World Health Organization

Vaccines and immunization for monkeypox

Interim guidance

16 November 2022

Contents

Executive Summary

The overarching goal of the global response to monkeypox is to stop the multi-country outbreak by interrupting human-to-human transmission, to protect vulnerable groups at risk of severe monkeypox disease and to minimize zoonotic transmission of monkeypox virus. Judicious use of vaccines can support this response. This interim guidance provides WHO recommendations on use of vaccines for monkeypox. This version of the guidance has been endorsed by the WHO Strategic Advisory Group of Experts on Immunization (SAGE) in October 2022.

General

- Monkeypox is an infectious disease caused by the monkeypox virus. This double-stranded DNA virus is a member of the *Orthopoxvirus* genus in the *Poxviridae* family, related to the virus which caused smallpox (eradicated in 1980).
- On 23 July, 2022 WHO declared the global monkeypox outbreak to be a public health emergency of international concern (PHEIC).
- Control of monkeypox outbreaks primarily relies on public health measures including surveillance, contact-tracing, isolation and care of patients for which vaccination is recommended as complementary intervention as outlined in these recommendations.
- Some interim vaccination recommendations provided here concern off-label use[1].

Summary of interim recommendations

- Based on currently assessed risks and benefits and regardless of vaccine supply, mass vaccination is not required nor recommended for monkeypox at this time.
- Human-to-human spread of monkeypox can be controlled by public health measures including surveillance, early case-finding, diagnosis and care, isolation and contact-tracing, and self-monitoring by contacts.
- In managing the response, vaccination should be considered an additional measure to complement primary public health interventions.
- All decisions around immunization with smallpox or monkeypox vaccines should be by shared clinical decision-making. At an individual level, vaccination should not replace other protective measures.
- Primary preventive (pre-exposure) vaccination (PPV): PPV is recommended for individuals at high-risk of exposure. Persons at highest risk of exposure in the current multi-country outbreak are gay, bisexual or other men who have sex with men (MSM) with multiple sexual partners. Others at risk may include individuals with multiple casual sexual partners; sex workers; health workers at risk of repeated exposure, laboratory personnel working with *orthopoxviruses*; clinical laboratory and health care personnel performing diagnostic testing for monkeypox; and outbreak response team members.

[1] The recommendations contained in this publication are based on the advice of independent experts who have considered the best available evidence, a risk–benefit analysis and other factors, as appropriate. This publication may include recommendations on the use of medicinal products for an indication, in a dosage form, dose regimen, population or other use parameters that are not included in the approved labelling. Relevant stakeholders should familiarize themselves with applicable national legal and ethical requirements. WHO does not accept any liability for the procurement, distribution and/or administration of any product for any use.

- The level of risk of exposure may vary between the groups and could be used in countries for prioritization in case of limited vaccine supply.
- Post-exposure preventive vaccination (PEPV) is recommended for contacts of cases ideally within four days of first exposure (and up to 14 days in the absence of symptoms).

Introduction

In April 2022, a Strategic Advisory Group of Experts (SAGE) on Immunization Working Group on smallpox and monkeypox vaccines was established to advise the World Health Organization (WHO) on the use of monkeypox vaccines and update the 2013 recommendations on the use of smallpox vaccines.[2]

This updated interim guidance has been developed on the basis of the advice issued by SAGE at its meeting on 4 October 2022. This guidance builds on initial interim guidance published on 24 June and updated on 24 August 2022.

Changes from earlier version

This is an updated version of the interim guidance on vaccines and immunization for monkeypox published on 24 August 2022. The current version is based on GRADEd evidence of a rapid review performed by WHO. The rapid review evaluated the safety, immunogenicity, efficacy and effectiveness of smallpox vaccines (ACAM2000, MVA-BN, LC16) against monkeypox (MPX) in subjects with high risk of exposure to monkeypox virus (MPXV), with emphasis on different population groups. The rapid review investigated the effects of vaccines when used as primary preventive (pre-exposure) vaccination (PPV) of persons with a high risk of exposure to MPX and post-exposure preventive vaccination (PEPV) of close contacts of MPX cases, as defined in the WHO interim guidance on Surveillance, case investigation and contact-tracing.

