

Guidance on the Use of Mpox Vaccines

Revised edition



PAHO



Pan American
Health
Organization



World Health
Organization
REGIONAL OFFICE FOR THE
Americas

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ACRONYMS

ESAVI	Event supposedly attributable to vaccination or immunization
FDA	US Food and Drug Administration (FDA)
MVA	Modified vaccinia Ankara
PAHO	Pan American Health Organization
SAGE	Strategic Advisory Group of Experts on Immunization
TAG	Technical Advisory Group on Vaccine-preventable Diseases
WHO	World Health Organization

INTRODUCTION

Smallpox eradication was certified in 1980. Mpox has been endemic in Central and West African countries since it was first detected in 1958 (1). It is a zoonosis; cases are often found close to tropical rainforests where various animals carry the orthopoxvirus that causes the disease. In endemic countries, most mpox infections in humans result from a primary animal-to-human transmission. Human-to-human transmission can result from close contact with respiratory secretions, skin lesions of an infected person, or recently contaminated objects. Transmission can also occur via the placenta from mother to fetus or through close contact during and after birth. (2)

As of 21 May 2022, 12 non-endemic countries in two World Health Organization (WHO) regions had reported 92 confirmed cases of mpox. By 26 August 2022, 96 non-endemic countries in all six WHO regions had reported 45 198 confirmed cases of mpox, including 6 deaths. During the same period, endemic countries reported 350 confirmed cases and 6 deaths. In the Region of the Americas,¹ 29 countries and territories reported 23 479 confirmed cases (48%) and 3 deaths (2,3).

Several observational studies on first generation vaccines demonstrated that smallpox vaccination was around 85% effective in preventing mpox (4). At the present time, the original (first-generation) smallpox vaccines are no longer available.

A second-generation smallpox vaccine (ACAM2000®) was subsequently developed, which has been used to immunize and protect personnel at high risk of occupational exposure, such as laboratory workers and those whose work in endemic areas (5, 6). A third-generation vaccine based on a modified attenuated vaccinia virus (Ankara strain) was approved for the prevention of mpox in 2019.

Smallpox and mpox vaccines are developed in formulations based on the vaccinia virus, which offer some cross-protection for the immune response to orthopoxviruses. However, the availability of vaccines is limited.

1 Daily update of the regional epidemiological situation. Pan American Health Organization. Monkeypox cases – Region of the Americas. Washington, DC: PAHO. Available from: <https://shiny.pahobra.org/monkeypox/>

On 31 May 2022, the VIII Ad Hoc Meeting of the Technical Advisory Group (TAG) on Vaccine-Preventable Diseases of the Pan American Health Organization (PAHO) (8) was held to address the outbreak of mpox in several countries. The meeting's recommendations were:

- Vaccination should only be offered to close contacts of a confirmed case of mpox.
- Post-exposure vaccination (ideally within four days of exposure) may be considered by some countries for close contacts at high risk of exposure.
- PAHO should establish clear guidelines on which mpox vaccine should be made available to close contacts of confirmed cases, based on their risk of infection and the risk of developing adverse effects.
- Most people aged 50 years and older would have received the smallpox vaccine and should only receive a single dose of a third-generation vaccine as a booster.
- There is not a sufficient supply of vaccines; however, there is currently no need for mass vaccination.

On 14 June 2022, the World Health Organization (WHO) published interim guidance on vaccines and vaccination against mpox with the advice and support of its Ad-hoc Working Group on Smallpox and Mpox Vaccines of the Strategic Advisory Group of Experts (SAGE) (9). This interim guidance includes:

- Mass vaccination against mpox is not required, nor is it recommended at this time.
- For case contacts, post-exposure prophylaxis (PEP) with an appropriate second- or third-generation vaccine is recommended, ideally within four days of first exposure to prevent the onset of disease.
- The SAGE recommends pre-exposure vaccination (PrEP) for at-risk healthcare workers, laboratory personnel working with orthopoxvirus, clinical laboratory personnel performing diagnostic tests for mpox, and others who may be at risk under national policy.
- Vaccination programs must be backed by thorough surveillance and contact tracing, and accompanied by a strong information campaign and robust pharmacovigilance in the context of collaborative vaccine effectiveness studies with standardized protocols and data collection tools.
- Decisions on use of smallpox or mpox vaccines should be based on a full assessment of risks and benefits on a case-by-case basis.



On 23 July 2022, the WHO Director-General declared the mpox outbreak a public health emergency of international concern (PHEIC) (10). A coordinated response was launched, aimed at interrupting transmission and protecting vulnerable groups, and a number of recommendations were made, including vaccination.

These temporary recommendations apply to different groups of countries, based on their epidemiological situation, patterns of transmission, and capacities. These recommendations include different aspects such as: the implementation of a coordinated response, community engagement and protection, surveillance and public health measures, clinical management, and infection control, among others. WHO recommends use of the vaccine for countries that have imported cases of mpox in the population and/or human-to-human transmission of monkeypox virus, including in key population groups and communities at high risk of exposure.

The overall goal of the global response to mpox as a PHEIC, is to stop human-to-human transmission and minimize zoonotic transmission of the monkeypox virus wherever it occurs.

The use of vaccines can contribute to this response. However, vaccination should be considered a measure to complement primary public health interventions that include surveillance, early case detection, diagnosis and care, isolation and contact tracing and follow-up, and self-monitoring to reduce contacts.

This document aims to provide useful accessible, and understandable information about mpox vaccines in order to facilitate deployment of vaccination strategies in the context of the current epidemiological scenario and based on the recommendations of the VIII Ad Hoc Meeting of the PAHO Technical Advisory Group (TAG) on Vaccine-Preventable Diseases (8).

This guidance offers a conceptual framework for available vaccines, supporting immunization program managers at the national and subnational levels and vaccinators in technical operations for vaccine utilization.

To facilitate updates, this document is organized around the various components required for deployment and includes relevant information on vaccines, administration techniques, the information system, events supposedly attributable to vaccination or immunization (ESAVI; also known as adverse events following immunization [AEFI]), waste management, and indications for vaccination.

1. MPOX

1.1 DESCRIPTION

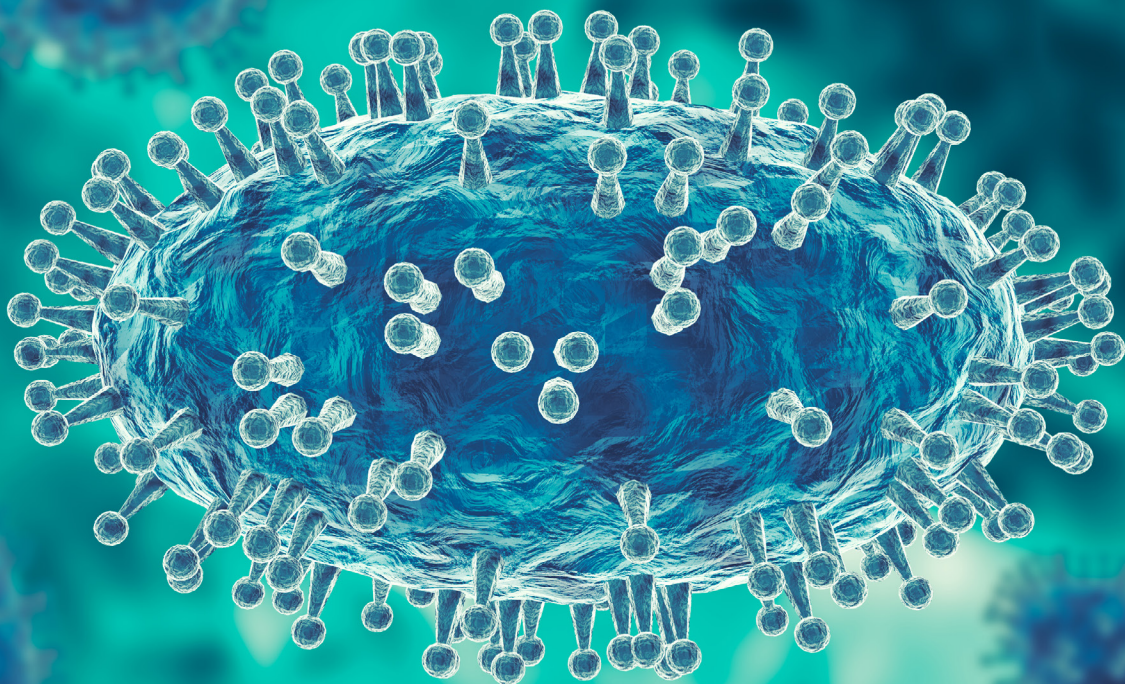
Mpox is a rare zoonotic viral disease caused by the monkeypox virus, which belongs to the genus *Orthopoxvirus*. Also belonging to this genus is the variola virus (which causes smallpox), the vaccinia virus, and the cowpox virus, among other poxviruses.

Mpox was first identified in colonies of monkeys bred for research in 1958 in Africa and was first detected in humans in 1970 in the Democratic Republic of Congo. It primarily occurs in Central and West Africa, often in proximity to tropical rainforests, although it has been increasingly appearing in urban areas. It has been endemic since it was first detected. The first outbreaks outside endemic areas were detected in the United States in 2003 (1).

It is usually a self-limiting disease, it is milder than smallpox and most people recover within several weeks; however, in some cases serious illness or death can occur.

There are two known clades of monkeypox, one in West Africa (WA) and one in the Congo Basin (CB) region (11). Historically, the CB clade has been more virulent, with a case fatality ratio (CFR) ranging from 1% to 10%, while the WA clade is associated with an overall lower mortality rate of < 3% (12, 13). It is important to note that mortality can vary substantially in different settings.

As of 12 August 2022, clades from the Congo Basin (Central Africa) and West Africa have been named clade I and clade IIa, respectively. The group of variants circulating during the current outbreak corresponds to the clade IIb (14).



1.2 CLINICAL AND EPIDEMIOLOGICAL ASPECTS

Table 1 shows the general characteristics of mpox.

