Mpox: emergence following smallpox eradication, ongoing outbreaks and strategies for prevention

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Purpose of review
This review focuses on the temporal relationship between the discontinuation of the global smallpox eradication effort with the rise of mpox in Africa and worldwide. It also discusses the global 2022 clade II mpox epidemic and the current 2024 clade I mpox outbreak. Newer findings on viral evolution and pathogenesis, plus current and future strategies for disease prevention, are reviewed.

Recent findings
The temporal association between the incidence of mpox and the World Health Organization's Global Smallpox Eradication Program (GSEP) is presented. The 2022 global mpox epidemic is discussed. Recent data show that clade IIb monkeypox virus (MPXV)-2022 has novel genetic features supporting a greater propensity for mutations that may be responsible for enhanced human-to-human transmissibility, increased disease severity and accelerated viral evolution. In 2023, another outbreak of mpox began in Africa, this time due to the potentially more virulent MPXV clade Ib strains. This outbreak remains ongoing in Africa, and clade Ib mpox cases have recently been reported elsewhere including the United States and Great Britain. The World Health Organization has deemed mpox to be a global public health emergency. Two smallpox vaccines are approved for mpox prevention in the United States; a third smallpox vaccine and an improved diagnostic test have recently received WHO Emergency Use authorization. Newer mRNA-based vaccines for evolving orthopoxvirus infections are discussed.

Summary
Vaccination to prevent smallpox provides immunologic cross-protection against infection with other members of genus *Orthopoxvirus*, including mpox. Discontinuation of the global smallpox eradication program in the 1980s and the subsequent waning of herd immunity contributed to the 2022 multinational epidemic of human clade IIb mpox infections. A second multinational outbreak with clade Ib MPXV is ongoing. Vaccination against smallpox remains the gold standard for mpox prevention, however newer multiepitope mRNA-based vaccines are in development and hold promise for prevention of mpox and other orthopoxvirus outbreaks.

Keywords
monkeypox, mpox, orthopoxvirus, smallpox

INTRODUCTION

Monkeypox, now known as mpox, is a viral illness with clinical characteristics comparable to smallpox, including a scaring vesicular rash on the skin, mucous membranes or genitals, fever, and swollen lymph nodes. Though most cases are mild and self-limiting, others may be severe and life-threatening especially in children, pregnant women and those with immune deficiencies, including HIV/AIDs. Complications include secondary infections, pneumonia, sepsis and encephalitis. Transmission is typically via exposure to infected mammals (animal-to-human) or by respiratory droplets or contact with blister contents from infected humans (human-to-human).

The name 'monkeypox' originated after a pox-like illness was observed in laboratory monkeys in 1959. Small rodents (e.g., squirrels, mice) – not monkeys – were subsequently recognized as the natural monkeypox virus (MPXV) reservoirs, whereas humans and nonhuman primates were

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KEY POINTS

- Due to antigenic similarities among members of the orthopoxviruses, immunization against smallpox (variola) virus confers cross-protection against monkeypox (mpox) virus (MPXV).
- Cases of human mpox in African countries increased following the cessation of the World Health Organization's Global Smallpox Eradication Program in 1979.
- In 2022, a multinational outbreak of human clade II mpox occurred and was associated with MPXV strains having a greater propensity for genetic mutation and different epidemiologic features.
- Beginning in 2023, human mpox cases due to the more virulent clade Ib MPXV have been reported in Africa and non-African countries, including the United States and Great Britain.
- Novel genetic traits in recent MPXV strains suggest the virus may be undergoing accelerated evolution leading to higher transmissibility and increased disease severity.
- Following the 2022 outbreak and again in 2024, the World Health Organization (WHO) declared mpox a 'public health emergency of international concern' and in 2024 authorized a more rapid diagnostic test and a third mpox vaccine for Emergency Use.
- Newer vaccine strategies, including multiepitope mRNA-based vaccines, are currently being clinically evaluated and hold promise against evolving orthopoxviruses.

considered incidental hosts. In 2022, the WHO suggested the name be changed to mpox; in this review the two names will be used interchangeably.

