Monkeypox policy brief series

The WHO/Europe monkeypox (MPX) policy brief series summarizes policy recommendations, knowledge and interim technical guidance on key policy areas around the monkeypox public health emergency of international concern (PHEIC) in the WHO European Region. The first brief in the series provides an overarching set of considerations for the monkeypox response.

This second policy brief is aimed at decision makers and policy planners, including national immunization programme managers in the WHO European Region, and to be used as a reference for planning related to vaccination against monkeypox. It contains a description of available vaccines, brings together WHO and other international agencies’ recommendations, summarizes the vaccination strategies implemented by countries that were among the first to adopt such strategies in the WHO European Region and provides guidance on the decision-making process.

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Abbreviations

AEFI adverse event following immunization
ECDC European Centre for Disease Prevention and Control
GACVS Global Advisory Committee on Vaccine Safety
IHR International Health Regulations
MPXV monkeypox virus
MVA-BN Modified Vaccinia Ankara-Bavarian Nordic vaccine
NITAG national immunization technical advisory group
PrEP HIV pre-exposure prophylaxis
STI sexually transmitted infection
US FDA United States Food and Drug Administration
Background

Monkeypox is an infectious disease caused by the monkeypox virus (MPXV). This double-stranded DNA virus is a member of the Orthopoxvirus genus in the Poxviridae family and is related to the virus which caused smallpox (eradicated in 1980).

Monkeypox is a zoonotic disease. Human monkeypox cases have been reported since 1970, with rising frequency in recent years. Routes of human-to-human MPXV transmission include direct contact with infectious skin or mucocutaneous lesions, direct contact with respiratory droplets (and possibly short-range aerosols) through prolonged face-to-face contact or indirect contact through contaminated objects or materials, also described as fomite transmission. Vertical transmission (mother-to-child) has also been documented in previous outbreaks. The incubation period is usually from 6 to 13 days, but can range from 5 to 21 days (1).

From early May 2022 through 16 August 2022, a total of 19,429 cases of monkeypox were identified in 43 countries and areas in the WHO European Region. Based on case reports submitted by countries in the European Region, circulation has been ongoing since as early as March 2022.

Among cases for which age and/or gender is known, the largest proportion of cases were between 31 and 40 years old (7602/18917 – 40%) and male (16065/16241 – 98.9%). Among cases with known HIV status, 38% (2749/7322) were HIV-positive. Among cases that reported symptoms, the majority presented with a rash (8937/11587 – 77.1%) and systemic symptoms such as fever, fatigue, muscle pain, chills or headache (7495/11587 - 65%). 505 cases were hospitalized (5.8%), of which 179 cases required clinical care. Three cases were admitted to an intensive care unit, among whom one for reasons unrelated to monkeypox infection (2). The outbreak in the Region is being driven by close skin-to-skin contact occurring predominantly during sexual activity. Some (57) cases were reported to be health workers, however no occupational exposure has been reported (2). The current assessment is that occupationally acquired infections are rare in the presence of standard and transmission-based precautions and could be mitigated with implementation of appropriate infection prevention and control procedures during sample collection from skin lesions.

Monkeypox outbreak response relies on the combined impact of public health measures, including prevention, early detection, contact tracing, and isolation and care of patients. WHO has provided interim guidance on surveillance, investigation and contact tracing for monkeypox to ensure early detection and identification of those at risk and to break chains of transmission (3).

A monkeypox prevention and control strategy includes a vaccination component, tailored to the epidemiological context, availability of vaccines, and with consideration of individual risks and exposures.

1 WHO is currently following a process to formally rename the virus according to its mandate to assign names to new and existing diseases under the International Classification of Diseases.
Vaccines

Vaccines against smallpox are inferred to be effective in preventing or minimizing the severity of monkeypox based on available immunogenicity data from clinical studies and efficacy data from animal challenge studies. Some countries have maintained strategic stockpiles of first-generation smallpox vaccines. These vaccines are not recommended for monkeypox, as they do not meet current safety and manufacturing standards. Second- and third-generation smallpox vaccines are available for use against monkeypox. A protective immune response may not be elicited in all vaccine recipients.

