Commentary

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Monkeypox (Mpox) vaccines and their side effects: the other side of the coin

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On the verge of smallpox eradication, human monkeypox (Mpox) – as recommended by the WHO (https://www.who.int/news/item/28-11-2022-who-recommends-new-name-for-monkeypox-disease) – was discovered in the Democratic Republic of Congo (DRC), in the year 1970, when sporadic cases were reported in rural areas of DRC[1]. It is a zoonosis without any identified definitive reservoir host. Other than DRC, it has been reported from adjacent West and Central African countries, including Nigeria, Cameroon, Sierra Leone, the Republic of Congo, and Liberia[2]. For decades the virus was restricted to this part of the world only, unless outbreaks started getting reported from different nonendemic countries since early May 2022. The number of cases increased so much globally that WHO declared this multicountry outbreak as a Public Health Emergency of International Concern on 23 July 2022[3]. As of 23 November 2022, the total number of confirmed Mpox cases is 80,850, with 55 deaths involving 110 countries, out of which 103 are nonendemic[3].

Mpox belongs to the family *Poxviridae*, genus *Orthopoxvirus*, which is like the smallpox virus; therefore, smallpox vaccines can give protection against Mpox also due to cross-reactivity.

Mpox has two clades (clade I: Central African clade; clade II: West African clade), out of which clade II is responsible for the current outbreaks mostly. This dreaded situation is almost leaning toward a new pandemic, which can be substantially hypothesized on waning immunity toward *Orthopoxvirus*, particularly of younger population who are not immune for the same, due to the cessation of smallpox vaccination. Even though the disease is self-limiting for most of the patients, there is a constant threat of no specific treatment and a high secondary rate of 9.28% in unvaccinated persons.

HIGHLIGHTS

- Currently there are three options (ACAM2000, MVA-BN, LC-16) available for Mpox vaccination.
- According to the US Food and Drug Administration, the incidences of myocarditis/pericarditis have been found to be 1 in 175 new ACAM2000 vaccine recipients.
- JYNNEOS produces fewer serious adverse events than ACAM2000.

Therefore, to curb the number of cases, WHO revised the strategy of the 2013 smallpox vaccination to use available smallpox vaccines for Mpox vaccination on 24 June 2022 and revised on 24 August 2022[4].

Currently, there are three options (ACAM2000, MVA-BN, LC-16) available for Mpox vaccination, out of which ACAM2000 is a second-generation and MVA-BN and LC-16 are third-generation smallpox vaccines. All three vaccines are approved to be used against Mpox by different jurisdictions, but their availability varies in different geographical areas. Out of the three vaccines, MVA-BN, popularly known as JYNNEOS (other brand names – Imvamune and Imvanex), is approved by the US FDA for the prevention of both smallpox and monkeypox, and it is the prime vaccine being used against Mpox in the United States. However, ACAM2000 is US FDA-approved against smallpox and available for Mpox vaccination use under the Expanded Access Investigational New Drug (EA-IND) protocol sponsored by the Centers for Disease Control and Prevention[3].

JYNNEOS (BARDA, Bioshield) is the only vaccine currently approved (since 2019) against Mpox. It is a replication-deficient live virus vaccine containing a weakened (nonreplicating) *Orthopoxvirus* – Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN) virus. It is approved for use in individuals above 18 years of age, two doses of 0.5 ml by the subcutaneous route, 4 weeks apart. But on the 9th of August 2022, US FDA authorized the administration of the vaccine by intradermal route for a high-risk population of at least 18 years, which requires less amount (one-fifth, 0.1 ml) of vaccine dose, to increase the vaccination coverage[5]. However, for younger individuals (< 18 years), the recommended route remained subcutaneous. This decision was taken based on the findings of a clinical trial conducted by Frey *et al.*[6], in the year 2015, which showed the same amount of immune response produced by the intradermal route but with a lesser amount of vaccine than the subcutaneous route.

The vaccine was initially developed to tackle any probable bioterrorist attack by smallpox in immunocompromised

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individuals as an alternative to an older vaccine ACAM2000. Later it was approved for Mpox also to be used in endemic areas in high-risk individuals.

ACAM2000 (Acambis, Canton, Massachusetts) is a replication-competent live vaccinia virus vaccine, derived by plaque purification from previously licensed calf lymph-produced vaccine – Dryvax (Wyeth Pharmaceutical Inc, Philadelphia, Pennsylvania) and further passaged three times in Vero cell lines. It is considered to be a second-generation replicating smallpox vaccine, approved for use by US FDA since 2007[7,8].

This vaccine is not approved for Mpox but can be used for the same under US FDA's EA-IND mechanism, which requires informed consent along with additional IND requirements. This vaccine is administered as a single dose, percutaneously by using a bifurcated needle–multiple punctures (scarification) technique[9]. One dose of ACAM2000 vaccine contains virus concentration ranging from 1.0 to 5.0×10^8 plaque-forming units (PFU)/ml or $2.5–12.5 \times 10^5$ PFU/dose as well as 2% albumin USP and trace levels of neomycin and polymyxin B.

LC-16 (KM Biologics, Japan) is an attenuated partially replicating Lister strain of vaccinia[10]. It is administered as a single dose, as ACAM2000 using a bifurcated needle–scarification method. It is a third-generation smallpox vaccine.