The first known case of human mpox was described in 1970. During implementation of the WHO's Global Smallpox Eradication Program (GSEP), mpox infections were rare. Decades of study (described below) demonstrated that the smallpox vaccine provided protection against mpox. Such cross-protection is attributed to antigenic similarity among members of the genus *Orthopoxvirus* which includes the smallpox virus (variola), vaccinia virus, cowpox virus and MPXV [1].

For decades after cessation of the GSEP in 1979, mpox infections were sporadic and were largely limited to areas of west and central Africa, including in the Democratic Republic of the Congo (DRC). Occasionally, imported or travel-related cases occurred elsewhere. However, in 2022, a sudden global human mpox outbreak occurred with remarkable rates of human-to-human transmission. These cases were attributed largely to clade IIb MPXV and were reported in scores of countries including the United States [2]. Global vaccination efforts and other public health measures helped contain this outbreak. In 2023, infections due to clade I MPXV emerged in Africa and beyond. Historically, the case fatality rates are higher with clade I infections [3], and thus this new expanding outbreak is of particular concern.

This review summarizes the incidence of human mpox infection during and after the successful global eradication of smallpox. It also highlights the novel genetic characteristics of the recently isolated MPXV strains. The current status of global mpox infections and available vaccine strategies are also discussed. Lastly, novel multivalent nucleic-acid based vaccines under development are highlighted.

SMALLPOX ERADICATION AND THE RISE OF MPOX INFECTIONS

Important epidemiological studies over several decades confirmed that the emergence of mpox temporally correlated with the cessation of global smallpox eradication efforts. The chronology of these studies is described below.

Smallpox eradication efforts (1967–1979)

The eradication of smallpox was announced in Nairobi, Kenya, by the World Health Organization (WHO) on October 26, 1979 – exactly 2 years after the last naturally occurring case of smallpox and nearly 11 years after the WHO launched its 10-year Global Smallpox Eradication Program (GSEP) in 1967 [4].

During the planning phase of the GSEP in the 1960s, Arita and Henderson [5] highlighted the importance of establishing that no animal reservoir of smallpox existed. To this end, they believed it was essential to understand the epidemiology of any pox-like illnesses among nonhuman primates. Only highly scattered reports of supposed smallpox in primates during the 19th century could be found. Considering the massive extent of human smallpox, including in areas with many nonhuman primates, the paucity of reports of nonhuman primate smallpox was deemed striking. In fact, there had been no documented pox-like outbreaks in nonhuman primates at least since 1936 [5]. Therefore Henderson *et al.* concluded that a nonhuman primate smallpox reservoir was highly unlikely but that active surveillance for such reservoirs should be included in the eradication program.

Monkeypox emergence (1959–1979)

Monkeypox was first described in 1959 when 31 cases occurred in cynomolgus monkeys shipped

from Singapore to Copenhagen [6]. No animals died and no transmission to humans was documented. The causative agent was identified and resembled both variola and vaccinia viruses but induced more necrotic lesions in rabbit skin. From 1960 to 1969, 10 additional small monkeypox outbreaks were documented in subhuman primates in captivity; most often these were in monkeys imported for early virus vaccine research [5–7]. A smallpox-like virus was isolated in six of these outbreaks and was named monkeypox. It was thought at the time that humans were likely nonsusceptible to monkeypox.

In 1973, Henderson and Arita [8] reported that from 1970 to 1973, 13 humans in scattered smallpox-free areas of Africa had illnesses similar to smallpox but without human-to-human transmission, and in each case MPXV was identified. The first of these cases occurred in 1970 in the Democratic Republic of the Congo (DRC) where there had been no smallpox cases for 2 years. Most of the 13 cases occurred in young nonsmallpox-vaccinated children in small remote villages. In contrast, most of the older family members had received the smallpox vaccine and none developed monkeypox.

The WHO's final report on the eradication of smallpox in 1979 included a discussion on human monkeypox because of the clinical similarities between these poxvirus infections [9]. The report noted that monkeypox had never been recognized in monkeys in the wild although monkeypox-specific antibodies were found in several primate sera out of several thousand screened [9]. Furthermore, it was reported that from 1970 to 1979, 45 cases of human monkeypox were identified in west and central Africa, the majority in the DRC and in unvaccinated children less than 10 years of age with rare person-to-person transmission [9].

