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Mpox global health emergency: Insights into the virus, immune responses, and advancements in vaccines

PART II: Insights into the advancements in vaccines

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Abstract

Mpox is currently a global health emergency. This review (Part II) aims to provide insights into Mpox vaccines and their advancements, offering easily digestible information for healthcare workers and researchers. Current Mpox vaccines are all live-attenuated, previously approved for smallpox, and are classified into non-replicating (Modified Vaccinia Ankara-Bavarian Nordic or MVA-BN) and replicating vaccines (Lister clone16m8 KM Biologic or LC16m8KMB and Acambis2000 or ACAM2000). Replicating vaccines offer long-lasting immunity but are contraindicated for immunocompromised individuals and those with extensive dermatitis. Replicating vaccines are administered as a single dose via epicutaneous scarification, while the non-replicating vaccine is given as two subcutaneous doses. Regulatory approvals in various countries are based on animal challenge studies, with limited effectiveness data available. Only LC16m8 is approved for children in Japan, while the others are approved for individuals aged 18 and older. Clinical trials are currently investigating the efficacy and safety of MVA-BN, particularly in children and for post-exposure prophylaxis (PEP). Novel Mpox vaccines that provide cross-protection against orthopoxviruses are needed, with DNA, subunit, and mRNA platforms under development. MPXV-neutralizing antibody-inducing target antigens for vaccine development include the outer envelope antigens of extracellular enveloped virus (EEV): A35R and B6R, and the inner membrane antigens of intracellular mature virus (IMV): M1R, A29L, H3L, and E8L. Two mRNA vaccines are currently in early clinical stages. Importantly, the COVID-19 pandemic underscored the importance of addressing vaccine disparities and improving global access. Transformative approaches are being explored to overcome this challenge and to enhance access in low- and middle-income countries.

Key words: Monkeypox virus, Mpox, MPXV, Vaccine, Novel Platform, PEP (Post-Exposure Prophylaxis)

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Introduction

The causative agent of Mpox, MPXV, belongs to the genus *Orthopoxvirus* in the *Poxviridae* family, which includes the variola virus that causes smallpox in humans, as well as the cowpox and vaccinia viruses. These viruses share several common characteristics and coding antigens. As a result, the immunity conferred by infection with these viruses exhibits considerable cross-reactivity and can provide partial cross-protection. The eradication of the variola virus from the human population using the vaccinia virus vaccine demonstrated that an effective immune response can be induced against *Orthopoxvirus* infections.

The recent Mpox outbreak in 2022, caused by MPXV clade II outside the endemic regions of Africa, ignited strong interest in evaluating the effectiveness of the vaccinia virus vaccine against Mpox and spurred the development of newly designed vaccines specific to MPXV. Both pre-exposure vaccination for high-risk individuals and post-exposure vaccination within a short window after contact have been found to offer significant protection against MPXV infection. With updated information on the genomes of emerging MPXV strains, protective immune responses, and new vaccine platforms such as mRNA technology, it is highly anticipated that more effective Mpox vaccines will emerge in the near future.

This review summarizes the current status of Mpox vaccines that are approved for use worldwide, the immune responses they induce, and provides updates on newly developed Mpox vaccines at various preclinical and clinical trial stages.

Update on current vaccines against Mpox

To contain the Mpox outbreak in 2022 and the more recent declaration of Mpox as a global health emergency, vaccination with third-generation smallpox vaccines, particularly MVA-BN, has been recommended by both national and international guidelines.[1-3]

Replicating and non-replicating vaccines

Currently, there are three available smallpox vaccines that can be used for Mpox vaccination, all are live-attenuated virus vaccines, including two third-generation vaccines: Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN), which is approved in many countries, and LC16m8, primarily available in Japan. One second-generation vaccine, ACAM2000, is also in use. Additionally, the Aventis Pasteur Smallpox Vaccine (APSV) is an investigational vaccine authorized by the U.S. FDA for emergency use. As summarized in **Table 1**, these vaccines can be categorized based on replication competency into non-replicating and replicating vaccinia vaccines.

MVA-BN is the only non-replicating vaccinia vaccine, offering a major safety advantage as it can be administered to individuals with immunocompromised conditions, active atopic dermatitis, active exfoliative dermatitis, and during pregnancy. However, to achieve a similar level of specific immune induction comparable to replicating vaccinia vaccines, MVA-BN requires two doses administered subcutaneously, with a 4-week interval between doses.

All replicating vaccinia vaccines are typically given percutaneously via scarification, using a bifurcated needle with 15 punctures to the deltoid area, and the site was covered with 2 occlusive bandages.[4] There is no clinical data on other alternative routes of administration. Although a study in mice has shown that replicating vaccinia vaccine given intramuscularly induced a comparable protective efficacy with local side effects.[5] The comparison between non-replicating and replicating vaccinia vaccines is shown in **Table 1**.

Table 1. Current Mpox vaccines classified by viral replicating competency.

Type of Vaccines	Non-Replicating	Replicating
Vaccine for Mpox	**MVA-BN** (JYNNEOS®, Imvamune®, Imvanex®) It was approved by the Food and Drug Administration (FDA) in 2019 and by the European Medicines Agency (EMA) in 2022	**LC16m8 KMB, ACAM2000, APSV** (Aventis Pasteur Smallpox Vaccine)
Dosing	2 doses × 4 weeks interval	Single dose only
Route	Subcutaneous (Intradermal route has also approved by EMA)	Percutaneous by scarification with bifurcated needle
Advantage	The virus doesn't replicate in human cells, it's considered safer, especially in vulnerable populations	Only the LC16 KMB (approved and available only in Japan) has extensive safety data in children and approved for use in children
Safety	Warning of systemic reaction and syncope. Post marketing surveillance, myocarditis and pericarditis, although very rare, have been reported.[6]	**ACAM2000**: There are some rare serious adverse effects have been reported and warning: myocarditis and pericarditis at a rate of 5.7 per 1000 primary vaccinees (95% CI: 1.9-13.3),encephalitis, encephalomyelitis, encephalopathy, progressive vaccinia, generalized vaccinia, severe vaccinial skin infections, erythema multiforme major (including STEVENS-JOHNSON SYNDROME), eczema vaccinatum resulting in permanent sequelae or death.[7] **APSV**: The risks of serious complications are low, occur more frequently in persons receiving their first dose and in young children. The most frequent serious complications are encephalitis, progressive vaccinia, and eczema vaccinatum.[8] **LC16 KMB**: has been administered to over 100,000 infants and 3,000 adults with no serious adverse reactions.[9] Rare serious complication has been reported: anaphylaxis, convulsion.
Contraindication	Allergic to vaccine components	Immunocompromised persons, active atopic dermatitis, active exfoliative dermatitis, pregnancy, and persons with multiple cardiac risk factor.