Table 1. Characteristics of mpox

Causative agent	The monkeypox virus is a member of the genus <i>Orthopoxvirus</i> . It is a double-stranded DNA virus.
Natural host of the virus	It is not certain, but it is suspected that there may be several species of small rodents such as squirrels, Gambian pouched rats, African dwarf dormice, and non-human primates, among others.
Transmission route	Transmission can occur from animal to human, from human to human, from contaminated environments to humans, and less frequently, from human to animal. Human-to-human transmission can occur by direct contact with mucocutaneous infectious lesions or with the organic fluids of the lesions, fomites, and through respiratory droplets. During pregnancy, the virus can cross the placenta and cause intrauterine exposure of the fetus and congenital infection of the newborn.
Signs and symptoms	The febrile phase of the disease usually lasts from 1 to 3 days, with severe headache, lymphadenopathy, back pain, myalgia, and severe asthenia. The febrile stage is followed by the skin eruption (exanthema) stage, lasting for 2 to 4 weeks. Lesions evolve from macules (lesions with a flat base) to papules (raised firm painful lesions) to vesicles (filled with clear fluid) to pustules (filled with pus), followed by scabs or crusts. The lesions vary in size from 0.5 to 1 cm in diameter and in number. They tend to be centrifugal, starting on the face and extending to the palms of the hand and soles of the feet, and may involve oral mucous membranes, conjunctiva, cornea and/or external genitalia. Cases descriptions in the present outbreak indicate that lesions are most often located in the genital, perianal, and perioral areas, possibly due to the pattern of transmission. In 20% of cases the febrile phase is not observed. It can cause severe proctitis, pharyngitis, or eye lesions.
Incubation period	From infection to onset of symptoms is 7 to 14 days, but can vary from 5 to 21 days.
Transmission period	The period from the appearance of the first prodromal symptoms, or in cases that begin with rash, from the day before its appearance, until the lesions have completely healed, the scabs have fallen off, and a new layer of skin has formed.
Diagnosis	Confirmed by laboratory from samples of skin lesions, using polymerase chain reaction (PCR) or genomic sequencing techniques.

<p>Prevention</p>	<p>The main prevention strategy is to reduce exposure to the virus by decreasing close and direct physical contact with skin lesions, scabs, or body fluids of an infected person.</p> <p>In health facilities, patients with suspected mpox infection should be isolated, with contact and droplet precautions in place. Hand hygiene and use of personal protective equipment should be increased.</p> <p>Some studies reported that vaccines used during the smallpox eradication program also provided protection against mpox in 85% of those vaccinated. Third-generation vaccines have shown good immunogenicity when administered pre-exposure; there is limited evidence that the vaccine prevents or modifies the course of the disease when administered post-exposure.</p>
<p>Treatment</p>	<p>There is no specific proven treatment for monkeypox virus infection. Symptoms usually resolve spontaneously; symptomatic and supportive management should be performed, as well as follow-up and treatment of possible complications. Appropriate measures should be implemented for the care of skin lesions to prevent secondary bacterial infections. Specific therapies are still in the experimental phase. Currently, there are four antivirals (tecovirimat, brincidofovir, cidofovir and NIOCH-14) and intravenous vaccinia immune globulin in development with potential utility for the treatment of mpox. WHO recommends that if there is a decision to use one of these, it be done within the framework of randomized studies or under a Monitored Emergency Use of Unregistered and Investigational Interventions (MEURI) protocol. Tecovirimat (TPOXX®, manufactured by SIGA) is the only intervention approved on an exceptional basis by the US Food and Drug Administration (FDA) to treat mpox within the MEURI framework.</p>

Sources:

World Health Organization. Clinical management and infection prevention and control for monkeypox: Interim rapid response guidance, 10 June 2022. Geneva: WHO; 2022. Available from: (<https://www.who.int/publications/i/item/WHO-MPX-Clinical-and-IPC-2022.1>)

Pan American Health Organization. Control of Communicable Diseases Manual. Official report of the American Public Health Association, 19th edition. Washington, DC: PAHO; 2011. Available (in Spanish) from: <https://www.paho.org/es/noticias/20-5-2011-control-enfermedades-transmisibles-19a-ed>

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Pan American Health Organization. Opciones terapéuticas para la viruela símica. Síntesis de la evidencia. Rapid Review, September 2022. Washington, DC: PAHO; 2022. Available from: <https://iris.paho.org/handle/10665.2/56406>

1.3 DIFFERENTIAL DIAGNOSIS

Various infections and skin diseases should be considered for differential diagnosis of mpox. Both clinical and epidemiological data and specific laboratory studies can lead to different diagnoses (15). In the current outbreak, cases of both mpox and other sexually transmitted infections have been simultaneously reported. Therefore, diagnosis of an infection such as syphilis or lymphogranuloma venereum should lead to investigation of possible infection with the mpox virus (16). Table 2 describes the characteristic lesions that correspond to each of the diseases that require differential diagnosis with mpox.

Table 2. Characteristics of the lesions caused by selected diseases, for differential diagnosis with mpox

DISEASE	DESCRIPTION OF LESIONS
Herpes simplex	Very painful polycyclic lesions that evolve to crusts, usually in people with a history of herpes virus infection.
Primary or secondary syphilis	<ul style="list-style-type: none">• Primary: firm, painless chancre with a clean base.• Secondary: roseola or disseminated papules that affect the palms and the soles of the feet.
Varicella	Starts on the upper back as asynchronous papules that evolve into vesicles and scabs.
Impetigo	Meliceric (yellowish) crusts, sometimes with blisters, caused by bacterial infection.
Hand, foot, and mouth disease	Although it is common in childhood, it can occur in adults. Caused by various enteroviruses. Fever, and lesions on the mucosa, mouth, palms, and buttocks.

Source:

Pan American Health Organization. Guidance on clinical suspicion and differential diagnosis of monkeypox: provisional technical note, June 2022. Washington, D.C.: PAHO; 2022. Available from: https://iris.paho.org/bitstream/handle/10665.2/56218/PAHOPHEIMS220011_eng.pdf?sequence=1&isAllowed=y



1.4 CLINICAL CHARACTERISTICS OF MPOX AND OTHER VACCINE-PREVENTABLE DISEASES

Clinical diagnosis of mpox is often inaccurate, so laboratory studies are necessary for differential diagnosis with other vaccine-preventable diseases such as varicella (chickenpox) and measles.

The PAHO publication *Surveillance, case investigation, and contact tracing for monkeypox: interim guidance—25 August 2022* provides definitions of mpox cases and deaths for surveillance purposes (17). Table 3 shows the clinical features of mpox, varicella, and measles.

Table 3. Clinical features of some vaccine-preventable exanthematous diseases

SYMPTOMS	MPOX	VARICELLA	MEASLES
Fever	≥38°C	Up to 39°C	Up to 40.5°C
Type of lesions	Macules, papules, vesicles, pustules present at the same stage in any area	Macules, papules, vesicles in various stages	Non-vesicular rash at different stages
Development of lesions	Lesions appear 1 to 3 days after fever. Slow development, from 3 to 4 weeks	Lesions appear in first 2 days	Lesions appear in 5-7 days and last 2-4 days
Spread of lesions	Appear on the head, more numerous on the face and limbs, then on the palms of the hands and soles of the feet. In the current outbreak in non-endemic countries, the lesions have been located in the genital, perianal, and perioral areas.	Appear on the face, are more numerous on the body, and absent on palms and soles	Appear on the head and spread; may reach the hands and feet
Classic characteristics	Lymphadenopathy	Itchy rash	Köplik spots
Mortality	Between 1 and 10%. The case fatality rate of the current outbreak is much lower.	Low	Varies widely

Source:

Adapted from World Health Organization. *Introducción a la viruela del mono: prevención y control*. Geneva: WHO; 2020. Available in Spanish from: <https://openwho.org/courses/viruela-del-mono-introduccion>.

2. SMALLPOX AND MPOX VACCINES

2.1 OVERVIEW

The first smallpox vaccine authorized in the United States by the Food and Drug Administration (FDA) was Dryvax® in 1931. Referred to as “first-generation”, it contained live vaccinia viruses, lyophilized, produced by infecting the abdominal skin or lymph of inoculated animals. It had 85% efficacy in preventing mpox (4); it was administered by multiple punctures with a bifurcated needle. Production was discontinued following the eradication of smallpox.

Subsequently, production of second- and third-generation vaccines began, with modern cell culture techniques that follow current standards of good manufacturing practices.

The second-generation vaccine (ACAM2000®, FDA-authorized) uses virus variants obtained by plaque purification of the same strain as the first-generation smallpox vaccine; it is a replicating virus vaccine. Third-generation vaccines have been developed to decrease the replication capacity of the virus. These include the non-replicating modified vaccinia Ankara (MVA), from a highly attenuated strain of poxvirus (chorioallantois vaccinia virus Ankara or CVA) (5); and the minimally replicating LC16m8 vaccine, derived from cells of a strain of vaccinia virus grown in rabbit kidney cells, authorized in Japan since 1975. This is the only smallpox vaccine approved for use in children (18, 19).

Currently, the government of the Russian Federation is developing a fourth-generation vaccine, VACDelta6, highly immunogenic, using an attenuated strain (1421ABJCN) with six genes inactivated by genetic engineering (19).

The supply of second- and third-generation vaccines is for limited use at this time since they were produced as part of the strategic reserves of countries for eventual smallpox events, so strategies are being developed for their access.



2.2 COMPARISON BETWEEN SMALLPOX AND MPOX VACCINES

Table 4 shows the characteristics of smallpox vaccines and second- and third-generation mpox vaccines.

Table 4. Characteristics of the second-generation smallpox vaccine (ACAM2000®) and third-generation mpox vaccines (MVA-BN and LC16m8)

	Second-generation	Third-generation	
	ACAM2000®	MVA-BN	LC16m8
Virus	Vaccinia virus (sequence-homologous clone of Dryvax®)	Chorioallantois vaccinia virus Ankara (CVA)	Modified vaccinia virus of the Lister strain
Vaccine type	Live replicating virus vaccine.	Non-replicating live attenuated virus vaccine.	Minimally replicating live attenuated virus vaccine.
Preparation	Cell cultures		

Source:

Pan American Health Organization. VIII Ad Hoc Meeting of PAHO's Technical Advisory Group (TAG) on Vaccine-Preventable Diseases. Washington, DC: PAHO, 2022. Available from: <https://iris.paho.org/handle/10665.2/56102?locale-attribute=en>

2.3 SECOND-GENERATION VACCINES (ACAM2000®)

This vaccine uses the same strains as the first-generation smallpox vaccine, with an improved manufacturing process. It is a replicating vaccine, which means it can replicate and spread to other parts of the body and can eventually infect people who are in direct contact with the vaccinee. The risk of side effects in the contacts of vaccinated people is the same as for the vaccinee, so the inoculation site requires special care to prevent spread.