Monkeypox (1980–1986)

Although accumulating data suggested that smallpox vaccination likely also prevented monkeypox infections, the Global Commission concluded that continued smallpox immunization beyond 1980 to prevent monkeypox was not justified. Monkeypox became the most important human orthopoxvirus infection, but remained rare. Smallpox vaccination was officially terminated in 1980 in the DRC, but recommendations were to continue to assess the possible public health importance of monkeypox in the absence of ongoing mass smallpox vaccination. WHO then supported active human monkeypox surveillance from 1981 to 1986 [9]. These studies suggested MPXV was very unlikely to persist in humans and therefore was not likely to become a major public health problem [10]. Continued surveillance in the DRC was recommended until 1989 [11].

Monkeypox follow-up, the surveillance years in DRC (2005–2007)

Rimoin *et al.* [12] conducted active monkeypox surveillance in the DRC from 2005 to 2007, ~30 years after cessation of the smallpox vaccination campaigns in the DRC. Active surveillance was carried out in the same health zones as the 1981–1986 program. They found a 20-fold higher incidence of confirmed human monkeypox (14.42 versus 0.72 per 10 000 population in 2005–2007 and 1981–1986, respectively). This increase was associated with living in rural forested areas, male gender, age <15 years, and no prior smallpox vaccination [12]. Evidence of prior smallpox vaccination was associated with a much lower incidence of monkeypox (0.78 versus 4.05/10 000 population in vaccine recipients and unvaccinated, respectively).

During the earlier active surveillance period of 1981–1986, prior smallpox vaccination provided 85% protection against human monkeypox while by 2005–2007, <4% of the population had clinical evidence (scar) of vaccination. This demonstrated that smallpox vaccine-induced immunity was long-lasting. Indeed, even 25 years postvaccination, individuals appeared to be at markedly reduced risk of developing human monkeypox [12].

Re-emergence of human monkeypox (2003–2022)

Human monkeypox spread slowly from its endemic regions of west and central Africa to other regions of that continent. Cases increased in the DRC and later in Nigeria where no cases had been recognized for 40 years. Subsequently, sporadic infection emerged in the United Kingdom, Israel, Liberia, Singapore and South Sudan [13]. In 2003, a large cluster of human mpox infections (71 cases) occurred in the mid-western United States (Illinois, Wisconsin and Indiana) when imported Gambian pouched rats transmitted infection to co-caged prairie dogs which were then sold as pets [14,15].

In early 2022, several highly prescient papers warned of a possible global monkeypox resurgence [13]. Accumulating evidence also suggested a change in mpox transmissibility, demographics and epidemiology. Specifically, the median age of patients at presentation increased from 4 years in the 1970s, to 21 years from 2010 to 2019. Two distinct viral clades were also emerging and were associated with different case fatality rates (CFR): the central (Congo Basin) African clade (clade I) was associated with a 10.6%

CFR versus 3.6% for the west African clade (clade II). Cessation of smallpox vaccination with resultant loss of cross-protection against monkeypox as well as the increase in global travel were considered important contributors to this emergence [2,13].

In May 2022, a large multinational outbreak of human mpox was recognized [2]. By October of that year, more than 27 000 cases were diagnosed in the United States with many times that number worldwide, prompting the WHO to declare a global health emergency. All 50 states in the United States were involved with at least five deaths, generally in individuals with immune deficiency. This outbreak was largely attributed to MPXV clade IIb. In response to this outbreak, more than 936 000 doses of the MVA-BN smallpox vaccine (Jynneos) were given in the United States for mpox prevention, largely to healthcare workers, first responders and others deemed at high risk of exposure. Worldwide health emergency measures including vaccination helped curb this outbreak, and the WHO rescinded its emergency declaration in May 2023. At present, clade IIb mpox infections are still reported, albeit at significantly lower levels.

In September 2023, an outbreak with clade Ib MPXV began. The DRC was heavily affected, with six provinces reporting cases. All occurred following close social or sexual human-to-human contact. In addition, five countries outside of Africa have also reported travel-associated clade Ib MPXV cases, including Sweden, Thailand, Germany, India and the United Kingdom [16]. In November 2024, the California Department of Public Health confirmed the first known case of clade I mpox in the United States. This case occurred in an individual who had traveled from Eastern Africa where the strain is endemic. Florida's Department of Health reports 185 confirmed mpox cases thus far in 2024 (through 11/17/2024) though clade information has yet to be determined.