Vaccine effectiveness

The vaccine effectiveness of pox-vaccines against Mpox is summarized in **Table 2**. MVA-BN (marketed as JYNNEOS®, Imvamune®, and Imvanex®) has more recent data than the others. The mean vaccine effectiveness (VE) of MVA-BN, when administered subcutaneously (SubQ) in two doses, ranges from 66% to 85.9%, while for a single dose, it ranges from 35.6% to 76%.[10-13] Among immunocompromised individuals, the effectiveness is 70.2% (95%CI = -37.9 to 93.6). The reported VE of ACAM2000 is 85%. The VE of intradermal (ID) administration, an alternative route approved by the European Medicines Agency (EMA) for the MVA-BN vaccine, is 80.3% (95%CI = 22.9 to 95.0).[11] When MVA-BN was administered heterologously (SubQ and ID), the mean VE ranged from 75% to 86.9%[10,11] Only the LC16 KMB vaccine has extensive safety data for children in Japan and is recommended for use in this population. MVA-BN is currently recommended for individuals aged 18 and older.

Immune reponses of MVA-BN vaccination in previous smallpox vaccinated-individuals

A recent study showed that a single dose of the MVA-BN vaccine in individuals previously vaccinated for smallpox induced significantly higher levels of specific IgG and neutralizing antibodies compared to two doses given to vaccine-naïve individuals. In contrast, the specific T-cell response was significantly higher in vaccine-naïve individuals than in those with prior vaccination experience.[14]

Cross protection of prior smallpox vaccination against Mpox

Studies suggest that smallpox vaccination is 80.7% effective in preventing human Mpox, and the immunity it provides is long-lasting. Furthermore, smallpox vaccination reduces the risk of contacting human Mpox by 5.2-fold. Two cross-sectional studies conducted in the Democratic Republic of the Congo (DRC), involving around 1,800 Mpox cases, found that unvaccinated participants had a 2.73 to 9.64-fold higher risk of contacting Mpox compared to vaccinated individuals.[15] This is likely due to high sequence homology between orthopox viruses and long-lasting of the wide breadth of immune responses.

Immune responses in MVA-BN vaccinees in recent Mpox infection

Recent MPXV infection induced strong serum antibody responses to both MPXV proteins and native proteins from a viral isolate. In contrast, vaccine recipients showed negligible gene-level plasmablast and antibody responses, with sera displaying only moderate binding to recombinant orthopoxviral proteins (A29L, A35R, E8L, A30L, A27L, A33R, B18R, and L1R) and native proteins from the 2022 Mpox outbreak strain. However, MVA-BN (JYNNEOS) vaccine recipients exhibited robust orthopoxviral $CD4^+$ and $CD8^+$ T-cell responses.[16]

Immune reponses and safety of MVA-BN vaccine in HIV-infected individuals[17]

Very few data available in people living with HIV (PLWH). However, some studies have shown that the MVA smallpox vaccine was as safe and well tolerated in HIV-infected subjects with CD4 counts as low as 200 cells/μL as in healthy individuals, regardless of their previous smallpox vaccination status. In brief, a phase 2 trial conducted between 2006 and 2009,[18] a total of 579 volunteers: 439 vaccine-naïve subjects (88 healthy subjects, 351 PLWH) and 140 vaccine-experienced subjects (9 healthy subjects, 131 PLWH) received at least one vaccination. The study demonstrated that MVA 2 doses has a favorable safety and immunogenic profile in HIV-infected vaccinia-naive and vaccinia-experienced populations with CD4 counts of 200–750 cells/μL. In other study also confirmed this findings.[18]

Side effects

MVA-BN, a non-replicating vasccine, has fewer local and systemic side effects. These include injection site reactions, myalgia, headache, fatigue, nausea, and chills. In contrast, higher rates of fever (up to 20%), lymphadenopathy (up to 60%), and satellite lesions (up to 15%) have been reported among individuals who received viral replicating vaccines. (**Table 2**)

Safety

The risk of serious side effects is rare. For the MVA-BN vaccine, there is a warning regarding systemic reactions and syncope. Post-marketing surveillance, although is rare, has reported cases of myocarditis and pericarditis.[6] The LC16m8 KMB vaccine has been administered to over 100,000 infants and 3,000 adults with no serious adverse reactions.[9] However, rare serious complications, including anaphylaxis and convulsions, have been reported. Some rare serious adverse effects have been reported for the ACAM2000 vaccine, with warnings including myocarditis and pericarditis at a rate of 5.7 per 1,000 primary vaccinees (95%CI: 1.9-13.3), encephalitis, encephalomyelitis, encephalopathy, progressive vaccinia, generalized vaccinia, severe vaccinial skin infections, erythema multiforme major (including Stevens-Johnson Syndrome), and eczema vaccinatum, which may result in permanent sequelae or death.[7] The risks of serious complications with the Aventis Pasteur Smallpox Vaccine (APSV) are low but occur more frequently in individuals receiving their first dose and in young children. The most frequent serious complications include encephalitis, progressive vaccinia, and eczema vaccinatum.[8]

Table 2. Update on current vaccines for Mpox (as of Sepetember 2024).