*MVA-BN*

The third-generation live attenuated non-replicating smallpox vaccine, Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN) was approved as a smallpox vaccine in Canada and in the European Union in 2013. Approval was further extended to active immunization against both smallpox and monkeypox in the United States (2019), Canada (2020) and in the European Union (2022), as well as other countries. Several countries are currently in this approval process. The vaccine is made available under several brand names (Imvanex®, Imvamune® or Jynneos®) in different markets. MVA-BN is administered to adults as two 0.5 ml dose subcutaneous injections, separated by at least 28 days. Maximum immune response is reached 14 days after the second dose. The European Medicines Agency (EMA) has stated that national authorities may decide as a temporary measure to use Imvanex as an intradermal injection at a lower dose while supply of the vaccine remains limited (4). The United States Federal Drug Administration (US FDA) has issued emergency authorization for such a dose-sparing strategy of 0.1 ml (one fifth of the vial) to be administered intradermally, based on results of an immunogenicity study on healthy adults comparing this strategy against a standard subcutaneous dose (5).

*LC16m8*

The third-generation live attenuated replicating smallpox vaccine, LC16m8, manufactured by KM Biologics was licensed for active immunization against smallpox in Japan in 1975, but was not used in the national smallpox eradication programme because routine smallpox vaccinations were halted in the country in 1976. In 2022 the approval in Japan was extended for the prevention of monkeypox. LC16m8 generates neutralizing antibody titers to multiple poxviruses, including vaccinia, monkeypox, and variola major, and broad T-cell responses, indicating that it may have efficacy in protecting individuals. LC16m8 is the only smallpox vaccine approved for use in infants and children. Maximum immunity is reached 4 weeks after a single 0.01 ml dose, administered by the percutaneous route (scarification) through 15 punctures with a bifurcated needle.
**ACAM2000**

The second-generation live attenuated replicating smallpox vaccine, ACAM2000, is licensed by the US FDA for immunization against smallpox disease (6). It has been made available for the prevention of monkeypox disease under an Expanded Access Investigational New Drug application for individuals who decide in consultation with their health care provider that the potential benefits of vaccination outweigh potential risks from ACAM2000 adverse events (7).

Effectiveness of ACAM2000 against monkeypox is unknown, but it is suggested by one study (8) that its precursor, the first-generation vaccine Dryvax, was 85% effective against monkeypox. Maximum immunity is reached 4 weeks after a single dose, administered by the percutaneous route (scarification) through 15 punctures with a bifurcated needle.

Table 1 provides brief descriptions of vaccines approved for use against monkeypox and/or smallpox. Detailed information on the third- and second-generation vaccines is available in WHO Interim guidance on vaccines and immunization for monkeypox (9).

**Vaccine safety**

In 2015, the WHO Global Advisory Committee on Vaccine Safety (GACVS) reviewed the evidence on the safety of replicating and non-replicating smallpox vaccines (10). Based on this review, the GACVS continues to recommend that any use of smallpox vaccines be guided by the anticipated risk versus benefit presented during various outbreak or exposure scenarios.

**MVA-BN**

MVA-BN is characterized by its lower reactogenicity compared to other smallpox vaccines. The most common adverse reactions observed in clinical trials were injection site reactions, such as pain, erythema, swelling, induration and pruritus, and common systemic reactions, such as fever, headache, nausea, myalgia, chills and fatigue, which were mild to moderate in intensity and resolved without intervention within seven days following vaccination. There are no specific contraindications to this vaccine other than serious allergy to a vaccine component. Following vaccination, persons with atopic dermatitis may experience more intense local skin reactions and other general symptoms, as well as a flare-up or worsening of their skin condition.

**LC16m8**

The expected response to vaccination with LC16m8 is characterized by development of a vesicular or pustular reaction (‘take’) at the site of inoculation, resulting in a pitted scar after 14–21 days. LC16m8 is characterized by lower virulence and replication competency than the second-generation vaccine ACAM2000. The majority of vaccine recipients exhibit symptoms of local or systemic reactogenicity. Reported major reactions include axillary lymph node tenderness, tenderness at the inoculation site, swollen axillary lymph nodes and low-grade fever. Rare cases of rash, allergic dermatitis
and erythema multiforme suspected to have been caused by vaccination have been documented. Very rare cases of eczema vaccinatum, autoinoculation, vaccinia virus infection have been documented among 10 578 children, vaccinated in 1974, whose clinical symptoms could be observed. No vaccine-related serious adverse events associated with LC16m8 were identified in conducted clinical trials and studies (11, 12).

