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PROTOCOL TEMPLATE

to be used as template for observational study protocols for

Cohort event monitoring (CEM) for active safety surveillance after vaccination with mpox vaccines

Work Package: [WP10]

V 1.0 [Draft] - [17/09/2024]

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Safety Platform for Emergency vACcines

DOCUMENT INFORMATION

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Project acronym	SPEAC	Full project title	Safety Platform for Emergency Vaccines
CEPI Project Lead	Rebecca Chandler		
CEPI Project Manager	Thomas Cole		
CEPI Contract Manager	Dorota Zdankewicz		

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This protocol template has been adapted by the Safety Platform for Emergency Vaccines (SPEAC) from the World Health Organization (WHO) protocol template for CEM with COVID-19 vaccines. https://cdn.who.int/media/docs/default-source/3rd-edl-submissions/who_covid_protocols_cem_template.pdf.

DOCUMENT HISTORY

NAME OF DOCUMENT	DATE	VERSION	CONTRIBUTOR(S)	DESCRIPTION
Protocol template	17-Sep-2024	V1.0	SPEAC Executive Board	Creation of the document

1. How to use this template to develop a CEM study protocol

The protocol template should be completed by adapting it to the specific country(ies) and study population(s). The sections of the protocol template to be adapted have been marked with blue square brackets.

It is important also to note that the adult informed consent form (ICF) template, provided in this template, and the informed consent process must be adapted to local situations, local languages and special populations (e.g., minors, pregnant women, elderly individuals lacking full capacity, migrants, prisoners, sex workers) that require a tailored approach to consent. This includes possible surrogate decision- makers, such as parents or guardians for young children, or study advocates for inclusion of prisoners, or orphans and additional forms, such as assent forms, as well as tailoring to correspond to the study information provided to participants during the consent process.

All protocols developed using this template should be reviewed by the appropriate committee(s), including the relevant ethics committees and institutional review boards, at a national level, or at the level of the study sites, or at the institution of the sponsor, as required by applicable laws and regulation.

2. Suggested process

- Step 1: Constitute a study coordination team consisting of representatives from the immunization program, national regulatory authority, pharmacovigilance center, chair or representative of the national adverse events following immunization (AEFI) committee, and academia.
- Step 2: Identify the role and responsibilities of the different institutions and nominate a person to lead and coordinate the process of protocol development and obtain the consensus of the study coordination team. Complete section 7 of the template with this information.
- Step 3: Define the target population, identify study sites, review list of adverse events of special interest (AESI) for the mpox vaccine(s) in use, and complete the protocol (including informed consent forms and data collection tools). If technical assistance from Africa CDC, Safety Platform for Emergency Vaccines (SPEAC), or other partners is required at this stage, send an e-mail request to <TBA>.
- Step 4: Discuss the draft protocol with the study coordination team and study site representatives to obtain their input and endorsement and then finalize the protocol.
- Step 5: The final protocol should be re-reviewed by experts to ensure that it is scientifically

sound, and should then be reviewed by the national ethics committee or the independent ethics committee (IEC) or institutional review board (IRB) of participating institution(s)

- Step 6: Develop the study procedures, data management plan and statistical analysis plan.

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Start of CEM study protocol template

Cohort event monitoring (CEM) study for active safety surveillance after vaccination with mpox vaccines

THIS PROJECT HAS BEEN FUNDED IN WHOLE BY CEPI

1 TITLE PAGE

Abbreviated study title	MPOX-CEM-[COUNTRY]- [NUMBER]
Full study title	Cohort Event Monitoring (CEM) study for active safety surveillance in [PRIORITY GROUP OF INTEREST] after vaccination with mpox vaccines in [COUNTRY]
Study ID	
Research question and objectives	
Country(ies) of study	
Protocol version	
Date of protocol version	
Protocol authors	

2 TABLE OF CONTENTS

3 PROTOCOL SIGN-OFF

This protocol has been discussed, reviewed and approved by the following experts:

- [NAME]
- [NAME]
- [NAME]
- [NAME]
- [NAME]
- [NAME]
- [NAME]

Protocol title:
Cohort event monitoring (CEM) study for active safety surveillance in [PRIORITY GROUP OF INTEREST] after vaccination with mpox vaccines in [COUNTRY]

Version: [Version number]

4 DOCUMENTATION OF PROTOCOL AMENDMENTS

Version	Version date	Reason for new version

5 STUDY TEAM AND RESPONSIBILITIES

Study team

	Role	Organization	Name
Research team	Principal investigator		
	Project manager		
	Data monitor		
	Other research staff		
Study site(s)	Investigator		
	Study coordinator		
	Other research staff, include clinicians who will evaluate reported adverse events		
Others, as applicable			
Sponsor			

Responsibilities

Organization/Capacity	Responsibilities

6 ABBREVIATIONS

AE	Adverse event
AESI	Adverse event of special interest
CDC	Centers for Disease Control and Prevention
CEM	Cohort event monitoring
CIOMS	Council for International Organisations of Medical Sciences
MPOX	Mpox
DMP	Data management plan
EMA	European Medicines Agency
GEP	Good epidemiological practice
ICF	Informed consent form
IEC	Independent ethics committee
IRB	Institutional review board
MedDRA	Medical Dictionary for Regulatory Activities
NIP	National Immunisation Programme
PT	Preferred term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCRI	Self-controlled risk interval
SIR	Standardized incidence ratio
SPEAC	Safety platform for emergency Vaccines
VAED	Vaccine-associated enhanced disease
WHO	World Health Organization

7 SYNOPSIS

Full title of study	Cohort Event Monitoring (CEM) study for active safety surveillance in PRIORITY GROUP OF INTEREST] after vaccination with mpox vaccines in [COUNTRY].
Background and rationale	Vaccines approved for use in national immunisation programmes (NIPs), are considered safe and efficacious based on demonstrable evidence from randomized controlled clinical trials. They are, however, not completely free of risks, and occasional adverse events will inevitably occur following vaccination at the population level. Given vaccines are often recommended for otherwise healthy individuals, the key to success for NIPs is public trust in vaccine safety. Thus, systematic vaccine safety surveillance is indispensable for ensuring safety of vaccines and public trust. mpox vaccine pharmacovigilance should start simultaneously with the implementation of plans for immunisation with mpox vaccines. This protocol describes a cohort event monitoring (CEM) study designed to capture adverse events occurring in a cohort of [PRIORITY GROUP OF INTEREST FOR THIS STUDY] vaccinated with [VACCINE/MPOX vaccines] during routine clinical practice in [COUNTRY] for the purpose of signal detection.
Objectives	The overall aim of this observational study is to monitor the safety of MPOX vaccines in [PRIORITY GROUP OF INTEREST FOR THIS STUDY] in [COUNTRY] for the purpose of safety signal detection as soon as the vaccine is used in routine vaccination programmes. **Specific objectives** 1. To estimate the incidence of and risk factors for serious adverse events (SAEs) in all enrolled vaccinated individuals after each MPOX vaccine dose, by mpox vaccine brand. 2. To estimate the incidence of and risk factors for adverse events of special interest (AESIs) in all enrolled vaccinated individuals after each mpox vaccine dose, by mpox vaccine brand. 3. To estimate the incidence of mpox in all enrolled vaccinated individuals, to assess the real-world effectiveness of the mpox vaccines.

