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Review Article

The resurgence of a neglected orthopoxvirus: Immunologic and clinical aspects of monkeypox virus infections over the past six decades

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ABSTRACT

Monkeypox is a zoonotic *Orthopoxvirus* which has predominantly affected humans living in western and central Africa since the 1970s. Type I and II interferon signaling, NK cell function, and serologic immunity are critical for host immunity against monkeypox. Monkeypox can evade host viral recognition and block interferon signaling, leading to overall case fatality rates of up to 11%. The incidence of monkeypox has increased since cessation of smallpox vaccination. In 2022, a global outbreak emerged, predominantly affecting males, with exclusive human-to-human transmission and more phenotypic variability than earlier outbreaks. Available vaccines are safe and effective tools for prevention of severe disease, but supply is limited. Now considered a public health emergency, more studies are needed to better characterize at-risk populations and to develop new anti-viral therapies.

1. Epidemiology

In 1958, monkeypox virus (MPXV) was isolated from a large colony of monkeys with non-fatal dermatitis in Denmark. [1] Subsequent studies have revealed that the name "monkeypox" is a misnomer, as rodents comprise the largest animal reservoirs. [2,3] Due to concerns that the name of the virus is stigmatizing, [4] efforts to change the virus's name are underway at the time of this review's publication. [5] Initially thought to solely affect animals, MPXV was first identified in humans in the early 1970s when a 9 month-old infant in the Democratic Republic of the Congo (DRC) presented with what appeared to be an acute case of smallpox. [6] This discovery led to the identification of additional patients with MPXV in the DRC. [7] MPXV is endemic to Africa and there are two major clades with varying severity: the case fatality rate of the Central African clade is 10.6%, while that of the Western African clade is 3.6%. [8,9] The growing incidence of MPXV has been attributed to cessation of widespread smallpox vaccination after the eradication of smallpox in 1980. [10] Global interest in MPXV was low until 2003, when a young girl was hospitalized with the virus in Wisconsin, USA after being infected from a prairie dog bite. [11–13] The infection spread to a total of 72 patients in multiple states, and was eventually traced back to a shipment of exotic animals from Ghana. [11] Outbreaks in Africa continued after this time, with the highest rates reported from the DRC. [9] After 2018, MPXV was discovered in Europe and Asia in travelers from Nigeria. [14–16] In 2022, the WHO declared a Public Health Emergency of International Concern after monkeypox cases were identified in 70 countries [17] and the United States Department of Health and Human Services declared the current outbreak a Public Health Emergency. [18] By August 2022, over 15,000 in the United States and 44,000 cases worldwide were reported, [19] with 13 total deaths reported worldwide from the 2022 MPXV outbreak. [20] The current outbreak has disproportionately affected men more so than earlier outbreaks. [18,21–23] More recent cases have affected older individuals, with the median age of affected individuals in Africa increasing from 4 years in the 1970s to 21 years in the 2010s. [9]

2. Host immune response

MPXV belongs to the *Orthopoxvirus* genus of DNA viruses, which includes variola (the cause of smallpox), vaccinia, ectromelia (the cause of mousepox), and cowpox virus. Orthopoxviruses replicate within monocytes, macrophages, dendritic cells, epithelial cells, and

Abbreviations: CMV, cytomegalovirus; DRC, Democratic Republic of the Congo; FDA, Food and Drug Administration; HIV, human immunodeficiency virus; IFN, interferon; MOPICE, monkeypox inhibitor of complement enzyme; MVA, Modified Vaccinia Ankara; MPXV, monkeypox virus; NK, natural killer; PKR, protein kinase R; TNF, tumor necrosis factor; VIGIV, vaccinia immune globulin.

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fibroblasts. [24] Viral entry occurs when orthopoxviruses bind to host cell-surface glycosaminoglycans and undergo endocytosis. Viral replication in the host cell's cytoplasm generates multiple types of infectious viral particles: cell-associated enveloped virions, extracellular enveloped virions, and intracellular mature virions. [25] Cell-associated enveloped virions remain attached to the host cell membrane and generate actin tails to spread between host cells. [25] Extracellular enveloped virions dissociate from the host cell and disseminate among host tissues. Intracellular mature virions are stable viral particles released by lysed cells that enable transmission among hosts. [25] Both innate and adaptive immunity contribute to the recognition and clearance of the Orthopoxviruses.