Studies in animal models have shown that LC16m8 protects the host against viral challenges and has a good safety profile, including low neurotoxicity and lack of severe adverse events in immunodeficient animals, which is markedly different from the first-generation vaccines.

No specific clinical evaluation of LC16m8 in immunocompromised (e.g., HIV-positive) individuals and/or those suffering from active skin barrier disorders that are linked to immune function (e.g., eczema) is available, therefore the LC16m8 vaccine should be used with caution in any person who is immunocompromised, has atopic dermatitis, or who has experienced an allergic reaction to any vaccine component. Anyone who is breastfeeding should consider continuation or discontinuation of breastfeeding basing on benefits and risks assessment.

The vaccine is contraindicated in people who have an illness causing severe abnormality in immune function or are undergoing immune-suppressive treatments, have generalized skin disease, are pregnant or have ever experienced anaphylaxis due to the components of the vaccine (product ingredients include gelatin, Streptomycin sulfate and erythromycin lactobionate) (13).

**ACAM2000**

ACAM2000 has a higher reactogenicity than the third-generation vaccines. The expected response to vaccination with ACAM2000 in primary vaccinees is the development of a major cutaneous reaction by day 6-8, which is considered as evidence of a successful ‘take’ and acquisition of protective immunity followed by development of a scar. However, any prior smallpox vaccination may modify (reduce) the cutaneous response upon revaccination. Virus is shed from the vaccination site during the period starting with the development of a papule (day 2−5); shedding ceases when the scab separates and the lesion is re-epithelialized, about 14−21 days after vaccination.

Common side effects of ACAM2000 include inoculation site reactions (erythema, pruritus, pain and swelling), lymphadenitis and systemic reactions, such as malaise, fatigue, fever, myalgia, and headache. Serious adverse events associated with ACAM2000 include rare progressive vaccinia, generalized vaccinia, skin infections, erythema multiforme including Stevens-Johnson syndrome, and eczema vaccinatum. Cardiac manifestations such as myocarditis and pericarditis and neurological manifestations, such as post-vaccinial encephalitis, encephalomyelitis or encephalopathy, have been reported.

ACAM2000 is contraindicated for anyone with a history of a severe allergic reaction to vaccine components (vaccine contains neomycin and polymyxin B) or who:

- has an immune deficiency disorder,
- has eye disease treated with topical steroids
• has three or more major cardiac risk factors (hypertension, diabetes, hypercholesterolemia, heart disease at age ≤50 years in a first-degree relative or smoking)
• has atopic dermatitis/eczema or other acute or exfoliative skin conditions,
• is pregnant or breastfeeding or
• is under 12 months of age.

The above groups are at an increased risk for serious problems if they become infected with the vaccine virus, either by being vaccinated or by being in close contact with a person who was vaccinated.

Safety and effectiveness of ACAM2000 have not been established in people under 16 years of age.

Vaccine supply

The third- and second-generation vaccines are procured nearly exclusively for national government reserves and not available for commercial use. The global supply of these vaccines is currently constrained. To ensure vaccine equity, WHO is establishing coordination mechanisms to maximize rapidity and efficiency in making vaccines available where they are needed.

Considerations for developing a monkeypox vaccination policy

Summary of current published and interim guidance and recommendations

Excerpts from WHO Interim guidance on vaccines and immunization for monkeypox (August 2022) (9)²:
• Mass vaccination for the general population is not recommended to control outbreaks of monkeypox at this time.
• Where appropriate second- or third-generation vaccines are available, post-exposure vaccination is recommended for contacts of cases based on risk of exposure assessment, ideally within four days of first exposure (and up to 14 days in the absence of symptoms). Experts believe that vaccination shortly after exposure may prevent the disease or make it less severe. Considerations for risk assessment of contacts of monkeypox cases are provided in the Interim guidance.
• Where appropriate second- or third-generation vaccines are available, primary preventive (pre-exposure) vaccination is recommended for individuals at high-risk of exposure including: individuals but not limited to those who self-identify as gay or bisexual or other men who have sex with men (MSM) or other individuals with multiple sexual partners; and health workers at high risk of exposure, laboratory personnel working with orthopoxviruses, clinical laboratory