Methods

This guidance is based on the results of a rapid review and quality appraisal of the retrieved literature, conducted July-September 2022. The full rapid review as well as the GRADE and Evidence to Decision tables are available on the SAGE website.

Declarations of interest were solicited from all external contributors and assessed for any conflicts of interest. The composition of SAGE and a summary of the declared interests of members can be found on the SAGE website. The composition and their declared interests of the Working Group on Smallpox and monkeypox vaccines can be found here.

Background

While monkeypox is a zoonotic disease, human cases of monkeypox have been reported since 1970, with rising frequency in recent years. Two clades of monkeypox virus have been identified, Clade I

[2] Meeting of the Strategic Advisory Group of Experts (SAGE) on Immunization. November 2013: conclusions and recommendations. Available at www.who.int/publications/i/item/WER8901https://www.who.int/publications/i/item/WER8901, accessed 3 August 2022.

and Clade II.[3] While the ongoing 2022 monkeypox multi-country outbreak has been associated with Clade II of monkeypox virus, which is less virulent than Clade I, historically outbreaks have been driven by Clade II and Clade I. From 1 January to 7 October 2022, over 71237cases of monkeypox and 26 deaths have been reported to WHO from over 107 countries/areas or territories from all 6 WHO regions. Currently, most cases reported are MSM in connected social and sexual networks.

Currently, there are three vaccines considered in the response to the ongoing monkeypox outbreak. All three vaccines were developed against smallpox, and evidence of their protection against monkeypox is overall limited. These are ACAM2000, a second-generation smallpox vaccine, and two third-generation vaccines, MVA-BN and LC16. All three vaccines have been approved in several jurisdictions for prevention of monkeypox. There are supply constraints in some countries at this time, owing to several issues including regulatory, policy, price, product preference, and supply availability issues.

Some countries have maintained strategic supplies of smallpox vaccines procured for the Smallpox Eradication Programme (SEP) which concluded in 1980. These first-generation vaccines, held in national reserves, are not recommended for monkeypox at this time, as they do not meet current safety and manufacturing standards.

Key evidence is summarized in the background document on vaccines and immunization for monkeypox and can be found here.

General goal and principles for the use of vaccines against monkeypox

The overarching goal of the global response to monkeypox is to stop the multi-country outbreak by interrupting human-to-human transmission (with a focus on population groups at high risk of exposure), to protect vulnerable groups at risk of severe monkeypox disease and to minimize zoonotic transmission of monkeypox virus. Vaccines against monkeypox can support this response.

Further to the Temporary Recommendations issued by the Director-General, WHO proposes the following principles to underpin the recommendations *(1)*:

- The WHO interim guidance should be broad to guide national authorities in development of their own monkeypox vaccination policies and strategies to support readiness and response.
- In 2013, WHO provided recommendations on the use of smallpox vaccines. These additional updated interim recommendations from WHO apply to the prevention and control of monkeypox only. They will be updated as more information becomes available.
- Established principles of human rights, inclusion and the dignity of all individuals and communities should support the planning for and implementation of these recommendations.

Summary of the evidence

Vaccine performance

A rapid review undertaken by WHO identified 39 studies that evaluated the safety, immunogenicity and effectiveness of smallpox vaccines (MVA-BN, LC16 and ACAM2000) against monkeypox in subjects with high exposure to MPX virus, with emphasis on different population groups. For

[3] Clade I of monkeypox virus was previously known as the Congo Basin or Central African clade and Clade II was previously known as the West African clade. Monkeypox: experts give virus variants new names (who.int).

detailed information see the background document on vaccines and immunization for monkeypox here.

The rapid review found no peer-reviewed clinical studies evaluating the clinical effectiveness of primary preventive vaccination with MVA-BN, LC16 and ACAM2000 versus no vaccination against monkeypox.

However, a recent preprint, published on 23 September 2022, indicated that one dose of MVA-BN was effective in preventing monkeypox infections. The study recruited male subjects at high risk for monkeypox virus infection and commenced on 31 July 2022, when the vaccination campaign was initiated, and participants were followed until 12 September 2022 *(2)*. 1,970 subjects of whom 873 (44%) were vaccinated with one dose of MVA-BN, completed at least 25 days of follow-up. 18 infections were confirmed in the study cohort, 3 in vaccinated and 15 in unvaccinated persons (40.0 versus 6.4 per 100,000 person days). VE was estimated at 79% (95% CI: 24%-94%).