Study design	Active mpox vaccine safety surveillance through an observational prospective single-arm cohort study that will be conducted in sentinel sites affiliated with vaccination centres in [COUNTRY].
Study period	There will be an enrolment period from the date of the study start until a predefined number of individuals have been enrolled. The time point for

	enrolment is first vaccination with any authorized mpox vaccine in participating study sites. Each subject enrolled will be actively followed-up until 3 months after their last mpox vaccine dose.
Population	Participants will be recruited among [PRIORITY GROUP OF INTEREST FOR THIS STUDY], vaccinated at [PLACE OF VACCINATION] participating in this CEM study. Study participation will be strictly voluntary. **Inclusion criteria** • Written informed consent (according to local normative); • [PRIORITY GROUP OF INTEREST FOR THIS STUDY] vaccinated with the first dose of any mpox vaccine at one of the vaccination centers or other sites of vaccination participating in the study. **Exclusion criteria** • Individuals already vaccinated with any mpox vaccine before study enrolment, irrespective of the brand. • Individuals unable to comply with study procedures. • Individuals already infected with monkeypox virus (self-reported or confirmed by a health worker)
Variables	**Exposure of interest** Vaccination with the first dose of any of the mpox vaccine brands that are available in [COUNTRY]. The mpox vaccine brand, dose, date of vaccination and batch number will be recorded. Details on the second dose will also be collected if it is administered. **Outcomes** • SAEs • AESIs • Any reported adverse events (AEs) • mpox disease
Data sources	Data collection is a mix of investigator site data entry and subject self-reported data through [A MOBILE APP/WEBLINKS/TELEPHONE CALLS/PAPER DIARY].

Sample size	The target study size of the entire CEM is 10,000 individuals vaccinated with one or more dose(s) of a mpox vaccine. This study size can rule out events occurring with a frequency of at least 1 per 3,333 if no event is observed, with at least 95% confidence.
Data analyses	Participation rates and demographic characteristics will be summarized using descriptive statistics. The mean/median and standard deviation/range will be summarized for age at enrolment, overall and stratified by sex and by country,

	when appropriate. Frequencies and percentages of outcomes will be provided by age group, sex and country when appropriate. Analyses of SAEs and AESIs will include all individuals. The frequencies and proportions of individuals with identified SAEs and AESIs will be calculated by time since vaccination, in weeks. For proportions, 95% confidence intervals will be calculated using an exact method. For SAEs and for AESIs with an unknown risk window, observed-to-expected analyses will be performed. The observed incidences for AESIs and SAEs will be compared with expected incidences obtained from the most appropriate sources (e.g., clinical trials, epidemiological studies). The expected rates will be age-stratified, and standardized incidence ratios (SIRs) will be calculated. For AESIs with a known risk window, a self-controlled risk interval (SCRI) analysis will be performed. The control interval will be the follow-up time after the risk window for the AESI. Incidence of severe mpox disease (including secondary infection, sepsis, pneumonia, encephalitis, myocarditis, with suspected and laboratory-confirmed mpox, hospitalization for mpox, requiring intensive care unit (ICU) admission, or mpox disease resulting in death) will be calculated by dose, by timing between doses, and by time since each vaccination in months.
Periodic reporting	Interim analyses will be performed at prespecified interval(s).
Ethics	This non-interventional study will be conducted in accordance with the international ethical guidelines for epidemiology studies published by the Council for International Organizations of Medical Sciences (CIOMS) [2], the Declaration of Helsinki and its amendments [3], good epidemiological practice (GEP) guidelines and any applicable national laws and guidelines [SPECIFY AS APPROPRIATE]. Data protection and privacy regulations will be strictly observed in capturing, forwarding, processing, and storing individuals' data.

	Written informed consent will be obtained from all participating individuals (according to the local normative). The study protocol and informed consent forms will be reviewed and approved by [NAME OF ETHICS COMMITTEE(S)/NAME OF INSTITUTIONAL REVIEW BOARD(S)].

8 BACKGROUND AND RATIONALE

Mpox is an infectious disease caused by the Monkeypox virus (MPXV), a species of the *Orthopoxvirus* genus along with Variola virus (smallpox), Vaccinia virus, Cowpox virus, and others. The virus was initially identified in 1958 in laboratory monkeys in Denmark. Human disease was first identified in 1970 in a a nine-month old boy in the Democratic Republic of the Congo (DRC) (Ref: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2480792/) and since then most cases have been reported across Central and West Africa. MPXV is divided genetically into two clades – Clade I (formerly known as Congo Basin clade) which can be classified into subclades Ia and Ib, and clade II (formerly known as West African clade), which can be classified into subclades IIa and IIb. Historically, clade I appears to be more virulent, with a case fatality rate (CFR) ranging from 1% to 10%, with recent outbreaks having a death rate of 1-3.3%. Clade II, which caused the global outbreak in 2022 has a case fatality rate of <1% (Ref: https://www.cdc.gov/poxvirus/mpox/about/index.html). It is important to note the mortality may differ based on setting and access to medical countermeasures and high-quality supportive care. A person with mpox can spread it to others until the rash and lesions have fully healed. Person to person transmission of mpox occurs via direct contact with skin or mucosal lesions, indirect contact with infected objects, vertical transmission from persons who are pregnant to their child, and from direct contact with animals or their body fluids. It–MPXV can be transmitted from animal to humans, human to human, and from the environment to humans (Bunge EM et al., 2022, WHO, 2022).

