# Background document for the SAGE October 2022 session on monkeypox vaccines

## Background document to the Vaccines and immunization for monkeypox interim guidance

16 November 2022

World Health Organization

Note: This background document was developed to inform the initial recommendation-making process. It will not be updated on a regular basis.

# Contents

## Introduction

In April 2022, a Strategic Advisory Group of Experts (SAGE) on Immunization Working Group on smallpox and monkeypox vaccines was established to advise the World Health Organization (WHO) on the use of smallpox vaccines and update the 2013 recommendations on smallpox vaccines. In May 2022, a multi-country outbreak of monkeypox began and rapidly spread around the world. In response to the 2022 monkeypox multicounty outbreak, an interim guidance on vaccines and immunization for monkeypox was published on 24 June 2022 and updated on the 24th of August.

This background document has been prepared by the SAGE working group on smallpox and monkeypox vaccines to inform the discussions of SAGE at its 3-7 October 2022 meeting.

Declarations of interest were collected from all external contributors and assessed for any conflicts of interest. Summaries of the reported interests can be found on the SAGE meeting website and SAGE Working Group website.

The working group met between April 2022 and September 2022 via teleconferences. A rapid review has been prepared by WHO to complement the 2013 review with the latest available evidence.

The rapid review evaluated the safety, immunogenicity, efficacy and effectiveness of smallpox vaccines (ACAM2000, MVA-BN, LC16m8) against monkeypox in subjects with high risk of exposure to monkeypox virus, in different population groups. The rapid review investigated the effects of vaccines in the following scenarios:

- Primary preventive (pre-exposure) vaccination (PPV) of persons with a high risk of exposure to monkeypox
- Post-exposure preventive vaccination (PEPV) of close contacts of MPX cases

## Epidemiology of the 2022 monkeypox multi-country outbreak

From 1 January through 26 September 2022, 65,295 laboratory-confirmed cases of monkeypox and 26 deaths have been reported to WHO from 105 countries/territories/areas in all six WHO Regions. In week 37 (12-18 September) days, 25 countries reported an increase in the weekly number of cases, with the highest increase reported in Chile. There are 32 countries that have not reported new cases in the 21 days preceding week 37

The number of weekly new cases reported globally decreased by 22% in week 37 (12 -18 September) (n=3794 cases) compared to week 36 (5-11 September) (n=4863 cases). The majority of cases reported in the past 4 weeks were notified from the Region of the Americas (80.3%) and the European Region (18.6%) (Table 1).

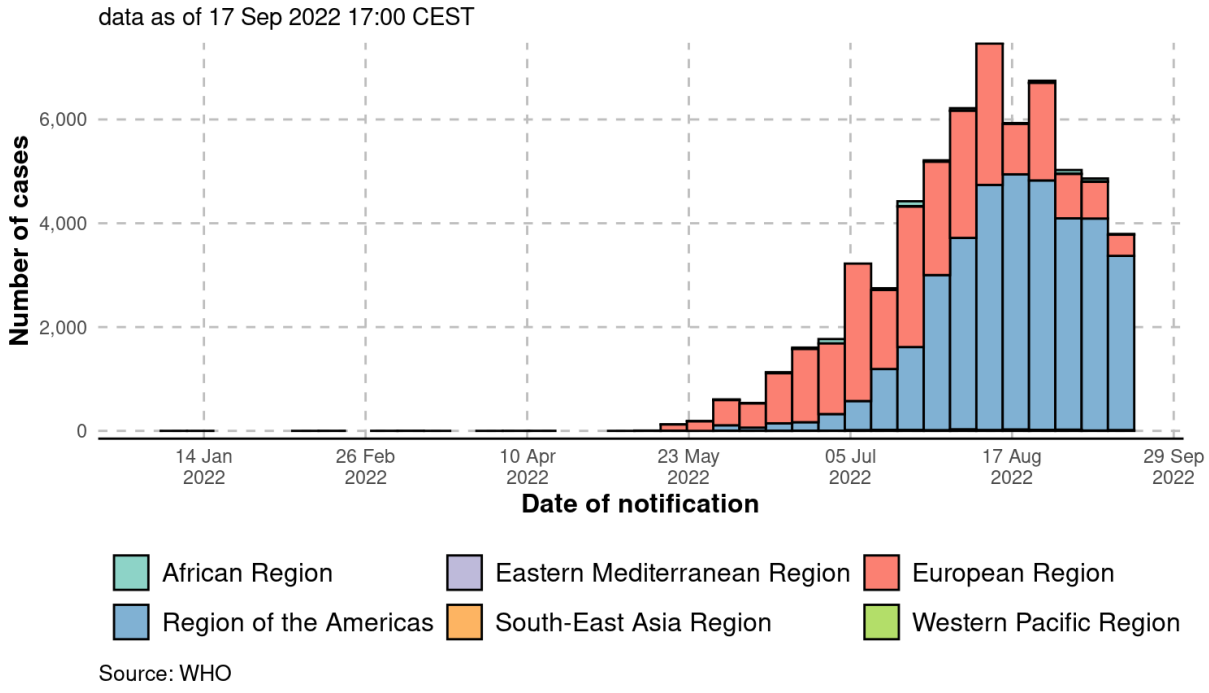
The outbreak continues to affect young men, with 97.4% (31295/32125) of cases with available data on gender being men with a median age of 35 years (Interquartile range: 30-42 years). Fewer than 1% (293/33,363) of cases with age data available are aged 0-17 years, out of which 86 (0.3%) were aged 0-4 years. This proportion differs between regions, with the largest proportion of cases aged 0-17 being reported from the Region of the Americas (164 /293; 56%).

