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Commentary

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Smallpox Vaccines for Monkeypox: Is Emergency Vaccination Imminent?

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Abstract

Monkeypox virus (MPXV) is a contagious disease that has been endemic in central and west Africa since 1970, characterized by symptoms such as fever, headache, and skin rash. While there is no approved treatment for MPXV infections, vaccination has proven effective in limiting its transmission, and previous smallpox vaccinations may also provide protection against monkeypox. However, the dependence of monkeypox on animal hosts makes eradication more complicated than with smallpox. Research should focus on assessing the safety of the vaccines, their duration of immunity, and their efficacy against the prevalent strains of monkeypox. The virus's accelerated rate of mutation poses additional challenges, as does the fact that it can be transmitted through animals, making eradication more complex than with smallpox. A comprehensive global immunization strategy is needed to address these complexities and draw on lessons learned from past eradication efforts.

Monkeypox virus (MPXV) belongs to the *Orthopoxvirus genus.*[1] Since the first documented case in 1970, the virus has been endemic to central and west Africa. The World Health Organization (WHO) has declared 2022 to be a Public Health Emergency of International Concern (PHEIC) due to the unprecedented global outbreak that year, where from May 13, 2022, up until 19 September, more than 62 000 cases of human monkeypox were reported in 104 countries in the world (among them 97 countries where the monkeypox virus was not endemic).[2] Although various antiviral medications have demonstrated success in recent trials, there is still no treatment approved in the USA for MPXV infections.[3]

With an unvaccinated smallpox case fatality rate of 11% among patients and a rate of 15% among children under 4 years old, the Democratic Republic of the Congo recorded the largest number of cases of monkeypox. However, vaccination has proven to be a crucial tool in controlling the spread of monkeypox, especially in the regions where the disease is endemic like central and western Africa areas (especially in the Democratic Republic of the Congo, Liberia, Sierra Leone, Nigeria, and Ivory Coast) that are characterized by high mean annual precipitations and low altitude.[10]

MPXV can propagate through human-to-human transmission via direct contact with an infected persons' skin lesions or through respiratory droplets. Following an incubation period that ranges from 5-21 days, MPXV infection can present with fever, extreme headache, lymphadenopathy, and myalgia. A maculopapular rash appears 1-3 days after the appearance of fever and is concentrated more on the face and extremities and can also be found on mucous membranes. Although monkeypox is typically self-limiting with symptoms lasting from 2-4 weeks, it can cause a more severe illness in children and those who are immunocompromised.[1] To make the diagnosis of monkeypox, the only method approved by the Food and Drug Administration (FDA) is by taking a swab from the monkeypox lesion and sending it for polymerase chain reaction (PCR).[1,4]

Yet, no treatment has been approved for MPXV infections in the USA, though several antiviral agents have shown promising efficacy in recent trials.[1] Since MPVX and smallpox viruses are closely related, previous smallpox vaccination can confer immunity to monkeypox with 85% effectiveness.[5] These smallpox vaccines are derived from the vaccinia virus which also belongs to the *Orthopoxvirus genus.* The US's Strategic National Stockpile (SNS) has 3 vaccines against the smallpox virus; Aventis Pasteur smallpox vaccine (APSV), ACAM2000™ (Acambis, Inc.™), and JYNNEOS™ (Imvamune or Imvanex).[6] Among these, ACAM2000® and JYNNEOS™ are approved for use against the monkeypox virus. Though both are live vaccines, they differ in how they provide immunity. ACAM2000® is a replication-competent vaccinia vaccine while JYNNEOS™ is a replication-deficient Modified Vaccinia Ankara (MVA).[7]

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As it is replication-competent, ACAM2000® causes a "take" reaction at the injection site 6-8 days after vaccination. This reaction occurs when the virus has inoculated and replicates at the injection site to form a lesion. A "take" signifies the production of antibodies and the development of immunity.[6] However, ACAM2000® can cause serious adverse effects such as myocarditis and pericarditis. Thus, it is approved under the Expanded Access Investigational New Drug (EA-IND) protocol; typical adverse reactions may manifest as signs and symptoms at the site of inoculation, lymphadenitis, and constitutional symptoms like malaise, fatigue, fever, muscle pain, and headache.[7] Personnel involved in vaccine preparation and administration should wear protective gloves and take care to avoid any contact between the vaccine and the skin, eyes, or mucous membranes. All materials, including the vaccine vial, stopper, diluent syringe, reconstitution needle, administration needle, and any associated gauze or cotton, should be disposed of in specialized biohazard containers that are both leak-proof and puncture-proof. These containers must then be appropriately disposed of to prevent any potential hazards. JYNNEOS™, on the other hand, lacks an observable take reaction due to its inability to replicate.[6] As such, JYNNEOS™ has relatively milder adverse effects such as fatigue, headache, and muscle pain.[7] There is a need for a worldwide immunization strategy against monkeypox (MPX). Important research requirements include investigating vaccination safety, duration, and interactions with COVID-19 vaccines, as well as assessing effectiveness against MPXV clade 1, which is common in the DRC. Strategies support pre-exposure prophylaxis targeting high-risk groups, especially frontline workers.[11]

Although the current vaccines have high efficacy against monkeypox, their effectiveness may taper off if the virus is allowed to spread rapidly. Compared to RNA viruses, DNA viruses mutate less frequently with mutation rates of 1-2 base pairs per year. Genetic analysis from the monkeypox outbreaks in Nigeria from 2017-2022 shows that monkeypox has been mutating at a faster rate of 47 base pairs per year.[9] These mutations are not random. They are caused by the enzyme APOBEC3 in the host cells as an anti-viral, innate immune system mechanism.[9] There is no significant threat that these mutations can confer a beneficial virulent property to the virus, but the accelerating rate of mutations is an issue that should be considered.[9]

After the eradication of smallpox in the 1970s, routine vaccination against smallpox was stopped as people born after its eradication did not need the vaccine. Recent monkeypox outbreaks, where the majority of infections were reported in the newer generations, indicate that previous smallpox vaccination seems to have a protective effect on the older generations. However, evidence suggests that the protection wanes as decades pass.[7] In Nigeria for instance, a substantial resurgence of monkeypox in 2017 was reported, which appears to have been driven by a combination of population growth, accumulation of unvaccinated cohorts, and decline in smallpox vaccine immunity.[13] In addition, recent decades witnessed prosperity in terms of international travel, which could be regarded as a risk factor for the potential emergence of mutated monkeypox variants. For instance, Brannen et al. found a 4.5 (1.05-19.39) odds of influenza hospitalization associated with international travel, largely associated with areas endemic with monkeypox.[8]

Monkeypox is an infectious disease that is difficult to eradicate due to its dependence on animals. Unlike smallpox, which has no animal reservoir, monkeypox has an animal reservoir, which makes its eradication more challenging. The role of animal hosts in the persistence of monkeypox distinguishes it from smallpox.[12] However, with routine vaccinations, we can mitigate the mutations and limit the virus's spread. Other preventive measures can also be adopted, including cleaning hands regularly with soap and water or alcohol-based hand rub, avoiding close contact with people who have suspected or confirmed monkeypox, and using proper personal protective equipment during care for suspected patients.

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