Vaccine for Mpox (and smallpox)	MVA-BN JYNNEOS®[6] Imvamune® Imvanex®	LC16 KMB[19]	ACAM2000®[7]	Aventis Pasteur Smallpox Vaccine (APSV)[8]
Vaccine generation	Third	Third	Second	Second
Type of virus	Modified vaccinia Ankara	Attenuated vaccinia virus	Attenuated vaccinia virus	Attenuated vaccinia virus
Virus strain	Vaccinia strain MVA-584	Vaccinia strain LC16m8	New York City Board of Health vaccinia strain (ACAM1000)	New York Board of Health vaccinia strain
Replication competency	No	Yes	Yes	Yes
Approval	US, Candada, Europe, US, others (should refer to each specific country regulatory authority)	Japan	US, Canada, Australia, Singapore	Is an investigational vaccine. U.S. FDA authorized as IND/EUA
Long-term storage	Shelf life: 3 years at −20°C, 5 years at −50°C, 9 years at −80°C	• Store powder between −35° and −20°C • Do not expose to light. • Shelf life: 10 years	Stored at -15°C to -25°C If necessary, lyophilized ACAM2000 may be stored up to 18 months at 2-8°C	Stored at -20°C[4]
Storage in clinic	Unopened containers: 2–8°C for up to 24 weeks.	Unopened containers: 2–8°C for up to 24 weeks. After reconsititution, at room temperature should be used in 24 hours	After reconstitution: At room temperature (20-25°C), may be administered within an 8 hour At 2-8°C, may be stored no longer than 30 days	N/A
Dose and administration	2 Doses by subcutaneous route, 4 weeks interval Note: Intradermal route also showed similar effectiveness	Single dose by the percutaneous route (scrarification)	Single dose by the percutaneous route (scrarification)	Single dose by the percutaneous route (scrarification)
Immunogenicity	• Seroconversion rate after 2 doses administration was 90.8% • Vaccinia-neutralizing antibody (NAb) responses with Geometric mean neutralizing antibody titer (GMT) = 152.8 [95%CI 133.3-175.0] at 2 weeks after the second dose. • The median lesion areas of the major cutaneous reaction were 0 mm^2 in the MVA group versus 76.0 mm^2 in the ACAM2000-only group[6]	• Major cutaneous 'take' lesions in vaccinia-naïve ~95%, and previously vaccinated ~80% to 95% • Induces vaccinia-neutralizing antibodies in 85-90% vaccinia-naïve and 60% in previously vaccinated persons • MPXV-neutralizing antibodies ~70%	• Vaccination success "Take" rate = 96% in vaccinia-naïve persons; and 84% in vaccinia-experienced persons. (Defined by a positivemajor cutaneous reaction with a pustule).[7] • GMT of NAb titer = 166 and 286, respectively.[7] • IFN-γ-ELISPOT assay (> 15 SFC) postive 100%[22]	• Vaccinia-neutralizing antibody titers, GMT= 626[23] • IFNγ ELISPOT mean = 460 (95%CI = 53-3627) spots forming cells/10^6 cells. • based on previous report, the success rate of vaccination "take" is 100%[4]

Table 2. (Continued)

Vaccine for Mpox (and smallpox)	MVA-BN JYNNEOS®[6] Imvamune® Imvanex®	LC16 KMB[19]	ACAM2000®[7]	Aventis Pasteur Smallpox Vaccine (APSV)[8]
Vaccine Effectiveness (VE)	**1 Dose, subcutaneous route** VE varies from studies: • 35.8% (95%CI, 22.1-47.1)[10] • 75.2% (95%CI = 61.2 -84.2)[11] • Up to 75%[12] • 76% (95%CI 64-88%)[13] • 78.23% (95%CI: 62.8–87.3%)[24] **2 Doses:** VE varies from • 66.0% (95%CI, 47.4 -78.1)[10] • 85.9% (95%CI, 73.8-92.4)[11] • Up to 80%[12] • 82% (95%CI 72-92%)[13] **Among immunocompromised persons:** 70.2% (95%CI = -37.9-93.6)	Data not available	There are no recent studies conducted to assess the exact effectiveness of ACAM2000 against Mpox virus and very little information regarding its efficacy and safety amongst pregnant women and no information regarding children. One recent observational study reported 85% protection against Mpox.[25]	NA for Mpox
Intradermal administration data	EUA approved for intradermal administration. Vaccine Effectiveness by intradermal route (ID): 80.3% (95%CI, 22.9-95.0)[11] Heterologous route (SubQ and Intradermal): mean %VE 75-86.9%[10,11] ID route is likely associated with syncope.[26]	NA	NA	NA
Pediatric use	MVA-BN indication: ≥ 12 yrs (EMA Sep 2024 and WHO Oct 2024)	Safety in children is acceptable, based on use in approximately 50,000 children in 1970s[19]	Not recommend in children age < 12 months	NA
Side Effects	Injection site reactions, myalgia, headache, fatigue, nausea, and chills[27]	Injection site pain, pruritus, lymphadenopathy, fever, headache, myalgia, diarrhea, joint pain, rash, and fatigue	Injection site pain, pruritus, lymphadenopathy, fever, headache, myalgia, rash, fatigue[27]	Injection site reaction, Overall, 60% axillary lymphadenopathy, 15% satellite lesions, and 20% Fever[4]

Table 2. (Continued)

Vaccine for Mpox (and smallpox)	MVA-BN JYNNEOS®[6] Imvamune® Imvanex®	LC16 KMB[19]	ACAM2000®[7]	Aventis Pasteur Smallpox Vaccine (APSV)[8]
Safety	Warning of systemic reaction and syncope. Post marketing surveillance, myocarditis and pericarditis have been reported.[6] Nonetheless, MVA-BN continues to have better cardiac safety than older, replicating vaccines.[26]	LC16m8 has been administered to over 100,000 infants and 3,000 adults with no serious adverse reactions.[9] Rare serious complication has been reported: anaphylaxis, convulsion.	There are some rare serious adverse effects have been reported and warning: myocarditis and pericarditis at a rate of 5.7 per 1000 primary vaccinees (95%CI: 1.9-13.3), encephalitis, encephalomyelitis, encephalopathy, progressive vaccinia, generalized vaccinia, severe vaccinial skin infections, erythema multiforme major (including STEVENS-JOHNSON SYNDROME), eczema vaccinatum resulting in permanent sequelae or death.[7]	The risks of serious complications are low, occur more frequently in persons receiving their first dose and in young children. The most frequent serious complications are encephalitis, progressive vaccinia, and eczema vaccinatum.[8]
Contraindication	Allergic to vaccine components	Immunocompromised persons, pregnancy, active exfoliative dermatitis, acute illness, allergic to vaccine ingradients	Immunocompromised persons, active atopic dermatitis, active exfloliative dermatitis, pregnancy Persons with multiple cardiac risk factors	Immunocompromised persons, pregnancy, active atopic dermatitis,
Duration of effectiveness	It has been estimated that effectiveness may remain more than 59% for up to 10 years, even after a single dose.[19] For persons who received primary series and who are at ongoing risk for occupational exposure to more virulent orthopoxvirus e.g., Variola virus and Monkeypox virus), should receive a booster dose every 2 years; For who are at ongoing risk for occupational exposure to less virulent orthopoxviruses, (e.g., Vaccinia virus or Cowpox virus, should receive booster doses of JYNNEOS at least every 10 years after the primary series.[21]	Anti-vaccinia neutralizing antibody persisted for decades after LC16 vaccination.	For persons working with more virulent orthopoxviruses, (Variola and Mpox viruses) a boost dose is recommended every 3 years. However, a recently preferred option is MVA-BN (JYNNEOS) due to its safety profile, with boosters recommended every 2 years.[21]	NA

Contraindications

All replicating competent vaccines (ACAM2000, LC16m8 KMB, and APSV)[7,19,20] are contraindicated in immunocompromised persons, active atopic dermatitis, active exfoliative dermatitis, pregnancy, and persons with multiple cardiac risk factors. Because there are a risk of increasing of generalizd vaccinia, progressive vaccinia, severe disability, neurological sequelae, and/or death. For individuals with active atopic dermatitis, active exfloliative dermatitis, there is a risk of eczema vaccinatum (a localized or systemic spread of vaccinia virus, it is often with fever and lymphadenopathy, and it can be fatal). And the vaccinees who received these replicating competent vaccines should avoid and prevent transmission by close contact to persons with immunocompromised persons, active atopic dermatitis, active exfloliative dermatitis, and pregnancy.[5]