Among cases with sexual orientation reported, 90.9% (13940/15339) identified as men who have sex with men. Of all reported types of transmission, a sexual encounter was most commonly reported, with 10,215 of 11,242 (90.9%) of all reported transmission events.

Among cases with known HIV status, 42.2% (7709/17,444) are HIV positive. It must be noted however, that information on HIV status is not available for the majority of cases.

415 cases were reported to be health workers. However, most were infected in the community and further investigation is ongoing to determine whether the remaining infections were due to occupational exposure. Several countries have reported single cases of health workers infected with monkeypox virus through needle-stick injuries.

*Table 1. Number of cumulative confirmed monkeypox cases reported to WHO, by WHO Region, from 1 January 2022 to 17 September*




*Epidemiology in West and Central Africa*

Since 1970, human cases of monkeypox have been reported in 9 countries in the WHO African region: Cameroon, Central African Republic, Congo, Côte d'Ivoire, Democratic Republic of the Congo, Gabon, Liberia, Nigeria, and Sierra Leone *(1)*. The true burden of monkeypox in these countries is not known. Notably, while the ongoing 2022 monkeypox outbreak has been associated with Clade II (formerly known as the West African clade) of monkeypox virus, which is less virulent than Clade I (formerly known as the Congo basin clade), historically outbreaks have been driven by Clade II and Clade I.

Historically, the sexual component of transmission in the countries in West and Central Africa has been thought to contribute less to human-to-human transmission of monkeypox than has been observed in the ongoing global outbreak. It should also be noted that there is limited testing capacity for monkeypox in many of these countries, which has led to under ascertainment of monkeypox cases.

In 2022, as of 19 Sep 2022, there have been 495 confirmed cases of monkeypox reported in these countries and 10 deaths. These represent 1% and 43% of global cases and deaths respectively.

In addition, 173 (35% of all cases) detailed cases have been reported to WHO. Of those cases with detailed data, 110 male cases (64.3%) and 61 female cases (35.7%) have been reported. The median age is 25 (IQR: 11 - 35). Of the 168 cases where age was available, there were 65 (38.7% of total) cases reported aged 0-17, out of which 21 (12.5% of total) were aged 0-4. There are currently no detailed cases for which transmission or exposure setting detail is available.

For updated information a public global epidemiology report is available online.

## Monkeypox

Monkeypox is an infectious disease caused by the monkeypox virus (MPXV). This double-stranded DNA virus is a member of the *Orthopoxvirus* genus in the Poxviridae family, related to the virus which caused smallpox (eradicated in 1980). While monkeypox is a zoonotic disease, human monkeypox has been reported since 1970, with cases of monkeypox rising in recent years. The increase in human monkeypox incidence has been associated with the decreasing population immunity to orthopox viruses after cessation of worldwide smallpox vaccination campaigns *(2)*. Spread of monkeypox from person to person has been known in the past to generally require prolonged close contact, such as face-to-face contact in close proximity, or skin-to-skin physical contact. Such exposure can occur in a range of settings including at home, in social or sexual networks, or in the health care setting.

## Clinical manifestations

Monkeypox can cause a range of clinical signs and symptoms. The initial phase of clinical illness typically lasts 1 to 5 days, during which time patients may experience fever, headache, back pain, muscle aches, lack of energy and lymphadenopathy – which is a characteristic of this disease. This is followed by a second phase, which typically occurs 1 to 3 days after fever subsides with the appearance of a rash. The rash presents in sequential stages – macules, papules, vesicles, pustules, umbilication before crusting over and desquamating over a period of 2 to 3 weeks *(3)*. Monkeypox can also present with fewer typical features, such as less severe illness, fewer or less widely disseminated lesions, appearance of lesions before constitutional symptoms such as fever, or appearance of lesions in different stages of development. Such atypical features are being observed in the current outbreak. A person with monkeypox may be infectious from the onset of any symptoms until all scabs have fallen off, leaving intact skin underneath. Resolution of skin lesions may take up to four weeks from prodrome onset.

Monkeypox is usually self-limiting, and most people recover within a few weeks. The risk of severe disease and complications such as secondary infection, sepsis, pneumonia and encephalitis may be increased in immunocompromised persons, young children and pregnant women *(4) (5, 6)*. In this outbreak, new clinical complications have been observed such as severe proctitis.

## Smallpox and monkeypox vaccines and regulatory status

Smallpox vaccines produced and successfully used during the intensified smallpox eradication programme (SEP) are called first-generation vaccines in contrast to smallpox vaccines developed at the end of the eradication phase or thereafter and produced by modern cell culture techniques. Second generation smallpox vaccines (ACAM2000) use the same vaccinia virus vaccine strains employed for manufacture of first-generation vaccines. The term third generation refers to more attenuated smallpox vaccine strains specifically developed as safer vaccines towards (LC16m8) or after (MVA-BN) the end of the eradication phase by further passage in cell culture or animals.