In May 2022, an unexpected mpox outbreak emerged and rapidly spread around the world, leading to sustained human-to-human transmission of MPXV clade IIb outside its historical ecological niche. Given the global health risk, the World Health Organisation declared the outbreak a Public Health Emergency of International Concern (PHEIC), the highest alert they can issue on July 23 2022. In response to the PHEIC, the international community mobilized to engage at-risk communities and deploy medical countermeasures, helping to quell the outbreak in affected communities in the United States and Europe. As a result of swift action, global cases declined and the PHEIC was lifted in May 2023, with the WHO calling for continued prioritization of efforts in Africa.
Mpox has historically been found in Central and West Africa, with the Democratic Republic of the Congo reporting the most cases from 1970 – 2021 (Ref: https://pubmed.ncbi.nlm.nih.gov/36656790/). In 2023 African countries witnessed an increased from approximately 8,000 cases in 2022 to about 15,000 in 2023, with DRC at the heart of the outbreak. In DRC, cases were occurring in areas that had not previously reported any, such as Kinshasa and sexual transmission of clade I was reported for the first time along with the detection of a new variant known as clade Ib in South Kivu (Masirika LM et al., Eurosurveillance Mar 2024). The clade Ib outbreak initially occurred among sex workers and has

now expanded to their contacts, including children with more information needed to clarify the role of this new variant compared to clade Ia which is endemic in DRC. Clade Ia is characterized by increased morbidity and mortality, especially among children, although more information still needs to clarify the role of each clade in this outbreak (Masirika LM et al., 2024; Vakaniaki EH et al, Nat Med 2024; Masirika LM, JIDC 2024). The outbreak has expanded to border communities and internally displaced people (IDP) camps, and cases imported to other countries in the region have resulted in local transmission in those countries with a high proportion of cases and fatalities reported in children and adolescents < 15 years of age.

According to the World Health Organization (WHO), from 1 January to 8 September 2024, a total of 25 093 suspected mpox cases, including both tested and untested cases, and 723 deaths among suspected cases, were reported in Africa. The three countries reporting the most suspected mpox cases in 2024 are the Democratic Republic of the Congo (21 835 suspected cases, 717 suspected deaths), Burundi (1489 suspected cases, no deaths), and Nigeria (935 suspected cases, no deaths). Since the beginning of 2024, the number of confirmed mpox cases in Africa has been steadily rising, mainly driven by the outbreaks in the Democratic Republic of the Congo (see Figure 2), which account for around 90% (5160 of 5759 cases) of confirmed cases on the continent. To date, clade Ib MPXV in Africa has been detected in the Democratic Republic of the Congo, Burundi, Kenya, Rwanda and Uganda, while clade II MPXV has been reported in over 115 countries globally including West Africa, northern and southern Africa As a dynamic situation, extensive contemporaneous updates can be accessed at a variety of sites, including the WHO Global Dashboard (Ref: https://worldhealthorg.shinyapps.io/mpx_global/#35_Symptomatology). Amid the escalating mpox outbreak in the DRC and across Africa, the Africa CDC declared the crisis its first ever Public Health Emergency of Continental Security on August 13, 2024. Simultaneously, recognizing the growing risk of international spread and the urgent need for global coordination, the WHO convened the International Health Regulations (IHR) Emergency Committee on August 14, 2024. Acting on the committee's recommendations, the WHO Director-General declared the outbreak a Public Health Emergency of International Concern (PHEIC) — the highest level of global health alert.

Vaccination for prevention of mpox

While there is no vaccine developed specifically for mpox, immunity to vaccines developed for smallpox offer some cross-protection against other orthopoxviruses, including MPXV. The Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN) vaccine was approved for use in adults at risk for mpox in the US in 2019 and has since been approved for use in the EU/EEA, UK, Canada and Switzerland; and approved under Emergency Use Authorization in other countries since the global mpox clade IIb public health emergency beginning in 2022. Animal studies (Hatch GJ et al., 2013, Keckler MS et al.,2020) have shown that vaccines developed for smallpox are effective in protecting against infection and

severe disease with limited human epidemiology supporting these observations (Jezek Z et al., 1986, Fine PEM et al.,1988, Rimoin AW et al., 2010). In November 2022 and again in March 2024, WHO's Strategic Advisory Group of Experts on Immunization (SAGE) recommended primary preventive vaccination for individuals at high risk of exposure and prompt post-exposure primary prophylaxis using vaccination (PEP or PEPV) for contacts of cases. SAGE issued a strong call to action to promote mpox vaccination and vaccine research, to facilitate equitable access to vaccination (Ref: https://www.who.int/groups/strategic-advisory-group-of-experts-on-immunization). On June 26, 2024, the medicine regulatory authority of DRC approved the emergency use of mpox vaccines MVA-BN, manufactured by Bavarian Nordic, and LC16m8 (LC16), manufactured by KM Biologics. On 13 September 2024, WHO prequalified the MVA-BN vaccine for mpox and is reviewing the regulatory dossiers for the LC16 vaccine and discussing dossier submissions with the manufacturer of the ACAM2000 vaccine.

Cohort event monitoring (CEM) enrolls a group of people receiving a vaccine or taking a drug (i.e., medication) in a prospective cohort study and then systematically records data on all adverse events of interest that occur in those patients during a specified follow-up period with periodic inquiries, AEs may be pre-specified or spontaneously reported. CEM involves obtaining a denominator of persons exposed to medication(s) of interest and allows for calculation of rates. Sentinel site CEM focuses on fewer sites and can provide high-quality data from a smaller population with the added benefit of logistical ease. CEM is especially useful in LMICs, because of the lack of large, linked data sources that provide denominator data. Examples of CEM in LMICs include cohort studies of AEFIs associated with the administration of a pentavalent DTP-hepatitis B vaccine/Hib vaccine conducted in Ghana, Guatemala, and India (Dodoo AN et al., 2007, Arora NK et al., 2020) and AEFIs following administration of Japanese Encephalitis vaccine in an endemic district in Sri Lanka (De Alwis KN et al., 2014) During COVID-19 pandemic CEM was implemented in many settings, with several template protocols that were made available (ShamaeiZadeh PA et al., 2024). Tools to collect data differ, but methods always include recruitment at vaccination point, consent, and periodic follow-up post-vaccination to solicit AEs. Acknowledging that routine passive reporting systems might not be sufficient to allow rapid assessment and appropriate public health response during MPOX vaccine introduction, active safety surveillance via CEM is recommended.

In [COUNTRY], vaccination with mpox vaccines as part of the NIP is expected to start in [XXX]. It is expected that vaccination will take place with [VACCINE BRAND], a [VACCINE PLATFORM e.g. live viral vector, live attenuated non-replicating viral] vaccine, manufactured by [MANUFACTURER]. The vaccine is indicated for [AGE GROUP], and is contraindicated for persons with [CONTRAINDICATION]. [Any known safety concerns]. At its initiation, there will be limited supplies of the mpox vaccines. [PRIORITY GROUP OF INTEREST FOR THIS STUDY] will be (among) the first groups to be vaccinated,

other priority groups are [PRIORITY GROUPS]. [PRIORITY GROUP OF INTEREST FOR THIS STUDY] will be primarily vaccinated at [PLACE OF VACCINATION]. As one or more vaccines may be used in [COUNTRY], identification of vaccine brand will be an important aspect of post-marketing pharmacovigilance activities.