Durability of vaccine effectiveness

The durability of protection provided by smallpox vaccines, such as MVA-BN (JYNNEOS), against Mpox is still under study, but evidence suggests that protection may last for several years or even decades. It has been estimated that effectiveness may remain more than 59% for up to 10 years, even after a single dose.[19] For persons who received primary series and who are at ongoing risk for occupational exposure to more virulent orthopoxvirus e.g., Variola virus and MPXV, should receive a booster dose every 2 years. For who are at ongoing risk for occupational exposure to less virulent orthopoxviruses, (e.g., Vaccinia virus or Cowpox virus, should receive booster doses of JYNNEOS at least every 10 years after the primary series.[21]

Post-Exposure Prophylaxis (PEP) vaccination to prevent Mpox disease

To prevent transmission and controlling the spread of monkeypox in those at high risk of infection, the World Health Organization (WHO) recommends PEP vaccination with Mpox vaccines for individuals with a history of high-risk contact with confirmed, probable, or suspected Mpox cases.[28] High-risk contacts include exposure to skin or respiratory secretions, body fluids (such as vesicular or pustular lesion fluid), or potentially infectious materials. These high-risk contacts may include 1) inhalation of droplets or dust while cleaning contaminated rooms; 2) mucosal exposure from splashes of body fluids; 3) physical contact with someone who has monkeypox, including direct contact during sexual activities; 4) sharing a residence (permanently or temporarily); 5) enetrating sharps injury from a contaminated device or through contaminated gloves.

Timing of PEP vaccination is likely to be most effective if given within 4 days of exposure for up 14 days. As summarized in **Table 3**, two vaccines have been studied for their PEP effectiveness: MVA-BN and LC16 KMB. Most of the available data comes from studies on MVA-BN, with effectiveness estimates ranging from 20% (95%CI: -24% to 65%)[13] to 88.8% (95%CI: 76.0% to 94.7%).[29] This highlights the importance of further research, particularly with larger populations, to better understand the effectiveness of these vaccines for PEP in controlling the spread of Mpox.

Table 3. Pre-exposure prophylaxis (PrEP) and PEP with Smallpox vaccines to prevent Mpox disease.

Vaccination Purpose	PrEP Vaccination	PEP Vaccination
Indication	• Health workers at risk of repeated exposure • Persons in the same household • Known contacts of persons with Mpox • Close community with someone who has Mpox • Persons who have multiple sex partners • Sex workers • Laboratory personnel working with orthopoxviruses • Clinical laboratory personnel performing diagnostic testing for monkeypox • Outbreak response team members	• Closed contact persons
Type of vaccine	• MVA-BN: JYNNEOS®, Imvamune®, Imvanex® • LC16 KMB	• MVA-BN, non-replicating vaccine • LC16 KMB (limited data)[30]
Dose, route admisnistration	MVA-BN: • 2 Doses for MVA-BN -subcutaneous route; may also give intradermally LC16 KMB: • Single dose, by the percutaneous route using the multiple puncture technique (scarification)	MVA-BN: • 2 doses subcutaneous injection, 4 weeks apart LC16 KMB: • A single dose by scarification
Administration Timing	Pre-exposure	• Vaccine should ideally be given within 4 days after the contact • In case symptoms are not delevoped, the vaccine can be given for up to 14 days
Efficacy against Mpox	See detail in **Table 2**	Varies from studies: • 20% (95%CI -24-65%)[13] • 88.8% (95% CI: 76.0–94.7)[29]

Future Mpox vaccines in preclinical research and development

Although MVA-BN and traditional vaccinia-based vaccines have proven effective against Mpox, there remain significant safety concerns, particularly with live-attenuated vaccinia-based vaccines. This concern is particularly pertinent for vulnerable populations, such as children, pregnant women, and immunocompromised individuals. These groups face higher risks of complications from live-virus vaccines, making it essential to develop newer, safer vaccine technologies.

New platforms like subunit vaccines with potent adjuvants and mRNA vaccines are being explored for Mpox due to their potential to induce effective immune responses with better safety profiles. The rapid scalability of mRNA technology, as demonstrated during the COVID-19 pandemic, presents a strong case for its use in future outbreaks, especially if Mpox were to escalate into a global pandemic.

According to the WHO Mpox Vaccine Tracker - List of vaccine candidates in research & development, 30 August 2024, there are a total of 46 reported preclinical studies, whereas 26 reports are from 2022 onward. Five technology platforms are in development: mRNA, vaccinia, subunit, DNA and MVA. For last 3 years, mRNA vaccine is the most common among those platforms which is approximately 60%, followed by subunit vaccines, **Figure 1**.[31]

Viral antigens as immune targets for vaccine R&D

Viral antigen targets selected for the DNA, subunit or mRNA R&D include M1R, H3L, E8L, A29L, A35R, and B6R.[31] M1R, H3L, E8L and A29L are key proteins in the membrane of intracellular mature virion (IMV), while A35R, and B6R are the component in the envelope of extracellulae enveloped virion (EEV) (**Figure 2**). These protein are crucial for the virus to infect host cells.[32] From previous studies on the vaccinia virus (VacV), the A27L, H3L, and D6L proteins—homologs of A29L, H3L, and E8L in Mpox—are essential for binding to host cell molecules, facilitating viral entry or movement within infected cells (B6R).

Thus, neutraling antibodies against these proteins could inhibit MPXV infection and spreading. Major immune target antigens have been investigating to develop novel Mpox vaccines as they are the target of neutralizing antibodies. Immunization with the combination of these protein provided protection and/or prolonged suvival after viral challenge.[33-35] However, recent data demonstrated that H3L protein plays a role in cellular pathogenicity by inducing cellular injury in both human and mouse cells through transcriptional disturbances and chromatin remodeling.[36] Hence, the inclusion of H3L in vaccine formulations may require further study to avoid potential side effects caused by the vaccine. Their homology to recent outbreak Mpox clades and Variola virus are summarized in **Table 4**.