Indirect surveillance data in the Democratic Republic of the Congo (2005–2007) indicated that among individuals born before 1980 (end of the official national smallpox vaccination program), people vaccinated against smallpox with first-generation vaccines had a 5.2-fold lower risk of monkeypox than those unvaccinated (0.78 vs. 4.05 per 10,000), which represented a smallpox pre-exposure vaccine effectiveness against monkeypox of 80.7% (95% CI: 68.2–88.4%) *(2)*. Another surveillance study among 338 subjects in the same country (1981-1986) suggested that Dryvax (a first generation vaccine) was 85% effective against zoonotic monkeypox *(7)*.

MVA-BN is administered as a 2-dose subcutaneous injection (0.5ml dose) given 4 weeks apart. LC16m8 and ACAM2000 are both administered as a single dose using the scarification method with a bifurcated needle.

In 2013, MVA-BN was approved for prevention of smallpox (in Canada and in the European Union). In 2019, MVA-BN was approved for the prevention of smallpox and monkeypox in the USA. In the same year, Canada extended the indication to monkeypox. On 22 July 2022, the European Union recommended extending the indication of smallpox vaccines to include protecting adults from monkeypox. LC16m8 vaccine was approved for the prevention of monkeypox in August 2022 in Japan. ACAM2000 vaccine is approved by the FDA for immunization against smallpox and made available for use against monkeypox under an Expanded Access Investigational New Drug (EA-IND) protocol. Table 2 outlines the vaccines currently available and their regulatory status.

Table 2: Smallpox and monkeypox vaccine options and regulatory status

| **Vaccine (Manufacturer)** | **Licensed for smallpox (country, type, date)** | **Licensed for monkeypox (country, type, date)** | **Considerations** | **Presentation** | **Injection materials** |
|---|---|---|---|---|---|
| **MVA-BN (Bavarian Nordic)** Third generation | EU (Imvanex): has been authorised under exceptional circumstances (2013)<br>Canada (Imvamune): Full MA (2013)<br>USA (Jynneos): Full MA (2019) | USA (Jynneos): Full MA (2019)<br>Canada (Imvamune):Full MA (2019)<br>EU (Imvanex): has been authorized under exceptional circumstances (2022) | Two doses four weeks apart. Liquid-frozen formulation, approved for use in the general adult population. The USA has granted emergency authorization for use in individuals 18 years and below (August 2022). | Liquid frozen or lyophilized (freeze-dried) Single dose vials (Multidose vials possible) | Needle and syringe (sub-cutaneous administration) (0.5ml).<br>The USA has granted emergency use authorization for intradermal administration (0,1ml). |
| **LC16 (KM Biologics)** Third generation | Japan - Full MA (1975) | Japan: MA (August 2022) | Single dose. Approved for use in infants and children (all ages) as well as adults | Freeze-dried Multidose vials | Bifurcated needle |
| **ACAM2000 (Emergent BioSolutions)** Second generation | Multiple countries - Approved | USA - EIND for PEPV | Single dose. Approved for use in adults aged 18 – 64 years of age. | Freeze-dried Multidose vials | Bifurcated needle |

# ACAM2000

ACAM2000, a second-generation smallpox vaccine, is derived from a clone of Dryvax, purified, and produced using modern cell culture technology.

## Immunogenicity and effectiveness of ACAM2000 against monkeypox infection

*Vaccination take rate and vaccinees with seroconversion*

A rapid review performed by WHO did not find studies evaluating immunogenicity of ACAM2000 against monkeypox. However, several studies described ACAM2000 take rates, which is the formation of a typical post-vaccinal skin reaction, and the proportion of vaccinees reaching non MPXV specific seroconversion.

The clinical development program of ACAM2000 encompassed six clinical studies *(8)*. In two phase I clinical studies conducted in healthy vaccinia naïve adults aged 18-29 years it was confirmed that vaccination with ACAM2000 results in high take rates of nearly 100%.

Two clinical studies, one in vaccinia-naïve and one in revaccinees, compared a dose range of 1.3-2.2 x10^8 PFU/ml of ACAM2000 vaccine with Dryvax (a first-generation vaccine) given in a dose of 1.5x10^8 PFU/mL. In vaccinia-naïve subjects, the take-rates were 96% and 99% for ACAM2000 and Dryvax, respectively. In the clinical study in vaccinia-experienced subjects, success rates of 84% and 98% were obtained in the ACAM2000 and Dryvax groups, respectively *(8)*.

The proportion of ACAM2000 vaccinees that reached seroconversion (non-MPXV specific) ranged from 76% to 97% (four RCTs, n= 317 vaccinees) *(9-12)*.

*Clinical effectiveness against monkeypox infection*

The rapid review found no clinical studies evaluating the clinical effectiveness of primary preventive vaccination with ACAM2000 versus no vaccination against monkeypox. ACAM2000 clinical effectiveness against monkeypox is inferred from indirect evidence.