Side effects of the ACAM2000 vaccine

ACAM200 vaccine is known to cause side effects like injection site pain, lymph node pain, pruritus, and other flu-like symptoms[11]. Other common side effects can be – itching, myalgia, headache, sore arm, rash, fever, and fatigue[12] (https://www.fda.gov/media/75792/download). Getting this vaccine is not like having a single shot of the vaccine; it requires 15 small pokes to be made on the skin by using a bifurcated needle. The vaccination site should be taken care of until the scab falls off; otherwise, there is a potential chance of spreading the live virus from the vaccination site to other parts of the body or to other persons. The scab usually falls off after 2–4 weeks, so till that time period, the vaccinated person becomes a potential source of spreading the infection, particularly to the immunocompromised persons. Accidental ocular vaccinia can occur in some of the exposed persons leading to symptoms like – painful watery eyes with blurred vision, scarring of cornea, keratitis, and blindness (https://www.fda.gov/media/75792/download). Severe and long-term side effects like myopericarditis have been reported to be found in approximately every 20 individuals out of 100,000 ACAM2000 vaccine recipients[13]. Neurological events were reported in about two individuals out of 100,000 ACAM2000 vaccine recipients. According to US FDA, the incidences of myocarditis/pericarditis have been found to be 1 in 175 new ACAM2000 vaccine recipients[9]. Few clinical trials reported the rate of myopericarditis to be 5.7 per 1000 new vaccines without any identifiable cause[14,15]. Some of the serious but rare long-term side effects are – infected blister over the vaccination site, severe allergic reaction (eczema vaccinatum), disseminated infection to the other parts of the body (progressive vaccinia), encephalitis, encephalomyelitis, and encephalopathy, and even death[3,16]. Risk factors for serious side effects can be – underlying skin diseases/allergic conditions, cardiac diseases, immunocompromised status, smoking, high blood pressure, high blood sugar/cholesterol, pregnancy, lactation, use of steroid eye drops, etc. There is a risk of stillbirth or fetal death due to ACAM2000 vaccination in pregnant women (https://www.fda.gov/media/75792/download). Besides, the risk of inadvertent inoculation of ACAM2000 live vaccinia virus from lactating mothers to infants is a critical concern. Individuals allergic to neomycin and polymyxin B are at an increased risk due to the presence of these antibiotics in ACAM2000.

Side effects of the MVA-BN vaccine

Till now, JYNNEOS seems to be a safer option to opt for vaccination against Mpox, which has been duly approved for the same too. But studies are yet to be done to know the complete safety profile and immunogenicity of the vaccine. However, it has been found to be safe in immunocompromised patients like transplant recipients, patients with HIV, and atopic dermatitis[17,18]. In different clinical trials of the vaccine injection site, reactions like redness, firmness/tightening, pain, induration, itching, sore throat, myalgia, headache, chills, and nausea have been reported, which are manageable and less severe than side effects of ACAM2000 vaccine. A report by Rao *et al.*[19] states, according to recommendations of the Advisory Committee on Immunization Practices – USA, there is a low-level certainty about the fact that JYNNEOS produces fewer serious adverse events than ACAM2000, after analyzing three randomized controlled trials and 15 observational studies, including total of 5775 subjects. A recent retrospective cohort study by Sharff *et al.* documented 10 cases of cardiac events occurring after the administration of the JYNNEOS vaccine during July–October 2022 in a population cohort of Northwestern United States (Oregon). However, the direct association of those events with the vaccine could not be assessed completely[20]. WHO states that local adverse events were frequently reported in MVA-BN vaccines (up to 99%). However, there were no cases of serious adverse events like myopericarditis or requiring hospitalization reported among 9713 MVA-BN vaccines from 19 clinical studies[4]. Due to the evidence of lesser side effects, the Advisory Committee on Immunization Practices recommended JYNNEOS as a substitute for ACAM2000 for immunizing those at risk of contracting the *Orthopoxvirus* on 3 November 2021[3].

Side effects of the LC16m8 vaccine

Mild to moderate local and systemic adverse events are very common with this vaccine. However, serious adverse events like encephalitis and symptomatic myocarditis were not reported in clinical trials and cohort studies[21,22]. The vaccine is not recommended for widespread vaccination among immunocompromised and atopic dermatitis patients, although preclinical evidence supports the use of the LC16m8 vaccine in these individuals[23,24].

Conclusion

At present mass immunization of population against Mpox is not justified, as all people are not at a heightened risk of the disease. Preexposure prophylaxis is recommended for close contact and high-risk populations like children, immunocompromised patients, men having sex with men – the gay population, persons with multiple unprotected sexual partners, healthcare workers and

laboratory persons working with Mpox[15]. Postexposure prophylaxis is recommended for close contact with cases within 4 days of contact. For pregnant and breast-feeding females and children, nonreplicating MVA-BN vaccines should be administered.

Even though to control the Mpox outbreaks, vaccination is the key, prior to getting a vaccination, a few key points should be considered regarding the risk–benefit ratio and vaccine safety and accuracy. We do not have studies to conclude firmly about the above-mentioned aspects for which results and data of further research on available Mpox vaccines are awaited.

Ethical approval

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Author contribution

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Conflicts of interest disclosure

There were no conflicts of interest.

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