Table 5 shows the characteristics of the ACAM2000® vaccine

Table 5. Characteristics of the ACAM2000® vaccine

Composition	<ul style="list-style-type: none"> • Live replicating virus vaccine. • Derived from the cloning of Vaccinia Dryvax® virus, purified and cultured in monkey kidney (Vero) cells. • Contains traces of neomycin and polymyxin B.
Production laboratory	Emergent
Regulatory status	Approved by the FDA in 2007 for the prevention of smallpox.
Efficacy	<ul style="list-style-type: none"> • Efficacy was evaluated by comparing the immune response with the Dryvax® vaccinia virus vaccine. • 96% seroconversion
Storage	<p>Store between -15°C and -25°C. Prior to reconstitution it can be stored between +2°C to +8°C for 18 months.</p> <p>After reconstitution, it can be administered during a 6- to 8-hour workday at room temperature (+20°C to +25°C).</p> <p>Once reconstituted, unused vaccine can be stored at refrigeration temperature (+2°C to +8°C) for up to 30 days; then it must be discarded as biohazard material.</p> <p>The diluent for the vaccine should be stored at room temperature (+15°C to +30°C).</p>
Presentation	<ul style="list-style-type: none"> • Multi-dose vial • Lyophilized powder of live virus purified with non-active excipients. Diluent packed in a 3 ml vial. • After reconstitution, each vial contains approximately 100 doses (0.0025 ml/dose) containing 2.5 to 12.5 x 10⁵ plaque-forming units. • Vaccine and diluent vial caps are not made of natural rubber latex.
Indications	For active immunization against smallpox in people at high risk of contracting the disease.
Schedule and dosage	<ul style="list-style-type: none"> • Schedule: 1 dose • Dosage: 0.0025 ml drop of reconstituted vaccine • Prior to administration, the vial should be removed from cold storage and brought to room temperature before reconstitution; once reconstituted it can be administered within up to 6 to 8 hours if kept at room temperature (20°C to 25°C). • The reconstituted vaccine should be a clear to slightly cloudy, colorless liquid, and free of foreign matter. If particles or discoloration are observed, do not use the vial and dispose of it safely.

Administration route	Percutaneous (multiple punctures with stainless steel bifurcated needle), in the deltoid muscle area of the non-dominant arm.
Mild adverse events	<p>Involuntary inoculation of the vaccine in other sites of the body is the most frequent complication of vaccination; the most common sites are: face, nose, mouth, lips, genitals and anus.</p> <p>Local adverse events: itching at the injection site (93.3%–100.0%), pain in the lymph nodes (81.1%), pain at the injection site (77.8%).</p> <p>Systemic adverse events: fatigue (68.9%), headache (60.0%), myalgia, malaise, and gastrointestinal disorder—most common being nausea, diarrhea, constipation and vomiting (4%–58.9%).</p>
Serious adverse events	<p>Serious events detected include: inadvertent inoculation, generalized vaccinia, progressive vaccinia, eczema vaccinatum, ocular vaccinia, encephalitis, myocarditis, and pericarditis.</p> <p>Risks (severe disability, permanent neurological sequelae and/or death) are higher in vaccinated people with a history of or current heart disease, eye disease treated with topical steroids, congenital or acquired immunodeficiency disorders, treatment with immunosuppressive medications, eczema or a history of eczema, or other acute or chronic exfoliative skin conditions, as well as in children under 12 months of age, and pregnant people.</p>
Contraindications	<ul style="list-style-type: none"> • History of a severe allergic reaction (anaphylaxis) to a previous dose or component of the ACAM 2000® vaccine. • In a context of high risk of contracting smallpox, the risk of serious complications of vaccination should be weighed against the risks of a possibly fatal smallpox infection. • People with severe immunodeficiency, including bone marrow transplants, or people with primary or acquired immunodeficiency who require isolation, should not receive the ACAM 2000® vaccine. • Use of the vaccine for an event is contraindicated in: <ul style="list-style-type: none"> ○ People with congenital or acquired immunodeficiency disorders, including those taking immunosuppressive medications and people living with HIV (particularly untreated and with CD4<200 cells). ○ People with a history of atopic dermatitis, eczema, or other acute or exfoliative skin conditions). ○ Infants under 12 months of age. ○ Pregnancy and breastfeeding: ○ Eye disease treated with topical steroids.

<p>Precautions</p>	<p>People at higher risk of serious complications from vaccination are often at the highest risk of death from smallpox. The risk of serious complications from vaccination should be assessed against the risks inherent to the disease.</p> <p>Three or more major cardiac risk factors (hypertension, diabetes, hypercholesterolemia, heart disease at age ≤ 50 in a first-degree relative, or smoking).</p>
<p>Concurrent use with other vaccines</p>	<p>There are no data evaluating the simultaneous administration of ACAM2000® with other vaccines. In the experience with the first-generation vaccine Dryvax®, it can be administered at the same time with other antigens, but at different sites. It has recently been recommended to avoid co-administration with other live vaccines, and to separate vaccination by at least 28 days.</p>
<p>Use of the vaccine in special populations</p>	<p>Pregnancy: has not been studied in pregnant people. Live vaccinia virus vaccines can cause fetal harm when given to pregnant people. Congenital infection has been observed, occurring mainly during the first trimester, after vaccination with live vaccines against smallpox vaccinia, although the risk may be low. The only situation in which vaccination of pregnant people should be considered is when exposure to smallpox is considered likely.</p> <p>Breastfeeding: has not been studied in this population group. It is not known whether the vaccine virus or antibodies are secreted into human milk. Live vaccinia virus can be inadvertently transmitted from a nursing person to a child.</p> <p>Pediatric use: The safety and efficacy of this vaccine in children under 16 years of age have not been established. The evidence for its use is from data from studies in older adults and with first-generation vaccines.</p> <p>Over 65 years: There are no published data to support the use of this vaccine in populations of this age group</p>

Sources:

Food and Drug Administration. ACAM2000. Silver Spring; FDA; 2019. Available from: <https://www.fda.gov/vaccines-blood-biologics/vaccines/acam2000>.

Centers for Disease Control and Prevention. Smallpox vaccination and adverse reactions guidance for clinicians. MMWR. 2003;52(4). Available from: <https://www.cdc.gov/mmwr/pdf/tr/tr5204.pdf>.

Centers for Disease Control and Prevention. ACAM2000 Vaccine. Atlanta: CDC. ACAM2000®. Vaccine. Available from: <https://www.cdc.gov/poxvirus/monkeypox/interim-considerations/acam2000-vaccine.html>.

World Health Organization. WHO advisory committee on variola virus research: report of the twenty-second meeting, Geneva, 4-5 November 2020. Geneva; WHO; 2021. Available from: <https://apps.who.int/iris/handle/10665/341197>.

Note: FDA: Food and Drug Administration

[Annex 1](#) provides information on vaccine administration procedures; [Annex 2](#) contains the informed consent form; and [Annex 3](#), an illustrative brochure on the cutaneous reaction to the ACAM2000® vaccine.



2.4 THIRD-GENERATION MVA-BN VACCINE

This vaccine is prepared with more attenuated vaccine strains developed through successive subcultures in cell lines of avian origin; the vaccinia virus has been modified and has lost its ability to replicate in mammalian cells.

Table 6 describes the characteristics of the non-replicating attenuated virus vaccine produced with a modified Ankara-Bavarian Nordic strain (MVA-BN).

Table 6. Characteristics of the MVA-BN vaccine

Composition	Non-replicating live attenuated virus vaccine. Developed from a highly attenuated strain of poxvirus (chorioallantois vaccinia virus Ankara or CVA). It is grown in fibroblasts of chicken embryos, suspended in a whey-free medium that does not contain material of animal origin.
Production laboratory	Bavarian Nordic
Regulatory Status	The MVA-BN vaccine is approved in Canada, Europe, and the United States (Imvamune [®] , Imvanex [®] , and Jynneos [®] respectively) for the prevention of smallpox and mpox.
Efficacy	<ul style="list-style-type: none"> • Vaccination with MVA induced a detectable response after two weeks of the first dose with an increase in neutralizing antibodies two weeks after the application of the second dose. • 98% seroconversion.
Storage	<p>The shelf life of the Jynneos[®] vaccine depends on the expiration date and storage temperature:</p> <ul style="list-style-type: none"> • When stored at $-50^{\circ}\text{C} \pm 10^{\circ}\text{C}$, the approved shelf life is 5 years. When thawed and stored between $+2^{\circ}\text{C}$ to $+8^{\circ}\text{C}$ it can be used up to 24 weeks. • If the storage temperature is between $-25^{\circ}\text{C} \pm 5^{\circ}\text{C}$, the approved shelf life is 3 years. When thawed and stored between $+2^{\circ}\text{C}$ to $+8^{\circ}\text{C}$ it can be used up to 12 hours. • It must be kept protected from light and after thawing it cannot return to freezing temperatures.