2.1. The innate immune response

Orthopoxviruses induce an immune response via multiple DNA-sensing mechanisms, including cyclic GMP–AMP synthase, DNA-dependent protein kinase, interferon gamma inducible protein 16, and Toll-like receptor (TLR) 9. The DNA sensors activate STING, leading to activation of the interferon (IFN) and nuclear factor kappa B (NF-κB) signaling pathways. [26] Orthopoxviruses produce double stranded RNA (dsRNA) intermediates that activate protein kinase R (PKR) and TLR3. [27] PKR and TLR both activate the NF-κB and IFN pathways. Additionally, PKR inhibits mRNA translation via phosphorylation of eukaryotic translation initiation factor 2A complex. [28]

Natural killer (NK) cells are important for controlling MPXV. A study of infected rhesus macaques revealed that MPXV infection leads to robust proliferation of all NK cell subsets in the blood and lymph nodes. [29] Although wild mice are highly susceptible to MPXV, most inbred strains of laboratory mice are resistant to orthopoxviruses, although the resistance loci remain unknown. [30] The CAST/EiJ mouse strain is one of the few laboratory mouse strains extremely vulnerable to orthopoxviruses [31,32] due to low numbers of NK cells [33] and a deficient IFN-γ response. [34] The administration of either IL-15, which induces proliferation of NK cells, or IFN-γ protects these mice from lethal MPXV infection. [33,35]

2.2. The adaptive immune response

After initial recognition and early innate response, the adaptive immune response is key for viral clearance. $CD14^+$ monocytes are the most abundant hematopoietic antigen presenting cells capable of presenting MPXV antigens to $CD4^+$ and $CD8^+$ T cells, which subsequently orchestrate cytokine production, lysis of infected cells, and the host's serologic response. [36] The cellular response of infected hosts has been studied in different subsets of T cells. One study of infected rhesus macaques identified two MPXV $CD8^+$ T cell specific epitopes from the F8L protein, which is a component of the virus's DNA polymerase. [37] MPXV are also recognized by Vγ2Vδ2 T cells, the predominant subtype of gamma delta T cells in blood. [38] Vγ2Vδ2 T cells recognize a diversity of non-peptide antigen and can undergo recall expansion characteristic of an effector memory T cell response. [38] Vaccinia-immunized rhesus macaques infected with MPXV expanded their Vγ2Vδ2 T cell population, with increased IFN-γ production and trafficking to lung tissue. The T cell response alone is insufficient for protecting macaques against lethal MPXV challenge: T cell-depleted, but not B cell-depleted, macaques survived a lethal monkeypox challenge following vaccination. [39] This underscores the critical contribution of the serologic response to immunity against MPXV infection.

An in-depth serological assessment in cynomolgus macaques identified Orthopox-specific IgM within the six day incubation period prior to emergence of the rash. [40] Antibodies against each of the two MPXV clades showed cross-reactivity between clades. [40] The anti-MPXV IgG in these primate produced recognized 23 distinct Orthopoxvirus proteins. In contrast, antibodies found in humans vaccinated against smallpox were specific to only 14 Orthopoxvirus proteins, indicating that smallpox vaccination generates a more limited serologic response against MPXV than natural infection. During the 2003 outbreak in the United States, a study compared MPXV infections in individuals with a history of the smallpox virus vaccination to those in unvaccinated individuals. [41] Both groups developed detectable IgM and IgG antibodies within the first week of infection. The unvaccinated group developed a more rapid increase in IgM within the first two weeks of infection, and had detectable levels lasting 126 days, compared to 77 days. [41] However, vaccinated patients showed a more robust IgG response within the first 56 days, with IgG positivity lasting 147 days compared to 139 days in unvaccinated patients. [41]

3. Evasion of host immune response

A notable characteristic of orthopoxviruses is their ability to evade the host innate and adaptive immune response [42,43]. Monkeypox is no exception, with multiple virulence factors (Fig. 1). Knowledge of how MPXV infection evades TLR3 has been revealed by transcriptional studies of infected cells. Live MPXV infection of primary human fibroblasts and macrophages in vitro caused cell death without changes in in gene expression. In contrast, cellular infection with killed MPXV virus induces expression of the interferon responsive genes, demonstrating that the capacity for immune evasion is specific to live virus. Live MPXV infection suppressed TLR3 signaling, demonstrated by reduced expression of TNF-α, IL-1α, IL-1β, CCL5, IL-6, and interferon-responsive genes. [44] This mechanism of immune evasion is relevant to individuals co-infected with human immunodeficiency virus (HIV), since intact TLR3 signaling contributes to control of HIV replication through induction of type I IFN and NF-κB signaling. [45] Additionally, MPXV expresses the A47R protein, [46] which has structural similarities to vaccinia virus proteins that bind to interleukin-1 receptor associated kinase 2 and TNF receptor associated factor 6, two cytoplasmic proteins needed for TLR3-mediated activation of NF-κB. [47,48]