The effectiveness of vaccines against monkeypox is further inferred from indirect evidence and animal studies.

Indirect surveillance data in the Democratic Republic of the Congo (2005–2007) indicated that among individuals born before 1980 (end of the official national mass smallpox vaccination program), people vaccinated against smallpox with first generation vaccines had a 5.2-fold lower risk of monkeypox than those unvaccinated (0.78 vs. 4.05 per 10,000), which represented a smallpox pre-exposure vaccine effectiveness against monkeypox of 80.7% (95% CI: 68.2–88.4%) *(3)*.

Protective efficacy of vaccines was also evaluated in various animal studies using mouse, rabbit and monkey models. Data from these studies demonstrated that mice, rabbits and monkeys were protected against lethal challenges with monkeypox virus when immunized with smallpox vaccines (see background paper).

Vaccine safety

MVA-BN

Local and systemic adverse events (AE) were frequently reported in MVA-BN vaccinees (up to 99%). However, there were no cases of myopericarditis or serious adverse events (SAE) requiring hospitalization reported among 9713 MVA-BN vaccinees from 19 clinical studies (see background paper).

ACAM2000

Information regarding the safety of ACAM2000 has been derived from clinical trial experience and observational studies including military personnel. ACAM2000 safety data from large population-based programs is limited.

Local and systemic AE in ACAM2000 vaccinated subjects were very frequently reported in up to 99% of the vaccinated subjects. Although AE were generally mild to moderate, ACAM2000 can be associated with rare but serious AE, such as myopericarditis. The rapid review reported a total of 269 cases of myocarditis across 8 studies (n=1,743,620 vaccinees, or an estimate based on these

studies of 15.4 cases per 100,000 doses). Five cases of generalized vaccinia, one case of eczema vaccinatum, one case of progressive vaccinia and five cases of autoinoculation were reported in four studies (n=843,744 vaccinees, overall 1.4 events per 100,000 doses) (see background paper).

LC16

The safety of LC16 was described in one RCT and two cohort studies *(4-6)*. Local and systemic AE in LC16 vaccinees were very frequent (reported in up to 99% of the vaccinees) but mild to moderate. Myopericarditis, pericarditis or myopericarditis were not detected while serious vaccine-related AE were very rare or not present (see background paper).

The rapid review undertaken by WHO found one phase III, open-label RCT that randomised 440 vaccine-naive participants to two doses of MVA-BN followed by ACAM2000 (n=221) versus one dose of ACAM2000 alone (n=219), comparing MVA-BN (via subcutaneous route) with ACAM2000. Based on the results of this one RCT, MVA-BN is likely associated with fewer local and systemic AE compared to ACAM2000. Analysis based on the same RCT was not powered to detect differences in the risk of myopericarditis or other serious adverse events (SAE) between MVA-BN and ACAM2000 vaccinees *(7)*.

The vaccine safety profiles vary by product and need consideration when deciding on the choice of vaccine (see recommendation 3).

Recommendations

Recommendation 1: Primary preventive (pre-exposure) vaccination (PPV)

Primary preventive (pre-exposure) vaccination (PPV) is recommended for groups at high risk for exposure to monkeypox in the current multi-country outbreak.

Persons at highest risk of exposure in the current multi-country outbreak are gay, bisexual or other men who have sex with men (MSM) with multiple sexual partners. Others at risk may include individuals with multiple casual sexual partners; sex workers; health workers at risk of repeated exposure; laboratory personnel working with *orthopoxviruses*; clinical laboratory and health care personnel performing diagnostic testing for monkeypox; and outbreak response team members (as designated by national public health authorities). The level of risk of infection may vary between the groups and could be used by countries for prioritization in case of limited vaccine supply.

For groups at risk of developing more severe disease if they are infected with monkeypox virus, including children, pregnant women and immunocompromised persons, vaccination against monkeypox as a PPV measure is not recommended on the basis of their higher risk of severe disease. If, however, they are at high risk of exposure, persons in these groups should be prioritized for PPV.