Presentation	<p>Single-dose vial</p> <ul style="list-style-type: none"> • Each 0.5 ml dose is formulated to contain 0.5×10^8 to 3.95×10^8 infectious units of live MVA-BN virus. • Each dose may contain residual amounts of host cell DNA, gentamicin, and ciprofloxacin. • It is a sterile vaccine formulated without preservatives. The caps on the vials are not made of natural rubber latex.
Indications	<p>Prevention of smallpox and mpox in people 18 years of age and older at high risk of contracting smallpox or mpox.</p>
Schedule and Dosage	<ul style="list-style-type: none"> • Primary schedule: two doses with an interval of 4 weeks between the two doses • For those previously vaccinated against smallpox or mpox: one dose (0.5 ml). • Thaw at room temperature, when thawed, the contents are a milky suspension of light yellow to pale white color. The single-dose vial should be gently swirled (not shaken) for at least 30 seconds to ensure homogeneity, and not used if foreign particles are observed in the bottle.
Administration route	<p>Subcutaneous.</p>
Mild adverse events	<ul style="list-style-type: none"> • The most common local adverse events are pain, erythema, swelling or induration at the injection site. • Among the systemic events detected are: headache, fatigue, nausea or myalgia, tachycardia, and palpitations.
Serious adverse events	<p>Cases of myocarditis and/or pericarditis after vaccination have not been identified in studies.</p>
Contraindications	<p>Severe allergy to a previous dose or to vaccine components</p>
Concurrent use with other vaccines	<ul style="list-style-type: none"> • So far, there are no data on the administration of the vaccine concurrently with other vaccines. • Given the potential risk of myocarditis and/or pericarditis after receiving orthopoxvirus vaccines, a 4-week interval is recommended between vaccination for COVID-19 with mRNA vaccine and vaccination against orthopoxvirus

Use of the vaccine in special populations

Pregnancy: The effect of Jynneos® on embryofetal and postnatal development was evaluated in developmental toxicity studies conducted in animals, which revealed no evidence of harm to the fetus.

Lactation: It is not known whether the vaccine is excreted in breast milk. No data are available to assess effects on either the infant or on milk production/excretion.

Pediatric use: The safety and efficacy of this vaccine in children under 16 years of age have not been established.

Over age 65: Jynneos®' clinical studies did not include a sufficient number of subjects aged 65 years or older to determine whether they respond differently than younger subjects.

People with immunosuppression: Immunocompromised persons, including those receiving immunosuppressive therapy, may have a decreased immune response.

Sources:

Food and Drug Administration. Jynneos®. Package Insert. Available from: <https://www.fda.gov/media/131078/download>.

UK Health Security Agency UK. Green book: chapter 9. Government Digital Services; 2022. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1106454/Green-Book-chapter-29_Smallpox-and-monkeypox_26September2022.pdf.

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Verheust C, Goossens M, Pauwels K, Breye D. Biosafety aspects of modified vaccinia virus Ankara (MVA)-based vectors used for gene therapy or vaccination. Vaccine. 2012;30(16):2623-2632. Available from: <https://doi.org/10.1016/j.vaccine.2012.02.016>.

Nota: MVA: Modified vaccinia Ankara (MVA); DNA: deoxyribonucleic acid; mRNA: messenger ribonucleic acid; COVID-19: coronavirus disease 2019.

[Annex 4](#) lists the procedures for subcutaneous vaccine administration; [Annex 5](#) offers information on the MVA-BN vaccine; and [Annex 6](#) provides information on intradermal administration, provided by the FDA and European Medicines Agency.

3. BIOSAFETY AND HAZARDOUS WASTE MANAGEMENT

Health personnel should follow all biosafety recommendations to reduce the risk of accidental exposure, in accordance with national and international regulations.

3.1 BIOSAFETY MEASURES DURING VACCINATION WITH MVA VACCINE

The extreme attenuation of the virus used in the MVA vaccine and its history of safe use make it possible to manage this virus at containment level 1 in the clinical setting.

No laboratory-acquired infections have been reported as a result of exposure to MVA strains or recombinant vectors derived from them.

When administered subcutaneously, any spread that occurs at the puncture site due to viral particles found on the skin near the puncture site has a minimal impact on environmental risk, given that it is a non-replicating vaccine (34).

Cottons used after vaccination should be disposed of as hazardous biowaste.

3.2 TREATMENT OF MVA VACCINE WASTE

Vaccine residues are susceptible to the action of a variety of chemical disinfectants, such as formaldehyde, glutaraldehyde, ethanol, isopropanol, and peracetic acid. The MVA vaccine has the same susceptibility profile to disinfection as the infectious vaccinia of the Lister Elstree strain (20).

In addition to chemical disinfection, steam sterilization is still very effective in inactivating these viruses. It is recommended that liquid and solid waste (potentially) infected by MVA, as well as disposable materials, be inactivated prior to disposal in accordance with current national regulations.

3.3 RECOMMENDATIONS FOR THE DISPOSAL OF MPOX VACCINE MATERIALS AND VIALS




The treatment and disposal of hazardous waste will depend on the conditions and regulations governed by the standards of each country, through laws and protocols that must be available and known to managers in each institution.



3.4 CONTAMINATED MATERIALS GENERATED BY THE ADMINISTRATION OF MPOX VACCINES

Table 7 described contaminated materials, according to type of smallpox and mpox vaccine.

Table 7. Contaminated materials according to type of smallpox and mpox vaccine

Second-generation (ACAM2000®) materials		Third-generation(MVA-BN) materials	
BIOLOGICAL PRODUCTS AND SHARPS	CONTAMINATED MATERIALS	BIOLOGICAL PRODUCTS AND SHARPS	CONTAMINATED MATERIALS
<ul style="list-style-type: none"> • Bifurcated needle • Used, empty, and expired vials • Use strong, puncture-proof containers for sharps and hazardous materials 	<ul style="list-style-type: none"> • Needle wrappers • Gloves, PPE • Wipes or swabs • Gauze • Table drapes 	<ul style="list-style-type: none"> • Used, empty, and expired vials • Injection syringe, 23-25G^{5/8} needles 	<ul style="list-style-type: none"> • Syringe wrappers • Wipes or swabs • Gauze • Table drapes
	 Use red bags for disposal of hazardous biowaste	 Use strong, puncture-proof containers for sharps and hazardous materials	 Use red bags for disposal of hazardous biowaste

Sources:

Food and Drug Administration (FDA). ACAM2000. Package Insert. Available from: [https://www.fda.gov/files/vaccines%2C blood %26 biologics/published/Package-Insert--ACAM2000.pdf](https://www.fda.gov/files/vaccines%2C%20blood%26%20biologics/published/Package-Insert--ACAM2000.pdf)

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3.5 TRATAMIENTO PRÁCTICO DE RESIDUOS Y ELIMINACIÓN DE VIALES CONTAMINADOS CON LA CEPA MVA

It is recommended that liquid and solid waste (potentially) infected by MVA, as well as disposable materials, be inactivated before disposal.

Table 8 describes waste treatment and disposal of potentially contaminated vials, according to the type of health facility.

Table 8. Waste treatment activities, according to the type of health facility

Health facilities	Issues
Health facilities located in low-density populated areas	<ul style="list-style-type: none">• On-site incineration, if available, or• Safe burial on site, or• Sterilization with chlorine before transporting it to a recycling or waste disposal facility.
Health facilities located in high-density populated areas	<ul style="list-style-type: none">• Off-site transportation to a larger facility with treatment capacity, a municipal incinerator, or landfill after sterilization.
In temporary vaccination sites or mobile settings	<ul style="list-style-type: none">• Always ensure off-site transportation of all waste to the reference health center for storage and treatment.• Label the waste, complete the required registration/report form, and store it in a safe area until it can be transported to the facility designated for waste storage or disposal.• On-site treatment/disposal should be avoided.

Source:

World Health Organization. Standard operating procedure (SOP): waste management of used COVID-19 vaccines vials and ancillary supply. Geneva: WHO; 2021. Available from: <https://www.afro.who.int/sites/default/files/2021-05/SOP%20Waste%20management%20of%20Covid-19%20Vaccines%20%281%29.pdf>.



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4. INFORMATION SYSTEM

4.1 OVERVIEW

The **overall objectives** of a vaccination monitoring system include:

- Monitor the number of doses administered according to the variables of person, time, place and characteristics of the biologic product, to ensure traceability of the administered dose and take specific actions when necessary.
- Integrate monitoring of vaccination progress with other relevant information systems, such as the epidemiological surveillance system and AEFI/ESAVI.
- Monitor the equitable application of vaccines, according to the epidemiological situation of each country and territory.
- Ensure that the required forms and documents are adapted and available to ensure complete and timely recording of vaccine doses administered.
- Facilitate the availability of information for analysis and use in decision-making (e.g., impact assessment, vaccine effectiveness, potential epidemiological studies, vaccine and supply management surveys, surveillance of adverse effects of special interest (AESI), and ESAVI surveillance, among others).
- Give vaccinees a vaccination card or certificate (paper or digital), or if they have a health card or booklet, add information on the vaccine applied, in order to document this information for future verification and allow the person to complete the vaccination series according to schedule.
- Establish processes to continuously monitor data quality, which provides reliable information for decision making.

The target population to be vaccinated will depend on the guidelines adopted by each country. Decision-making based on this information will depend largely on the doses administered and recorded through the various information systems that exist. This points to the importance of adapting the data sources and recording instruments to ensure that the descriptive variables prioritized by each country will be captured, allowing for better analysis and monitoring of the data.

Since vaccination will not be done massively or by cohorts of recipients, special attention will need to be paid to the variables required to **identify the vaccination targets and to monitor both the eligibility criteria of people exposed to the virus, as well as the period between exposure and vaccination**. This will make it possible to evaluate eligibility as well as the timeliness of post-exposure vaccination.


Having detailed information on vaccinated individuals, their contacts, and eligibility, will facilitate follow-up.



4.2 VARIABLES TO CONSIDER FOR PROPER RECORD-KEEPING ON VACCINATION

Table 9 describes the data to be recorded for the 'person' variable.

Table 9. Data to be recorded for the 'person' variable

Variable	Type of data	Description	Further information	Use
Person 	Unique identifier	<ul style="list-style-type: none"> National identity document number Passport number 	Unique identifier that the country has or must create for each person, integrated with other systems, such as: ESAVIs, epidemiological surveillance, assessment of vaccine effectiveness, etc.).	Identify each vaccinated person.
	Age in years	e.g., 45 years	Countries with electronic information systems can tie alerts to age restrictions indicated by the manufacturer.	Follow up on vaccinees and conduct analyses by age group.
	Sex	<ul style="list-style-type: none"> Male Female 		Monitor vaccine administration by sex.
	Eligibility criteria	Post-exposure vaccination: type of contact	<ul style="list-style-type: none"> Confirmed case contact Occupational exposure 	Analyze people who have been exposed to the virus according to eligibility criteria.
	Likely date of exposure	Day, month, and year	Complements eligibility criteria and measures timeliness of vaccination, whether performed within 4 days post-exposure (recommended) or later.	To assess whether post-exposure vaccination was within the timeframe expected to be most effective.



