VIII Ad Hoc Meeting of PAHO’s Technical Advisory Group (TAG) On Vaccine-Preventable Diseases

Technical Briefing on the Multi-Country Monkeypox Outbreak

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31 May 2022
Virtual
VIII Ad Hoc Meeting of PAHO’s Technical Advisory Group (TAG) On Vaccine-Preventable Diseases

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Introduction

Monkeypox has been endemic in central and west Africa since its first detection in 1958 in the Democratic Republic of the Congo (1). However, since 13 May 2022 multiple countries in Europe have reported the sudden and unexpected appearance of monkeypox. To date, 27 non-endemic countries across four WHO regions have reported cases. Of these, four are countries in the Americas. Multiple suspected cases in these and other countries are currently under investigation (2).

The following report summarizes the epidemiological data to date, reviews available information on monkeypox vaccines, and provides recommendations to Member States of the Americas on how to minimize viral transmission and approach vaccination operations.

Epidemiology of the disease (3)

Monkeypox virus is an Orthopoxvirus that causes a disease with symptoms similar, but less severe, to smallpox. While smallpox was eradicated in 1980, monkeypox continues to occur in countries of Central and West Africa. Two distinct clades are identified: the West African clade and the Congo Basin clade.

Monkeypox is a zoonosis. Cases are often found close to tropical rainforests where various animals carry the virus including squirrels, rodents, dormice, and monkeys. Most human monkeypox infections in endemic countries result from a primary animal-to-human transmission. Human-to-human transmission does occur, with the longest documented chain of transmission being six generations. Transmission occurs through contact with bodily fluids, lesions on the skin or on internal mucosal surfaces, such as in the mouth or throat, respiratory droplets, and contaminated objects. Close contact with infected people or contaminated materials should be avoided. While human-to-animal transmission is rare, it should be considered as a possible link in the transmission chain.

Monkeypox presents with fever, an extensive characteristic rash, and usually swollen lymph nodes. Caregivers need to distinguish monkeypox from other illnesses such as chickenpox, measles, bacterial skin infections, scabies, syphilis, and medication-associated allergies.

The incubation period of monkeypox can range from 5 to 21 days. The febrile stage of illness usually lasts 1 to 3 days with symptoms including fever, intense headache, lymphadenopathy, back pain, myalgia, and intense asthenia. The febrile stage is followed by the skin eruption 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 case fatality rate of the disease has varied between 0% and 11% in documented cases and has been higher among young children and people with HIV (4, 5). The West African clade, which has been documented in cases of the recent outbreak (6), is associated with an overall mortality rate lower than 3% (7).
Prevention and control of human monkeypox rely on raising awareness in communities and educating health workers to prevent infection, detect cases, and stop transmission.

It is important to note that much of the information available on monkeypox was developed in a setting of high population levels of smallpox vaccination. Forty years after smallpox eradication and the end of all vaccination activities, there are many questions on how the Monkeypox virus will behave under current conditions. The World Health Organization (WHO) and the Pan American Health Organization (PAHO) will update their guidance as additional information becomes available.

Monkeypox epidemiological update – World (as of 4 June 2022) (2)

As of 4 June 2022, a total of 780 confirmed cases in 27 countries cases were reported across four WHO regions. As of 2 June 2022, there have been no deaths associated within the current monkeypox outbreak in non-endemic countries. However, cases and deaths continue to be reported from endemic countries.

Epidemiological investigations are ongoing. Reported cases thus far have no established travel links to endemic areas. Transmission may have been amplified by a point source event or events, and retrospective investigations are still ongoing. The sudden and unexpected appearance of monkeypox (within several non-endemic countries where this disease has never been reported or where there have only been cases linked to endemic countries) suggests that there has been undetected transmission for some time.

Current evidence suggests that those who are most at risk are those who have had close physical contact with someone with monkeypox while they are symptomatic, even before the appearance of lesions. Based on currently available information, cases have mainly but not exclusively been identified among men who have sex with men (MSM) seeking care in primary care and sexual health clinics. Countries are beginning to report cases of apparent community transmission, including some cases in women.

To date, all cases whose samples were confirmed by polymerase chain reaction (PCR) have been identified as being infected with the West African clade. The first reported sequence is close to a West Africa strain from cases imported from Nigeria in 2018–2019.

Monkeypox epidemiological update – Americas (as of 2 June 2022) (8)

As of 2 June 2022, 82 confirmed cases and 14 suspected cases were reported in the Region of the Americas. Beyond the number of cases, there are hardly any epidemiologic data available from countries – possibly to minimize discrimination for the population groups currently affected. Information on ongoing investigations is not available either.