Multiple mechanisms enable the virus to evade the Type I IFN response. MPXV-infected cells secrete MPXVB16, a soluble IFNα/β binding protein that sequesters Type I IFNs from binding to IFN receptors. [49,50] IFNα/β binding proteins have been considered a vaccine target based on studies in which mice immunized against IFNα/β binding proteins are protected against lethal mousepox infection. [50] NK cells are an important source of Type I and II IFNs. MPXV reduces the efficacy of NK cell-mediated clearance by reducing the expression of chemokine receptors important for NK cell migration, NK cell cytotoxicity, and the secretion of IFN-γ and TNF-α secretion, all of which occur within the first week of infection. [29] Additionally, MPXV expresses the F3 protein, which binds to dsRNA viral intermediates and prevents recognition of viral dsRNA by PKR. [51]

Monkeypox inhibitor of complement enzyme (MOPICE) inhibits the host's complement response. MOPICE is present in the more virulent clade from Central Africa, but has not been identified in the West African clade, to which the 2022 outbreak belongs. [52] Expression of MOPICE in the West African clade did not increase its virulence to that of the Central African clade, [53] demonstrating that MOPICE is not the sole determinant of differences in viral virulence between the two clades. The function of MOPICE has been derived from studies of similar proteins in variola and vaccinia viruses, which inhibit activation of the classical and alternative complement pathways by cleaving C4b and C3b. [54] However, evasion of the host's complement response enables increased viral replication and a more robust adaptive immune response. Rhesus macaques infected with MOPICE-deficient MPXV had increased viral loads, higher levels of anti-MPXV antibodies, and increased T cell expression IFN-γ and TNF-α – all of which facilitate resolution of the infection. [55]

4. Clinical presentation of MPXV infection

MPXV transmission occurs via large respiratory droplets and direct

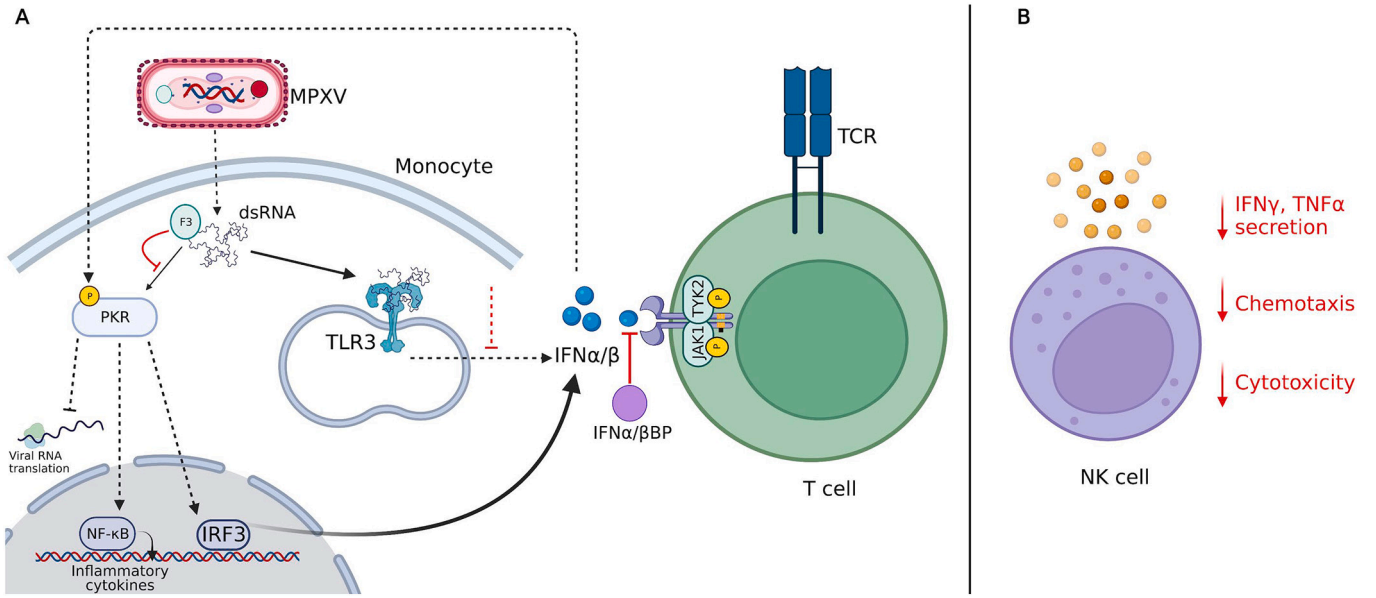

Fig. 1. Mechanisms utilized by MPXV to evade host immunity. **A)** Following viral entry into monocytes and production of viral dsRNA intermediates, the F3 protein binds these intermediates and sequesters them away from PKR, preventing downstream antiviral mechanisms, while the TLR3 response to these intermediates is also reduced. IFNα/βBP prevents binding of type I IFN on the cell surface. **B)** NK cells demonstrate decreased chemotaxis, IFNγ and TNFα secretion, and cytotoxicity during MPXV infection.