Source:

Pan American Health Organization. Tools for monitoring coverage of integrated public health interventions. Vaccination and deworming of soil-transmitted helminthiasis. Washington, DC: PAHO; 2021. Available from: <https://www.paho.org/en/documents/tools-monitoring-coverage-integrated-public-health-interventions-vaccination-and>

Note: ESAVI = event supposedly attributable to vaccination or immunization.

Table 10 describes the data to be recorded on the 'time' and 'location' variables.

Table 10. Data to be recorded on the vaccination 'time' and 'location' variables

Variable	Type of data	Description	Further information	Use
Location 	Home address of person vaccinated	<ul style="list-style-type: none"> Address Municipality Region/province/state 	Seek the highest level of disaggregation according to the structure determined by each country.	Monitor vaccine distribution/administration among regions and by different levels according to home address (where the person lives) and location (where the vaccine is administered)
	Health facility where the person was vaccinated	<ul style="list-style-type: none"> Facility name Municipality Region/province/state 	If performed through an extramural vaccination point, this must also be recorded.	
	Name of the person who administered the vaccine	Full Name	Verify that the person who administered the vaccine is enrolled in the electronic immunization registry.	<ul style="list-style-type: none"> This is part of vaccination traceability. Provides information during an ESAVI investigation process.
Time 	Date of birth	Day/month/year	Date format will vary by country.	Assess appropriateness of administering the vaccine according to age established by the manufacturing laboratory.
	Date of vaccination	Day/month/year	<ul style="list-style-type: none"> Date format will vary by country. The EIR can capture the date on which the record was entered into the system, which permits assessment of the timeliness of recording the information. 	Monitor the number of people who accessed the vaccine in a certain period of time (day, week, month, year).



Source:

Pan American Health Organization. Tools for monitoring coverage of integrated public health interventions. Vaccination and deworming of soil-transmitted helminthiasis. Washington, DC: PAHO; 2021. Available from: <https://www.paho.org/en/documents/tools-monitoring-coverage-integrated-public-health-interventions-vaccination-and>

Note: ESAVI: Event supposedly attributable to vaccination or immunization

Table 11 describes the data to be recorded for the 'vaccine' variable.

Table 11. Data to be recorded for the 'vaccine' variable

Variable	Type of data	Description	Further information	Use
Biological 	Vaccine available	Trade or generic name of the available vaccine(s)		<ul style="list-style-type: none"> • Monitor the administration of available biologics. • Contribute to impact studies of vaccines according to vaccine effectiveness. • Monitor potential vaccine safety problems. • Evaluate compliance with indications (e.g., post-exposure vaccine response time) and contraindications for the vaccine, based on the type of vaccine. • Integration with epidemiological surveillance system, ESAVI surveillance, and vaccine inventories.
	Dose level	Dose of the vaccine administered	Vaccine will be single- or multi-dose depending on manufacturer	
	Lote	Unique numerical or alphanumeric identification of the administered vaccine.	Provides information regarding manufacturing methods, controls carried out in the production stages, product specifications, among others.	
	Expiration date	Day/ month/year	Vaccine shelf life; the product will expire on the date indicated.	
	Manufacturing laboratory	Name of laboratory manufacturing the vaccine		
Unused vaccine 	Why the vaccine was not used	<ul style="list-style-type: none"> • At request of the person • Medical contraindication 	It can also be indicated whether the medical contraindication is temporary or permanent.	Makes it possible to formulate vaccination strategies and follow up on those who have temporary medical contraindications

Source:

Pan American Health Organization. Tools for monitoring coverage of integrated public health interventions. Vaccination and deworming of soil-transmitted helminthiasis. Washington, DC: PAHO; 2021. Available from: <https://www.paho.org/en/documents/tools-monitoring-coverage-integrated-public-health-interventions-vaccination-and>

Note: ESAVI: Event supposedly attributable to vaccination or immunization

4.3 COMPLEMENTARY RESOURCES

The following are complementary resources to support registration for vaccination.

Electronic Immunization Registry (EIR): Practical Considerations for Planning, Development, Implementation and Evaluation, 2018.

This document aims to help administrators of the expanded program on immunization (EPI) and their teams to use EIR information systems, based on different experiences collected worldwide and especially in the Region of the Americas.

Contains practical considerations for vaccination planning, development, implementation, and evaluation (21).

Tools for monitoring coverage of integrated public health interventions. Vaccination and deworming of soil-transmitted helminthiasis.

This document provides useful information for the systematic follow-up, monitoring, and analysis of vaccination activities, so that corrective measures can be implemented if necessary (22).

Monitoring COVID-19 vaccination: Recommendations on the collection and use of vaccination data.

This publication provides guidance on the minimum and optional data to be collected as vaccines are deployed and delivered; key performance indicators and their intended use, to measure the performance of key components of the immunization system and to take corrective action where necessary; and the use of information systems to collect, store, analyze, and disseminate any relevant information (23).



5. SURVEILLANCE OF ADVERSE EVENTS

5.1 OVERVIEW

An ESAVI is any unfavorable, unintended medical occurrence (sign, abnormal laboratory finding, symptom, or illness) which follows immunization and which does not necessarily have a causal relationship with the vaccination process or the vaccine itself (24).

The definition as a supposedly attributable event emphasizes the uncertainty in the causal relationship between an adverse event and a vaccine at the time of notification. It is important to recognize that an ESAVI, while having a temporal association with the application of a vaccine, **does not necessarily imply a cause-and-effect relationship**. Causality will be determined by an investigation and analysis of the event, according to a structured methodology, by committees of experts with the capacity to perform such an analysis.

The overall objective of ESAVI surveillance at the national level is the early detection, reporting and analysis of ESAVIs, so that a rapid and effective response can be organized to minimize the negative impact on the health of individuals and on the immunization program; as well as preventing the occurrence of additional events and their recurrence.

5.2 KEY POINTS FOR ESAVI SURVEILLANCE

These are key points for ESAVI surveillance:

- A mpox vaccine safety surveillance plan should be in place that considers coordination between national immunization programs, national pharmacovigilance centers, and epidemiological surveillance units.
- Mpox vaccination will be carried out in the context of a public health emergency, which requires preparing the system to properly carry out the activities of the surveillance cycle.
- Serious ESAVIs should be reported as soon as possible, and no more than 48 hours after detection. Once reported, investigation of the case will begin, ensuring the collection of as much information as possible so that the national vaccination committee has the elements required to determine the causality of the case.
- Non-serious ESAVIs should be reported within seven days of detection.
- All ESAVI notification forms, both serious and non-serious, will have at least the key variables suggested for each (24).
- Conduct full and extensive investigation of serious ESAVIs and determine whether a risk-based investigation is necessary for non-serious ESAVIs (24).
- Document all adverse events and the standard ESAVI/AEFI reporting form according to the rules and protocols of each country. Information collection tools should be designed to minimize the possibility of errors in the recording of data.

5.3 COMPLEMENTARY RESOURCES

PAHO is working on a short guide for ESAVI surveillance of the mpox vaccine that will include the details of response preparedness. Until it is published, please consult the PAHO/WHO *Manual for Surveillance of Events Supposedly Attributable to Vaccination or Immunization in the Region of the Americas* (24).

This regional manual describes in detail the principles and procedures for carrying out ESAVI monitoring; explains the processes of detection, notification, investigation, and causality analysis, among others; and offers links to model forms for reporting and investigating such events.



6. RECOMMENDATION FOR POST-EXPOSURE VACCINATION ACCORDING TO RISK LEVEL

At the current state of the mpox outbreak, WHO and the TAG have indicated that mass vaccination is not recommended or necessary.

Post-exposure vaccination (ideally within four days of exposure) may be considered by some countries for high-risk close contacts.

The risk of exposure to contacts of people with confirmed or probable mpox is classified according to the nature of the potential exposure. The risk to the individual is categorized according to the likelihood of exposure and existing medical conditions that may put a person at increased risk of serious illness.

WHO defines high-risk contacts **as persons whose skin or mucous membranes have been directly exposed to the skin or respiratory secretions of a person with confirmed or probable mpox, their body fluids, or potentially infectious material (including clothing or bedding), without using proper personal protective equipment (PPE).**



6.1 CLASSIFICATION OF CONTACTS ACCORDING TO TYPE OF EXPOSURE

Table 12 shows risk classification of contacts, according to exposure to a confirmed or probable cases of mpox.

Table 12. Risk classification of contacts according to type of exposure

High risk	Medium risk	Low or minimum risk
<p>Direct exposure to the skin, mucous membranes, or respiratory secretions of a person with confirmed, probable, or suspected mpox, their body fluids (e.g., vesicular lesion or pustular fluid), or potentially infectious material (including clothing or bedding) if not using proper PPE.</p>	<p>No direct contact but proximity in the same room or indoor space as a person with symptomatic mpox, if not using proper PPE.</p>	<p>Contact with a person with confirmed, probable, or suspected mpox or an environment that may be contaminated with the mpox virus, while using proper PPE.</p> <p>Community contact, such as being in an outdoor setting with a symptomatic case without proximity or physical contact.</p> <p>No known contact with a symptomatic case of mpox in the past 21 days.</p> <p>Laboratory personnel handling routine blood samples or other specimens that are not directly related to smallpox diagnostic tests.</p>

Source:

World Health Organization: Vaccines and immunization for monkeypox: Interim guidance, 16 November 2022. Geneva: WHO; 2022. Available from: <https://www.who.int/publications/i/item/WHO-MPX-Immunization-2022.2-eng>.

Note: PPE = personal protective equipment

Given that mpox vaccination is a complementary measure to help stop transmission, and considering the post-exposure vaccination strategy and limited supply of vaccines, it is necessary to identify contacts of confirmed or probable mpox cases to offer them the vaccine, and also to monitor for any early signs of disease. Contacts can be identified through case investigation, contact tracing, or risk exposure assessments.