Specific considerations apply as to vaccine choice for special population groups at high risk of severe disease (see Recommendation 3 on vaccine choice).

Mass vaccination is not recommended for outbreaks of monkeypox at this time, and vaccination is not recommended for the general public.

Recommendation 2: Post-exposure preventive vaccination (PEPV)

Post-exposure preventive vaccination (PEPV) is recommended for contacts of cases, ideally within four days of first exposure (and up to 14 days in the absence of symptoms). (Criteria to assess risk of exposure can be found under implementation considerations.)

Children, pregnant women and immunocompromised persons may be at risk of developing more severe disease when infected with monkeypox virus. In case of limited vaccine supply, these populations, if exposed, should be offered vaccination in priority.

Specific considerations apply as to vaccine choice for special population groups at high risk of severe disease (see Recommendation 3 on vaccine choice).

Recommendation 3: Choice of vaccine and vaccination for special populations

For healthy adults, non-replicating vaccine (MVA-BN), minimally replicating vaccines (LC16) or replicating vaccinia-based vaccines (ACAM2000) are appropriate for use.

MVA-BN is administered as a 2-dose subcutaneous injection (0.5ml dose) given at least 4 weeks apart. LC16 and ACAM2000 are both administered as a single dose using the scarification method with a bifurcated needle.

For individuals for whom replicating (such as ACAM2000) or minimally replicating (LC16) vaccine is contraindicated (i.e. severe immune deficiency), the non-replicating (MVA-BN) should be used; likewise for individuals for whom there are warnings or precautions because of e.g. immunosuppression therapies or atopic dermatitis, the non-replicating (MVA-BN) vaccines should be used.

Vaccine recipients must be informed that the level and duration of protection is currently unknown, and that it takes approximately 2 weeks from time of finalizing a complete series (2 doses) of vaccination with MVA-BN for peak immunity to develop. For the minimally and non-replicating vaccines peak immunity is expected to occur 4 weeks after vaccination (1 dose).

Immunocompromised persons, including people living with HIV

For purposes of this interim guidance, immunocompromised persons include those with active cancer, transplant recipients, immunodeficiency, and active treatment with immunosuppressives. It also includes people living with HIV (PLWH) with a current CD4 cell count of <200 cells µl. Persons with immune suppression, who are at high risk of infection or who are exposed to a monkeypox case should be prioritized for MVA-BN vaccination. Vaccination should follow a careful evaluation of risks and benefits and shared decision-making between the individual and their health care provider.

According to the package leaflet, the use of ACAM2000 is contra-indicated in persons with severe immune deficiency. Severe localized or systemic infection with vaccinia (progressive vaccinia) may occur in persons with weakened immune systems. The use of LC16 is contra-indicated in persons with severe immune deficiency or medical treatment that results in immune suppression.

The WHO rapid review found no clinical studies on MVA-BN focusing on this population. However, a study in 24 hematopoietic stem cell transplant recipients concluded that MVA-BN was safe, well tolerated, and immunogenic in hematopoietic stem cell transplant recipients *(8)*. A phase II trial evaluating three MVA-BN dosing regimens for safety, tolerability, and immunogenicity in persons with HIV who had a history of AIDS, concluded that MVA-BN was well tolerated and immunogenic among the study participants *(9)*.

Pregnancy

During pregnancy, where consideration is given to primary or post-exposure preventive vaccination, non-replicating vaccine (MVA-BN) should be used. ACAM2000 should not be used in pregnancy. Live vaccinia virus vaccines can cause fetal harm when administered to a pregnant woman. Congenital infection, principally occurring during the first trimester, has been observed after

vaccination with live vaccinia smallpox vaccines, although the risk may be low. Generalized vaccinia of the fetus, early delivery of a stillborn infant, or a high risk of perinatal death has been reported. Pregnant women who are close contacts of ACAM2000 vaccinees may be at increased risk because live vaccinia virus can shed and be transmitted to close contacts.

There are no data available to assess the risk of minimally replicating (LC16) vaccines in pregnant women. No development and reproductive toxicology studies have been performed.