contact with skin lesions or bodily fluids. [56] MPXV can be spread by completely asymptomatic carriers, thereby adding to challenges in diagnosis. [57] The viral incubation period can be as long as 21 days (Fig. 2). [8,21,58,59,61] Patients then develop a prodrome of fever, chills, lethargy, myalgias, headache, and back pain that lasts up to 4 days, followed by development of the characteristic rash. [8,21,58,59,59,62–66] The MPXV rash classically begins as a macular exanthem, which evolves into painful monomorphic papules, vesicles, pustules, and finally scabbed lesions [8,21,22,58,59,62–65,67–73]. Lesions may be ulcerated, necrotic, or hemorrhagic and spread in a centrifugal distribution; they may affect any body part, including the palms, soles, and anogenital areas. [8,67,18,21,23,58,62–64,68,70,72,74,75] The rash typically lasts 12 to 35 days and is present for the duration of the illness. [8,13,58,59,68,75] In a study of 1057 individuals, aged one month to 79 years, infected with MPXV from 2011 to 2015, all patients had a rash. [63] All but six patients presented with fever before the onset of the rash, and about one third of patients were bedridden, suggesting that these symptoms are the most consistent among all ages. [63] In contrast, a study of the 2017–2018 outbreak in Nigeria found more variability in the clinical presentation of 51 hospitalized patients, as 65.7% of patients presented with rash without a prodromal period. [66]

Additional symptoms of MPXV infection include vomiting, diarrhea, cough, mucositis, pharyngitis, dysphagia, pruritus, conjunctivitis, blepharitis, photophobia, rhinorrhea, scrotal edema, and proctitis. [8,13,21,59,63,64,66,67,69,70,72,73,75] Lymphadenopathy is present in the majority of cases and can differentiate MPXV from acute varicella, measles, and smallpox infections. [8,21,59,63,68,70,72,75] In 2017, investigators sought to better define the clinical presentation of MPXV, particularly in comparison to the phenotypically similar varicella zoster virus (VZV). [67] Features with a sensitivity exceeding 80% for MPXV included: a rash with uniform, deep-seated lesions on the extremities, palms, and soles, lymphadenopathy, and fatigue. However, no single symptom occurred in >32% of patients, further underscoring variability in the clinical phenotype.

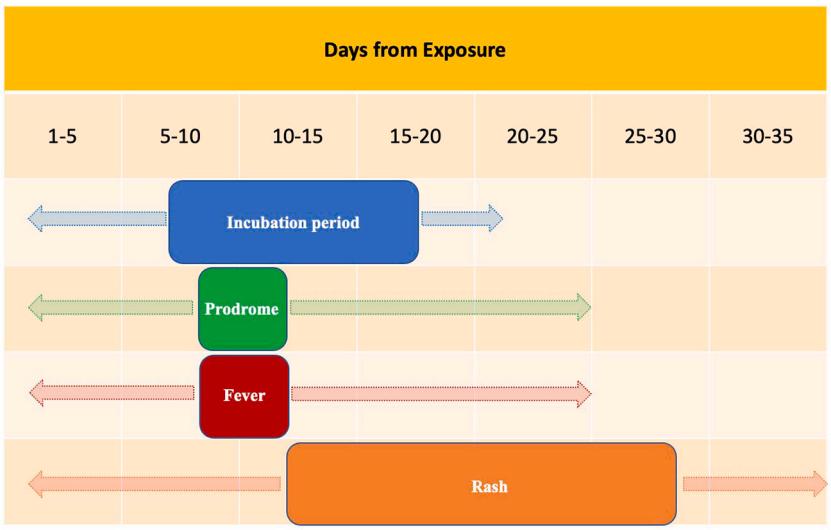

Fig. 2. Progression of clinical symptoms after MPXV infection. The classic presentation of an infection with monkeypox virus starts with an incubation period of about 7–17 days, followed by a prodromal period of 1–4 days, characterized by fever, myalgias, and fatigue. The fever resolves as the characteristic rash presents, typically around 12 days after exposure. The rash evolves for the duration of the illness, usually resolving by 28 days after exposure. The arrows represent the spectrum of phenotypes that have been described, with more variability and shorter incubation periods in the 2022 outbreak.

