National Advisory Group
on Immunisations (NAGI)
Enquiries: Prof Anne von Gottberg
E-mail: annev@nicd.ac.za

20 June 2024

The Ministry of Health, Republic of South Africa
Office of the Minister

SUBJECT: RECOMMENDATIONS ON MPOX VACCINE

Dear Honorable Dr MJ Phaahla

PROBLEM STATEMENT

Since 9 May 2024, 11 new mpox cases have been reported in South Africa (five in KwaZulu-Natal, five in Gauteng, and one in Western Cape). Two of these individuals have died. Whilst clinical and epidemiological data are still being collated for the most recent cases, all eleven are young adult males (23-39 years), and the first five cases for whom information is available are reported to be gay, bisexual, or other men who have sex with men (GBMSM). The first seven individuals for whom information is available are living with HIV. None of the cases reported recent international travel.

These new cases have occurred in the context of the ongoing global mpox outbreak and are the first cases in South Africa since August 2022 (five epidemiologically unlinked cases were reported in May-August 2022, during the initial phase of the global outbreak). Notably, there were no mpox cases confirmed in the country in 2023. The first three cases in this 2024 outbreak, for which sequencing results are available, are confirmed to be associated with monkeypox virus (MPXV) clade IIb (the sub-clade responsible for the global outbreak). The past two years have seen increasing MPXV transmission in the WHO African Region, particularly in the Democratic Republic of the Congo, with high morbidity and mortality in children under the age of 15 years in endemic areas and new

outbreaks in previously unaffected areas, the latter associated with sexual transmission of a new lineage of MPXV clade I.

Based on this, the key decisions required are:

i) Whether mpox vaccines should be obtained and made available for use in South Africa.
ii) If made available, whether vaccines should be used for pre-exposure vaccination and/or post-exposure vaccination.
iii) If made available, which population groups should be considered for mpox vaccination.

BACKGROUND

South African outbreak May 2024

On 9 May 2024, the National Department of Health (NDoH) reported a new case of mpox in a 35-year-old male in Gauteng Province (GP). This was the first reported case of mpox in South Africa since August 2022. Since then, additional cases have been reported in GP, KwaZulu-Natal (KZN), and Western Cape (WC). As of 18 June 2024, there are now a total of 11 confirmed cases (KZN – 5, GP – 5, WC - 1).

Although clinical, epidemiological and laboratory data are still being collated for the recently reported cases, information available at present includes:

- All 11 confirmed cases are males, aged 23-39 years.
- The first five confirmed cases are GBMSM; details of later cases are pending.
- The first seven confirmed cases are people living with HIV (full details of antiretroviral therapy, CD4+ count and viral loads pending).
- None of the first five confirmed cases reported recent international travel, nor known contact with anyone with recent travel.
- The first three KZN cases are epidemiologically linked, through sexual networks.
- The first seven confirmed cases with full information were classified as severe, having been hospitalised with extensive cutaneous ± mucosal disease.
- Some of the cases have received treatment with tecovirimat (obtained under section 21 approval).
- Sequence data confirms MPXV clade IIb for the first three cases.
- Two cases have died (one case from GP and one from KZN).

Global and regional context

In 2022, the geographic expansion of MPXV across non-endemic regions resulted in the first global mpox epidemic, which was declared a public health emergency of international concern (PHEIC) by the WHO from July 2022 to May 2023. As of 30 April 2024, 97 208 laboratory-confirmed cases and 186 deaths have been reported to WHO from 117 countries. Whilst the overall number of new cases declined following the peak in August 2022, cases continue to be reported around the world[1,2].

Except for countries in Central and West Africa, the global outbreak continues to primarily affect GBMSM, with no evidence of sustained transmission beyond these networks. Of all reported types of transmission, sexual encounter remains the most reported exposure. The global outbreak has been associated predominantly with MPXV clade IIb.