The person who administers the mpox vaccine must follow the pertinent instructions for its administration, after a clinical, epidemiological, and laboratory evaluation of a case, and also a risk-benefit analysis, using the protocols established by the health authorities in each country and under the indications of a medical professional.



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GLOSSARY

Contraindication to vaccination

A specific situation in which a vaccine should not be administered, because a person's conditions increase the risk of a serious adverse reaction.

Event Supposedly Attributable to Vaccination or Immunization

Any unfavorable, unintended health situation (sign, abnormal laboratory finding, symptom, or illness) which follows vaccination or immunization and which does not necessarily have a causal relationship to the vaccination process or the vaccine itself.

Non-serious ESAVI

Any ESAVI that does not endanger the life of the vaccinated person (or the embryo, fetus or newborn in the event that the vaccinated person is pregnant), that disappears without treatment or with symptomatic treatment, that does not force the affected person to be hospitalized and that does not cause disability or disorders in the long term.

Precautions

A condition in a vaccinated person that could increase the chance or severity of a serious adverse reaction, or that could compromise the vaccine's ability to induce immunity. In general, vaccine administration is deferred when there is a precautionary condition. However, situations may arise where the benefit of vaccine protection outweighs the risk of an adverse reaction and a provider may decide to administer the vaccine.

Public Health Emergency of International Concern

A public health emergency of international concern (PHEIC) is "an extraordinary event which is determined to constitute a public health risk to other States through the international spread of disease and to potentially require a coordinated international response."²

Ring vaccination

Strategy to vaccinate people who were in contact with a confirmed case, with the aim of interrupting any possible chain of transmission.



2 World Health Organization. International Health Regulations (2005), third edition. Geneva: WHO; 2005. Available from: <https://www.who.int/publications/i/item/9789241580496>.

Serious ESAVI

An ESAVI that meets any of the following conditions: results in death, endangers life, requires hospitalization of the patient or prolongs existing hospitalization, results in persistent or significant disability, or is suspected of causing a congenital anomaly or stillbirth, or is suspected of causing a miscarriage.

Vaccine

A biological product that generates or enhances immunity to a particular disease. In addition to the antigen, it contains multiple components (excipients) and each component may have unique safety implications.

Viral replication

The ability of the virus in the vaccine to continue replicating and spreading to other parts of the body and eventually have the ability to infect people who are in direct contact with vaccinated people.

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ANNEX 1. PROCEDURES FOR THE ADMINISTRATION OF ACAM2000® VACCINE

Warning: If the person who administers the vaccine is at high risk of serious adverse events from a replicating mpox vaccine, he or she should **NOT** handle or administer the ACAM2000® vaccine.

Provide the user with information on the vaccine to be administered. If the country requires the use of informed consent for the application of this vaccine, give the user the informed consent form (see Annex 2), and then proceed step by step, as follows:

Step 1. Vaccine preparation³

- Prepare the materials and supplies required for the preparation and administration of the vaccine: bifurcated needle, disposable gloves, gauze, containers, and a puncture-proof container for biohazard contaminated materials and sharps, etc.
- Cover the work table where the vaccine will be handled with a semipermeable absorbent material, which will provide an additional barrier.
- Wear personal protective equipment (PPE): gloves, gown, surgical mask, and eye protection.⁴
- Remove the vaccine vial from the refrigerator; bring to room temperature of 20°C-25°C before reconstitution. The diluent for reconstitution is kept at room temperature, for immediate use.
- Steps for reconstitution of the vaccine:
 - Wash your hands and change gloves between each vaccinee, to prevent the spread of the virus; avoid contact between skin and vaccine.
 - Remove the flip cap seals from the stoppers on the vaccine and diluent vials.
 - Clean the rubber stopper with the swab moistened with alcohol and wait for it to dry.

3 Sources: Food and Drug Administration. ACAM2000 : package insert. Available from: <https://www.fda.gov/files/vaccines%2C%20blood%20%26%20biologics/published/Package-Insert--ACAM2000.pdf>; Centers for Disease Control and Prevention. Smallpox vaccination and adverse reactions guidance for clinicians. MMWR. 2003;52(4). Available from: <https://www.cdc.gov/mmwr/pdf/rr/rr5204.pdf>; European Medicines Agency. EMA recommends approval of Imvanex for the prevention of monkeypox disease. EMA News, 18/09/2022. Available from: <https://www.ema.europa.eu/en/news/emas-emergency-task-force-advises-intradermal-use-imvanex-jynneos-against-monkeypox>; Centers for Disease Control and Prevention. ACAM2000 medication guide. Atlanta: CDC. Available from: <https://www.fda.gov/media/75800/download>; Centers for Disease Control and Prevention. Video on administering the smallpox vaccine. Atlanta: CDC. Available from: Administering ACAM2000 Smallpox Vaccine Videos | Smallpox | CDC; Fulginiti VA, Papier A, Lane M, Neff JM, Henderson DA, Henderson DA, et al. Smallpox vaccination: a review, part I. Background, vaccination technique, normal vaccination and revaccination, and expected normal reactions. Clin Infect Dis. 2003;37(2):241-250. Available from: <https://doi.org/10.1086/375824>.

4 Pan American Health Organization. How to don and doff personal protective equipment (PPE). Washington, D.C.: PAHO; 2019. Available from: <https://www.paho.org/en/file/90487/download?token=iPlkbVVU>.

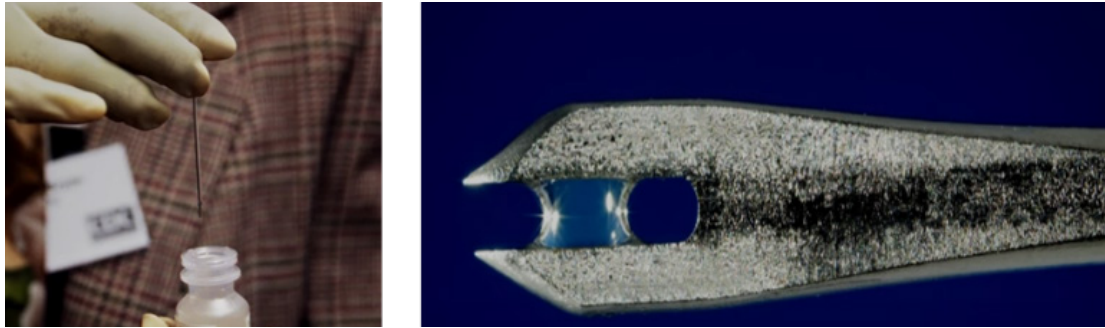
- Using aseptic technique, with a sterile one-milliliter syringe and 2.5-gauge 5/8-inch needle, draw up 0.3 milliliters from the diluent and transfer the entire contents of the syringe to the vial of ACAM2000 vaccine. The bottle of the diluent may contain more volume than necessary. Use only 0.3 ml to reconstitute the vaccine. Discard the syringe in the biosafety box.
- On the surface of the work table, gently swirl the vial of reconstituted vaccine to mix the contents. Try not to get the product on the rubber stopper.
- Visually inspect the reconstituted vaccine. It should be a clear to slightly cloudy, colorless liquid, and free of foreign matter. If particles or discoloration are observed, do not use and dispose of the vial safely as a biohazardous material.
- Record the date and time of reconstitution on the vial. Once reconstituted, the vial should be used within the first 6 to 8 hours. After that time, it is discarded according to the standards, as a biohazardous material.

Step 2. Vaccine administration⁵

- Check the full name of the person to be vaccinated and briefly mention the characteristics of the vaccine to be given.
- Clean the skin around the deltoid muscle with swabs moistened with soap and water; let dry. Do not use alcohol because it could inactivate the vaccine virus.
- Carefully inspect the bifurcated needle packaging to ensure it is intact. Do not use the bifurcated needle if the wrapper is open, damaged or tampered with; dispose of it in a container for biohazard sharps.
- Remove the stopper from the vial of previously reconstituted vaccine and proceed to:
 - Remove the bifurcated needle from its packaging, being careful not to touch the forked end of the needle.
 - Dip the bifurcated end of the needle into the reconstituted vaccine solution. Do not insert the top of the needle that has been in contact with your fingers into the vaccine vial; do not re-dip the needle into the vaccine vial if it has touched skin. The needle will pick up a drop of vaccine inside the fork (Figure A1-1).

5 Sources: Food and Drug Administration. ACAM2000 : package insert. Available from: <https://www.fda.gov/files/vaccines%2C%20blood%20%26%20biologics/published/Package-Insert---ACAM2000.pdf>; Centers for Disease Control and Prevention. Smallpox vaccination and adverse reactions guidance for clinicians. MMWR. 2003;52(4). Available from: <https://www.cdc.gov/mmwr/pdf/rr/rr5204.pdf>; Centers for Disease Control and Prevention. ACAM2000 medication guide. Atlanta: CDC. Available from: <https://www.fda.gov/media/75800/download>; Centers for Disease Control and Prevention. Video on administering the smallpox vaccine. Atlanta: CDC. Available from: [Administering ACAM2000 Smallpox Vaccine Videos | Smallpox | CDC](#); Fulginiti VA, Papier A, Lane M, Neff JM, Henderson DA, Henderson DA, et al. Smallpox vaccination: a review, part I. Background, vaccination technique, normal vaccination and revaccination, and expected normal reactions. Clin Infect Dis. 2003;37(2):241-250. Available from: <https://doi.org/10.1086/375824>.

Figure A1-1. A: Needle inserted into the vial; B: a drop collected in the fork



A

B

Source:
Centers for Disease Control and Prevention. Administering ACAM2000 smallpox vaccine videos, chapter 2, part B: vaccine administration. Atlanta: CDC.
Available from: <https://www.cdc.gov/smallpox/clinicians/administering-acam2000.html>.