Efficacy data from animal challenge studies suggest that the ACAM2000 vaccine may be effective against monkeypox. In one study, three groups of macaques were vaccinated with 1 dose of ACAM2000, 1 dose of MVA-BN or 2 doses of MVA-BN. After challenge with a lethal dose of monkeypox virus at 28 days following the last vaccine dose, vaccine efficacy against death compared to an unvaccinated control group was 100% for the ACAM2000 and 2-dose MVA-BN groups, and 67% for the 1-dose MVA-BN group *(13)*.

## Safety of ACAM2000

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

Common local adverse events (AE) reported were injection site pain (up to 77%), redness (up to 74%), pruritus (up to 97%), injection site swelling (up to 48%) and rash (up to 20%) *(9-11, 14)* (n=13,952 vaccinees).

Systemic AE were frequently reported in 848,417 ACAM2000 vaccinees, including muscle pain (up to 60%), fatigue (up to 49%), malaise (up to 37%), fever (up to 37%), pyrexia (up to 11%), chills (up to 17%), rigors (up to 21%), exercise tolerance decreased (up to 11%), dyspnoea (up to 4%), lymph node pain (up to 73%), headache (up to 60%), nausea (up to 23%), vomiting (up to 7%), diarrhoea (up to 23%) and constipation (up to 6%) *(9-11, 14, 15)*.

*Vaccine-related serious adverse events*

The rapid review reported a total of 269 cases of myocarditis across 8 studies (n=1,743,620 vaccinees). A meta-analysis found an overall incidence of myopericarditis of 131 cases per 100,000 ACAM2000 vaccinees, 95% CI 28 to 607. No cases of post-vaccinial encephalitis or post-vaccinial encephalomyelitis were reported with ACAM2000. Five cases of generalized vaccinia, one case of eczema vaccinatum and one case of progressive vaccinia were reported in four studies (n=843,744) *(15)*. A total of five cases of autoinoculation (unintentional transfer of vaccinia virus from the vaccination site to another place on the vaccinee's body) were described in the studies informing this outcome in 843,714 vaccinees *(9, 14, 15)*. Two out of 1,732,264 ACAM2000 vaccinees deaths were considered to be related to vaccination. One subject showed myocarditis (dilated cardiomyopathy), infarction/necrosis of the liver and haemorrhage/necrosis of the right adrenal gland *(15)*. The other death was attributed to rhabdomyolysis without myocarditis evidence at autopsy *(16)*.

## ACAM2000 in children

The safety and effectiveness of ACAM2000 has not been established in children. The use of ACAM2000 against smallpox in all pediatric age groups is supported by evidence from the controlled studies of ACAM2000 in adults and with additional historical data with use of live vaccinia virus smallpox vaccine in pediatrics. Before the eradication of smallpox disease, live vaccinia virus smallpox vaccine was administered routinely in all pediatric age groups, including neonates and infants, and was effective in preventing smallpox disease. During that time, live vaccinia virus was occasionally associated with serious complications in children, the highest risk being in infants younger than 12 months of age. Vaccinated persons who have close contact

with infants may inadvertently transmit ACAM2000 live vaccinia virus to infants. ACAM2000 Product Insert (fda.gov)

### ACAM2000 in pregnancy and during breastfeeding

ACAM2000 has not been studied in pregnant women. Live vaccinia virus vaccines can cause fetal harm when administered to a pregnant woman. Congenital infection, principally occurring during the first trimester, has been observed after vaccination with live vaccinia smallpox vaccines, although the risk may be low. Generalized vaccinia of the fetus, early delivery of a stillborn infant, or a high risk of perinatal death has been reported. Pregnant women who are close contacts of vaccinees may be at increased risk because live vaccinia virus can shed and be transmitted to close contacts.

ACAM2000 has not been studied in lactating women. It is not known whether vaccine virus or antibodies are secreted in human milk. However, live vaccinia virus can be inadvertently transmitted from a lactating mother to her infant. Infants are at high risk of developing serious complications from live vaccinia smallpox vaccination. ACAM2000 Product Insert (fda.gov)

### ACAM2000 in immunocompromised individuals

ACAM2000 may cause serious adverse events in smallpox naïve immunocompromised individuals and is contra-indicated in immunocompromised individuals. ACAM2000 Product Insert (fda.gov)

## LC16m8

LC16m8 is a third-generation smallpox vaccine, modified attenuated lister strain of vaccinia.

### Immunogenicity and effectiveness of LC16m8 against monkeypox infection

*Vaccination take rate and vaccinees with seroconversion*

A rapid review performed by WHO did not find studies measuring immunogenicity of LC16m8 against monkeypox. However, three studies described LC16 take rates and the proportion of adult vaccinees reaching non MPXV specific seroconversion.

The proportion of vaccinees with a take ranged from 90% to 100% between 6- and 14-days following immunization *(17-19)* (n=3614) and the proportion of LC16m8 vaccinees that reached seroconversion (non-MPXV specific) ranged from 60% to 100% at 30 days from vaccination (n= 331 vaccinees) *(17-19)*.

*Clinical effectiveness against monkeypox infection*

There are no studies reporting the clinical effectiveness of LC16m8. LC16m8 clinical effectiveness against monkeypox is inferred from indirect evidence. Protective efficacy was evaluated in various animal studies using mouse, rabbit and monkey models. Data from these

studies showed that mice, rabbits and monkeys were protected against lethal challenges with monkeypox virus when immunized with LC16m8 *(8)*.