This protocol describes a cohort event monitoring (CEM) study designed to capture adverse events occurring in a cohort of [PRIORITY GROUP OF INTEREST FOR THIS STUDY] vaccinated with [VACCINE/MPOX vaccines] during routine clinical practice in [COUNTRY] for the purpose of signal detection and estimation of incidence and risk factors. The site-specific protocol will include informed consent forms (ICFs) in [LOCAL LANGUAGE(S).

9 OBJECTIVES

The overall aim of this observational study is to monitor the safety of mpox vaccines in [PRIORITY GROUP OF INTEREST FOR THIS STUDY] in [COUNTRY] for the purpose of safety signal detection as soon as the vaccine is introduced.

The specific objectives are to:

1. Estimate the incidence of and risk factors for SAEs in all enrolled vaccinated individuals after each mpox vaccine dose, by MPOX vaccine brand;
2. Estimate the incidence of and risk factors for AESIs in all enrolled vaccinated individuals after each mpox dose, by MPOX vaccine brand;
3. Estimate the incidence of mpox in all enrolled vaccinated individuals, to assess the real-world effectiveness of the mpox vaccines.

10 METHODS

10.1 Study design

Active mpox vaccine safety surveillance through an CEM observational prospective single-arm cohort study that will be conducted through [PLACE OF VACCINATION] under the [NAME OF NATIONAL HEALTH AUTHORITIES]. Study participants will be actively followed up until 3 months after their last MPOX vaccine dose.

10.2 Study population

Participants will be recruited among [PRIORITY GROUP OF INTEREST FOR THIS STUDY] vaccinated at [PLACE OF VACCINATION] participating in this CEM study. Study participation will be strictly voluntary.

10.2.1 Inclusion criteria

- Written informed consent.
- [PRIORITY GROUP OF INTEREST FOR THIS STUDY] vaccinated with the first dose of any mpox vaccine at one of the vaccination centers participating in the study.

10.2.2 Exclusion criteria

- Individuals already vaccinated with any MPOX vaccine before study enrolment, irrespective of the brand.
- Individuals unable to comply with study procedures (illiterate, [to be completed as per study set up: e.g., use of mobile phone for data collection).
- Individuals already infected with MPXV (suspected or laboratory confirmed).

10.2.3 Withdrawal from the study

Participants will have the right to withdraw from the study for any reason at any time. A participant will be considered lost-to-follow-up after [NUMBER] unsuccessful attempts to contact them by phone, followed by [NUMBER] unsuccessful attempts to contact their next of kin. The attempts to contact will be documented.

All attempts will be made to determine the underlying reason for withdrawal and, where possible, the primary underlying reason will be recorded. Withdrawn participants and those lost-to-follow-up will not be replaced after the enrolment period has ended. Should a participant decide to withdraw from the study, data collected up to the time of withdrawal will not be withdrawn and will be used in the analyses.

10.3 Study sites

[Paragraph describing the health facilities in which the study will be conducted]
Study sites are defined as [groups of] vaccination centres where mpox vaccines are administered to [STUDY POPULATION OF INTEREST], i.e., sentinel sites.

Criteria for the selection of sentinel sites will be based on scoping information from IQVIA, DRC partners, and Africa CDC, and could consist of the following criteria: (a) provides mpox vaccinations; (b) mpox suspected cases exceeding a threshold number as determined by the

Ministry of Health; (c) availability of sufficient human resources at the sentinel site.

Table 1. Study sites with site principal investigators and contact details

Site	Site Principal investigator	Email	Phone number

10.4 Study period

10.4.1 Start of study and duration of follow-up

There will be an intensive enrolment period soon after the date of the start of the mpox vaccine deployment until the predefined target number (study sample size) of enrolled individuals has been reached. The time point for enrolment will be first vaccination with any authorized mpox vaccine in one of the participating sites. Study recruitment will be monitored during the study to assess whether recruitment goals are being reached.

Each individual will be followed-up for 3 months after the first dose of mpox vaccine. If a second dose is administered within 1 months of the first dose, the subject will be followed up till 3 months after the second dose. A 3-month follow-up period was chosen because this covers the most common risk windows for AESIs (42 days), with a similar amount of time after the risk window, to be used as a control period.

10.4.2 Study completion and end of study

Participants will be considered to have completed the study when they have completed the follow-up surveys 3 months after their last mpox vaccine dose. End of study is defined as the point at which the last subject enrolled has reached the 3 months follow up period.

10.5 Sample sizes

10.5.1 Sample size for overall cohort

To guide the decision for suitable sample sizes, sample sizes were calculated taking into consideration different event frequencies. Table 2 shows the sample sizes required to rule out an event with a given frequency with 95% confidence. If no event is observed with 30,000 participants, events with a frequency of 1 per 10,000 would be ruled out with 95% confidence. Studies conducted following the

same protocol in different countries will provide strengthened evidence on MPOX vaccine safety.

Table 2. Sample sized required to rule out events with the indicated frequency if no event is observed with 95% confidence.

Sample size	Event frequency
10,000	**1 per 3,333**
20,000	1 per 6,666
30,000	1 per 10,000

The probability of observing at least one event was calculated based on a binomial distribution as shown in Figure 1 (example shown for sample sizes up to 60,000). This figure shows the probabilities of observing at least one event in different scenarios corresponding to different sample sizes and event frequencies. The two vertical dotted lines correspond to sample sizes of 10,000 and 30,000, respectively. The horizontal dotted lines correspond to a 95% probability of observing at least one event. With a sample size of 10,000, it is likely (probability ~ 95%) to observe at least one event with an event frequency of 1 per 3,333. A sample size of 10,000 will enable to observe at least one event with an event frequency of 1 per 3,333 people whilst a sample size of 30,000 will enable to observe at least one event with an event frequency of 1 per 10,000 people, with 95% confidence.