- The Public Health Agency of Canada reported 58 confirmed cases on 2 June 2022, of which 51 were identified in the province of Quebec (9).
• The United States Centers for Disease Control and Prevention (US CDC) reported a total of 21 confirmed cases in the country (10).

• Mexico reported one confirmed case of monkeypox on 29 May 2022, with epidemiological link to the Netherlands (11).

• In Argentina, two confirmed cases have been reported. At least one has an epidemiological link to countries in Europe (12).

• In Uruguay, according to a 2 June 2022 press release from the Ministry of Health, four suspected cases of monkeypox have been identified in the country among persons with history of travel to countries that have reported confirmed or suspected cases.

• Costa Rica provided further information regarding the first suspected case of monkeypox in the country. The case corresponds to a 21-year-old female with history of travel to Norway and onset of symptoms on 27 May 2022. A total of seven contacts have been identified.

Diagnostics capacity in the Americas

Detection of viral DNA by PCR is the preferred laboratory test for monkeypox. The best diagnostic specimens are directly from the rash – skin, fluid or crusts, or biopsy where feasible. Antigen and antibody detection methods may not be useful as they do not distinguish between orthopoxviruses.

Currently, countries in Latin America and the Caribbean do not have PCR capacity specific for monkeypox. WHO and PAHO have developed guidelines for laboratory diagnostics, and are working to acquire and distribute the necessary primers and probes (13, 14). PCR capacity should gradually become available by mid-June 2022. In the meantime, a few countries are using a PCR generic for orthopoxviruses followed by molecular sequencing.

Definition of a close contact (15)

A close contact is defined as a person who, in the period beginning with the onset of the source case’s first symptoms, and ending when all scabs have fallen off, has had one or more of the following exposures with a probable or confirmed case of monkeypox:

• Face-to-face exposure (including health workers without appropriate personal protective equipment [PPE]).

• Direct physical contact (including health workers without appropriate PPE), including sexual contact.

• Contact with contaminated materials such as clothing or bedding (including health workers without appropriate PPE).

Routine vaccination is recommended for laboratory personnel who directly handle: 1) cultures; or 2) animals contaminated or infected with replication competent vaccinia virus, recombinant vaccinia viruses derived from replication-competent vaccinia strains (i.e., those that are capable of causing clinical infection and producing infectious virus in humans), or other orthopoxviruses that infect humans (e.g., monkeypox, cowpox, variola). Clinical laboratory personnel performing
diagnostic testing for orthopoxviruses, health workers in care for patients infected with orthopoxviruses, and response teams at high risk of exposure are also recommended for routine vaccination. Laboratory personnel who perform routine chemistry, hematology, and urinalysis testing for the general public, including for patients with suspected or confirmed Orthopoxvirus infections, are not included in this recommendation because their risk for exposure is very low (16, 17).

Recommended practices for surveillance, contact tracing and isolation (19)

- The key objectives of surveillance and case investigation for monkeypox in the current context are to: a) rapidly identify cases and clusters in order to provide optimal clinical care; b) isolate cases to prevent further transmission; c) identify and manage contacts, including quarantine of close contacts who develop symptoms; d) protect frontline health workers; and e) tailor effective control and prevention measures.
- Immediate actions should focus on: a) informing those who may be most at risk for monkeypox virus (MPXV) infection with accurate information; b) stopping further spread; and c) protecting frontline workers.
- Clinicians should report suspected cases immediately to public health authorities.
- If monkeypox is suspected, case investigation should consist of clinical examination of the patient with appropriate PPE, questioning the patient about possible sources of infection, and safe collection and dispatch of specimens for MPXV laboratory examination.
- Any individual that meets the suspected case definition for monkeypox should be offered testing.
- As soon as a suspected case is identified, contact identification and contact tracing should be initiated.
- Contacts should be monitored at least daily for the onset of any signs/symptoms for a period of 21 days from last contact with a patient or their contaminated materials during the infectious period.
- Quarantine or exclusion from work are not necessary during the contact tracing period as long as no symptoms develop. Quarantine or self-isolation following contact with a case should begin the moment of experiencing any feelings of being unwell such as fever, headache or body aches. Such contacts should seek immediately health care.