## Safety of LC16m8

Three studies reported on the safety of LC16m8 *(17-19)*.

Common local AEs reported were rash (up to 2.4%), movement limitation (up to 12%), lymphadenopathy (up to 36.8%), local erythema (up to 78.0%) and induration (up to 100%) (n=3614 vaccinees) *(17-19)*.

Systemic AEs included constitutional symptoms such as fatigue (up to 0.7%) and fever (up to 7%) among LC16m8 vaccinees *(17)* in one cohort study with 268 vaccinees. Information was not provided on common systemic AEs reported in other studies such as headache, malaise, chills, nausea and muscle pain for the overall populations examined in the included studies.

### *Vaccine-related serious adverse events*

Two studies (n= 3346) reporting on cardiac events found no symptomatic myocarditis, pericarditis or myopericarditis among LC16m8 vaccinees *(18, 19)*. No cases of encephalitis (n=3488), eczema vaccinatum, progressive vaccinia or generalized vaccinia (n=3614) were reported after LC16m8 immunization *(17-19)*. Two observational studies reported autoinoculation of up to 0.4% among LC16m8 vaccinees (n=3489) *(17, 18)*. Studies reporting on cardiac events found no symptomatic myocarditis, pericarditis or myopericarditis among LC16m8 vaccinees (n= 3346) *(18, 19)*.

## LC16m8 in children

One study focused on the effects of LC16m8 in children, including a cohort of over 50,000 0-7-year-olds vaccinated with the LC16m8 strain smallpox vaccine between 1974 and 1975 *(20)*. The study was conducted in two stages. The first consisted of 10,578 subjects in whom measurements of potential AEs, including body temperature, and immunogenicity by take were actively monitored for a month following immunization. The study informed the licensure of LC16m8 for the Japanese Ministry of Health & Welfare licensed in December 1975. The second study comprised 30,466 subjects whose clinical observations for immunogenicity and safety were monitored daily for a month following immunization.

The study determined the immunogenicity of LC16m8 with the appearance of a take. The proportion of LC16m8 vaccinees reaching the formation of a take at one month was 97% (range: 95-98%) among LC16m8 vaccinees in both studies following immunization. In a subsample of 532 vaccinees, hemagglutination inhibition (HI) antibody titers were measured between 1- and 6-months following immunization. The study reported no significant

differences between the LC16m8 strain and Lister strain regarding the antibody value distribution.

Systemic AEs among 10,578 vaccinees from the first study, included fever (up to 7.0%) and post-vaccinal exanthem (up to 0.08%). Satellite vesiculation (up to 0.3%) and temporary benign febrile convulsions (up to 0.05%) were infrequent among 40,004 LC16m8 vaccinees from both studies.

Vaccine-related SAEs were not frequently reported, including eczema vaccinatum among 10,578 vaccinees from the first study (up to 0.01%) and autoinoculation (0.1%, range: 0.09-0.1%) among 40,004 vaccinees from both studies. Serious neurological AEs, such as encephalitis and serious skin disorders, were not detected among the vaccinees from both studies (n=50,000).

## MVA-BN

MVA-BN, a third-generation smallpox vaccine, (modified vaccinia Ankara-Bavarian Nordic) is a highly attenuated vaccinia virus.

A rapid review performed by WHO did not find peer-reviewed studies addressing immunogenicity or efficacy of MVA-BN against monkeypox. However, a recent pre-print article measured MPXV neutralizing antibodies in recently MVA-BN vaccinated individuals. Another pre-print article described effectiveness of one dose MVA-BN vaccination against monkeypox.

### Immunogenicity and effectiveness of MVA-BN against monkeypox infection

There are no peer-reviewed studies addressing immunogenicity of MVA-BN against monkeypox based on MPXV neutralizing antibodies available. However, a recent preprint posted on 1 September 2022, measured MVA-, vaccinia virus (VACV)- and MPXV-reactive binding and neutralizing antibodies with validated in-house assays in three cohorts: historically smallpox-VACV vaccinated, MPXV PCR-positive, and recently MVA-BN-vaccinated individuals. MPXV neutralizing antibodies were detected across all cohorts in individuals with MPXV exposure as well as those who received historic VACV vaccination. However, two dose MVA-BN immunization in subjects not previously exposed to MPXV or historic vaccination yielded relatively low levels of MPXV neutralizing antibodies. Furthermore, an intradermal regimen dose-sparing technique led to lower antibody levels, whereas a third MVA vaccination boosted the antibody response *(21)*.

*Vaccinees with seroconversion*

The proportion of MVA-BN vaccinees that reached seroconversion (non-MPXV specific) was over 98% (n=1222). Peak antibody response (full immunization) was achieved 2 weeks after receipt of the second dose of MVA-BN vaccination series *(12)*.

*Clinical effectiveness against monkeypox infection*

While MVA-BN efficacy studies were aimed at understanding its protective efficacy against smallpox, many of the licensing studies have been conducted using challenge with monkeypox virus. Protective efficacy of MVA-BN was evaluated in animal studies using established animal models and compared to first- and second-generation vaccines *(8)*. In one study, three groups of macaques were vaccinated with 1 dose of ACAM2000, 1 dose of MVA-BN or 2 doses of MVA-BN. After aerosol challenge with a lethal dose of monkeypox virus at 28 days following the last vaccine dose, vaccine efficacy against death compared to an unvaccinated control group was 100% for the ACAM2000 and 2-dose MVA-BN groups, and 67% for the 1-dose MVA-BN group *(13)*.