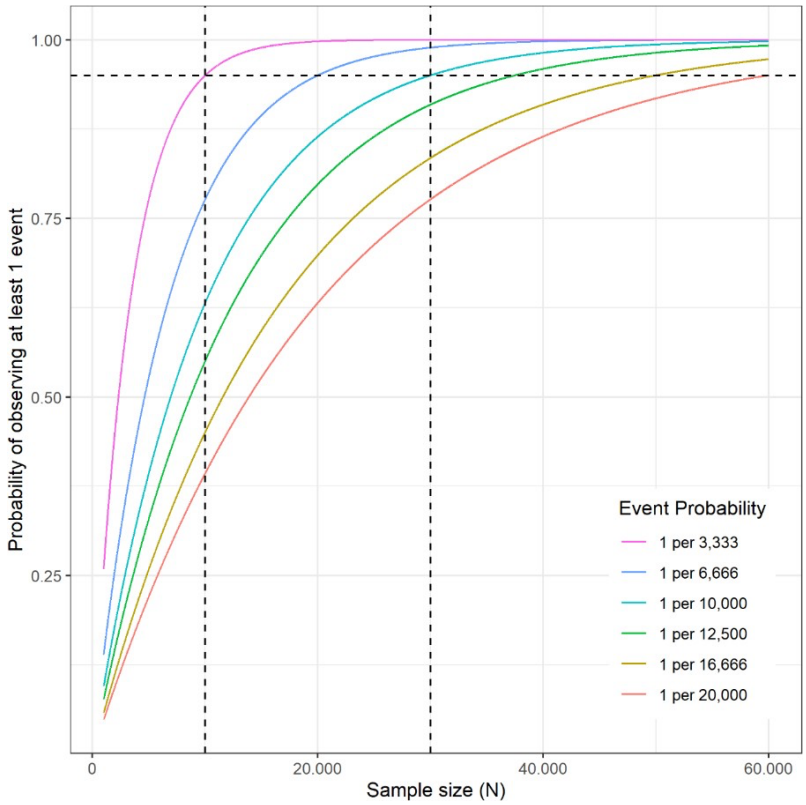


Figure 1. Probability of observing at least one event assuming a given event probability, by varying sample sizes up to 60,000. The horizontal dotted lined correspond to a 95% probability of observing at least one event.

The sample size required to rule out a given relative risk (RR) with 95% confidence if no event is observed in the risk window was calculated, taking into account the background incidence rate and the length of the risk window for some AESIs.

10.6 Study variables

Study staff will collect data for covariates and vaccination on the day of vaccination. All participants will complete questionnaires through [A MOBILE APP/WEBLINKS/TELEPHONE CALLS/PAPER DIARY] at day 7, day 30, day 60 and day 90 after vaccination (Appendix 2).

10.6.1 Exposure of interest

Vaccination with the first dose of any of the mpox vaccine brands that are available in [COUNTRY]. The mpox vaccine brand, dose, date at vaccination and batch number will be recorded. If a second dose is administered within 1 months of the first dose, same details on the second dose will also be

collected.

10.6.2 Study outcomes

10.6.2.1 Serious adverse events

A serious adverse event (SAE) is any untoward medical occurrence that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

10.6.2.2 Adverse events of special interest

The list of AESIs is shown in Appendix 1.

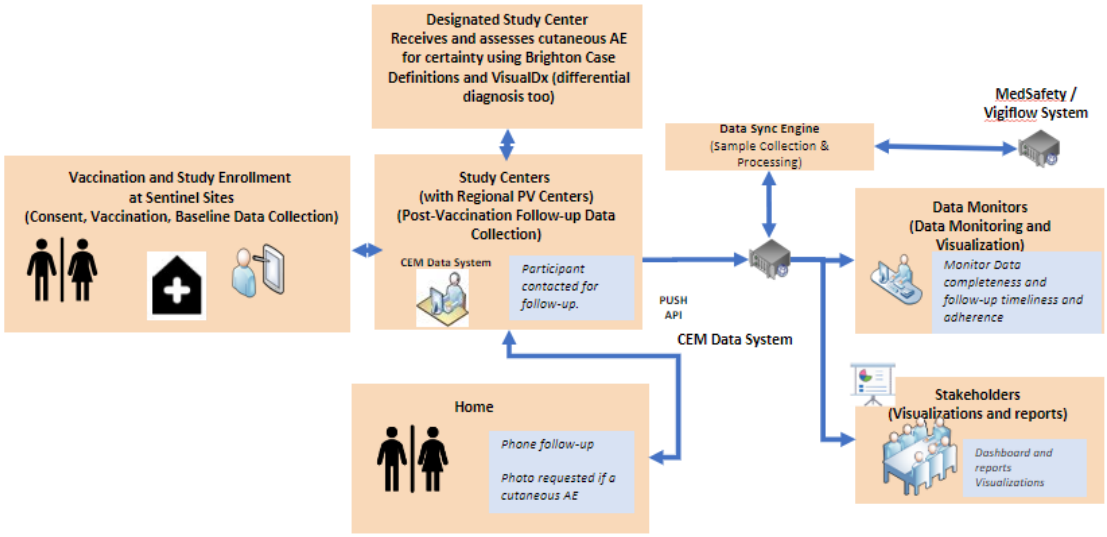
10.6.2.3 Mpox disease

Occurrence of mpox disease will be solicited throughout follow-up to collect Information on (Appendix TBD):

- laboratory-confirmed diagnosis or not:
- hospitalization for mpox disease;
- intensive care necessary or not; and
- mpox resulted in death.

10.7 Study flow: data sources and data collection

Figure. CEM study flow.



Data will be collected at the time of enrolment, at time of vaccination, and during follow-up. Data collection by the study site staff at the time of enrolment and vaccination will take place through [AN ELECTRONIC TOOL OR OTHER MEANS] at the site. Data collection by the participants during follow-up will take place through [A MOBILE APP/WEBLINKS/TELEPHONE CALLS/PAPER DIARY]. All data variables are listed in APPENDIX.

The CEM study flow is depicted in the Figure. Follow-up of patients would be initiated by study personnel who will phone patients at prespecified time intervals and record presence and absence of specified AEs. In the event of a cutaneous AEFI, a photograph will be requested to be transmitted to the study site where it will be evaluated for certainty, potentially facilitated with the clinical support system, VisualDx. In collaboration with International Network of Special Immunization Services (INSIS), biological samples for later multi-OMICs analysis may be collected at recruitment into the CEM after specific informed consent among participating sites.

10.7.1 Vaccination and enrolment

Potential participants will be informed about the study through [APPROPRIATE ROUTE, e.g. occupational health service department for healthcare workers, or study staff at vaccination centre],

and study staff will be available to answer any questions. Enrolment will take place immediately after vaccination, the study staff will collect the signed ICF, complete the participants' baseline information (demographic and medical) and contact information for the participant and their next of kin (Appendix 2), and record the details of. A unique participant identifier will then be generated.