Available human data on MVA-BN administered to pregnant women are insufficient to determine vaccine-associated risks in pregnancy. However, four development and reproductive toxicology animal studies in rats and rabbits have shown no evidence of harm to the fetus. In addition, safety in pregnant women has been shown for the MVA vectored Ebola vaccine Mvabea® (MVA-BN-Filo). MVA-BN can be used in pregnant women when the benefits of vaccination to the pregnant woman outweigh the potential risks. To help pregnant women make this assessment, they should be provided with information about the risks of monkeypox virus infection in pregnancy, the potential benefits of vaccination in the local epidemiological context and the current limitations of the safety data in pregnant women.

Breastfeeding women

For women who are breast-feeding, where consideration is given to primary or post-exposure preventive vaccination, non-replicating (MVA-BN) vaccines should be used. ACAM2000 should not be used in lactating women. It is not known whether vaccine virus or antibodies are secreted in human milk but live vaccinia virus can be inadvertently transmitted from a lactating mother to her infant.

There are no data available to assess the risk of minimally replicating (LC16) vaccines in breast-feeding women.

MVA-BN vaccine can be used in breastfeeding women. This is based on the following considerations: breastfeeding offers substantial health benefits to breastfeeding women and their breastfed children. Data are not available on the potential benefits or risks of the MVA-BN vaccine to breastfed children. However, safety in pregnant women has been shown for the MVA vectored Ebola vaccine Mvabea® (MVA-BN-Filo). In addition, as MVA-BN vaccine is a non-replicating live virus vaccine, it is biologically and clinically unlikely to pose a risk to the breastfeeding child. WHO does not recommend discontinuing breastfeeding because of vaccination.

Infants and children

For children, where consideration is given to vaccination for post-exposure preventive vaccination, non-replicating (MVA-BN) or minimally replicating (LC16) vaccines should be used. LC16 has been authorized for children in Japan, and MVA-BN has obtained emergency use authorization in children in the USA. However, in most countries, MVA-BN is approved for 18 years and above. Use in children in those countries would be off-label.

While MVA-BN has not been specifically studied in a clinical trial in children, the same non-replicating MVA viral vector is used as a platform for other vaccines including MVA-BN-filo (marketed as Mvabea®) against Ebola virus disease (EVD). This EVD vaccine is approved in the European Union for adults and children aged one year and older.

MVA-BN can be used in children when the benefits of vaccination to children outweigh the potential risks. To help parents make this assessment, they should be provided with information about the risks of monkeypox virus infection in children, the potential benefits of vaccination in the local epidemiological context and the current limitations of the safety data in children.

ACAM2000 should not be used in infants. ACAM2000 has not been studied in infants or children. Infants are at high risk of developing serious complications from live vaccinia smallpox vaccination. Vaccinated persons who have close contact with infants, e.g., breastfeeding women, must take precautions to avoid inadvertent transmission of ACAM2000 live vaccinia virus to infants. LC16 has been authorized for children in Japan.

Vaccination in previously smallpox-vaccinated individuals

Some individuals, in particular older adults (>50 years), may have been vaccinated against smallpox vaccines in the context of global smallpox eradication (in general, before 1980).

WHO recommends that individuals, should they be eligible for PPV or PEPV, be vaccinated irrespective of previous smallpox vaccination and/or visible smallpox scar.

Recommendation 4: Vaccination in the case of limited supply

Prioritization

In case of limited vaccine supply, close contacts of monkeypox cases at risk of developing severe disease, such as children, pregnant women and immunocompromised persons, including those on immunosuppressive therapy or living with poorly controlled HIV, should be prioritized for receipt of vaccine following analysis of risks and benefits on a case-by-case basis.

In assessing eligibility for primary preventive (pre-exposure) vaccination, national authorities should consider who may be at high risk of exposure for infection and the possible nature of the exposure. As the level of risk varies between the different high-risk groups (see recommendation on PPV), vaccination strategies could prioritize groups for vaccination as determined by the local epidemiological context of monkeypox.