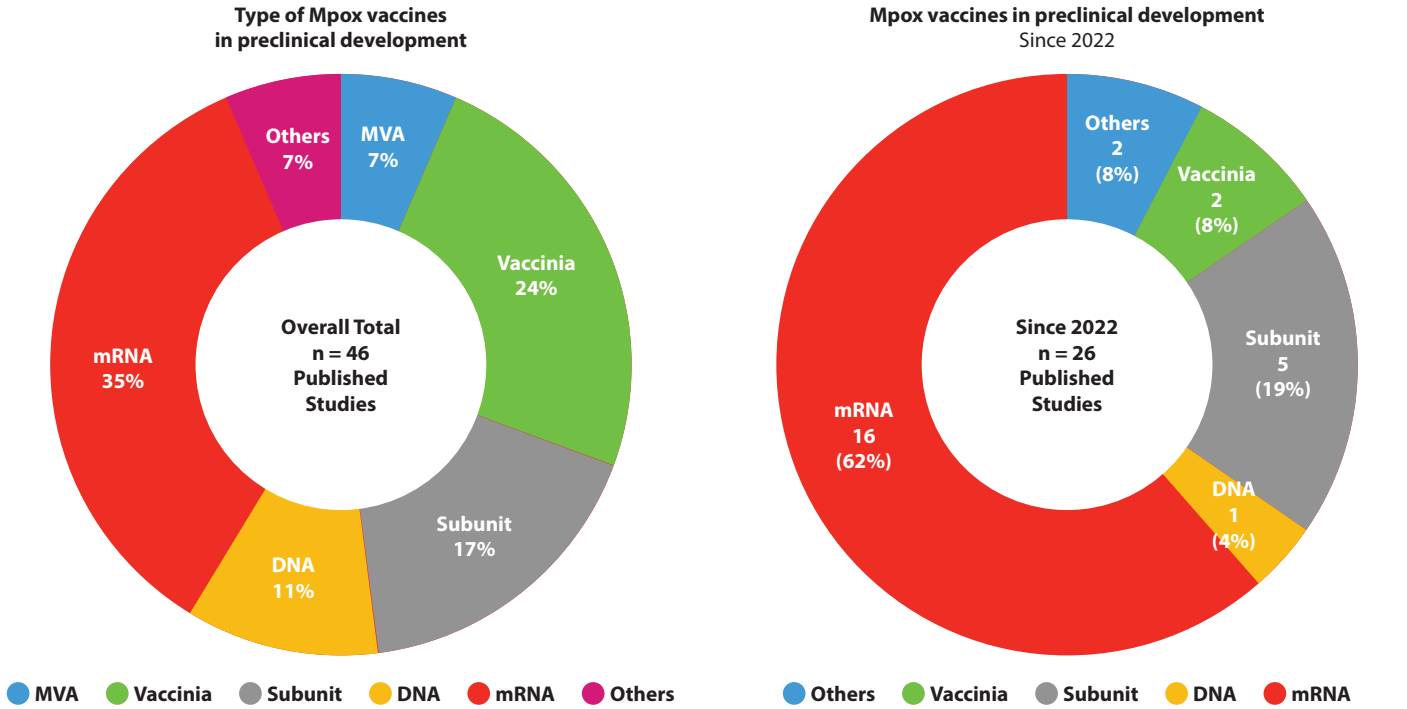

Figure 1. Mpox vaccines in preclinical development (data sourse from the WHO Mpox Vaccine Tracker - List of vaccine candidates in research & development, 30 August 2024).

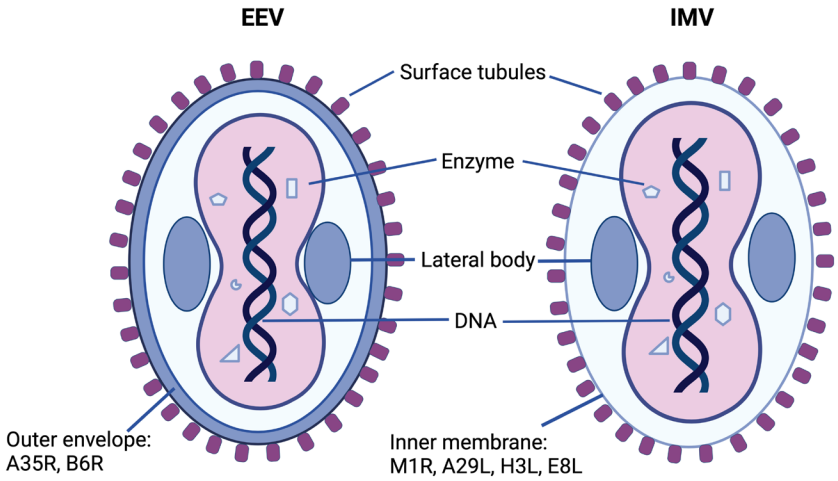

Figure 2. Major MPXV antigens of extracellular enveloped virus and intracellular mature virus, potential immune targets for novel Mpox vaccine development, *created with Biorender*.

Table 4. Mpox virus target antigens as potential selection for vaccine development and its homology to the current outbreaking clades and variola virus

MPXV Selected Antigen	Location	Homology Clade 1b (PP601220.1) vs clade 2 (OP328310)	Homology Clade 2 vs Variola virus (VARV: DQ437581)
M1R	IMV membrane	100%	Identity: 248/250 (99.2%) Similarity: 250/250 (100.0%) 57L, I242V
A35R	EEV envelope	96.2% E67K, A88V, U181V, 182KTMN185 Deletion	Identity: 168/185 (90.8%) Similarity: 172/185 (93.0%) L35I, 67E, S73 del, V75T, S81L, 88A, D95K, K97Q, L112F, K117Q, S118L, E120S, A128T, S164T
B6R	EEV envelope	100%	Identity: 294/317 (92.7%) Similarity: 308/317 (97.2%) H53Y, D87N, S95A, I96I, M97I, S100I, N102K, G103D, P132S, E132D, Y152H, M153I, V166A, S170T, I216I, I233V, I236I, V238I, D248E, M283V, I296V, V304N
A29L	IMV membrane	100%	Identity: 104/110 (94.5%) Similarity: 106/110 (96.4%) N27K, I30A, Y39D, I61V, E77D, 107R
E8L	IMV membrane	100%	Identity: 283/304 (93.1%) Similarity: 295/304 (97.0%) P2S, D18N, T23P, D25N, I52L, T64S, I65L, I114L, A118S, S143T, M146T, T163K, T168K, A181V, S205L, Q230E, V246A, K253R, A261T, F285Y, Q296R
H3L	IMV membrane	99.4% A4V, I111T	Identity: 306/325 (94.2%) Similarity: 313/325 (97.0%) T3A, N5-deletion, L26V, P45Q, N49D, K54N, A64V, H67Q, N75D, K118N, V125I, M144I, M169I, N172D, V174A, N252T, A264V, V266A, A275T

Current clinical developments of Mpox vaccines

The WHO has provided a very useful and updated dataset of Mpox Vaccine Traker (as of 30 August 2024). Up-to-date, as summarized in **Table 5**, 65 clinical trials ranging from phase 1 to 4 have been registered to the U.S. clinicaltrials.gov and the European clinicaltrialsregister.eu databases. In the early years before 2019, all of the trials were vaccinia-based or MVA-based vaccines to address the efficacy or effectiveness of the vaccines. The study groups were covered mainly adolescent and adults. Only one LC16m8 vaccine study conducted on 1 years old and older in Japan (started in 2014).