In November 2024, the United States Centers for Disease Control and Prevention (CDC) described results of their recent risk assessment regarding spread of clade I mpox [17]. This assessment included epidemiologic data from Central and Eastern Africa, data from the ongoing clade IIb mpox outbreak in the United States, and historical data on global clade I mpox outbreaks plus simulated clade I mpox outbreaks. The conclusions were that close-contact transmissions are unlikely to result in a large number of mpox clade I cases in the United States and that the risk to the general population in America remains low. In support of this notion, other countries that have reported clade Ib cases have not seen an onward spread of the virus, and viral spread in the United Kingdom has been limited to close household contacts.

Worldwide, there have been 115 101 lab confirmed mpox cases from January 1, 2022 to October 31, 2024 involving more than 123 countries [16]. According to the WHO's Multicountry External Situation Report published 9 November 2024 [16], mpox cases show a slight rising trend on the African continent, including those attributable to clade Ib. Furthermore, eleven other countries are now reporting clade Ib cases.

In light of the global spread of clade I mpox, the WHO again declared mpox a 'public health emergency of international concern' in November 2024. In addition, the WHO and partners, in collaboration with Member States, activated the Global Health Emergency Corps (GHEC) for the first time to provide support to countries facing mpox outbreaks [18]. In late 2024, WHO listed one additional vaccine (LC16m8; see below) and two new rapid diagnostic RT-PCR-based tests (Alinity m MPXV assay, Abbott Molecular Inc.; and Xpert Mpox, Cepheid) for emergency use to help stem the ongoing outbreaks. While vaccines are the mainstay of mpox prevention, novel therapeutic options are also being actively pursued [19▪].

GENETIC FEATURES OF MONKEYPOX VIRUS

The MPXV and other members of the genus *Orthopoxvirus* share a common genomic structure consisting of a linear, double-stranded DNA of approximately 200 kb encoding about 180 proteins. MPXV's genome consists of a central core region, variable regions at the left and right ends, and a tandemly repeated inverted terminal repeat [1]. MPXV's core region shares >90% sequence homology with other orthopoxviruses whereas species and strain-specific characteristics are often found in the variable regions at the ends of the genome [1]. There are two distinct clades (or subtypes) of MPXV: clade I (with subclades Ia and Ib) which historically has been associated with the Congo Basin, and clade II (with subclades IIa and IIb) found in west Africa. Genomic sequencing of representative isolates confirmed there is significant sequence diversity between the two clades [20]. Experimental studies in laboratory animals demonstrated that clade I strains were significantly more virulent than clade II strains [20], suggesting that human infections due to clade I strains would be more severe.

The 2022–2023 global outbreak was caused by MPXV clade IIb which exhibits multiple mutations in genes associated with virulence, host recognition, and immune evasion [21▪]. Compared to clade IIb strains isolated in 2018–2019, MPXV-2022 strains had higher numbers of single nucleotide polymorphisms (SNPs) which equated to an approximate

6–12-fold increase in the predicted nucleotide substitution rate [22▪,23]. These strains shared 46 common amino acid mutations which in turn affected 20 proteins [22▪]. Together, these data suggest that MPXV may be undergoing accelerated evolution which could explain the high transmissibility of mpox worldwide.

MONKEYPOX VIRUS PATHOPHYSIOLOGY AND TARGETS FOR INTERVENTION

Infection is mediated by the binding of viral proteins to host cell glycosaminoglycans, followed by endocytosis, uncoating of the viral core, and replication of its genomic DNA by viral DNA polymerase in the cytoplasm of the host cell. The mature brick-shaped virus particles are assembled in the cytoplasm and released upon cell lysis. The process can begin within 30 min of infection and be completed within 48 h, producing thousands of virus particles per cell. An excellent review of this complex process including a discussion of current and future pharmacologic strategies that target the various steps in MPXV pathophysiology has been recently published [19▪].

VACCINE STRATEGIES FOR MONKEYPOX VIRUS PREVENTION

The global interest in mpox prevention has grown following the 2022 surge in cases worldwide. No MPXV-specific vaccine has been developed to date. However, due to antigenic similarities, the smallpox vaccine is efficacious at preventing mpox infection. Yet most people under the age of 55 have not received the smallpox vaccine.