To increase the quality of the self-reported data, participants will be asked to report any physician-made diagnoses and, if they are hospitalized, to provide data from their discharge report, if available. In addition, the participants will be asked to return to the same vaccination centre to receive their second dose of mpox vaccine (if applicable).

10.7.2 Vaccination during the follow-up period

If participants receive a second MPOX vaccine dose during the follow-up period, details of the second vaccination are also collected (Appendix TBD).

10.7.3 Follow-up

Participants will be asked to return to the vaccination centre if any event occurs within seven days after immunization. The study team will call the participants on day seven and every month after vaccination until month three to ask if any event occurred. A specific form will be filled out to document each follow-up.
<TBA>

10.7.4 Identification of AESIs and SAEs

The diagnoses reported by the participants during follow-up will be coded using Medical Dictionary for Regulatory Activities (MedDRA) by [TO BE DEFINED BY STUDY TEAM]. SAES and AESIs will be identified using MedDRA codes by [TO BE DEFINED BY STUDY TEAM].

10.7.5 Pregnancy

Participants who are reported to be pregnant during follow-up will be referred to the [NATIONAL AEFI FOCAL POINT] for follow-up as per national guidelines. All pregnant women inadvertently exposed to MPOX vaccine should be followed up until delivery, and the pregnancy outcome documented in accordance with protocol (TBA).

10.7.6 Data collection at withdrawal/lost to follow-up

If a participant withdraws from the study or is lost-to-follow-up, the follow-up for that participant will be terminated early and the date of and, if possible, the reason for withdrawal/lost-to-follow-up will be recorded.

If a safety signal is detected, [DESIGNATED STUDY TEAM/NATIONAL AEFI FOCAL POINT/NATIONAL PHARMACOVIGILANCE CENTER] may decide to contact the healthcare provider of participant with the potential safety issue, for further investigation through [APPROPRIATE NATIONAL ROUTES].

10.8 Data analysis

The analysis plan will be fully described in a written and approved statistical analysis plan (SAP). All analyses will be documented in the final study report. Missing data will be acknowledged in the analyses and interpretation of data.

10.8.1 Descriptive analysis of demographics and baseline characteristics

Participation rates over time will be described. Demographic characteristics will be summarized. The mean/median and standard deviation/range will be given for age at enrolment, overall and stratified by sex and by country, when appropriate. Frequencies and percentages will be provided by age group, sex, and country, when appropriate.

10.8.2 Statistical analyses

The analyses of SAEs and AESIs will include data for all participants, while analyses of reactogenicity will include only data from the participants in the reactogenicity subset. Participants that completed the follow-up forms but do not report any event(s) will be considered as participants without event(s).

Diagnoses will be coded, using MedDRA preferred terms (PTs), by [TO BE DEFINED BY STUDY TEAM]. All analyses for AESIs will be at the PT levels. The frequency and proportion of participants reporting AESIs and SAEs will be calculated by time since vaccination (in weeks). For the proportions, 95% confidence intervals will be calculated using an exact method [11].

Observed-to-expected analyses will be performed for SAEs and AESIs with an unknown risk window. The observed incidences for AESIs will be compared with background rates from the most appropriate sources. Good quality national background rates will be used if available. If these are not available, good quality background rates from neighboring countries with comparable healthcare systems will be used. The expected rate will be age-stratified, and the standardised incidence ratio (SIR) will be calculated.

For acute AESIs with a known risk window (see APPENDIX 2: ADVERSE EVENTS OF SPECIAL INTEREST),

self-controlled risk interval (SCRI) analyses will be performed. The control interval will consist of the follow-up time after the risk window for the acute outcomes.

The incidence of mpox disease (any mpox disease diagnosed by a healthcare professional, laboratory-confirmed mpox, hospitalization for mpox, mpox requiring intensive care unit admission, mpox resulting in death) will be calculated by dose, by timing between doses, and by time since each vaccination in months. Participants with mpox symptom onset within [APPROPRIATE TIME INTERVAL] after vaccination may be excluded.

11 Data management

A data management plan (DMP) will be developed before data collection begins and will describe all functions, processes, and specifications for data collection, cleaning and validation.

Study staff will enter data in [APPROPRIATE TOOL] at several time points. Study staff will enter data on informed consent, contact details and covariates at the time of enrolment, data on the exposure at the time of vaccination, [DATA FROM THE QUESTIONNAIRE IF COLLECTED THROUGH TELEPHONE/PAPER-BASED DIARIES], and any data obtained in the event of additional follow-up after initial non-response. [TO DESCRIBE SPECIFICATIONS OF MEANS OF DATA COLLECTION, SOFTWARE IF ANY, DATA STORAGE]

Participants will complete the questionnaires through [A MOBILE APP/WEBLINKS/TELEPHONE CALLS/PAPER DIARIES]. The questionnaires will be available in [LANGUAGE]. [SPECIFICATIONS OF MEANS OF DATA COLLECTION, SOFTWARE IF ANY, DATA STORAGE TO BE DESCRIBE].

For all electronic data entry, automated quality checks will detect out-of-range or anomalous data, where applicable. User testing of any data entry methods, whether electronic or on paper, will be performed prior to deployment.

13.1.1 Data security

[PROCESSES FOR ANONYMIZATION, ACCESS, STORAGE, AND DESTRUCTION OF RAW DATA TO BE DESCRIBE].

The key-coded data obtained from this study will be stored in a secured database located in [COUNTRY]. Data will be handled in accordance with all applicable data protection and privacy laws. No unauthorized persons will have access to the data. Data will be archived for [XXX] years, as per national regulations, and will then be destroyed.

These security measures will also apply to the ICFs.

13.1.2 Data transfer

[PROCESS FOR DATA TRANSFER INCLUDING SECURITIY TO BE DESCRIBE]

13.1.3 Source documents

The data sources for the exposure of interest will be [TO BE COMPLETE AS APPLICABLE].

The data source for covariates will be the participants.

The data sources for the study outcomes will be the questionnaires completed by the participants (or their next of kin).

13.1.4 Data retention and archiving

Documents that individually and collectively permit evaluation of the study conduct and the quality of the data produced will be retained for [TIME PERIOD AS APPLICABLE] in accordance with good

pharmacoepidemiological practice guidelines [12] and [LOCAL REGULATIONS, to be detailed in the site-specific protocol]. This will include the analytical data, analyses programs, and all output generated.