Implementation considerations

Dose sparing options

Based on a study published in 2015, that concluded that intradermal administration of MVA-BN was considered non-inferior to subcutaneous administration of MVA-BN *(10)*, the US FDA issued an Emergency Use Authorization (EUA) for the use of MVA-BN for the active immunization by intradermal injection (0.1ml) for the prevention of monkeypox disease amongst adults aged 18 years and above, at high risk of infection. In the context of the national public health emergency declared in the US, this alternative regimen was approved to increase the number of available MVA-BN doses by up to five-fold. It must be noted however, that a high local reactogenicity is reported after ID administration, which can leave a prolonged visible mark at the injection site and may lead to increased stigma of vaccinated individuals. The European Medicines Agency Emergency Task Force also released a statement concluding that intradermal use of MVA-BN vaccine was acceptable in view of the outbreak situation and significant vaccine shortage, noting that the higher local reactogenicity following ID administration of MVA-BN may raise concerns regarding vaccination[4].

As indicated above, a pre-print from Israel showed that one dose of MVA-BN was effective in preventing monkeypox infections. In the case of supply shortages, authorities may consider offering MVA-BN using a delayed second dose.

Post-exposure prevention vaccination considerations

Persons who have had a two-dose primary preventive (pre-exposure) vaccination and who become exposed (contacts) should not receive PEPV but should monitor for any symptoms up to 21 days after the last exposure. Persons who have contact with a monkeypox case after their first dose and before their second dose, should receive their second dose as scheduled.

Exposure risk for contacts of persons with confirmed, probable or suspected monkeypox is classified by the nature of the potential exposure.

A contact is defined as a person who has been exposed to an infected person during the infection period i.e the period beginning with the onset of the index case's first symptoms and ending when all scabs have fallen off, and who has one or more of the following exposures with a probable or confirmed case of monkeypox *(11)*:

- direct skin-to-skin physical contact (such as touching, hugging, kissing, intimate or sexual contact)
- contact with contaminated materials such as clothing or bedding, including material dislodged from bedding or surfaces during handling of laundry or cleaning of contaminated rooms
- prolonged face-to-face respiratory exposure in close proximity
- respiratory exposure (i.e., possible inhalation of) or eye mucosal exposure to lesion material (e.g., scabs/crusts) from an infected person
- the above also apply for health workers potentially exposed in the absence of proper use of appropriate PPE

[4] European Medicnes Agency, Emergency task force statement ; ETF statement POSOLOGY- Imvanex (europa.eu)

Some countries have reported challenges with implementing post-exposure preventive vaccination of close contacts of monkeypox cases resulting in unused doses of vaccines. Challenges include unknown contacts of cases, tracing contacts within a 2-week period to be eligible for PEPV and limited resources. In these instances, authorities may consider offering PPV instead of PEPV.

Even where vaccine cannot be offered for supply, regulatory, choice of product, programmatic, timeliness for PEPV, safety considerations or other reasons, contact-tracing is important to identify those at risk and break chains of transmission, including identifying past events that may have contributed to risk of exposure. Symptom monitoring for contacts and isolation of newly diagnosed cases is essential to prevent onward spread of the disease, particularly given the atypical presentation of many cases.

National health authorities must ensure that information is provided to health personnel on administration of MVA-BN monkeypox vaccine via sub-cutaneous or intra-dermal injection, and on the use of bifurcated needles for administration of ACAM2000 or LC16. Instructions for smallpox vaccination with a bifurcated needle are provided here. Replicating smallpox vaccines such as ACAM2000 consist of live vaccinia virus; it is therefore important to follow special care instructions[5] for the vaccination site (available also in video form[6]) including covering the site with a light bandage.

Hand hygiene should be performed with soap and water or an alcohol-based hand rub before and after vaccine administration. The vaccination site must not be touched before it has healed and care must be taken so that others do not touch the vaccination site, particularly infants or young children. Further guidance on disposal of bandages and care and laundry of clothing can be found here.

Vaccination policy development

If not yet done, Member States are encouraged to convene their national immunization technical advisory groups (NITAGs) to review the evidence and develop policy recommendations for the use of vaccines for monkeypox as relevant to the national context. All countries are advised to strengthen the biological and epidemiological understanding of monkeypox in their context. With more precise characterization of infection, transmission patterns and disease, as well as ascertainment of risk and needs assessments, countries can determine their clinical and public health needs regarding vaccines, along with operational requirements, as well as research and development regarding public health measures, vaccines, antivirals, diagnostics, materials and supplies, and research needs to support policy.