For more recent data in last up to 6 years, since 2019, there are only 19 registered trials (**Figure 3**). Approximately up to 70% (13 of 19) are investigating MVA-BN with different objectives to address the vaccine efficacy against Mpox prospectively in various countries mainly in adults aged 18 years old or order. Notably, efficacy data in children is lacking, only a few trials are investigaitng in younger age groups, as shown in **Table 5**, i.e., the study number 57: at least aged 12 to 17 vs aged 18 to 50, and the study #65: aged 2 to 12 vs adults up to 50). Three large scale studies (in this case is defined by with a sample sixe of 3,000 or more) were registered: 1). The study #54: A prospective cohort in 4 countries to study the effectiveness of smallpox vaccines against Mpox with a sample size approximately 4,600. 2). the study #58 (N = 15,000) is a observational study to access the effectiveness of MVA-BN in Mpox at risk population conducted in Germany. 3). The study #61 is a randomized controlled trial of LC16m8 vaccine to compare immediate vs delayed (with 6 weeks versus after 6 weeks) vaccination to assess the safety and efficacy of the vaccine in individuals at risk of Mpox. This study is conducted in Columbia. Furthermore, proper designed studies to investigate the efficacy of "PEP" are needed, in this database only study #64 is a randomized-controlled PEP study with the sample size of 1,560 and relevantly children aged 2 to adults are included in the study to received either MVA-BN or a Typhoid vaccine.

Two mRNA-based vaccines have been registered in phase 1 and 2 clinical trials to assess their safety and immunogenicity for Mpox (studies #62 and #63). These trials are being conducted in the United States and the United Kingdom, reflecting a shift toward exploring newer vaccine technologies beyond the traditional live-attenuated platforms. The mRNA vaccines, known for their success in COVID-19 vaccines and RSV vaccine, these early stage trials, and their outcomes could provide valuable data for developing next-generation vaccines that may offer advantages in production scalability and adaptability to new viral threats.

Data on vaccine efficacy in children remain limited, with only a few trials including younger age groups. For instance: Study #57 compares individuals aged 12-17 years with those aged 18-50. Study #65 investigates the vaccine in children aged 2-12 compared to adults up to age 50, (**Table 5**).

Large-scale studies have also been registered: Study #54 (N = 4,600): A prospective cohort study across 4 countries to evaluate smallpox vaccines' effectiveness against Mpox. Study #58 (N = 15,000): An observational study in Germany to assess MVA-BN effectiveness in at-risk populations. Study #61: A randomized controlled trial of LC16m8 in Colombia to assess vaccine safety and efficacy through immediate versus delayed (6 weeks) vaccination.

Despite progress, there remains a need for well-designed trials on PEP. In the current database, only Study #64 investigates PEP in a randomized-controlled format, with a sample size of 1,560, including children aged 2 years and up, comparing MVA-BN with a typhoid vaccine. These studies highlight ongoing efforts to expand our understanding of Mpox vaccine efficacy across different age groups and populations at risk.

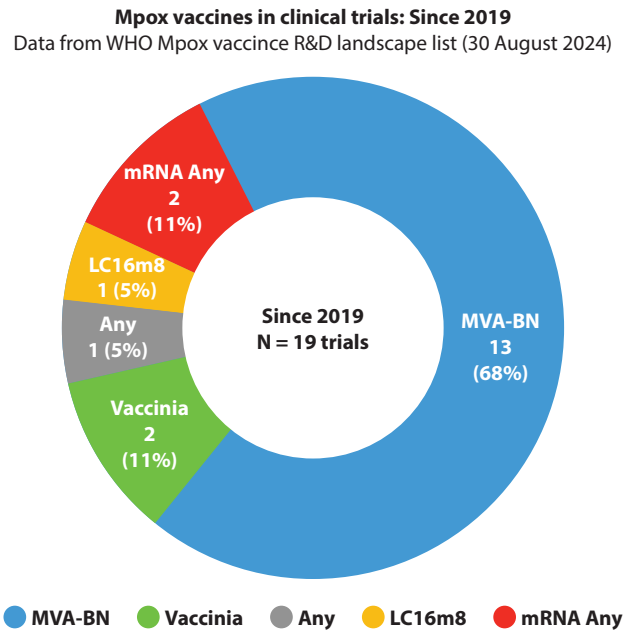

Figure 3. Mpox vaccines in clinical trials since 2019 (Data the WHO Mpox vaccine tracker - List of vaccine candidates in research & development, as of 30 August 2024)[31]

Table 5. Clinical trials of pox-vaccines against Smallpox and Mpox.
(adapted from the WHO Mpox vaccine tracker - List of vaccine candidates in research & development. 30 August 2024;[31] and clinicaltirals.gov[37] -last accessed -7 October 2024)