12 Quality assurance, monitoring and reporting

14.1.1 Monitoring

A site initiation [VISIT (PREFERRED IF FEASIBLE)/TELEPHONE CALL] will be conducted to ensure the site is ready to start data collection. Study staff will be trained on the study procedures.

[REMOTE/ON-SITE] monitoring of the study conduct will be performed throughout the study period to assess the accuracy and completeness of the data.

The study site may be subject to a quality assurance visit. If so, the site will be contacted in advance to arrange a monitoring visit. The investigator and site staff will guarantee direct access to all study documents for quality assurance monitors.

14.1.2 Interim analyses and reporting

Interim analyses will be performed by [TO BE DEFINED BY STUDY TEAM] on a weekly basis for the reactogenicity outcomes, as data will be collected daily. For the other outcomes, for which data will be collected weekly, interim analyses will be performed on a monthly basis.
Should the rates of adverse event be different from the expected rates (as per clinical trials data and reported in the summary product characteristic of a given product), the study team will have to inform the national regulatory authorities for regulatory review.

14.1.3 Final analyses and reporting

Final analyses will be performed and a full study report will be written within 4 weeks after database lock. Study results will be shared with the national regulatory authorities for regulatory review, and with the national immunization programme to inform policy decision.

13 Study management

This study will be performed by the investigator, with guidance, input, review and approval of the sponsor, including development of materials, recruitment, training and management of sites, electronic data capture and data management and analyses.

The Investigator and all study staff will conduct the study in compliance with the [NAME ETHICS COMMITTEE/NAME of INSTITUTONAL REVIEW BOARD] approved version of this protocol. All personnel involved in the conduct of this study must be qualified by education, training and experience to perform their tasks.

15.1.1 [NATIONAL PHARMACOVIGILANCE CENTRE/AEFI COMMITTEE/NATIONAL IMMUNIZATION PROGRAMME MANAGER/DEDICATED SCIENTIFIC COMMITTEE]

The [NAME OF NATIONAL PHARMACOVIGLANCE CENTRE/AEFI COMMITTEE/NATIONAL IMMUNIZATION PROGRAMME MANAGER/DEDICATED SCIENTIFIC COMMITTEE (to be detailed in the site-specific protocol)] will oversee the implementation and smooth running of the project. They will provide scientific, statistical and technical expertise, as needed.

15.1.2 Changes to the protocol

Changes to the protocol will be documented in written protocol amendments. Major amendments will usually require submission to the relevant institutional review board (IRB)/independent ethics committee (IEC) for approval. In such cases, the amendment will be implemented only after approval has been obtained.

Minor protocol amendments, including administrative changes, will be filed by the investigator at each participating site and will be submitted to the relevant IRB/IEC. Any amendment that could have an impact on an individual's agreement to participate in the study will requires the renewed informed consent prior to continued participation in the study.

15.1.3 Management and reporting of adverse events/adverse reactions

The study team will ensure that the healthcare workers in charge of vaccine administration in study sites are familiar with the national AEFI reporting and management processes as per national guidelines. The study team will liaise with the national immunization programme/national regulatory authorities to ensure that provisions are in place (including AEFI reporting forms, procedures, and training) for smooth implementation.

Adverse events will be assessed at the level of the population. No individual causality assessment will be done as part of the study.

Contact information of the participants and their healthcare providers will be collected, and consent will be sought to use this contact information in case the [NAME OF NATIONAL AEFI FOCAL POINT/NATIONAL PHARMACOVIGILANCE CENTER] needs to investigate any potential safety signals that arise from the study.

The study team will be responsible to ensure that all SAEs detected and reported in the context of this study will also be reported through the routine AEFI surveillance system to the responsible organization within the health ministry (NPI/national regulatory authorities/pharmacovigilance centre), to ensure appropriate healthcare, timely investigation, causality assessment and response

as per the country's protocol.

[Describe mechanisms/processes to ensure that all serious adverse events detected and reported in the context of this study, are also reported through the routine AEFI surveillance system to the responsible institution within the health ministry (NPI/ national regulatory authorities / pharmacovigilance centre), to ensure timely investigation, causality assessment and response as per the country protocol].

14 Ethical considerations

16.1.1 Guiding principles

To ensure the quality and integrity of research, this study will be conducted under the International Ethical Guidelines for Health related Research involving humans issued by the Council for International Organizations of Medical Sciences [2] , good epidemiological practice (GEP) guidelines, the ethical principles in the Declaration of Helsinki [3] and any applicable national laws, regulations and guidelines.

This is an observational study without medical intervention or change in the clinical and diagnostic practices. Therefore, there will be no direct benefit to the participants. Nevertheless, there will be potentially important societal benefits from this vaccine safety study. MPOX vaccines are key to controlling the pandemic. Close monitoring of the first cohorts vaccinated with MPOX vaccines will be important for these novel vaccines, to ensure safety and to maintain public confidence in vaccines.

16.1.2 Respecting participants' autonomy

The study will use self-reported data and data collected as part of healthcare provision at designated hospital(s). Participants will be informed about the study through [TO COMPLETE AS APPLICABLE] and will have the opportunity to ask questions to study staff. An ICF must be signed prior to the individual's participation in the study (APPENDIX 4: ADULT INFORMED CONSENT FORM). When signing the ICF, individuals agree that the study team will be able to contact designated hospital(s) at which they may have sought care during the study period. The purpose of this contact is to obtain medical confirmation of the adverse event that led to the hospital visit. The study-specific ICF will spell out the purpose of the data collection, the foreseeable uses of the data, the intended goal of such use, who has access to the data, the conditions and duration of data storage, and the ways in which the participant can contact the custodian and remain informed about future use. The ICF will explain that individual's participation is completely voluntary and that they can decide to withdraw at any time during the study.

[The adult ICF template and process will need to be adapted for special populations (e.g., minors, pregnant women, elderly patients lacking full capacity, migrants, prisoners) that require a tailored approach to consent, including possible surrogate decision-makers (e.g. parents or guardians, adult children) or study advocates (e.g. for inclusion of prisoners, orphans) and additional forms (e.g., assent forms), as well as tailoring some details provided to participants during consent].

16.1.3 Participant confidentiality

No data whatsoever will be used, either alone or in conjunction with any other information to establish the identity of any of the participants from whom data were obtained. All parties will ensure protection of participant personal data and will not include participant's names on any study forms, reports, publications, or in any other disclosures, except where required by law. Local data protection and privacy regulations [TO BE DETAILED IN THE SITE SPECIFICPROTOCOL] will be observed in capturing, forwarding, processing, and storing patient data.