The phenotypic variation during the 2022 outbreak has been attributed to differences in the MPXV genome from the two established clades in Africa. [76] Patients during the 2022 outbreak have had much shorter incubation periods, with development of skin lesions within 24 h of an encounter with an infected individual in the absence of a febrile prodrome. [23] Many patients have had no rash, while others have a mild rash without systemic symptoms; furthermore, the morphology of the rash is more variable during the 2022 outbreak. [21,22]

5. Diagnosis

Polymerase chain reaction testing is the gold-standard diagnostic test for MPXV infection. [8,58,59,68,70,77] PCR testing from skin lesion samples are the most reliable, although testing has been performed using blood, urine, feces, semen, saliva, as well as oral, nasal, and rectal swabs. [22,57,59,68,70] The overlap and longevity of IgG antibodies against members of the *Orthopoxvirus* genus has been a challenge for the diagnosis of acute MPXV infections. [8,59,61,68,77,78] In 2005 investigators found that measurement of anti-MPXV IgM between 5 and 77 days after rash onset had a sensitivity of 94.8% and specificity of 94.5% in vaccinated and unvaccinated patients. In unvaccinated and MPXV naïve patients, measurement of anti-MPXV IgG from day 14 onwards had a sensitivity of 100% and specificity of 88.5%. [78] In 2014, a monoclonal antibody specific to the heparin binding site of a MPXV envelope protein identified an epitope unique to MPXV, [79] thereby establishing the foundation for more specific serologic assays for MPXV infection. [80,81]

Data regarding laboratory findings in patients with acute MPXV is limited. Hypoalbuminemia is a common finding, and may be accompanied by transaminitis, reduced levels of blood urea nitrogen, lymphocytosis, and thrombocytopenia. [71,75] However, patients can have normal white blood cell counts and only modest elevations in C reactive protein levels. [23] Cytokine profiling of 19 serum samples from infected patients revealed elevations in MIP-1a, MIP-1B, IL-1RA, IL-6, and IL-15, irrespective of disease severity. [82] Patients with more severe disease had increased levels of IL-2R, IL-10, and granulocyte macrophage colony-stimulating factor, indicative of activated T cells, myeloid cells, and fibroblasts. [82]

6. Clinical outcomes and individuals at risk

Most patients with MPXV require only supportive care, though a smaller percentage may develop secondary complications. These include respiratory distress, bacterial skin infections or pneumonias, dehydration related to gastrointestinal losses or poor oral intake (secondary to mucositis), encephalitis, septicemia, ocular lesions leading to scarring or vision loss, seizures, acute kidney injury, myocarditis, or severe pain, with hospitalization rates ranging from 0% to 100% in different case series. [8,21,58,59,66,66,70,72,75] A report from 2022 investigating 528 patients with MPXV infections reports a 13% hospitalization rate and no deaths. [21] Patients with more severe lesions may also develop permanent cutaneous scarring after recovery, which is difficult to treat cosmetically. [8]

Severe illness has been associated with more lesions, secondary complications, illness acquired via a bite or scratch from an infected animal, and infections in children under 8 years of age. [8,58,59,68,69,75,83]. Unborn fetuses appear to be at particularly high risk, with multiple case reports detailing miscarriages and stillbirths. [66,71,83] Additionally, epidemiologic studies have noted a possible increased risk of MPXV in patients with compromised immunity. [59,68,73,83] Among studies of patients with preexisting Hepatitis C or HIV infections, [21–23,66,75] only one noted a difference in outcomes, with increased likelihood of secondary bacterial infections in patients with HIV. [66] The 2022 outbreak has been associated with a high concurrence of infection with HIV as well as other sexually transmitted infections. [21–23,68]. A review of 528 cases diagnosed in 2022 found that 29% of patients infected with MPXV had a concurrent sexually transmitted infection, and 218 patients were HIV positive. [21] However, patients with well-controlled HIV infections did not have more severe MPXV infections. [68] In contrast, the outcomes of MPXV infection in patients with congenital immunodeficiencies are unknown, although the known importance of Type I and II IFN signaling in the control of MPXV infection suggests that patients with defects in IFN signaling may be at increased risk for more severe MPXV infections.

7. Treatment

In a minority of MPXV cases, severe illness necessitates treatment with antibiotics for secondary infection and/or systemic antiviral therapies (Table 1). [8,21,66,68,70,73] A study conducted in 2006 compared the efficacy of post-exposure smallpox vaccination, cidofovir, and a related antiviral acyclic nucleoside phosphonate analogue for treating a fatal dose of MPXV in monkeys. [84] Both antiviral medications were successful at reducing disease severity, but post-exposure smallpox vaccination conferred no protection against mortality. Cidofovir is an anti-viral medication that inhibits DNA polymerase and is classically used to treat cytomegalovirus retinitis. Although the medication has been used in humans with MPXV, nephrotoxicity associated with cidofovir limits its usage. [8,21,73] Brincidofovir is a lipid conjugate of cidofovir with less nephrotoxicity. A case series from 2022 found that brincidofovir did not change clinical outcomes or viral loads, and was associated with transaminitis in all three patients who received it. [70] Tecovirimat is another anti-viral therapy that prevents viral release from cells via inhibition of p37, a viral envelope protein. Tecovirimat is FDA-approved for the treatment of smallpox infections, and is currently available for use in severe MPXV cases in patients of all ages under an Investigational New Drug protocol. [86]