A recent preprint, published on 23 September 2022, was a retrospective cohort study conducted in Israel to evaluate the effectiveness of one dose of MVA vaccine in male subjects at moderate to high-risk for monkeypox virus infection. The cohort included male subjects from the electronic medical records who answered one or more of the following criteria: (a) dispense of HIV-Pre-Exposure Prophylaxis medication (HIV-PrEP) since January 1,2022; (b) HIV-positive and also diagnosed with one or more of the following sexually transmitted infection (STI)s since January 1, 2022: active syphilis, chlamydia, or gonorrhea. The study commenced on July 31, 2022, when the MVA vaccination campaign was initiated, and participants were followed until September 12, 2022 *(22)*. Results indicated that one dose of MVA-BN was reasonably effective in preventing monkeypox infections. 1,970 subjects of which 873 (44%) were vaccinated with one dose of MVA-BN completed at least 25 days of follow-up. 18 infections were confirmed in the study cohort, 3 in vaccinated and 15 in unvaccinated persons (40.0 versus 6.4 per 100,000 person days). VE was estimated at 79% (95% CI: 24%-94%).

## Safety of MVA-BN

Common local AE reported were injection site pain (up to 85%), including movement limitation, redness (up to 61%), pruritus (up to 18%), swelling (up to 52%), induration and itching (up to 43%) (n=5921 vaccinees).

A phase III RCT comparing MVA-BN with ACAM2000, randomized 440 vaccine-naive participants to two doses of MVA-BN followed by ACAM2000 (n=221) versus one dose of ACAM2000 alone (n=219) found that all solicited local AEs (pain, erythema, swelling, induration, and pruritus) were more frequent in the ACAM2000-only group than in the MVA group during any MVA vaccination period and after ACAM2000 vaccination when preceded by MVA vaccination

(P<0.001 for all solicited adverse events). Injection site pain was the most prevalent local AE after MVA vaccination (110 out of 212; 52%), and erythema (191 out of 200; 96%) and pruritus (179 out of 200; 90%) after ACAM2000 vaccination *(12)*.

Systemic AEs were frequently reported in MVA-BN vaccinees, such as muscle pain (up to 43%), fatigue (up to 30%), malaise (up to 17%), fever (up to 2%), chills (up to 10.4%), headache (up to 34.8%) and nausea (up to 17.3%) (n=5457).

The above described study, comparing MVA-BN with ACAM2000 found that all solicited systemic AEs (headache, myalgia, chills, nausea, fatigue, and malaise) occurred more frequently in the ACAM2000-only group than in either MVA period (except pyrexia, which occurred equally in MVA period 1 and the ACAM2000-only group) *(12)*.

*Vaccine-related serious adverse events*

There were no cases of myopericarditis or SAE requiring hospitalization reported among 9713 MVA-BN vaccinees from 19 clinical studies. Post-vaccinial encephalopathy, encephalomyelitis, eczema vaccinatum, progressive vaccinia or generalized vaccinia were not reported after MVA-BN immunization.

*Adverse events reported through a surveillance database*

From April 2022 up until the 26th of August 2022, Vigibase, which is the global database of the WHO programme for international drug monitoring reported 360 adverse events after the use of the MVA-BN vaccine. The majority of events reported were from the US followed by the UK and France. Main events reported were incorrect route of administration and local injection site reactions such as pain, erythema ,swelling and itching. Twenty-three serious events were reported. Details about these serious adverse events were not available but they did not include cases of myocarditis.

### MVA-BN in children

While MVA-BN has not been specifically studied in a clinical trial in children, the same non-replicating MVA viral vector is used as a platform for other vaccines including MVA-filo (marketed as Mvabea™) against Ebola virus disease (EVD). This EVD vaccine is approved in the European Union for adults and children aged one year and older. The MVA viral vector platform is also being used to develop a vaccine against infection with respiratory syncytial virus. Data from nine published studies on MVA-BN as a viral vector platform for prevention of Ebola or RSV support the favourable safety profile of the product and some data suggest that immune response to MVA encoded antigens  is not altered by serving as a vector.

In a TB vaccine trial of approximately 1500 infants, aged approximately 5 to 6 months, MVA85A was very well tolerated. In a trial of 100 Gambian infants who received MVA85A and in a

further study of 100 infants who received MVA-malaria there was a tolerable safety profile *(23-25)*.

### MVA-BN in pregnancy and during breastfeeding

Available human data on MVA-BN administered to pregnant women are insufficient to determine vaccine-associated risks in pregnancy. However, four development and reproductive toxicology animal studies in rats and rabbits have shown no evidence of harm to the fetus. MVA-BN safety and efficacy has not been evaluated in breastfeeding women *(26)*. Data are not available to assess the impact of MVA-BN on milk production or the safety of MVA-BN in breastfed infants *(26)*.