² WHO Interim guidance of June 2022 is currently under review for possible revision and updating. Following publication of any global update, this policy brief on monkeypox vaccination in the WHO European Region will be updated accordingly.
personnel performing diagnostic testing for monkeypox, outbreak response team members (as designated by national public health authorities).

Excerpts from recommendations issued by the WHO Director-General based on the report of the Second meeting of the International Health Regulations (2005) (IHR) Emergency Committee regarding the multi-country outbreak of monkeypox (23 July 2022)(14):

- Consider the targeted use of second- or third-generation smallpox or monkeypox vaccines for post-exposure prophylaxis in contacts, including household, sexual and other contacts of community cases and health workers where there may have been a breach of personal protective equipment (PPE).
- Consider the targeted use of second- or third-generation smallpox or monkeypox vaccines for pre-exposure prophylaxis in persons at risk of exposure; this may include health workers at high risk of exposure, laboratory personnel working with orthopoxviruses, clinical laboratory personnel performing diagnostic testing for monkeypox and communities at high risk of exposure or with high-risk behaviours, such as persons who have multiple sexual partners.

Excerpts from European Centre for Disease Prevention and Control (ECDC) Rapid Risk Assessment (8 July 2022) (15):

Early diagnosis, isolation, effective contact tracing and vaccination strategies are key for the effective control of this outbreak.

- At this point, mass vaccination for monkeypox is not required nor recommended.
- When there is less effective tracing, mathematical modelling results indicate that targeted pre-exposure vaccination as prophylaxis for individuals at high risk would be the most effective strategy to use vaccines to control the outbreak. Prioritizing groups of men who have sex with men at higher risk of exposure, as well as front-line staff with a risk for occupational exposure should be considered in developing vaccination strategies.
- In settings with more effective contact tracing and higher vaccine uptake, post-exposure prophylaxis vaccination of close contacts of cases (e.g. sexual partners, household contacts, health care personnel and individuals with other prolonged physical or high-risk contact as defined by ECDC (16)) would be the most efficient vaccination strategy. Post-exposure prophylaxis vaccination of contacts and contacts of contacts, according to a ring vaccination scheme, could also be considered.

Current vaccination strategies in countries of the WHO European Region

To date, 22 countries of the WHO European Region offer post-exposure vaccination for people who had close contact with a monkeypox case. At least 15 countries currently offer or are planning to offer pre-exposure vaccination for people who can be exposed to orthopoxvirus in their work setting (certain laboratory personnel, health care and public health workers). At least 11 countries offer or plan to offer pre-exposure vaccination for people considered to be at highest risk of exposure (e.g., men who have
multiple male sexual partners, or sex workers). Among those at highest risk of exposure, some countries have placed particular focus on those who are at highest risk of severe complications (e.g., people with immune disorders).

Some strategies described by countries for identifying and reaching people at highest risk due to sexual practices include offering vaccination to people who regularly attend sexual health clinics, receive HIV pre-exposure prophylaxis (PrEP) and/or have a recently diagnosed sexually transmitted infection (STI); and offering vaccination to individuals determined by their primary care provider to be at high risk of exposure. Some countries have evaluated eligibility also based on self-reported behaviours linked to higher risk of exposure, such as sexual contact with multiple partners or attendance of group sex events or sex-on-premises venues. Prioritization of target groups is explicitly dependent on availability of vaccine and existing mechanisms to identify and reach those individuals who are at highest risk within each of the above categories. Some countries have prioritized administration of the first dose due to limited stock availability.

Experience in European countries to date with post-exposure vaccination of sexual and other high-risk contacts of monkeypox cases has revealed major challenges potentially limiting the effectiveness of this strategy. These include difficulties in identifying and reaching sexual contacts due to anonymity or reluctance to divulge partners due to stigma or other social and legal factors. In settings without highly effective contact tracing, modelling conducted by ECDC indicates that pre-exposure vaccination would be the most efficient and effective use of limited vaccine stock to prevent spread of monkeypox (16).