There are 2 smallpox vaccines licensed for use in the United States to prevent mpox. These include MVA-BN (developed by Bavarian Nordic; marketed as Jynneos and ACAM2000 (originally produced by Acambis; approved for mpox prevention in August 2024). The MVA-BN vaccine is a live, attenuated Modified Vaccinia Ankara (MVA) virus that does not replicate efficiently in humans and thus has a favorable safety profile; it requires two doses administered 28 days apart. The ACAM2000 vaccine contains a live, single plaque-purified vaccinia virus derived from the previously licensed smallpox vaccine in the United States (Dryvax, Wyeth Laboratories, Inc.). ACAM2000 was developed to replace Dryvax in the US Strategic National Stockpile and thereby improve preparedness against bioterrorism with smallpox [24]. ACAM2000 has similar immunogenicity and efficacy profiles compared to Dryvax. Like Dryvax, vaccination with ACAM2000 has been associated with myocarditis or pericarditis in some vaccinees. Its use in immunocompromised individuals or infants remains a concern. To prevent mpox, the CDC currently recommends that travelers to Africa and others at high risk for mpox receive the recommended two doses of the MVA-BN (Jynneos) vaccine.

On November 20, 2024, the WHO granted emergency use listing for a third mpox vaccine, the Japanese LC16m8 vaccine [25], for at-risk individuals over 1 year of age. The LC16m8 vaccine is an attenuated, replicating smallpox virus derived from the Lister strain of vaccinia [26]. This vaccine has been used in Japan since the 1970s, including in children, and had markedly less neurotoxicity than nonattenuated vaccines in nonclinical studies. It protects against both smallpox and mpox after a single dose and requires a bifurcated needle for administration [26]. Japan has committed to donating more than 3 million doses of LC16m8 vaccine to the DRC to stem the ongoing mpox outbreak in that country.

The unprecedented human-to-human transmission in the recent outbreaks and the emergence of divergent clades/subclades of mpox have spurred recent efforts to exploit both the versatility and the time- and cost-effectiveness of nucleic acid vaccines for mpox, and other related orthopoxviruses [27,28,29▪]. A 2024 preclinical report demonstrated efficacy of one such mRNA vaccine (BNT166, BioNTech) in preventing disease in laboratory animals [29▪]. Specifically, immunization with quadravalent vaccine BNT166a was 100% effective at preventing death and at suppressing lesions in a lethal clade I MPXV challenge in cynomolgus macaques. A Phase I/II clinical evaluation of BNT166's safety and immunogenicity is now underway (NCT05988203). In addition, an mRNA-lipid nanoparticle (LNP) vaccine expressing MPXV surface proteins (called mRNA-1769) [30▪], conferred protection against lethal clade I MPVX challenge in experimental animals and mitigated symptoms and disease duration. The current status of these and other novel vaccine strategies against orthopoxviruses has been recently reviewed [31].

CONCLUSION

The WHO's Global Smallpox Eradication Program utilizing mass vaccination, contact surveillance, and ring vaccination of contacts had remarkable global cooperation and success. The last naturally acquired case of smallpox occurred in 1977 and routine smallpox vaccination ended in 1980. The first human monkeypox case was diagnosed in 1970 in a smallpox-free region of Africa.

Careful epidemiologic studies demonstrated a temporal association between the discontinuation

of the smallpox eradication program with the rise in mpox. Subsequent work confirmed that smallpox vaccination provides cross-protection against mpox, and the dual protection is long-lived. Initially, officials concluded mpox was not a sufficient threat to public health to justify restarting routine smallpox vaccination. However, due to the ongoing multinational outbreaks since 2022, the use of smallpox vaccine as mpox prevention is now deemed warranted, especially for high-risk individuals and contacts. This approach, together with case identification and management, will hopefully stem the current clade Ib outbreak. Identification of the natural animal reservoir of MPXV may also facilitate eradication of mpox. Lastly, newer vaccine strategies including a universal multiepitope mRNA vaccine targeting evolving orthopoxviruses are currently under development and hold promise to stem future global outbreaks with these viruses.

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Conflicts of interest

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