WHO recommendations to date (4)

1. **Travel**: WHO does not recommend travel restrictions to any countries at this time.
2. **Therapeutics**: Treatment of monkeypox patients is dependent on the symptoms. Recently, tecovirimat, a new antiviral, was licensed by regulatory authorities in the European Union (European Medicines Agency [EMA]) (18) and in the United States of America (Food and Drug Administration [FDA]) (19) to treat smallpox, monkeypox and cowpox. The use of tecovirimat can be considered under investigational or compassionate
use protocols, particularly for those who have severe symptoms or who may be at risk of poor outcomes (such as immunosuppressed persons). However, this therapeutic option is not yet widely available.

3. **Vaccination**: Vaccination, where available, is being deployed as a preventive measure to persons who may have been exposed, such as household members as well as health workers and laboratory personnel without appropriate PPE. Post-exposure vaccination (ideally within four days of exposure) may be considered by some countries for higher risk close contacts such as health workers or family members in the same household. WHO is not recommending mass vaccination at this time.

**Description of the smallpox and monkeypox vaccines currently available**

The first FDA-licensed smallpox vaccine was Dryvax in 1931. This was a lyophilized live virus vaccine known as first-generation vaccines, made from lymph or skin from inoculated animals. Production was suspended following the eradication of smallpox. There are currently some other equivalent vaccines available. Smallpox vaccination demonstrated 85% efficacy in preventing monkeypox.

1. **ACAM2000 (20, 21):**
   a. **Description**: A second-generation vaccine derived from a clone of the vaccinia virus (Dryvax) that has been purified and produced using cell cultures. The vaccine contains the replicating live virus (vaccinia) and is administered to the surface of the skin by scarification. At the injection site an injury is generated, which then progresses to vesicles. The virus can continue to replicate and spread to other parts of the body and can eventually infect people who are in contact. ACAM2000 was approved by FDA for the prevention of smallpox. The vaccine is recommended for laboratory personnel working with *Orthopoxvirus* and military personnel at risk of exposure to this virus. This vaccine is not recommended for people with immune deficiencies and exfoliative skin disorders, such as eczema or atopic dermatitis.

   b. **Safety**: The majority of adverse events (AE) reported were mild or moderate in intensity. Injection site itching was the most commonly reported AE reported in 93.3%–100.0% of subjects. The next most reported AE were lymph node pain (81.1%), injection site pain (77.8%), fatigue (68.9%), headache (60.0%), myalgia (58.9%) and malaise (57.7%). Commonly reported gastrointestinal disorders subjects included nausea and diarrhea (14%), constipation (6%), and vomiting (4%). Since ACAM2000 is replication-competent, there is a risk for serious AE (e.g., progressive vaccinia and eczema vaccinatum, myopericarditis), but the underlying mechanism is unknown.

   c. **Efficacy**: Vaccine efficacy was assessed by comparing the immunologic response of ACAM2000 to another US-licensed live vaccinia virus smallpox vaccine, Dryvax, in two randomized, multi-center active-controlled clinical trials. In previously
vaccinated subjects, ACAM2000 was non-inferior to the comparator with regard to the strength of the neutralizing antibody immune response. Therefore, ACAM2000 was non-inferior to the comparator in the rate of major cutaneous reaction in those naïve to the vaccine, and the strength of the neutralizing antibody immune response in those previously exposed to vaccinia-based smallpox vaccines (22).

2. **JYNNEOS MVA-BN** (23):
   a. **Description**: Modified Vaccinia Ankara – Bavarian Nordic. It is a non-replicating live attenuated virus vaccine, originating from a highly attenuated strain of poxvirus (Chorioallantois Vaccinia Virus Ankara or CVA). The vaccine is administered subcutaneously, and two doses are required four weeks apart. The FDA approved it in 2019 for use in people over the age of 18 and it was specifically licensed to prevent monkeypox. Whereas is a non-replicating vaccine, there is no risk of spreading the virus.
   b. **Safety**: Data from multiple clinical trials show that MVA-BN has a favorable AE profile compared with 1st and 2nd generation vaccines that have been studied in the pre- and post-eradication era. In the phase 3 clinical trial, there were fewer AE of grade 3 or higher after both MVA vaccination periods in the MVA group than in the ACAM2000-only group (24). The vaccine was well tolerated, with no clinically relevant differences between the populations studied. No confirmed case of myopericarditis or any other cardiac inflammatory event in any MVA-BN clinical trial was observed.
   c. **Efficacy**: In a 2019 phase 3 efficacy trial (8), MVA vaccination induced a detectable response by week 2, with neutralizing antibodies peaking at week 6. This compares with a lower peak GMT in the ACAM2000 group at week 4. At day 14, the GMTs induced by a single MVA vaccination was equal to that induced by ACAM2000, and the percentages of participants with seroconversion were similar (90.8% and 91.8%, respectively).