One of the key observations during the global outbreak has been the association of severe, complicated mpox disease with advanced, uncontrolled HIV[3,4]. In an international observational study of mpox in 382 people living with HIV with CD4 count <350 cells/μL in 19 countries, May 2022 – Jan 2023, severe complications were more common in people with CD4 <100 cells/μL than in those with >300 cells/μL – this included necrotising skin lesions (54% vs 7%), lung involvement (29% vs 0%) and secondary infections and sepsis (44% vs 9%). 107 (28%) of 382 were hospitalised, of whom 27 (25%) died. All deaths were in people with CD4 <200 cells/μL (median 35 cells/μL), and all but one with unsuppressed viral load[4].

Concurrently with the global outbreak, there has been a notable increase in MPXV activity in the WHO African Region, especially in the Democratic Republic of Congo (DRC) [5-10]. Epidemiological data from the DRC has shown geographic expansion to non-endemic areas and increasing human-to-human transmission associated with sexual networks involving female and male sex workers with onward transmission to close household and non-household contacts[7,8,10]. This expansion has been linked to a new MPXV clade I lineage[9,10]. In addition, incidence in endemic areas continues to rise, including a documented cluster of the endemic strain of clade I MPXV among GBMSM. Limited access to testing in DRC means that most cases are not confirmed (~18% of clinically suspected cases are tested). In 2024 epi weeks 1-14, there have been 5133 suspected cases and 321 deaths (case-fatality ratio 6.3%). Children under 15 years old constitute the majority of both suspected cases (69.0%) and deaths (85.0%)[11].

Mpox vaccines

Smallpox and mpox vaccines available today are all based on live vaccinia virus[12]. Second-generation vaccines are replication competent, whereas third generation refers to more attenuated smallpox vaccine strains. Table 1 outlines the vaccines currently available and their regulatory status. None of these vaccines have been approved by South African Health Products Regulatory Authority (SAHPRA). None of the vaccines are WHO prequalified yet, and WHO does not hold any bulk supply of vaccines. WHO is, however, coordinating bilateral donations (from countries with stockpiles) and bulk procurement from manufacturers.

Table 1: Current mpox vaccine options[13]

Vaccine (Manufacturer)	Licensed for smallpox (country, type, date)	Licensed for mpox (country, type, date)	Considerations	Presentation	Injection materials
Orthopoxvac Fourth generation	Russian Federation (November 2022)	Russian Federation (November 2022)	Single dose	Not commercially produced yet	Needle and syringe (intradermal administration)
MVA-BN (Bavarian Nordic) Third generation	EU (Imvanex*): Full MA (2013) Canada (Imvamune): Full MA (2013) USA (Jynneos): Full MA (2019)	USA (Jynneos): Full MA (2019) Canada (Imvamune): Full MA (2019) EU (Imvanex*): Full MA (2022)	Two doses four weeks apart. Approved for use in the general adult population. The USA has granted emergency authorization for use in individuals under 18 years of age (August 2022).	Liquid frozen or lyophilized (freeze-dried) Single dose vials (Multidose vials possible)	Needle and syringe (sub-cutaneous administration) (0,5ml). 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: EA-IND	Single dose. Approved for use in adults aged 18 – 64 years of age.	Freeze-dried Multidose vials	Bifurcated needle

*MVA-BN vaccine is also licensed in Switzerland (as Jynneos, approved for 18 years and older for smallpox, mpox and vaccinia virus infections, 1 March 2024). Source: WHO, Background document for the SAGE March 2024 session on mpox vaccines and immunisation.

No randomised controlled trials have been conducted to investigate efficacy of mpox vaccines. Systematic reviews of the effectiveness and safety of available mpox vaccines

were conducted for the March 2024 meeting of The Strategic Advisory Group of Experts on Immunization (SAGE) [13]. Key findings are listed in Table 2 below.