Order	Vaccine(s)	Type of Platform	Year Start	Participant Location	Route of administration	Phase	Sample Size (n)	Age (years)	Trial Registration
1.	Dryvax	Vaccinia	2001	USA	Intradermal	2	680	≥ 18 < 32	NCT00026611
2.	ACAM1000	MVA -BN	2002	USA	Subcutaneous	2	274	≥ 18 < 29	NCT00053508
3.	Cell-cultured smallpox vaccine	Vaccinia	2002	USA	Subcutaneous	1	350	≥ 18 < 65	NCT00042094
4.	APSV: Aventis Pasteur smallpox vaccine	Vaccinia	2002	USA	Scarification	1, 2	330	≥ 18 < 32	NCT00038987
5.	MVA-TBC-M (MVA and Dryvax)	MVA and Vaccinia	2002	USA	IM	1, 2	195	≥ 18 < 30	NCT00046397
6.	Elstree-BN (Lister)	Vaccinia	2003	Germany	Scarification	1	50	≥ 18 < 32	NCT00189969
7.	Dryvax	Vaccinia	2003	USA	Scarification	N/A	69	≥ 18	NCT00325975
8.	Modified Vaccinia Virus Ankara	MVA	2003	USA	IM	1	80	≥ 31 < 60	NCT00053742
9.	ACAM2000	Vaccinia	2003	USA	Subcutaneous	2	357	≥ 28	NCT00053482
10.	ACAM2000 and Dryvax	Vaccinia	2003	USA	Subcutaneous	2	353	≥ 18 < 30	NCT00053495
11.	LC16m8 Smallpox Vaccine	LC16m8	2004	USA	Scarification	1, 2	154	≥ 18 < 35	NCT00103584
12.	ACAM3000	MVA	2004	USA	Subcutaneous	1	110	≥ 18 < 32	NCT00079820
13.	Dryvax	Vaccinia	2004	USA	Scarification	1	45	≥ 18 < 50	NCT00068198
14.	ACAM3000	MVA -BN	2005	USA	Subcutaneous	2	590	≥ 18 < 55	NCT00466245
15.	Smallpox Vaccine (LISTER Strain)	Vaccinia	2005	France	Scarification	2	230	≥ 18 < 25	NCT00258947*
16.	Imvamune (JYNNEOS)	MVA -BN	2005	USA	Subcutaneous	1, 2	151	≥ 18 < 55	NCT00189904
17.	Imvamune (JYNNEOS)	MVA -BN	2005	Switzerland	Subcutaneous	2	165	≥ 18 < 30	NCT00189956
18.	ACAM3000/Dryvax	MVA and Vaccinia	2005	USA	IM/SC/ID	1, 2	72	≥ 18 < 38	NCT00133575
19.	Smallpox Vaccine (LISTER Strain)	Vaccinia	2005	France	Scarification	2	230	≥ 18 < 25	EUCTR2005-002175-32-FR
20.	Smallpox Vaccine (LISTER Strain)	Vaccinia	2006	France	Not indicated	N/A	147	≥ 18 < 25	NCT00998543
21.	Imvamune (JYNNEOS)	MVA -BN	2006	USA	Subcutaneous	2	581	≥ 18 < 55	NCT00316589
22.	Imvamune (JYNNEOS)*	MVA -BN	2006	Germany	Subcutaneous	2	745	≥ 18 < 55	NCT00316524*
23.	Smallpox Vaccine (LISTER Strain)	Vaccinia	2006	France	Scarification	2	230	≥ 18 < 25	EUCTR2006-000715-19-FR*
24.	Imvamune (JYNNEOS)*	MVA -BN	2006	Unknown	Subcutaneous	2	745	≥ 18 < 55	EUCTR2005-001781-14-DE*
25.	MVA3000	MVA	2006	USA	Subcutaneous	1	2	≥ 18 < 35	NCT00282581

Table 5. (Continued)

Order	Vaccine(s)	Type of Platform	Year Start	Participant Location	Route of administration	Phase	Sample Size (n)	Age (years)	Trial Registration
26.	Imvamune (JYNNEOS) and Dryvax	MVA -BN; and Vaccinia	2007	USA	Scarification and subcutaneous	1, 2	206	≥ 18 < 38	NCT00437021
27.	ACAM2000	Vaccinia	2008	USA	Subcutaneous	4	14108	≥ 17	NCT00928577
28.	ACAM2000	Vaccinia	2008	USA	Subcutaneous	4	897227	≥ 17	NCT00927719
29.	CJ-50300	Vaccinia	2009	South Korea	Not indicated	3	88	≥ 19 < 60	NCT01056770
30.	Imvamune (JYNNEOS)	MVA -BN	2009	USA	Subcutaneous	2	91	≥ 18 < 38	NCT00879762
31.	Imvamune (JYNNEOS)	MVA -BN	2009	USA	Subcutaneous	2	120	≥ 56 < 38	NCT00857493
32.	CJ-50300	Vaccinia	2010	South Korea	Not indicated	3	145	> 32 -< 60, born < 1979	NCT01317238
33.	ACAM2000 for VIVIG production	Vaccinia	2010	USA	Percutaneous scrarification	3	25	≥ 18 < 65	NCT01158157
34.	Imvamune (JYNNEOS)	MVA -BN	2010	Germany	Subcutaneous	2	100	≥ 18 < 65	EUCTR2010-018334-51-DE
35.	Imvamune (JYNNEOS)	MVA -BN	2010	USA	Intradermal/ Subcutaneous	2	523	≥ 18 < 38	NCT00914732
36.	Imvamune (JYNNEOS)	MVA -BN	2010	USA	Subcutaneous	4	22	≥ 18 < 65	NCT03472014
37.	Imvamune (JYNNEOS)	MVA -BN	2013	Germany	Subcutaneous	2	342	< 12 years	EUCTR2012-005137-37-DE
38.	Imvamune (JYNNEOS)	MVA -BN	2013	USA	Subcutaneous	2	651	≥ 18 < 55	NCT01668537
39.	Imvamune (JYNNEOS)	MVA -BN	2013	USA	Subcutaneous	3	4005	≥ 18 < 40	NCT01144637
40.	LC16m8	Vaccinia	2014	Japan	Scarification	1	50	≥ 20	JPRN-jRCTs 031220171
41.	LC16m8	Vaccinia	2014	Japan	Scarification	2	150	> 1	JPRN-jRCTs 031220137
42.	Imvamune (JYNNEOS)	MVA -BN	2014	USA	Subcutaneous	2	87	≥ 18 < 45	NCT02038881
43.	ACAM2000	Vaccinia	2015	Canada	Percutaneous scrarification	4	3032	≥ 18 < 65	NCT02443623
44.	ACAM2000 and Imvamune	Vaccinia and MVA-BN	2015	South Korea	Subcutaneous	3	440	≥ 18 < 42	NCT01913353
45.	Imvamune (JYNNEOS)	MVA -BN	2017	Democratic Republic of the Congo	Subcutaneous	3	1600	≥ 18	NCT02977715
46.	Imvamune (JYNNEOS)	MVA -BN	2018	UK	Subcutaneous	N/A	120	≥ 18	NCT03745131

Table 5. (Continued)