### MVA-BN in individuals living with well-controlled HIV (CD4 ≥ 200)

MVA-BN was well tolerated and immunogenic in well-controlled HIV subjects (CD4 ≥ 200).

### MVA-BN in individuals living with uncontrolled HIV (CD4 < 200)

No clinical studies are available focusing on this population. A phase II trial evaluated three MVA-BN dosing regimens for safety, tolerability, and immunogenicity in persons with HIV who had a history of AIDS. This trial concluded that MVA-BN was well tolerated and immunogenic among the study participants. However, only 19% of the study subjects presented uncontrolled HIV (CD4 < 200), and disaggregated data for this population was not provided *(27)*.

### MVA-BN in immunocompromised individuals

Twenty-four hematopoietic stem cell transplant recipients were included in a dose-escalation RCT of MVA-BN administered subcutaneously on days 0 and 28. The study authors concluded that MVA-BN was safe, well tolerated, and immunogenic in hematopoietic stem cell transplant recipients *(28)*.

### MVA-BN in Individuals with a history or presence of atopic dermatitis, eczema or other exfoliative skin conditions

Two studies comparing SAEs in MVA-BN vaccinees with and without atopic eczema, reported inconclusive results (95% CI includes the potential for both meaningful benefit as well as meaningful harm) on AEs leading to study withdrawal (n = 692 vaccinees; RR 0.53, 95% CI 0.06 to 5.04; I2 = 0%) and cardiac AEs (n=632 vaccinees; RR 1.23, 95% CI 0.84 to 1.79) *(29, 30)*.

### MVA-BN in previously smallpox vaccinated individuals (adults>50 years old or adults with visible smallpox scar)

The frequency of MVA-BN AEs may be slightly higher in vaccinia-naïve subjects compared to experienced vaccinees. The following AEs seemed more frequent in vaccinia-naïve subjects compared to previously vaccinated subjects, although the differences seemed not clinically significant: injection site pain (85% vs 80%), muscle aches (43% vs 22%), headache (35% vs 28%), nausea (17% vs 10%), fever (2% vs 0.5%). On the contrary, injection site redness (61% vs 81%), swelling (51% vs 67%), induration (45% vs 70%) and fatigue (30% vs 34%) seemed less frequent among naive individuals.

## Monkeypox outbreak impact modelling

Model-based simulations of the initial phase of the monkeypox outbreak in the EU/EEA were performed by the European Centre for Disease Prevention and Control (ECDC) and the European Commission's Health Emergency Preparedness and Response Authority (HERA) *(31)*. The 2022 monkeypox outbreak was modelled using two groups of contacts of monkeypox cases (regular versus non-regular contacts) to allow different parameter values and interventions (e.g. contact tracing and vaccination strategies) for each group separately. Regular contacts were considered as household members and a small number of regular sex partners, and non-regular contacts as sporadic contacts at events with a larger number of individuals who have had no or infrequent contact before.

The modelling results suggest that the effective isolation of cases (at an assumed 90% effectiveness in preventing new secondary cases) and tracing the infected contacts of cases (at a probability of successfully finding 50% of newly infected regular contacts and 10% of non-regular contacts) make the likelihood of outbreak control by week 12 a little more than 50%.

The addition of PEPV or PPV vaccination at low uptake levels of 20% results in little increase of the chance to achieve outbreak control by week 12 (Figure 1, panel a). In contrast, a high uptake of 80% of PPV vaccination increases the effectiveness to achieve outbreak control by week 12 to more than 75%. Where a higher effectiveness of contact tracing can be achieved and combined with high vaccine uptake levels of 80% the chance of outbreak control by week 12 can be maximized, with PPV vaccination being the most effective strategy.

Limitations of this model include the assumption of a vaccine effectiveness against infection of 85% (derived from surveillance data from the 1980s *(2,4)*), and that the only outcome measure is the effect against transmission to achieve outbreak control.

Another modeling study of transmission during sexual activity between men suggests that one-time partnerships, which account for 3% of daily sexual partnerships and 16% of daily sex acts, would account for approximately 50% of daily MPXV transmission. A 40% reduction in one-

time partnerships might delay the spread of monkeypox and reduce the percentage of persons infected by 20% to 31% *(32)*.

## Post-exposure preventive vaccination

There is very limited evidence on whether vaccines can prevent or modify disease when given post-exposure.

No peer-reviewed data of clinical studies evaluating the effects of post-exposure vaccination of close contacts of MPX cases is available. A preprint was posted on 4 August 2022, describing 276 individuals who received one dose of MVA-BN after exposure with a PCR-confirmed monkeypox patient. Most of the patients were men (91%, n=250) and men who have sex with men (88%, n=233). Among the 276 vaccinated individuals, 12 (4%) had a confirmed monkeypox breakthrough infection with no severe infection. Ten out of 12 patients developed a monkeypox infection in the five days following vaccination and two had a breakthrough infection at 22 and 25 days *(33)*.

A study in prairie dogs investigated whether post-exposure vaccination with ACAM200 and MVA-BN vaccines was protective against monkeypox disease in different exposure scenarios. Animals were infected with a low ($10^4$ pfu (2× $LD_{50}$)) and high ($10^6$ pfu (170× $LD_{50}$) dose of monkeypox virus and vaccinated with MVA-BN or ACAM2000 either 1 or 3 days after challenge. The results indicated that post-exposure vaccination protected the animals to some degree from the low, but not the high viral challenge. In the low viral challenge, it was observed that administration of vaccine at 1 day was more effective than administration at 3 days post-exposure for both vaccines *(34)*.