Serologic therapies have also been considered for MPXV treatment. A study in 2016 found that orthopoxvirus-immune humans produced antibodies specific for a variety of epitopes shared by multiple types of orthopoxviruses, of which 54% were neutralizing. [87] Furthermore, mixtures of monoclonal antibodies more effectively neutralized orthopoxviruses than any single monoclonal antibody. Vaccinia immune globulin is a product that was initially used for some smallpox infections and vaccine-related complications. [88] It has been used clinically in some severe cases of MPXV, and been proposed for the treatment of patients with T cell lymphopenia ineligible to receive a live MPXV vaccine. [21,73] Although it is currently approved by the FDA for treatment of *Orthopoxvirus* infections during an outbreak, efficacy

Table 1
Therapies used for treatment of monkeypox virus. All of the following therapies have been used in pediatric and adult patients, although studies in children are limited.

Medication	Mechanism of action	Adverse events	FDA approved for MXPV
Brincidofovir	Viral DNA polymerase inhibitor; lipid conjugate of cidofovir	Diarrhea, nausea, vomiting, abdominal pain, transaminitis	No
Cidofovir	Viral DNA polymerase inhibitor	Nephrotoxicity, neutropenia, teratogenicity, decreased intraocular pressure, anterior uveitis, metabolic acidosis	Yes
Tecovirimat	Prevent viral release via inhibition of p37, a major envelope protein	Headache, nausea, abdominal pain, vomiting, neutropenia, infusion site reaction	Yes
Vaccinia immune globulin	Provides passive immunity to orthopoxviruses	Headache, nausea, dizziness, aseptic meningitis, hemolysis	Yes

regarding its use in MPXV is unknown.

8. Vaccines

Most available vaccines against Orthopoxviruses utilized today are based on vaccines against vaccinia, due to the cross-reactivity among antibodies to *Orthopoxvirus* (Table 2). Early surveillance data from the 1980s report 85% protection among vaccinated individuals, [89] although the protection conferred by childhood vaccination can be lower due to waning immunity with aging. [90] Multiple methods of delivery have been used for vaccine administration, with scarification being the first used for smallpox vaccination. Scarification is a process by which a vaccine is administered percutaneously into the dermis via multiple punctures using a bifurcated needle. [91] Studies of a vaccinia vaccine delivered via scarification or intramuscular (IM) administration in mice showed that severe disease and mortality was comparable in both groups after a vaccinia virus challenge. Mice who received the IM vaccine had less weight loss and reduced disease severity after the viral challenge. [92]

8.1. First generation, live viral vaccines

Dryvax is a live vaccinia strain grown on calf skin, administered via scarification, and was initially used in the United States prior to the eradication of smallpox. [93] A study in rhesus macaques showed that protection from lethal intravenous MPXV challenge depends on the serologic response to vaccination. [39] Dryvax has been associated with significant adverse events, including Stevens-Johnson syndrome, a combination of malaise, fever, myalgia, and headache known as acute vaccinia syndrome, vaccine-associated myocarditis or myopericarditis, secondary pyogenic infections at site of vaccine administration, auto-inoculation leading to vaccinia in a site other than the primary vaccination site, disseminated vaccinia, post-vaccination encephalitis, and eczema vaccinatum in patients with history of eczema. [94] These complications can, in rare cases, lead to death. [94] Due to safety concerns arising from this side effect profile, a second-generation vaccine, ACAM2000, has replaced Dryvax. [95]

8.2. Second generation, live viral vaccines

ACAM2000 is derived from plaque purification cloning from Dryvax under serum-free conditions. One study showed that ACAM2000 fully protects monkeys from lethal MPXV challenge, with no significant clinical signs of disease in vaccinated animals. Vaccinated monkeys had antibody titers comparable to those induced by Dryvax. [96] This replication-competent vaccinia strain was first approved in the US in 2007 for vaccination against smallpox in individuals at increased risk of exposure, and is now available for use for prevention of monkeypox under an Expanded Access Investigational New Drug application. [97] This vaccine is administered as one dose percutaneously via scarification. [98] Similar to Dryvax, ACAM2000 has multiple side effects, including inoculation site pruritus and pain, lymphadenitis, and acute vaccinia syndrome. Less common side effects are similar to those of Dryvax, resulting in a black box warning. [98] Vaccine-associated death is estimated to be 1 in 1 million unvaccinated individuals and 1 in 4 million vaccinated individuals. [98]

