Opinion

Trends in Pharmaceutical Sciences and Technologies 2025: 11(4):287-92.

A Pharmaceutical Perspective on the Potential of Monkeypox Outbreak to Tackle Future Pandemics

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Abstract

Pandemics have devastating effects on human societies, leading to wreak havoc on economies and disrupting global education and health systems, slowing down sustainable development. Nevertheless, they may provide an opportunity to test ideas and technologies such as novel vaccine platforms and routes of administration in real-world scenarios. This comment highlights the role of the emerging outbreak of monkeypox (mpox) in the development of mucosal vaccines from previously approved platforms. A priority goal for next-generation mpox vaccines is to prevent transmission of the virus via the mucosal membranes, while improving protection against symptomatic disease. A robust immune response in the mucosal membranes can prevent infection, virus shedding and transmission. Since mucosal vaccines provide the opportunity to use non-invasive needle-free administration, their application is easier in low-income countries with weak health infrastructure. Additionally, compliance with mucosal vaccines is much higher in children. These vaccines require neither health workers for injection nor aseptic medium during administration. Moreover, mucosal vaccines are associated with reduced psychological stress and hesitancy compared with parenteral routes. This highlights the role of these vaccines in future pandemics, particularly for mass vaccinations.

Keywords: Monkeypox; Mucosal Vaccination; Pandemic; Vaccine.

Please cite this article as: Hossaini Alhashemi S, Taheri Z, Firouzabadi N, Dehshahri A. A pharmaceutical perspective on the potential of monkeypox outbreak to tackle future pandemics. Trends in Pharmaceutical Sciences and Technologies. 2025;11(4):287-92. doi: 10.30476/tips.2025.107208.1298

1. Introduction

The emergence of a new outbreak caused by a member of the Orthopoxvirus genus of the Chordopoxvirinae subfamily (monkeypox or mpox) has raised concerns among global health institutions; however, the consequences of the recently-emerged pandemic caused by SARS-CoV-2 remain challenging (1, 2). Mpox is a zoonotic viral infection that was first detected in monkeys shipped from Singapore to Denmark in 1958 (3). Despite the identification of the virus in a Danish lab in the late 50s and several reports confirming outbreaks among captive monkeys worldwide, no human outbreaks have been reported since 1970 (Figure 1). The first infected human case, a 9-year-old boy who had never received the smallpox vaccine, was reported early this year in the Democratic Republic of Congo (DRC)

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Received: 16/04/2025; Accepted: 01/09/2025

(4). Notably, other members of the family who had previously received the vaccine were not infected with mpox. The effectiveness of cross-protection by smallpox vaccination against mpox has been shown to be 85%. Between 1981-2017, some sporadic emergence of the disease was reported in West and Central African countries, particularly among children, with high fatality rates of 1-12 % (5-9). However, the disease has not attracted international attention since 2003, when mpox caused an infection in the U.S (10). Following the report of tens of thousands of new cases in more than hundred countries by 2022, the World Health Organization (WHO) declared a public health emergency of international concern (PHEIC) (11, 12). Considering the upsurge of mpox in several countries around the world, the WHO repeated the PHEIC in August 2024, highlighting the urgency of epidemiological surveillance as well as vaccination (Figure 1) (13). This timeline depicts key discoveries and events during the development of vaccines for the disease.

Although mpox has not yet reached global emergence and has not been characterized as a pandemic, there are some concerns associated with its spread worldwide, including travel-related cases outside endemic regions of Africa (14). Since the incubation period of the virus occurs within 1-3 weeks (15), a suspected case with no symptoms may leave the high-risk regions and arrive in another non-infected country within hours. This is one of the major concerns regarding the rapid spread of the virus. Another major feature of the current outbreak was the changes in human sexual behavior in recent decades. According to the results of the previous outbreak in 2022, one of the largest multinational outbreaks occurred among homosexual men. The mpox lesions are mainly present in mucosal tissues, including the genitalia, rectum, and oral cavity, facilitating their spread in the same-sex relationship. In addition, large respiratory droplets are the main route of disease transmission. These human-to-human transmission routes must be carefully considered for the development of potential future vaccines (16). The last but not the least concern in the current mpox outbreak is that the virus may establish itself in an animal reservoir outside the endemic regions of Central and West Africa. If the virus could find a small pet such as a dog as a new reservoir, this means that the disease could not be eradicated due to its presence in a non-human reservoir. Considering the global pet trade, illegal underground black market of small animals around the world and illegal construction encroaches on rainforests as well as the development of "urban jungles", deforestation and erosion of small farms into the jungles, the human population and wildlife may have closer contact and the virus may have a great opportunity to evolve and jump back to human as it happened in the case of