Factors to consider for decision making on pre- and post-exposure monkeypox vaccination strategies

Countries in the WHO European Region are in varied epidemiological stages of the outbreak, coinciding with the ‘groups’ described in the IHR Emergency Committee report (14). Their health care and immunization service delivery systems also vary widely. These factors will have significant bearing on the interventions and tools used in efforts to interrupt human-to-human transmission across the Region.

Countries should make decisions on vaccination of target groups against monkeypox, prioritize among these groups for effective use of available vaccines in the evolving context of limited global and national vaccine supply, and ensure equitable access to vaccines for people who are disproportionately affected by monkeypox. The decision-making process should involve each country’s national immunization technical advisory group (NITAG) and their national regulatory agency.

In order to design an appropriate vaccination strategy at service-delivery levels, all stakeholders within the Ministry of Health, other ministries and agencies, as well as other sectors of society including civil-society and community-based organizations should be involved, including groups and individuals relevant
to the current monkeypox outbreak that are not normally engaged in immunization-related policy issues, such as HIV/AIDS organizations and LGBTIQ+ advocacy groups.

Impactful allocation of resources will require vaccination strategies tailored to the national context that prioritize the highest-risk individuals and sub-groups among the broader at-risk populations.

Member States are encouraged to regularly revisit and revise these strategies.

Based on the available knowledge to date, the following factors could be considered for developing vaccination strategies:

- **Local epidemiology of monkeypox**, including number of probable and confirmed cases, clusters of cases, growth rate, hospitalizations and deaths in different populations, age groups and geographic locations. Consider potential limitations of data due to challenges with diagnostics, underreporting and/or limitations of case reporting forms (e.g., lack of nonbinary and transgender categories).

  In choosing target groups for prioritization, consider that:

  - while anyone can be infected with monkeypox regardless of gender or sexual identity, in the WHO European Region to date reported cases have been predominantly among men who have sex with men with multiple sexual partners (limited numbers of cases have been reported among other population groups, with no significant increase in growth rate);
  - self-reported risk factors may be useful to help identify individuals at the highest risk of exposure;
  - laboratory personnel working with orthopoxviruses, health care personnel who care for people with suspected or confirmed monkeypox, and health care personnel who administer replication-competent smallpox vaccines should be protected from the occupational risk of infection.

- **Evolving evidence on immunogenicity, effectiveness and safety of available smallpox and monkeypox vaccines; balance of risk from monkeypox disease compared to benefits/risks of the available vaccines for different population groups.**

- **Necessity of a joint risk-benefit analysis and shared clinical decision-making on vaccination between the individual and health care provider.**

- **Programmatic feasibility:**
  - Availability and rational use of different vaccine products

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3 LBGTIQ+ refers to lesbian, gay, bisexual, transgender, intersex and queer individuals.

4 Risk factors may include having multiple casual sexual contacts and/or sexual partners, attending sex on premises venues, ‘chemsex’ practices, occupational sex work (including occupational risk from work in sex on premises venues if personnel are regularly exposed to items (e.g. linens) or surfaces likely to be contaminated with body fluids or skin cells), use of HIV PrEP, or proxy markers such as recent STIs. (‘Chemsex’ refers to use of drugs that enhance or disinhibit sexual experiences, and which may be associated with riskier sexual behaviours.)
Feasibility and effectiveness of providing pre- and post-exposure vaccination to target populations.

- In prioritizing pre- and post-exposure vaccination strategies, consider that experience in the European Region to date has revealed limited capacity of many public health systems to identify contacts of monkeypox cases and reach them with post-exposure vaccination.
- In collaboration with relevant stakeholders and disease programmes within the Ministry of Health and other relevant ministries, consider whether existing mechanisms (such as sexual health clinics, HIV PrEP centres and outreach through community-based organizations) would be effective in reaching a large proportion of the highest-risk groups being targeted, or if there is a need to establish new vaccine delivery strategies.