3. **VACDelta6** (25):
   a. **Description**: Is a 4th generation vaccine against smallpox and other *Orthopoxvirus* infections. It is a cell-derived vaccine based on a strain of vaccinia virus with six inactivated virulence genes. Preclinical studies shown a significantly lower reactogenicity and neurovirulence compared to the original clonal LIVP variant. It induces generation of significantly higher levels of virus neutralizing antibodies compared to the original clonal LIVP variant. This vaccine is currently under development by the Russian Government.

4. **LC16m8** (26):
   a. **Description**: Licensed in Japan in 1975 for smallpox prevention. It is a 3rd generation vaccine, to be given in a prime / boost schedule. It is the only smallpox
vaccine approved for use in children. The shelf life of bulk vaccine substance was 5 years when stored at -80°C, and four years for the final product stored at -20°C. As part of Japan’s national strategic stockpile, this vaccine is not available to the general public. It is recommended for the general population only in case of a smallpox outbreak.

b. **Safety:** The safety of the vaccine had been confirmed in children, as well as in immunocompromised animal models. Vaccination had not yet been recommended for use in immunocompromised persons.

c. **Efficacy:** Preliminary findings indicated the efficacy profile of LC16m8 to be equivalent to Dryvax.

### Availability of smallpox and monkeypox vaccine on the global market

There are only two manufacturers of smallpox and monkeypox vaccines in the world. At this time, the doses are only available in the strategic stockpiles of a few countries, as well as in WHO’s physical reserve (27):

To date, there is no timeline as to if or when these vaccine doses may become available to the global community.
<table>
<thead>
<tr>
<th></th>
<th>1st generation</th>
<th>2nd generation</th>
<th>3rd generation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Virus</strong></td>
<td>Vaccinia virus. Lyophilized live virus vaccine, made from lymph or skin from inoculated animals.</td>
<td>Vaccinia virus, a clone of Dryvax. A replication-competent vaccine; produced using cell cultures.</td>
<td>Chorioallantois Vaccinia Virus Ankara or CVA. A non-replicating live attenuated virus vaccine, originating from a highly attenuated strain of poxvirus, produced using cell cultures.</td>
</tr>
<tr>
<td><strong>Name (Manufacturer)</strong></td>
<td>Dryvax (Wyeth)</td>
<td>ACAM2000 (Emergent)</td>
<td>MVA (Bavarian Nordic)</td>
</tr>
<tr>
<td><strong>Regulatory status</strong></td>
<td>FDA licensed 1931 for prevention of smallpox. Production was discontinued.</td>
<td>FDA approved 2007 for prevention of smallpox.</td>
<td>JYNNEOS, FDA 2019 IMVAMUNE (CAN) approved for prevention of smallpox and monkeypox. IMVANEX, (EU, EMA 2013: smallpox)</td>
</tr>
<tr>
<td><strong>Administration &amp; dosing</strong></td>
<td>Administered in a single dose by the percutaneous route using a bifurcated needle.</td>
<td>Administered in a single dose by the percutaneous route (scarification) using 15 jabs of a stainless-steel bifurcated needle.</td>
<td>Administered by subcutaneous injection in 2 doses (0.5 ml each) at 0 and 4 weeks for primary vaccinees. Subjects previously vaccinated against smallpox receive a single 0.5 ml dose.</td>
</tr>
<tr>
<td><strong>Recommended use (28)</strong></td>
<td>• Persons with a known smallpox virus exposure unless severely immunodeficient • Persons at high risk for smallpox infection (as defined by public health authorities) unless severely immunodeficient or relatively contraindicated.</td>
<td>Persons at high risk for smallpox infection without a known smallpox virus exposure with a relative contraindication to smallpox vaccination including: – Persons with atopic dermatitis (eczema) – Persons with immunocompromised states – Persons with vaccine or vaccine-component allergies</td>
<td></td>
</tr>
<tr>
<td><strong>“Take”</strong></td>
<td>“Take” occurs</td>
<td>No “take” after vaccination</td>
<td></td>
</tr>
<tr>
<td><strong>Inadvertent inoculation and autoinoculation</strong></td>
<td>Risk exists</td>
<td>No risk</td>
<td></td>
</tr>
<tr>
<td><strong>Contraindications (29)</strong></td>
<td>Atopic dermatitis, other active exfoliative skin conditions, immunosuppression, breastfeeding, serious vaccine component allergy, underlying heart disease</td>
<td>Serious vaccine component allergy</td>
<td></td>
</tr>
</tbody>
</table>
None of the vaccines currently available in the strategic stockpiles has received Emergency Use Listing (EUL) approval from the WHO. The WHO stockpile does not include 3rd generation vaccines against monkeypox. While 1st generation vaccines were used to eradicate smallpox, they can cause multiple adverse effects, including eczema vaccinatum, progressive vaccinia, and myopericarditis. Continued concerns over vaccine safety and fears of smallpox release have fueled research on safer, better-characterized vaccines. These concerns have advanced development of 2nd and 3rd generation vaccines. However, questions remain regarding the breadth and quality of response, protection of immunocompromised individuals (30).