- Administer the vaccine by percutaneous route, applying the multiple puncture technique to the skin with the bifurcated needle. It should not be administered by intramuscular, intradermal, subcutaneous, or intravenous route.
- Hold the bifurcated needle between the thumb and index finger, perpendicular to the skin (90°), with the drop removed from the vial on the clean surface of the arm skin. Rest the wrist of the hand holding the needle against the vaccinee's arm. Rapidly perform 15 jabs of the needle perpendicular to the skin, in a diameter of about 5 millimeters. The jabs should be vigorous enough so that drops of blood appear at the vaccination site (Figure A1-2).

Figure A1-2. A and B: Vaccine application technique using multiple punctures (percutaneous route)



A

B

Source:
Centers for Disease Control and Prevention. Administering ACAM2000 smallpox vaccine videos, chapter 2, part B: vaccine administration. Atlanta: CDC.
Available from: <https://www.cdc.gov/smallpox/clinicians/administering-acam2000.html>.

- Discard the bifurcated needle in a biohazard sharps container. Bifurcated needles are for single use only.

- Dry the vaccination site with sterile gauze, wipe any excess vaccine drops and blood from the skin, and discard the gauze in the biohazard container.
- Cover the vaccination site with sterile gauze without pressing. Use adhesive or paper tape to hold it. This will provide a barrier to protect against spread of the vaccine virus. Do not put ointments or creams on the vaccination site.
- Close the vaccine vial with the rubber stopper. Use the reconstituted vaccine within the first 6 to 8 hours.
- Discard gloves and wash your hands immediately with soap and water or use alcohol-based hand sanitizer. This will prevent spread of the vaccine virus if you have been in direct contact with contaminated materials used during vaccine administration.
- Provide post-vaccine recommendations:
 - Avoid rubbing or scratching the vaccination site.
 - Use sterile gauze to cover the vaccination site. This should be discarded safely (place in a red plastic bag, close tightly, and then place in the trash recipient).
 - Wash hands before and after touching the vaccination site and when removing gauze. The vaccinated person's hands or skin can get contaminated with vaccine virus and subsequently touch the mucosa of other people with whom the vaccinee is in contact.
 - The vaccine virus can be transmitted until a dry scab and scar has formed at the vaccination site.

Step 3. Interpretation of vaccination results

After vaccination, instruct the vaccinated person to return in 6 to 8 days to verify the results of vaccination. Explain that the vaccine acts in the skin and develops a skin reaction (provide visual material, see Annex 3).

A **successful response to vaccination**⁶ at the vaccination site consists of:

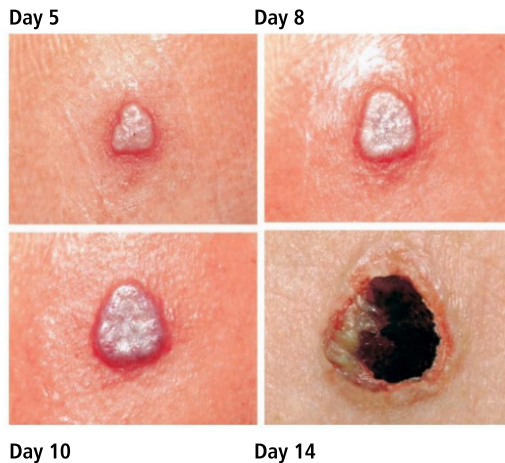
- **First dose:** A papule will form in 2 to 5 days in people who have received the first dose. Then, within 6 to 8 days later, the papule will become a vesicle with surrounding erythema, and then a pustule. The lesion will reach its maximum size at 8 to 10 days after vaccination. The pustule will then dry out, starting from the center outward, and form a scab that will separate in 2 to 4 weeks, leaving a pitted scar at the vaccination site. (Figure A1-3A).

6 Sources: Food and Drug Administration. ACAM2000: package insert. Available from: <https://www.fda.gov/files/vaccines%2C%20blood%20%26%20biologics/published/Package-Insert--ACAM2000.pdf>; Centers for Disease Control and Prevention. Smallpox vaccination and adverse reactions guidance for clinicians. MMWR. 2003;52(4). Available from: <https://www.cdc.gov/mmwr/pdf/rr/rr5204.pdf>; Centers for Disease Control and Prevention. ACAM2000 medication guide. Atlanta: CDC. Available from: <https://www.fda.gov/media/75800/download>; Centers for Disease Control and Prevention. Video on administering the smallpox vaccine. Atlanta: CDC. Available from: [Administering ACAM2000 Smallpox Vaccine Videos | Smallpox | CDC](#); Fulginiti VA, Papier A, Lane M, Neff JM, Henderson DA, Henderson DA, et al. Smallpox vaccination: a review, part I. Background, vaccination technique, normal vaccination and revaccination, and expected normal reactions. Clin Infect Dis. 2003;37(2):241-250. Available from: <https://doi.org/10.1086/375824>.

- **Persons previously vaccinated or revaccinated against smallpox:** may develop a skin reaction with lower intensity and faster progression. About 2 to 8 days after vaccination, they may develop an attenuated or modified skin reaction. (Figure A1-3B).

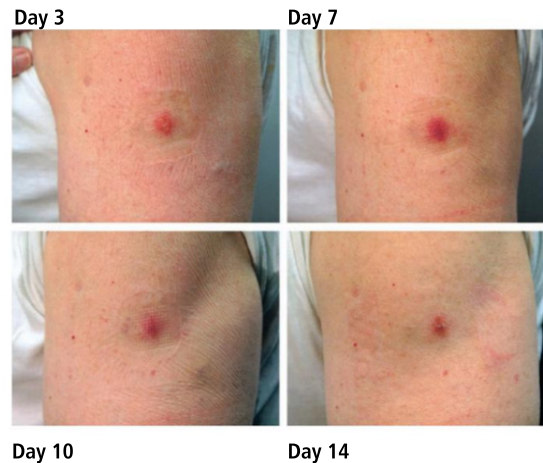
Figure A1-3. Vaccine response in primary and secondary vaccinees. A: Progression of major cutaneous reaction after primary vaccination; B: Progression of minor cutaneous reaction after revaccination

Figure 1: Progression of major cutaneous reaction after primary vaccination



A

Figure 2: Progression of minor cutaneous reaction after revaccination



B

Source:

Rao A. National Center for Emerging and Zoonotic Infectious Diseases. Meeting of the Advisory Committee on Immunization Practices. Background information to interpret GRADE tables and evidence to recommendations framework about Jynneos®, 29 September 2021. Available from: <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-09-29/02-Orthopoxvirus-Rao-508.pdf>.

- **Failed vaccination response:** Some people may have no response or develop erythema at the vaccination site, which may last only a few days. This may indicate that the individual has not had an adequate immune response, that they are immune for viral replication, that the dose of vaccine administered was lower than indicated, or that there was improper vaccination technique. Regardless, if a failed reaction is observed, vaccination procedures should be rechecked and the individual should be revaccinated.

Step 4. Records and follow-up on vaccinees

- Complete the records established by the country at the time of vaccination. The required data are: vaccination site, vaccine used, lot and expiration, and vaccination result (adequate or inadequate), among others. This information must be available to those in charge in case the vaccination status of the population and potential need for revaccination must be determined.
- Give the vaccinee a vaccination card or booklet and instructions for care of the vaccination site. Confirm personal contact information (phone number and email) for subsequent follow-up on the vaccinee.
 - Monitor the vaccination process (check the arm where the vaccine was given). Instruct the vaccinated person to return to the vaccination service for examination of the vaccinated arm 6 to 8 days after vaccination to check the progression and reading of the vaccine scar (see Annex 3).

ANNEX 2. EXAMPLE OF INFORMED CONSENT FORM

Date: _____ 2022 Time: _____

I, _____ have symptoms compatible with mpox; or I have tested positive in the last two weeks; or I am in clinical follow-up for mpox.
Yes () No ()

I have had contact with someone who tested positive for mpox in the last two weeks; or I am in quarantine.
Yes () No ()

I have been informed about (a) the benefits and possible adverse reactions to the mpox vaccine and (b) have voluntarily decided to receive the mpox vaccine. Yes () No ()

Signature or fingerprint:

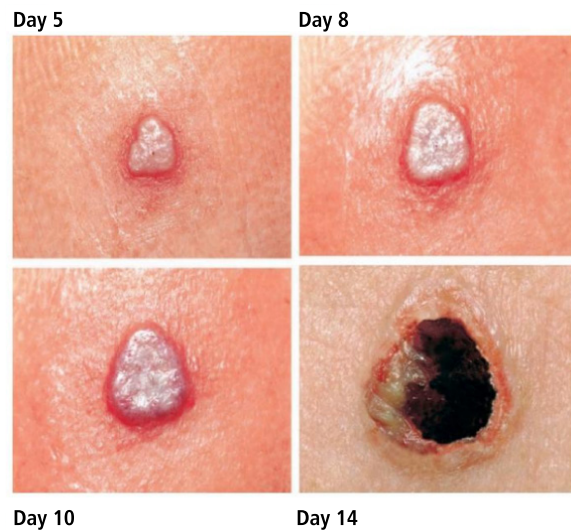
Signature and seal of the healthcare worker who administered and received this form:

.....

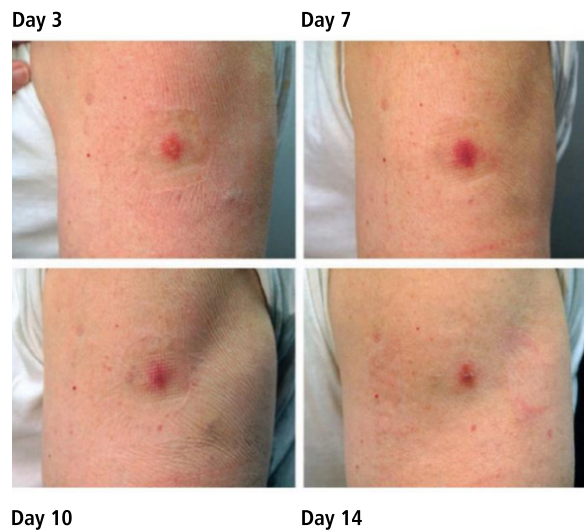
ANNEX 3. PROPOSED ILLUSTRATION OF LESION PROGRESSION IN THOSE WHO RECEIVE THE ACAM2000® VACCINE

Proposed illustration of the progression of the ACAM2000® vaccine, to be given to vaccinees

Major cutaneous reaction after primary vaccination



Minor cutaneous reaction after revaccination



Source:

Rao A. National Center for Emerging and Zoonotic Infectious Diseases. Meeting of the Advisory Committee on Immunization Practices. Background information to interpret GRADE tables and evidence to recommendations framework about Jynneos®, 29 September 2021. Available from: <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-09-29/02-Orthopoxvirus-Rao-508.pdf>.

