infarction [10]. However, in the later stages, enzymes normalize with T wave inversion in ECG. Quick recovery of patients was noted with no features of frank heart failure [10]. Furthermore, all patients had normal ECG after 3 months. Healthcare workers should note that some patients may continue to have exercise-related T wave inversion even after one year [10].

Severe fatal myocarditis following smallpox vaccination has been described [14,15]. However, an ecological study did not demonstrate a significant association between cardiac deaths and mass smallpox vaccination in New York City in 1947 [16].

Treatment approach for vaccinia-related myopericarditis includes use of non-steroidal anti-inflammatory agents (NSAIDs), limiting physical exertion for four to six weeks, treatment of heart failure as necessary, and steroid therapy [17].

Healthcare workers should take precautions and where possible, avoid smallpox vaccines among individuals with symptomatic or asymptomatic angina, cardiomyopathy, congestive cardiac failure, and previous myocardial infarction [18]. Moreover, the Bavarian Nordic's

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Table 1
Smallpox vaccines, cardiac adverse effects, precautions/treatment.

Vaccine	First generation (e.g., Dryvax)	Second generation vaccines (e.g., ACAM2000).	MVA-BN vaccine
Adverse effect	Myocarditis, pericarditis	Myocarditis, pericarditis	Myopericarditis not reported in a Phase II study [19]
Precautions/ treatment	NSAIDs, limiting physical exertion for four to six weeks, treatment of heart failure as necessary and steroid therapy	NSAIDs, limiting physical exertion for four to six weeks, treatment of heart failure as necessary and steroid therapy	Counseling on adverse event reporting for proper monitoring

MVA-BN vaccine is replication incompetent and hence safe in immunocompromised patients and those with atopic dermatitis. MVA-BN vaccine may have fewer adverse effects compared to the Dryvax and the ACAM2000 vaccines [19]. Cases of myopericarditis were not reported with the MVA-BN vaccine in a Phase II study [19].

With the smallpox vaccines currently used in selected persons for prevention of MPX, it suggested that a hotline and a card detailing the vaccine administered should be provided to those vaccinated to aid in reporting adverse events following immunization for proper monitoring [20].

Ethical approval

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Author contribution

RAF: the conception and design of the study. FMD, HMD and RAF: made the first draft. RAF: updated the manuscript. RAF: reviewed the final draft and edited final. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

Trial register number

1. Name of the registry:
2. Unique Identifying number or registration ID:
3. Hyperlink to your specific registration (must be publicly accessible and will be checked):

Guarantor

All authors.

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Data not available/not applicable.

Declaration of competing interest

No conflicts to declare.

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Farouq Muhammad Dayyab
Cardiac Intensive Care Unit, Mohammed Bin Khalifa Bin Salman Al Khalifa Cardiac Center, Awali, Bahrain
Global Research Group (GRG), Kafrelsheikh, Egypt

Haruna Muhammad Daiyab
Department of Medicine, Murtala Muhammad Specialist Hospital, Kano, Nigeria

Ramadan Abdelmoez Farahat*
Faculty of Medicine, Kafrelsheikh University, Kafrelsheikh, Egypt
Global Research Group (GRG), Kafrelsheikh, Egypt

* Corresponding author. Faculty of Medicine, Kafrelsheikh University, Kafrelsheikh, 33511, Egypt.
E-mail address: ramadan.med_2587@med.kfs.edu.eg (R.A. Farahat).