Order	Vaccine(s)	Type of Platform	Year Start	Participant Location	Route of administration	Phase	Sample Size (n)	Age (years)	Trial Registration
47.	VACΔ6 vaccine	Vaccinia	2019	Russia	Subcutaneous	1	60	≥ 18 < 40	NCT05762523
48.	Freeze-dried (FD) MVA-BN smallpox vaccine	MVA -BN	2019	USA	Subcutaneous	3	1129	≥ 18 < 45	NCT03699124
49.	VACΔ6 vaccine	Vaccinia	2021	Russia	Intradermal	2, 3	334	≥ 18 < 60	NCT05846243
50.	Imvamune (JYNNEOS)	MVA -BN	2022	USA	Subcutaneous	2	229	≥ 18 < 50	NCT05512949
51.	Imvamune (JYNNEOS)	MVA -BN	2022	USA	Subcutaneous	N/A	300	≥ 18	NCT05654883
52.	Imvamune (JYNNEOS)	MVA -BN	2022	Spain	Subcutaneous	N/A	100	≥ 18	NCT05562323
53.	Mpox vaccine	Any	2022	Chile, Panama, Peru, Spain	Any	N/A	4638*	≥ 18	NCT05522296
54.	IMVANEX, JYNNEOS	MVA-BN	2022	France	Subcutaneous	N/A	300	≥ 18	NCT05438953
55.	Imvamune (JYNNEOS)	MVA -BN	2022	France	Subcutaneous	N/A	330	≥ 18	NCT05627713
56.	Smallpox Vaccine	MVA-BN	2022	Belgium	Any	N/A	345	≥ 18	NCT05879965
57.	Imvamune (JYNNEOS)	MVA -BN	2023	USA	Subcutaneous	2	400	≥ 12–17** vs ≥ 18 < 50	NCT05740982
58.	Imvamune (JYNNEOS)	MVA -BN	2023	Germany	Subcutaneous	3	15000*	≥ 18	DRKS00029638
59.	Imvamune (JYNNEOS)	MVA -BN	2023	Democratic Republic of the Congo	Subcutaneous	4	500	≥ 18	NCT05734508
60.	Imvamune (JYNNEOS)	MVA -BN	2023	Brazil	Subcutaneous	4	746	≥ 15	RBR-10mpz6sd
61.	LC16m8 Vaccine	LC16m*	2023	Colombia	Scarification	3, 4	8686*	≥ 18 <55	NCT06223919
62.	BNT166a	mRNA	2023	USA, UK	IM	1, 2	64	1-45**, and 50-65	NCT05988203
63.	mRNA-1769	mRNA	2023	UK	IM	1, 2	351	18-49	NCT05995275
64.	Imvamune (JYNNEOS) as PEP Vaccination***	MVA -BN	2024	Democratic Republic of the Congo, Nigeria, Uganda	Subcutaneous	4	1560	≥2	NCT05745987
65.	MVA-BN	MVA-BN	2024	Unknown	Subcutaneous	2	460	2 -< 12** vs adults up to 50	NCT06549530

*Recent large scale studies, (Recent = since 2019)
**Recent studies included children and adolescent younger than 18 years old,
***Recnet study to investigate the efficacy of PEP

Licensure of future Mpox and Smallpox vaccines

The licensure of future Mpox and smallpox vaccines is anticipated to follow similar regulatory pathways as the currently approved vaccines, MVA-BN (Bavarian Nordic) and LC16m8 (KM Biologics). Both of these vaccines were approved based on surrogate endpoints, particularly lethal-challenge studies in nonhuman primates (NHPs), rather than traditional efficacy studies in humans.[19] Current Licensure Approach: MVA-BN (JYNNEOS), approved as a pre-exposure prophylaxis (PrEP) for Mpox in various countries, MVA-BN has demonstrated real-world effectiveness against clade IIb Mpox infections. It is replication-deficient, making it a safer option, especially for immunocompromised individuals and those in pediatric populations. LC16m8, a live-attenuated, replication-competent vaccine with more data in pediatric populations, LC16m8 has been approved based on its ability to induce protection in lethal animal challenge studies against clade I Mpox and other orthopoxviruses. Both vaccines have solid safety profiles, and their effectiveness against the more lethal clade I Mpox virus is inferred largely from animal studies, which simulate lethal viral challenges.

Challenges for novel Mpox vaccines approval

For future novel Mpox and smallpox vaccines, obtaining licensure may be challenging without traditional human efficacy trials. However, the regulatory approach is likely to continue relying on surrogate outcomes (e.g., animal challenge models), as seen with MVA-BN and LC16m8.

Given the absence of universally defined immune correlates of protection (CoP) for Mpox and smallpox, researchers are turning to markers such as 1) neutralizing antibodies; these are considered an important immune marker, as they can block the virus from entering host cells and 2) T-cell responses; $CD4^+$ and $CD8^+$ T cells are also believed to play a key role in mediating protection against both viruses.

Regulatory trends and future vaccine licensure

The success of the MVA-BN and LC16m8 vaccines, along with the use of immunobridging for other diseases (e.g., COVID-19),[38] suggests that regulators may approve new Mpox vaccines based on immunogenicity data and animal model efficacy in the future. The use of immune correlates of protection as has been applied in recent COVID-19 vaccine approvals, could help pave the way for novel Mpox vaccines to achieve licensure without requiring large-scale human efficacy trials.[39] Moreover, randomized controlled efficacy trials and real-world effectiveness studies are ongoing to further strengthen data, especially in underrepresented populations such as children, pregnant women, and immunocompromised individuals.

In summary, The future licensure of Mpox and smallpox vaccines is likely to continue leveraging data from animal studies and immune correlates, particularly in the absence of traditional efficacy trials. Regulatory authorities may increasingly rely on approaches similar to those used in the approval of COVID-19 vaccines, including the use of immunobridging and surrogate markers like neutralizing antibodies and T-cell responses.

Global access to Mpox vaccines: Lesson learned from the COVID-19 pandemic

Vaccine access disparities, which have persisted for decades, were starkly highlighted during the COVID-19 pandemic. Unfortunately, similar issues are expected to arise with Mpox vaccines. High-income countries, particularly those that develop and produce effective vaccines, often provide widespread and timely immunization for their populations, resulting in overstocked reserves. In contrast, low- and middle-income countries (LMICs) frequently face delays of a year or more and suffer from insufficient vaccine coverage.[40] Various international efforts, along with initiatives at the national level, have attempted to address these challenges and advocate for transformative approaches to improve global vaccine access and prepare for future pandemics.[41-43] These efforts have led to increased infrastructure and capacity-building initiatives in LMICs, particularly in the areas of vaccine research, development, and manufacturing.[44,45] Looking ahead, novel approaches that involve joint international and national funding, as well as regional and global collaboration in vaccine development and production, offer promising and sustainable strategies to ensure equitable global vaccine access.[41-43] These strategies are essential for both pandemic and non-pandemic preparedness in the future.

In Summary, Mpox, though is less contagious than smallpox, has become a global health emergency. Currently approved vaccines in various countries are based on previous live-attenuated smallpox vaccines, both non-replicating and replicating. Initial approvals were primarily based on cross-protection in lethal challenge in animal models along with limited effectiveness data. Real-world evidence has further supported the safety and effectiveness of these vaccines. However, data on their use in children and PEP remain limited, and are currently being investigated in larger-scale prospective studies. There is a need for novel Mpox-specific vaccines with improved safety and immunogenicity profiles. Subunit and mRNA vaccines are in development with at least 2 mRNA vaccines in early-phase clinical trials. To overcome vaccine disparity and improve global access, transformative approaches are being implemented in various regions.

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