ANNEX 4. PROCEDURES FOR THE SUBCUTANEOUS ADMINISTRATION OF THE MVA-BN VACCINE

Offer and explain the information sheet on the vaccine to be administered to the potential vaccinee (Annex 5). If the country requires use of informed consent for the application of this vaccine, give the patient the informed consent form (Annex 2), and then proceed step by step, as follows:

- Prepare the materials and supplies required for preparation and administration of the vaccine: syringes, needles, swabs, receptacles and a puncture-proof container for sharps, etc.
- Use the recommended personal protective equipment for regular schedule vaccine administration. This vaccine contains non-replicating live attenuated virus.
- Remove the vaccine vial from the refrigerator and thaw; keep at +2°C to +8°C, do not refreeze.
- Prepare the anatomical site for the application of the vaccine on the deltoid muscle of the non-dominant arm. No other site on the body has been studied or approved by the manufacturer for vaccine administration.
- Clean the skin of the deltoid with swabs moistened with soap and water; let dry. Do not use alcohol because it could inactivate the vaccine virus.
- Swirl the vial gently for 30 seconds before use. Check the appearance of the contents of the vial (homogenous suspension, milky to light yellow color).
- Prepare the sterile 23/25G x 5/8-inch injection syringe, type AD 0.5cc. You can also use a conventional 1cc decimal graduated syringe. Draw a 0.5 ml dose into the syringe.
- Pinch the skin into a fold and insert the metal needle with the bezel up at a 45-degree angle (Figure A4-1) and press the plunger gently into the body.

Figure A4-1. Subcutaneous application technique



© Agence France-Presse

- Remove the syringe and press the injection site with a dry swab; do not rub.
- Discard the syringe in the biosafety box without recapping the needle.
- Record vaccination correctly and completely (date of vaccination, vaccine, dose, lot, and expiration date) and in a timely manner in the documents or systems established by each country.
- Inform the vaccinee about possible post-vaccination events and the importance of completing the two-dose vaccination series, if required. Advise the vaccinee to immediately report any adverse events to their health care provider. Give them the vaccination card or booklet, including information on the vaccine administered, lot, expiration date, dose, whether another additional dose is needed, and surveillance should any event occur.

ANNEX 5. MPOX VACCINE FACT SHEET. MVA-BN

You are being offered a monkeypox virus vaccine **[complete with vaccine name]**, authorized by [insert name of relevant regulatory authority], consisting of 2 doses to be administered at 4-week intervals. Studies available to date show a good safety profile and produce a positive immune system response. You can ask the health personnel in charge about the characteristics of the vaccine, its benefits, risks, as well as the procedure for vaccination. You can also find this information at [www... \[national immunization program website\]](#) and the Pan American Health Organization (PAHO) website: <https://www.paho.org/en/monkeypox>.

You can voluntarily decide if you want to get the vaccine. Regardless of your decision, you should continue prevention measures against possible exposure to mpox. After vaccination, you will stay for 15 to 30 minutes under observation and then you can leave.

As with other vaccines, you may experience pain, slight swelling, or redness at the injection site after getting vaccinated. Some more generalized or severe reactions (such as malaise, headache, and muscle pain) may occur 48–72 hours after vaccination. In case of any discomfort or adverse reaction, you should contact the nearest health center.

We will not share your personal data. All your information will remain confidential. You will be given a document (card or certificate) where the vaccination is recorded and that you must keep to follow up and complete the vaccination schedule.

ANNEX 6. INTRADERMAL (ID) APPLICATION OF THE MVA VACCINE

BACKGROUND

On 9 August 2022, the US Food and Drug Administration issued an emergency use authorization for intradermal use of the Jynneos® vaccine in people 18 years of age and older classified as high risk for mpox infection. Data from a clinical study by Frey et al on the MVA vaccine has demonstrated an immune response similar to subcutaneous administration. People who received the vaccine intradermally received one-fifth (0.1 ml) of the subcutaneous dose (0.5 ml), but produced antibody levels similar to those who received the higher subcutaneous dose.⁷

With the use of the intradermal route, an increased risk of local reactions (longer lasting redness and thickening or discoloration of the skin) was detected.

On 19 August 2022, the European Medicines Agency revised information on the Imvanex® vaccine for ID application, indicating that it could be administered intradermally at a lower dose as a temporary measure to protect people at risk during the current outbreak of mpox while supply of the vaccine remains limited.⁸

PROCEDURE FOR INTRADERMAL ADMINISTRATION OF JYNNEOS® VACCINE⁹

Offer and explain to the user the information sheet on the vaccine to be administered (Annex 5). If the country requires informed consent for application of this vaccine, give the user the informed consent form (Annex 2), and then proceed step by step, as follows.

This route of application is indicated for people aged 18 and over.

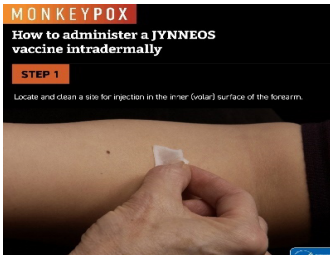

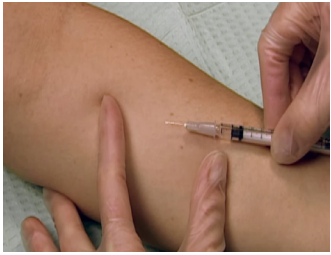
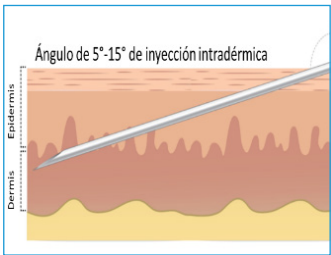

Figure A6 shows the procedure for intradermal administration of the Jynneos® vaccine.

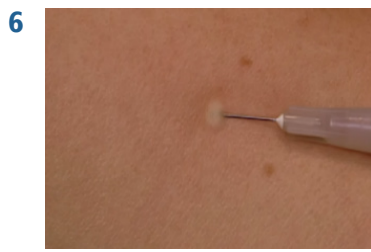
7 Food and Drug Administration. FDA Authorizes Emergency Use of Monkeypox JYNNEOS Vaccine, 9 August 2022. Silver Spring: FDA; 2022. Available from: <https://www.fda.gov/news-events/press-announcements/monkeypox-update-fda-authorizes-emergency-use-jynneos-vaccine-increase-vaccine-supply>.

8 European Medicines Agency. EMA recommends approval of Imvanex for the prevention of monkeypox disease. EMA News, 18/09/2022. Available from: <https://www.ema.europa.eu/en/news/emas-emergency-task-force-advises-intradermal-use-imvanex-jynneos-against-monkeypox>

9 Centers for Disease Control and Prevention. Interim clinical considerations for use of JYNNEOS during the 2022 U.S. monkeypox outbreak. Atlanta: CDC; 2022. Available from: <https://www.cdc.gov/poxvirus/monkeypox/health-departments/vaccine-considerations.html>; Fulginiti VA, Papier A, Lane M, Neff JM, Henderson DA, Henderson DA, et al. Smallpox vaccination: a review, part I. Background, vaccination technique, normal vaccination and revaccination, and expected normal reactions. Clin Infect Dis. 2003;37(2):241-250. Available from: <https://doi.org/10.1086/375824>.

Figure A6. 1-10: Procedure for intradermal administration of the Jynneos® vaccine

-
- 1**  Locate and clean a site for injection on the volar forearm.
 - 2**  Use the thumb and index finger to pull the skin taut.
 - 3**  Position the needle with the bevel facing up and insert the needle at a 5° to 15° angle into the dermis.
 - 4**  Illustration showing the location of the dermis.
 - 5**  Slowly inject 0.1 milliliters of the vaccine intradermally.
-



As the vaccine enters the dermis, a noticeable pale elevation of the skin, or wheal, will occur.



This is how the skin will look once the needle is removed.



Discard the syringe in a biosafety container.



Keep the vaccinee under observation for 15 minutes (or 30 minutes if they have a history of anaphylaxis to gentamicin, ciprofloxacin, chicken, or egg protein).

-
- 10 Inform the vaccinee about possible post-vaccination events and the importance of completing the two-dose vaccination series if required. Advise the vaccinee to immediately report any adverse event to their health care provider in the country, and give the vaccinee the vaccination card or booklet, including the vaccine administered, expiration, lot number, and dose. This will help if another dose is required and also facilitate surveillance of any event that may occur.
-

Sources:

Centers for Disease Control and Prevention. How to administer a Jynneos vaccine intradermally. Atlanta; CDC. Available from: <https://www.youtube.com/watch?v=TLv1mR6mECQ>; Centers for Disease Control and Prevention. Interim clinical considerations for use of JYNNEOS and ACAM2000 vaccines during the 2022 U.S. monkeypox outbreak. Atlanta: CDC; 2022. Available from: <https://www.cdc.gov/poxvirus/monkeypox/health-departments/vaccine-considerations.html>.

On 23 July 2022, the WHO Director-General declared the mpox outbreak a public health emergency of international concern (PHEIC) (10). A coordinated response was launched, aimed at interrupting transmission and protecting vulnerable groups, and a number of recommendations were made, including vaccination.

These temporary recommendations apply to different groups of countries, based on their epidemiological situation, patterns of transmission, and capacities. These recommendations include different aspects such as: the implementation of a coordinated response, community engagement and protection, surveillance and public health measures, clinical management, and infection control, among others. WHO recommends use of the vaccine for countries that have imported cases of mpox in the population and/or human-to-human transmission of monkeypox virus, including in key population groups and communities at high risk of exposure.

PAHO



Pan American
Health
Organization



World Health
Organization
Americas