[5] Written instructions on care of the smallpox injection site. USCDC. Available here : https://www.cdc.gov/smallpox/vaccine-basics/who-gets-vaccination.html#care-for, accessed 3 August 2022.

[6] Video instructions for the care of the vaccination site for replicating smallpox vaccines. USCDC. Available here: Chapter 3: How to Care for the Smallpox Vaccination Site and Prevent the Spread of Vaccinia Virus - YouTube, accessed 3 August 2022.

Research needs

All efforts should be made to administer vaccines for monkeypox within a framework of collaborative research, including randomized controlled trials (RCT).[7] Where observational study designs are considered, they should be carefully planned to minimize bias and include standardized data collection tools for clinical and outcome data.

Recommendations on addressing current knowledge gaps through further research. WHO recommends the following post-authorization monitoring activities and research:

- Vaccine safety:
  - safety surveillance and monitoring of serious adverse events, including in subpopulations;
  - studies on safety in pregnant and breastfeeding women;
  - safety studies in persons below the age of 18 years; and
  - safety data on vaccination in immunocompromised persons, including persons living with HIV and persons with autoimmune disease.

- Vaccine immunogenicity and effectiveness:
  - vaccine effectiveness in relation to 1 and 2 doses;
  - vaccine effectiveness over time;
  - correlates of initial protection and correlates of durability of protection;
  - assessment and reporting of breakthrough infections; and
  - vaccine effectiveness in previously smallpox vaccinated individuals.

- Evidence on dose-sparing options
  - extended interval between doses;
  - intradermal administration; and
  - use as a first vaccine in a prime-boost model with ACAM2000 or LC16 as a second dose (including assessment of safety profiles of such regimens).

- Behavioural insights research including research on beliefs about vaccine effectiveness, safety and relevance, willingness to limit high risk activities and willingness to delay a second vaccination dose.

- In addition, WHO recommends that research be conducted on epidemiology and burden of disease, in particular:
  - Evidence on the epidemiology and epi-zoonotic situation of monkeypox disease in previously affected countries and the relationship with animal vectors.

[7] WHO Monkeypox Research - What study designs can be used to address the remaining knowledge gaps for monkeypox vaccines? (https://www.who.int/news-room/events/detail/2022/08/02/default-calendar/who-monkeypox-research---what-study-designs-can-be-used-to-address-the-remaining-knowledge-gaps-for-monkeypox-vaccines, accessed 9 August 2022)

Table of updates

07 November 2022

Section	Rationale for update
Executive summary	Reflects the updated language used in the recommendations.
Background	The background section replaces the previous introduction section. Reflects the recent epidemiology
Summary of the evidence	A short 'summary of the evidence' section has been added. This section refers to a background document which can be found on the web and discusses the vaccines, vaccine safety and vaccine effectiveness in more detail. The summary of the evidence section replaces the previous background section.
Recommendation 1 Primary preventive vaccination (PPV)	This was the former Recommendation 5. Some changes to groups at risk of exposure were made: others with multiple *casual* sexual partners, *sex workers,* health workers *at risk of repeated exposure*; clinical laboratory *and health care personnel* performing diagnostic testing for monkeypox. Added to the recommendation that the level of risk of infection may vary between the groups and could be used by countries for prioritization in case of limited vaccine supply. Former recommendation 2 on vaccination outbreak response is included in the revised PEPV recommendation.
Recommendation 2 Post-exposure preventive vaccination (PEPV)	This was the former Recommendation 3. No change has been made.
Recommendation 3 Choice of vaccine and special populations	This was the former Recommendation 5 on special populations and former recommendation 6 on choice of vaccines are both combined into the new Recommendation 3.
Recommendation 4 Vaccination in the case of limited supply	Added to describe prioritization in the case of limited vaccine supply, includes former Recommendation 7 on vaccine supply
Implementation considerations	Summarizes the separate implementation sections from the previous guidance into one section. The former Recommendation 1 on vaccination policy development has been included in this section
References	The former 'additional smallpox and monkeypox resources' have been partly moved to the references section and partly moved to a separate document that can be found on the web (link to page),

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