Information on protective post-exposure efficacy also derives from several sets of data on secondary attack rates among vaccinated and unvaccinated family contacts of smallpox cases. The data indicate that the longer the time between exposure and vaccination the higher the risk that post-exposure vaccination is ineffective to prevent infection or to mitigate severity of smallpox disease. Based on historical data from the UK it was found that primary vaccination within 3-4 days after smallpox exposure and revaccination within one week after exposure may protect against disease and/or death *(8)*.

## Vaccine administration and dose sparing options

### Dose sparing options

A clinical study published in 2015, comparing intradermal (ID) and subcutaneous (SC) administration of MVA-BN concluded that the intradermal group was considered non-inferior to the subcutaneous group. After the second vaccination, geometric mean of peak neutralization titers were 49.5 and 59.5 for the SC and ID groups, respectively, and the maximum number of responders based on peak titer in each group was 142/149 (95.3%) and

138/146 (94.5%), respectively. At 180 days after the second vaccination, geometric mean neutralization titers declined to 10.2 and 10.4 with 39.2% and 35.2% of subjects remaining seropositive for the SC and ID groups, respectively *(35)* .

Following any vaccination, the proportion of subjects with measured erythema or induration at the injection site differed among groups. The proportions were 84.4%, and 100% for the SC, and the ID dose groups, respectively. Of these, 58.1% and 94.8% had severe local reactions (>30 mm), respectively. Local reactogenicity lasting at least 30 days, unexpected nodules and skin discoloration at the vaccination site, accounted for 389 (80%) of the adverse events reported as associated to vaccination and included 42/167 (25.1%), and 128/191 (67.0%) for the SC, and ID groups, respectively *(35)*.

Based on this study, the US FDA issued an Emergency Use Authorization (EUA) for the use of MVA-BN for the active immunization by intradermal injection (0.1ml) for the prevention of monkeypox disease amongst adults aged 18 years and above, at high risk of infection. In the context of the national public health emergency declared in the US, this alternative regimen was approved to increase the number of available MVA-BN doses by up to five-fold. The European Medicines Agency Emergency Task Force also released a statement concluding that intradermal use of MVA-BN vaccine was acceptable in view of the outbreak situation and significant vaccine shortage.

### Delayed second dose of MVA-BN vaccine

The role of MPXV neutralizing antibodies for protection against disease and transmissibility is currently unclear and no correlate of protection against MPXV infection has been identified yet.

A recent preprint, published on 23 September 2022, indicated that one dose of MVA-BN was effective in preventing monkeypox infections. 1,970 subjects of which 873 (44%) were vaccinated with one dose of MVA-BN completed at least 25 days of follow-up. 18 infections were confirmed in the study cohort, 3 in vaccinated and 15 in unvaccinated persons (40.0 versus 6.4 per 100,000 person days). VE was estimated at 79% (95% CI: 24%-94%). These preliminary results suggest a single dose of MVA-BN is associated with a lower risk of MPXV disease in high-risk individuals after 25 days of follow-up *(22)*.

## Access and availability of vaccines

WHO and some Member States hold strategic reserves of first-generation smallpox vaccines for health security preparedness in the event of a re-emergence of smallpox through natural, accidental or deliberate causes. These first-generation vaccines are not recommended for use for monkeypox.

Further to the above, three vaccine brands are available that have been licensed by various national regulatory authorities (see Table 2):

- MVA-BN (Bavarian Nordic, Denmark) : 16.4 million doses produced to date , sold to government entities
- LC16m8 (KM-Biologics, Japan) : up to 200 million doses produced, all within a national stockpile
- ACAM2000 (Sanofi Pasteur ) 100 million doses, all within national stockpiles

Currently only MVA-BN can be procured. However, the vaccines produced to date have already entirely been sold to countries. Hence, product delivery from current orders occurs up to a year after purchase.

WHO engages with vaccine manufacturers to encourage scaling of vaccine production and with vaccine procuring countries to equitably share vaccine supply for use in lower resource settings.

## Research gaps

Data on the effectiveness of vaccines in the prevention of monkeypox in clinical practice and in field settings are mostly not available and many unknowns remain on their clinical benefit and most appropriate use in different contexts. Safety information also remains limited with respect to special population groups. This applies to both PPV and PEPV. More information is also needed on the different dose-sparing options. All efforts should be made to administer vaccines for monkeypox within a framework of collaborative research and RCT protocols with standardized data collection tools for clinical and outcome data. This will allow the rapid generation of safety and effectiveness data for the use of vaccines for different purposes, in different at-risk groups and in different settings, and document their performance. When an RCT design is not possible, observational studies should be considered. Vaccines may be used under expanded access protocols such as Monitored Emergency Use of Unregistered and Investigational Interventions (MEURI). Such field- and practice-based research using standard protocols will also provide much needed information on transmission dynamics of monkeypox and clinical features of the disease. This should also include studies in countries with zoonotic transmission.

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