Two phase III clinical trials compared the efficacy of ACAM2000 to Dryvax. [99] The first trial included vaccinia vaccine naïve individuals, with 780 subjects receiving ACAM2000 and 257 receiving Dryvax. Using measures of cutaneous response to the vaccines, both were found to be effective at eliciting an immune response. The second trial included individuals who had previously been vaccinated against smallpox, with 1242 subjects receiving ACAM2000 and 405 subjects receiving Dryvax. [93] In this revaccinated cohort, Dryvax was more effective at eliciting higher titers of neutralizing antibodies. These results indicate that ACAM2000 and Dryvax are equally effective for vaccinia naïve individuals, but that Dryvax is superior for revaccination. Both Dryvax and ACAM2000 are live viral vaccines, which are contraindicated in immunocompromised individuals due to the risk of fatal, disseminated infections. [94,98] Live vaccinia vaccines are also not recommended for pregnant women (due to the risk of transmission to the fetus), patients with a history of eczema (due to the risk of eczema vaccinatum), and children younger than 18 years of age. Scarification with live vaccines can lead to transmission to immunocompromised contacts, leading to eczema vaccinatum in a close contact of one vaccinated individual. [100] Additional groups at risk for adverse reactions with ACAM2000 include those with anaphylaxis to the polymyxin B sulfate and neomycin components of the vaccine and individuals with a history of cardiac disease, due to the risk of vaccine-associated myocarditis estimated to occur at a rate of 5.7 per 1000 primary vaccinations. [98]

8.3. Third generation, attenuated vaccines

The Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN) vaccine is an attenuated, live vaccinia virus that is replication-incompetent in mammalian cells. This vaccine was initially used for smallpox eradication. [101] Since this attenuated vaccinia strain is unable to replicate, it is safer and has had a much more favorable side effect profile compared to first- and second-generation vaccines. The most common side effects

Table 2
Vaccinia vaccines used for protection against MPXV. EA-IND, expanded access for an investigational drug.

	Dryvax	ACAM2000	JYNNEOS	LC16m8
Type	Live, grown in calf skin	Live, grown in serum-free cell culture	Live attenuated, replication-incompetent	Live attenuated
Mode of delivery	Scarification	Scarification	Subcutaneous or intradermal	Scarification
Dosing	1 dose	1 dose	2 doses, given 4 weeks apart	1 dose
Cutaneous lesion at vaccination site	Yes	Yes	No	Yes
Approval for MPXV	No	Available under EA-IND	Yes	No
Serious adverse effects	Progressive vaccinia, eczema vaccinatum, autoinnoculation, myocarditis/myopericarditis, Steven-Johnson syndrome		None	Eczema vaccinatum, vaccinia infection
Precautions & contraindications	• Allergy to components, including neomycin or polymyxin B • Immunodeficiency • Infants <12 months • Eczema or other skin barrier disorders • Pregnancy • Cardiac disease • Corticosteroid eye drop use, due to the risk of ocular vaccinia through autoinoculation.		• Allergic reaction to components, including ciprofloxacin and gentamycin	• Immunodeficiency • Eczema or other skin barrier disorders

include injection site reactions, headache, myalgias, and lymphadenopathy. [102] As the MVA-BN vaccine contains low amounts of gentamicin (≤0.163 μg per dose) and ciprofloxacin (<0.005 μg per dose), individuals with a history of an allergic reaction to these antibiotics may require additional monitoring or consultation to consider the risks and benefits of vaccination. [102] Animal studies have shown no harm to the fetus during pregnancy. [102]

Studies have demonstrated the efficacy of MVA-BN against MPXV. A study in monkeys compared the immune response to MVA-BN versus Dryvax and found that MVA-BN generated more neutralizing antibodies and a more robust T cell response. Monkeys vaccinated with MVA-BN had mild or asymptomatic disease, with some developing transient skin lesions; in contrast, unimmunized monkeys developed large numbers of skin lesions and became severely ill or died. [103] Another study in rhesus macaques found that immunity to MPXV was induced more rapidly after one dose of MVA-BN than after Dryvax, [104] attributed to the higher dose of MVA-BN that can be safely administered. [104] A phase 3 clinical trial compared the efficacy of MVA-BN to that of ACAM2000 in 440 participants. [105] One group received one dose of ACAM2000; the other received two subcutaneous doses of MVA-BN given four weeks apart, followed by a challenge with ACAM2000 to assess attenuation of the ACAM2000-associated major cutaneous reaction. MVA-BN and ACAM2000 generated comparable peak serum neutralizing antibody titers. In addition, while ACAM2000-only subjects developed lesions with a median area of 76 mm^2 (95% confidence interval: 70–87 mm^2), MVA-BN vaccinated subjects had lesions with a median area of 0 mm^2 following ACAM2000 inoculation (95% confidence interval: 0–2 mm^2), indicating protection conferred by MVA-BN. Additionally, a small randomized controlled trial was performed to assess the immune response to MVA-BN vaccination in 24 individuals with a history of hematopoietic stem cell transplant recipients at least two years prior to study enrollment. Those receiving MVA-BN had greater neutralizing antibodies and vaccinia-specific T cell responses compared to the placebo group. [106] However, this study was limited by the lack of comparison to a control group without a history of transplantation. Additionally, as all individuals enrolled had a remote history of transplantation, no ongoing graft versus host disease, and no use of immunosuppressive therapies for at least 30 days prior to study enrollment, the findings of this study are not broadly generalizable to the immunocompromised population.