- Required training of health care workers on administration of MVA-BN vaccine using subcutaneous injection or intradermal injection for fractionated dosing, and/or on the use of bifurcated needles for administration of ACAM2000 and LC16m8 vaccines.
- Availability of trained staff and appropriate injection materials for intradermal injection for possible implementation of the MVA-BN dose-sparing strategy.

- Necessity of an effective and tailored communications and advocacy strategy that is based on behavioural insights and designed and implemented in partnership with communities and groups that are disproportionately affected as well as diverse partners already working with affected populations.
  - Such a strategy could include community outreach, education efforts and communication through multiple, appropriate channels focused on behavioural strategies to minimize risk of exposure, eligibility for vaccination, and risk and benefits of vaccination.
  - Innovative communications approaches may be needed, such as partnering with “dating apps” to disseminate prevention messages, including on monkeypox vaccination.

- Need to strengthen surveillance for adverse events following immunization (AEFIs) to ensure timely detection, reporting and causality assessment of all AEFIs following vaccination against monkeypox. Countries should also ensure timely reporting of AEFIs to the WHO global database.

The European Technical Advisory Group of Experts on Immunization will provide more detailed recommendations for NITAGs on monkeypox vaccination in due course.


Annexes

Annex 1: Description of vaccines approved for use against monkeypox and/or smallpox

<table>
<thead>
<tr>
<th>Smallpox vaccines</th>
<th>Description</th>
<th>Dose schedule</th>
<th>Administration method and presentation</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVA-BN (Bavarian Nordic)</td>
<td>Non-replicating vaccinia-based vaccine, third generation, authorized for smallpox and monkeypox.</td>
<td>Two doses, four weeks apart</td>
<td>Needle and syringe (sub-cutaneous administration with 0.5 ml or intra-dermal administration with 0.1 ml). Liquid frozen or lyophilized single-dose (0.5 ml vials).</td>
<td>There are no known specific contraindications for administering to persons with immune deficiencies, immunosuppression therapies, atopic dermatitis, who are pregnant or breastfeeding, or children.</td>
</tr>
<tr>
<td>LC16m8 (KM Biologics)</td>
<td>Minimally-replicating vaccine, third generation, authorized for smallpox and monkeypox.</td>
<td>Single dose</td>
<td>Bifurcated needle. Lyophilized multidose vials, containing after reconstitution with 0.5 ml of diluent, approximately 50 nominal doses of 0.01 ml of vaccinia virus (live).</td>
<td>Contraindicated in persons with an immunodeficiency or who is pregnant. Approved for use in infants and children. Was used to inoculate about 50,000 children in 1974 in Japan; in 10,578 of them clinical symptoms were observed.</td>
</tr>
<tr>
<td>ACAM2000</td>
<td>Replicating vaccine, second generation, authorized only for smallpox</td>
<td>Single dose</td>
<td>Bifurcated needle. Lyophilized multidose vials, containing after reconstitution with 0.3 ml of diluent, approximately 100 nominal doses of 0.0025 ml of vaccinia virus (live).</td>
<td>Contraindicated in persons with an immunodeficiency, pregnant and breastfeeding women, and infants and young children. Significant adverse event profile (e.g. cardiac and neurological manifestations).</td>
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Annex 2: Current knowledge gaps

- Data and evaluation on effectiveness of smallpox and monkeypox vaccines in pre- and post-exposure vaccination for preventing monkeypox infection, preventing severe symptoms and interrupting secondary transmission
- Correlates of protection
- Duration of protection after a complete vaccine dose series
- Effectiveness of alternative schedules, including interchangeability of full and fractionated doses, and one-dose schedules (full or fractionated) for MVA-BN compared to two full-dose schedule for both pre-exposure and post-exposure vaccination
- Safety of MBA-BN vaccine in broad range of immunocompromised groups, pregnant and breastfeeding people, children
- Co-administration with COVID-19 and other vaccines (e.g. feasibility, timing, spacing and safety)
- Population perceptions related to monkeypox and acceptance of vaccination to prevent the diseases
- Effective vaccination delivery strategies in various contexts to target highest-risk groups without generating stigma and discrimination
- Possible need for revaccination or booster doses for people (pre- or post-exposure vaccination) who have previously received smallpox vaccination