Table 2: Key findings from systematic reviews of mpox vaccine effectiveness and safety, presented to SAGE at March 2024 meeting[14]

Adapted from: https://terrance.who.int/mediacentre/data/immunization/SAGE_SlidedeckMarch_2024.pdf

Vaccine effectiveness

- Included human studies of efficacy/effectiveness of vaccines with activity against MPXV. Study type could include outbreak investigations, case-series retrospective cohorts, prospective cohorts, and randomised controlled trials (dates of search: 1 January 1970 – 3 November 2023)
- 35 studies identified (all involving MVA-BN vaccine) from 9 countries – involving 110,914 participants.
- Risk of bias was high, and overall Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) assessments were very low confidence.
- Effectiveness of **pre-exposure vaccination** with a **one-dose schedule** of MVA-BN against infection was **76%** (95% confidence interval [CI] 64-88) [12 studies]
- Effectiveness of **pre-exposure vaccination** with a **two-dose schedule** of MVA-BN against infection was **82%** (95% CI 72-92) [6 studies]
- Effectiveness of **pre-exposure vaccination** with MVA-BN (one- or two-dose schedule) **against hospitalisation** was **66%** (95% CI 54-78) [10 studies]
- Effectiveness of **post-exposure vaccination** with MVA-BN against infection was **20%** (95% CI -24-65) [7 studies]

Vaccine safety

- 48 studies
- GRADE certainty of evidence low to very low
- Local adverse events (AEs) (pain, erythema, swelling) and systemic AEs (fever, headache, fatigue) are commonly reported – local AEs less frequent with MVA-BN than ACAM2000.
- Serious adverse events have been rare – there have been no reported cases of generalised vaccinia with MVA-BN or LC16
- LC16 approved for use in children and adults in Japan; approval for use in children is based on several studies and administration in a total of more than 50,000 children.

SAHPRA Donation Policy allows rapid approval provided there is:

- Authorisation from a stringent regulatory authority (SRA, e.g., European Medicines Agency) or from WHO prequalification.
- Product is manufactured in a facility approved for vaccine manufacturing by an SRA including the European Union ensuring Good Manufacturing Practice (GMP).
- SAHPRA can issue Section 21 permits on a named-patient basis with motivation from a clinician, requiring regular reporting on patient progress e.g., tecovirimat.
- SAHPRA can approve products for a Section 21 stockpile allowing rapid access to drug or vaccine supported by retrospective reporting.
- In an emergency, SAHPRA can issue emergency licenses for vaccines, therapeutics or diagnostics.

FACTORS SUPPORTING THE SELECTION OF MVA-BN VACCINE

MVA-BN is:

a) a third-generation vaccine, documented better safety profile than second generation (e.g., ACAM2000) and preferred for our context in South Africa with high HIV prevalence.
b) the vaccine most widely used in the global outbreak, and for which we have robust effectiveness and safety data.
c) the vaccine known to be available through bilateral donations.
d) the vaccine approved in several jurisdictions for use in adults aged 18 years and above, which is the group currently at risk in South Africa.

RECOMMENDATIONS

Mpox vaccines

- The MVA-BN vaccine should be urgently procured for immediate use in the current outbreak, noting the available data on safety and effectiveness including in immunocompromised people and people living with HIV, pregnant and lactating women, and children.
- The MVA-BN vaccine should be used for both preventive pre-exposure vaccination and for post-exposure vaccination (optimally within 4 days but up to 14 days post exposure, in the absence of symptoms).
- A two-dose schedule (two doses 4 weeks apart) should be used for both pre-exposure and post-exposure vaccination.