MVA-BN, which includes the Imvanex, Imvamune and JYNNEOS vaccines, was approved in the US in 2019 for vaccination against smallpox and monkeypox as two subcutaneous doses administered four weeks apart. [107] In 2022, limited vaccine availability prompted the FDA to authorize the administration of JYNNEOS intradermally to expand vaccine availability. [108] This decision was based on studies showing that intradermal administration of one tenth the subcutaneous dose of MVA maintained a comparable antibody response in magnitude and kinetics [109] and attenuated the cutaneous response in response to a challenge with Dryvax. [110] A clinical trial published in 2015 compared the efficacy of a two-dose series of MVA given subcutaneously in either liquid ($n = 149$) or lyophilized form ($n = 145$), or intradermally at one fifth the subcutaneous strength ($n = 146$). The peak neutralization antibody titers induced by the lyophilized subcutaneous and liquid intradermal forms were comparable to the liquid subcutaneous form. The lyophilized form has the added benefit for a longer shelf life, while intradermal administration allows for five times the number of doses per vial. [111]

Current studies are investigating the efficacy of another vaccine based on the LC16m8 vaccinia strain. LC16m8 is a replicating, attenuated vaccinia strain with a truncated B5R membrane protein, leading to decreased production of extracellular enveloped virus. It is approved for use in Japan against smallpox, where it was administered as a single dose via scarification in thousands of children in the 1970s. [112,113] A study evaluating LC16m8 as a vaccine against MPXV in cynomolgus monkeys found that it was effective in preventing all symptoms after intranasal infection and most symptoms, other than small ulcers at area of inoculation, after subcutaneous infection [114]. A phase I/II clinical trial comparing vaccination with LC16m8 to Dryvax showed that LC16m8 produces neutralizing antibodies and T cell-specific responses against vaccinia, variola, and MPXV, albeit at levels that were two- to three-fold less than those induced by Dryvax. [115] Vaccination with LC16m8 has not yet been authorized for use against MPXV.

In addition to using vaccines as pre-exposure prophylaxis in which vaccination is given before MPXV exposure, the U.S. Centers for Disease Control and Prevention has employed a post-exposure prophylaxis strategy to manage the 2022 outbreak. Vaccination with ACAM2000 or JYNNEOS is recommended within four days of known MPXV exposure. [116] Post-exposure prophylaxis can be considered within 14 days of exposure to individuals in high risk groups, such as a history of eczema or immunocompromised immunity, with presumed exposure to MPXV. [116]

In addition to the first, second, and third generation vaccines, studies have also investigated DNA vaccines against MPXV as an alternative vaccination strategy that avoids use of live virus. The initial study of plasmid DNA encoding four vaccinia proteins administered to rhesus macaques via gene gun (which delivers a high concentration of DNA using compressed helium) showed protection against death after challenge with a lethal dose of MPXV virus. [79] Given the impracticality of administering vaccines via gene gun to humans, a subsequent study compared intramuscular vaccination with plasmid DNA encoding four vaccinia proteins, alone and in combination with the recombinant proteins encoded by the plasmid DNA. Intramuscular vaccination with plasmid DNA alone failed to protect the rhesus macaques from infection and death. The macaques vaccinated with recombinant proteins developed moderate to severe disease, but survived. Vaccination with a combination of plasmid DNA and recombinant proteins had mild disease that resolved within days and generated protective antibody titers for all four proteins. [117] Additional studies are needed for the development and testing of DNA viruses against MPXV.

9. Conclusions

The current outbreak of the monkeypox virus has revealed changes in this virus over time, from a zoonotic infection to one predominantly spread via human-to-human transmission. Despite changes in the clinical phenotype of MPXV, the 2022 outbreak has not been characterized by an increase in hospitalizations or deaths. As monkeypox utilizes mechanisms to evade innate and T-cell immunity, in-depth immunophenotyping and next-generation DNA sequencing of patients with severe infections may enable the identification of biomarkers for severe disease. The data on the efficacy of anti-viral therapies in humans remains fairly limited at this time. Vaccines may be the most important tool to gain control of the current outbreak, given the importance of the serologic response highlighted in earlier studies. This is a critical time for translational research, with the uncertainties of a quickly spreading virus providing impetus for expeditious and focused investigations.

Declaration of Competing Interest

All authors declare that no conflict of interest exists.

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