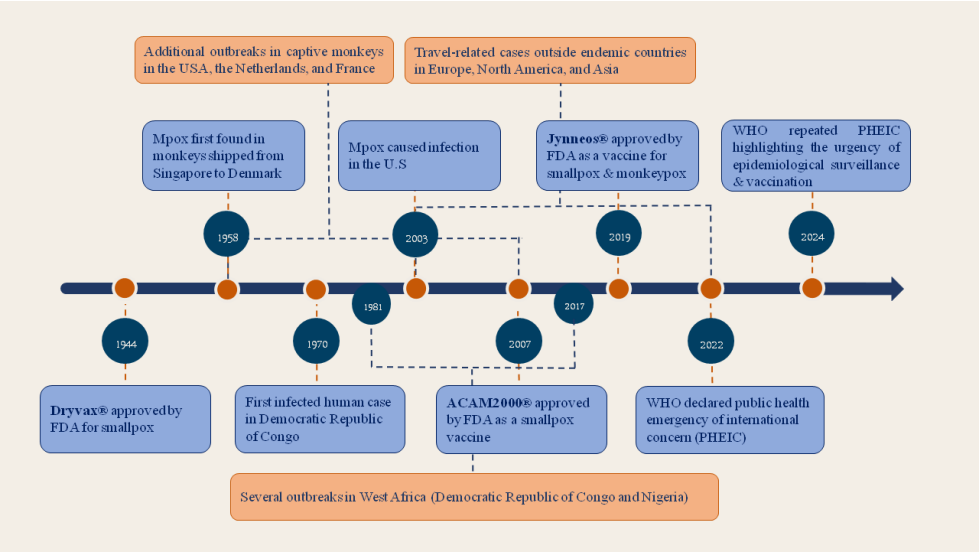

Figure 1. A brief history of the history of monkeypox outbreaks and development of vaccines.

yellow fever in colonial era in South America centuries ago (17). These points, along with the lessons learned from the latest pandemic of COVID-19 may pave the way for combating the disease and preventing its spread through the development of efficient, easy-to-use, and safe vaccines. However, the question remains as to how.

2. What was Learned from the Vaccine Development during the COVID-19 Pandemic?

By occurrence of the outbreak of SARS-CoV-2 and the declaration of a pandemic in early 2020 (18), great attention has been directed toward the development of vaccines based on various conventional platforms, including inactivated and live attenuated vaccines, as well as novel platforms such as viral-vector-based or mRNA/lipid nanoparticle (LNP) vaccines. As is clear, the major focus for the vaccine industry was the selection of an appropriate "platform" with the potential to achieve an efficient and safe vaccine with a reasonable price, promising stability, and optimal storage conditions as well as potential approval from regulatory agencies. In this competition, the platform used to create such a life-saving vaccine was considered a game-changer. The success stories of Moderna and BioNTech/Pfizer in one hand and the failures of Merck, Sanofi and GlaxsoSmithKline in the other hand was mainly based on the platforms used in the development of the vaccines (19). In terms of pharmaceutical perspective, a forgotten story in this context may be the dosage form and route of administration (RoA). This almost forgotten section of the industry might be a game-changer for future pandemics.