- Deployment of mpox vaccines should be accompanied by rigorous pharmacovigilance using existing systems (https://medsafety.sahpra.org.za/) to actively monitor for adverse events following immunisation. There should also be systematic collection of data on acceptability and uptake of vaccines; and research to assess the effectiveness of pre-exposure and post-exposure vaccination.
- The NDoH should urgently initiate discussions with the National Treasury about the options for vaccine procurement. Noting that this is an expensive vaccine (no costs are currently available in the SA setting) the NDoH is encouraged to explore the possibility of donations from the manufacturer and countries with stockpiles, with the support of WHO Geneva and the WHO regional and country office.
- These recommendations for vaccine choice and vaccine strategy will be reviewed and updated as necessary, depending on the progression of the outbreak and relevant new information about vaccine effectiveness, safety, availability and cost.

Groups to be offered vaccination

Noting that the current outbreak is so far concentrated in the GBMSM community, the following groups are recommended for vaccination. If the at-risk population changes, these recommendations will be updated.

Pre-exposure vaccination

- A staggered approach, initially targeting GBMSM and transgender people at highest risk of exposure in the districts with reported cases, including through dedicated health service points for key populations. Those at highest risk of exposure to mpox include people with a recent history of multiple sexual partners and those participating in group sex. Depending on the progression of the outbreak and the availability of vaccines, vaccination could then be expanded to other risk groups and other geographic areas.
- Health workers at risk of repeated exposure (e.g., frontline patient-facing workers in emergency departments and hospital wards used for care of mpox cases in affected districts).
- Laboratory workers at risk of repeated exposure (e.g., in laboratories where MPXV testing is being done).
- Consideration should be given in the future to travelers to Central and West African countries with ongoing outbreaks, but this is not part of the initial outbreak response.

Post-exposure vaccination

- Sexual contacts of persons with mpox – this includes contacts of any gender, not limited to GBMSM.
- Household contacts of persons with mpox, including pregnant and lactating women and children (youngest age group to be discussed with WHO).
- Health workers with documented contact with a confirmed mpox case and with one of the following exposures, as defined in the Standard Operating Procedure for contact tracing[15]: i) Face-to-face contact or was in a closed environment with a case without appropriate personal protective equipment (PPE); ii) Direct physical contact with skin/skin lesions; or iii) Contact with contaminated materials (e.g., clothing, bedding, utensils) or percutaneous injury with contaminated sharp (e.g., needle-stick injury).
- Laboratory workers at facilities with mpox cases.
- In areas where more than one household has an index case, consideration can be given to vaccinating adults and children in a geographically defined area of exposure.

Communication strategy

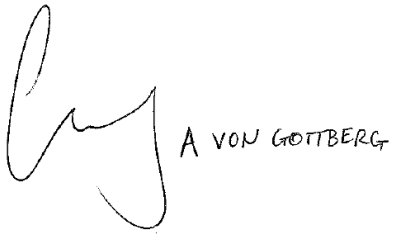
Risk communication and community engagement will be critical for the successful deployment of vaccines. A communications strategy should be developed for:

- Key populations: GBMSM, transgender people and sex workers (Presidents Emergency Plan for AIDS Relief partners should be engaged with the support of United States Agency for International Development and United States Centres for Disease Control and Prevention).
    - Essential information about mpox (how it spreads, activities associated with risk of exposure, clinical features, what to do if you have symptoms, treatment and prevention).
    - For communities where the vaccine will be deployed, additional information should be provided about mpox vaccines, and specifically about the goals of pre-exposure and post-exposure vaccination.
- Household contacts who will be offered post-exposure vaccination.

- Frontline health care workers and laboratory workers in high-risk settings who will be offered pre-exposure and post-exposure vaccination.
- Assessments to determine mpox vaccine acceptability in key populations to inform tailored messaging to optimise vaccine uptake.
- A national information campaign about clinical and laboratory diagnosis and management to be widely disseminated to health care workers in the public and private sector.

Thank you for your consideration.

Yours sincerely,



PROFESSOR ANNE VON GOTTBERG
CHAIRPERSON: NATIONAL ADVISORY GROUP ON IMMUNISATION (NAGI)

CC: Dr S Buthelezi (Director-General)
Mr Morewane (Acting Deputy Director-General: HIV, TB and MCWH)

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