Given the unusual increase in cases of monkeypox reported in the PAHO epidemiological alert of May 20, 2022, the Revolving Fund for Access to Vaccines (RFV) contacted the two manufacturers of this vaccine in order to investigate availability, delivery times, cold chain requirements, among other aspects.

TAG Recommendations

1. The TAG commends PAHO for its proactive response to the recent outbreaks of monkeypox in Europe and the Americas. TAG urges PAHO to monitor these outbreaks and their investigations closely and support enhancement of the preparedness and response of countries in order to curtail the spread of monkeypox in the Americas as soon as possible. PAHO will facilitate countries by, inter alia, preparing resource material for training health and frontline workers as well as risk communication, simplifying the WHO case definition, facilitating laboratory diagnostic capacity in countries and leading negotiations for access to vaccines, therapeutics and other essential items on behalf of the Region.
2. The TAG urges countries to review WHO’s recommendation (31) for monkeypox surveillance and control – including syndromic identification, notification, laboratory diagnostics, contact tracing and isolation/quarantine – and develop national guidelines to implement these operations. Countries must clearly define the characteristics of a close contact (32) of a monkeypox confirmed case (e.g., type of contact, time since last contact, travel history) and evaluate the risk of transmission (33). It is imperative that countries implement these operations thoroughly and interrupt all transmission chains as soon as possible, since this is the most effective and readily available option to stop the outbreak.

3. To avoid overburdening national laboratories that are still processing large quantities of COVID-19 samples, the TAG recommends that WHO and PAHO provide clear, simple algorithms for differential diagnostics of different rashes and skin lesions (with pictures). These guidelines must be disseminated widely in healthcare settings (including primary care, emergency rooms and dermatology clinics) and in the community to facilitate identification of suspected cases.

4. Countries must define and enforce infection prevention and control (IPC) measures in all settings where monkeypox cases are found in order to limit viral transmission including strategies for partners and household members of confirmed cases. Strict adherence to guidelines for the correct use of personal protective equipment (PPE) in health settings is strongly encouraged (34) especially for health personnel who offer care to suspected monkeypox cases.

5. The TAG urges the RFV to negotiate access to monkeypox vaccines on behalf of the 42 Member States and to procure vaccine doses for all countries based on their epidemiological situation. Negotiations must take into account technical regulatory criteria, vaccine effectiveness and safety, the limited availability of vaccine doses and price.

6. The TAG strongly endorses the WHO recommendation (35) that only close contacts of a confirmed monkeypox case should be offered vaccination. Post-exposure vaccination (ideally within four days of exposure) may be considered by some countries for high-risk close contacts (28). TAG recommends that PAHO establish clear guidelines regarding which Monkeypox vaccine should be made available to close contacts of confirmed cases, depending on their risk of infection and risk of developing adverse events. Most persons aged 50 years or older would have received the smallpox vaccination and should be given only a single dose of a 3rd generation vaccine as a booster. There is no place for mass vaccination currently, nor are there sufficient supplies of vaccine to do this.

7. The TAG recognizes that all monkeypox vaccines can generate adverse events. Therefore, when proposing vaccination to a close contact, countries must inform the person of the possible sequelae of vaccination and offer alternative infection control measures where feasible.
8. If countries use 3rd generation vaccines, the route of application is subcutaneous and requires no additional training for their administration. However, if countries use 2nd generation monkeypox vaccines, they should provide training to vaccinators in order to minimize programmatic errors and adverse events – since health personnel are not trained in the scarification administration technique required for this vaccine.

9. Ministries of Health should work closely with national and local civil society organizations to develop communication strategies that help prevent unnecessary risks while fostering community trust and engagement. Care must be taken to avoid stigmatizing language.

References


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