3. An Alternative Route of Administration: a New Answer to an Old Question

Almost the majority of vaccines used for comprehensive childhood vaccination, as well as COVID-19 vaccines, are based on parenteral administration, such as intramuscular (IM), subcutaneous (SC), and in some cases intradermal (ID) injections (20). In the case of mpox, Dryvax® and ACAM2000® vaccines are administered via scarification and multiple-puncture techniques with a bifurcated needle, respectively, whereas the Jynneos® vaccine, which is an attenuated non-replicating third-generation smallpox vaccine, is used subcutaneously (21). Since the eradication of smallpox in the 20th century, the global need for this vaccine has declined. However, threats such as bioterrorism and smallpox outbreaks have prompted some countries, including the United States, to invest in the development of new smallpox vaccines. Due to the cross-protection of smallpox against mpox, these vaccines are the only sources for immunization. Considering the inadequate vaccine capacity supply, even in high-income countries, and the problems related to the manufacturing ramp-up, tackling the threats posed by the new mpox outbreak must be addressed by alternative approaches. One of the strategies applied in the U.S. is dose-sparing of available FDA-approved vaccines. In this approach, the Jynneos® vaccine is administered in one S.C. injection instead of two recommended doses, or smaller volumes of the same vaccine are used via a different RoA (e.g., I.D. injection instead of the standard S.C. route). Although these efforts may reduce the need for sufficient available vaccines, holistic strategies are needed to combat the rising cases of mpox before the disease spreads worldwide and threatens the pandemic. One of these comprehensive approaches is based on the pharmaceutical perspective and recommends considering different RoA as well as dosage forms.

As mentioned earlier, the two main routes of human-to-human transmission of mpox are respiratory secretions and direct contact with the lesions. The common point is that the deposition of the droplets of the infected host on the mucosal membrane of the mouth or nose, as well as direct contact with lesions on mucosal membranes through direct and intimate contact (e.g., sexual activ-

ity via the rectum or genitalia) are the main routes of transmission (14, 22, 23). A priority goal for next-generation mpox vaccines is to prevent transmission of the virus via the mucosal membranes, while improving protection against symptomatic disease. Hence, mucosal vaccination could be a promising approach for achieving these goals. A robust immune response in mucosal membranes can prevent infection as well as virus shedding and transmission. Such mucosal vaccines have the potential to prevent direct and forward transmission by inducing durable immunity at the primary site of shedding, leading to a lower incidence of infection. This, in turn, resulted in a lower incidence of the emergence of new variants. Since mucosal vaccines provide the opportunity to use non-invasive needle-free administration, their application is easier in low-income countries with weak health infrastructure. Additionally, compliance with mucosal vaccines is much higher in children (24). These vaccines require neither health workers for injection nor aseptic media for administration. Moreover, mucosal vaccines are associated with reduced psychological stress and hesitancy compared with parenteral routes (25). This highlights the role of these vaccines in future pandemics, particularly mass vaccination. Since mpox can also be transmitted through sexual acts, focusing on vaginal and rectal formulations for mucosal vaccines beside the intranasal, sublingual, and oral routes is necessary. Notably, at least five mucosal vaccine candidates for COVID-19 have received authorization from regulatory authorities worldwide, and more than a dozen are in clinical trials, demonstrating the capability of these vaccines to be used in real-world scenarios. These formulations are based on sprays, nebulizers, inhalers, and droppers, as well as oral tablets or suspensions (26). Interestingly, various platforms of live attenuated, protein-based, and viral vectors, as well as DNA or RNA vaccines, have been formulated for mucosal delivery. This clearly shows that bench-to-bed translation of mucosal vaccines is a possible in the future (27).

4. Discussion

The COVID-19 pandemic provided a great opportunity to develop a novel platform for vaccines (mRNA/LNP) and also could answer the historical questions of "how mRNA can be translated to a vaccine" and "what are the risks of nano-delivery systems such as LNPs" (28). Since the preparedness for the future pandemics must be started today, current mpox outbreak can provide a similar opportunity for scientists to answer another old question: "how mucosal vaccination could be possible for the future pandemic?"

5. Conclusion

This comment highlights the role of the emerging outbreak of monkeypox (mpox) in the development of mucosal vaccines from previously approved platforms.It is suggested that the next generation of mpox vaccines based on mucosal routes might be able to prevent transmission of the virus efficiently, while improving protection against symptomatic disease.

Authors Contributions

Conceptualization: Samira Hossaini Alhashemi, Zahra Taheri, Negar Firouzabadi, Ali Dehshahri; writingoriginal draft preparation, Samira Hossaini Alhashemi, Zahra Taheri; writingreview and editing, Negar Firouzabadi, Ali Dehshahri; supervision, Ali Dehshahri. All authors have read and agreed to the published version of the manuscript.

Funding

No funding was received to assist with the preparation of this manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest.

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