16.1.4 Independent ethics committee/institutional review board

Participating study sites will submit the site-specific protocols to [NAME OF ETHICS COMMITTEE(S)/NAME OF INSTITUTIONAL REVIEW BOARD(S), following local regulations - to be detailed in the site-specific protocol] and will comply with any national ethics committee requirements.

Informed consent will be required from all participants or legal representatives.

15 Limitations

The exclusion of individuals who have already been vaccinated with mpox vaccine precludes the possibility to monitor effects of repeat vaccinations as part of this study. Sample size usually limits assessing uncommon adverse events. CEM studies are prone to loss-to-follow-up. Implementation in areas with difficult access and poor access to cell phones and the internet may make it difficult to monitor participants. Mobile populations and areas experiencing violent conflict may pose additional barriers to followup.

16 References

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17.

APPENDIX 1: MPOX ADVERSE EVENTS OF SPECIAL INTEREST

Based on SPEAC Mpox AESI list, v1.1, 17 September 2024 (https://speacsafety.net/tools/aesi-lists/mpox/).

This list of potential Adverse Events of Special Interest (AESI) that could follow vaccines to prevent Mpox was developed based on criteria established by the Safety Platform for Emergency Vaccines (SPEAC), which include:

1. A known association with immunization or a specific vaccine platform.
2. The occurrence during wild-type disease due to viral replication and/or immunopathogenesis.
3. A theoretical association derived from animal models.

Special populations, including pregnant women, children, adolescents, and immunosuppressed individuals, may experience an increased frequency and severity of any of the AESIs listed as relevant to all populations. There are also specific AESI that are of particular relevance to special populations, and these are listed according to the population. It is important to note that children, pregnant women and immunocompromised individuals may also have increased severity of expected local and systemic reactogenicity, as well as unexpected autoimmune conditions.

This list is based on the available data for mpox vaccines, which are to be used in response to the 2024 Public Health Emergency of International Concern (PHEIC) for mpox in Africa.

Body System	Possible AESI	Specific to mpox disease	Specific to vaccine platform	Published BC Case Definition	Completed Companion Guide	Simplified Data form ('RedCap ready')
Relevant to all populations						
Cardiac	Myocarditis/pericarditis	X	MVA-BN, LC16m8	YES	YES	YES
Dermatologic	Rash	X		YES	YES	YES
	Robust take		LC16m8	YES	YES	YES
	Generalized vaccinia		LC16m8	YES	YES	YES
	Eczema vaccinatum		LC16m8	YES	YES	YES
Dermatologic, Mucosal, and Ophthalmologic	Inadvertent inoculation (including ocular vaccinal infections)	X	LC16m8	YES	YES	YES
Dermatologic and Systemic	Secondary infections (bacterial)*	X	LC16m8	NO	NO	NO
Hematologic	Thrombocytopenia		any vaccine	YES	YES	YES
Immunologic	Anaphylaxis		any vaccine	YES	YES	YES
Neurologic	Encephalitis	X	LC16m8	YES	YES	YES
	Generalized convulsive seizure	X	any vaccine	YES	YES	YES
Ophthalmologic	Ocular Manifestations	X	LC16m8	NO	NO	NO
Respiratory	Pneumonitis/ARDS	X	LC16m8	YES†	YES†	NO†

Body System	Possible AESI	Specific to mpox disease	Specific to vaccine platform	Published BC Case Definition	Completed Companion Guide	Simplified Data form ('RedCap ready')
Relevant to pediatric populations						
Dermatologic	Severe Vaccinal Eruption or Local Reactogenicity (Hives, Erythema, Poor healing, Scarring)		MVA-BN, LC16m8	NO§	NO	NO
Dermatologic and Systemic	Secondary infections (bacterial)*	X	MVA-BN, LC16m8	NO	NO	NO
Neurologic	Febrile seizure	X	MVA-BN, LC16m8	NO¶	NO¶	NO¶
Relevant to pregnant populations**						
Maternal	Stillbirth	X	MVA-BN, LC16m8	YES††	YES	YES
	Spontaneous Abortion/Miscarriage	X	MVA-BN, LC16m8	YES	YES	YES
	Antenatal hemorrhage	X	MVA-BN, LC16m8	YES	NO	YES
	Preeclampsia/Eclampsia		MVA-BN, LC16m8	YES§§	NO	YES
Neonatal	Fetal Vaccinia (congenital infection)		MVA-BN, LC16m8	NO	NO	YES
	Congenital anomalies	X	MVA-BN, LC16m8	YES	NO	YES
	Preterm delivery/birth	X	MVA-BN, LC16m8	YES	YES	YES
	Neonatal vaccinia/mpox infection in infant of mother vaccinated in pregnancy	X	MVA-BN, LC16m8	YES¶¶	NO	YES
Relevant for people with HIV and other immunocompromised populations***						
Immunologic	Progression of HIV	X	MVA-BN, LC16m8	NO	NO	NO
	Opportunistic infections†††	X	MVA-BN, LC16m8	NO	NO	NO
	Progressive vaccinia		MVA-BN, LC16m8	YES	NO	NO

*Secondary bacterial infection of lesions or resulting in sepsis after vaccination should be captured.
†BC tools exist for ARDS, but not a digitalized data collection form. No BC tools exist for pneumonitis.
§BC tools do not exist for all the AESIs listed for special populations. However, there are other tools (e.g. toxicity grading scales) that may be applied.
¶BC tools exist for Generalized convulsive seizure and Fever.
**Guidelines for data collection exists as part of the GAIA project: https://brightoncollaboration.org/global-alignment-of-immunization-safety-assessment-in-pregnancy-gaia/
††The Stillbirth CD publication update is pending.
§§BC CD for hypertensive disorder of pregnancy
¶¶BC CD exists for Neonatal infection.
***Including malnutrition
†††Viral infection or live-attenuated viral vaccination can worsen immunosuppressive states.

References:

https://www.hosp.ncgm.go.jp/isc/vaccines/MNK/Vaccination_Procedure_Guideline_for_Lc16.pdf

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APPENDIX 2: CEM QUESTIONNAIRES

CEM AESI Questionnaire

Demographics

1. What is your age? _____ years/months
2. Sex: [ ] M [ ] F [ ] TGM [ ] TGF
    a. If F = YES, and Age > 10 years:
    Pregnancy status: [ ] Unknown [ ] Not pregnant [ ] Pregnant
    LMP: ___/___/___ (dd/mo/yr)
3. HIV status: [ ] Unknown [ ] Negative [ ] Positive
    a. If HIV positive:
    Last CD4: _____ Date: ___/___ (mo/yr)
    Last VL: _____ Date: ___/___ (mo/yr)
    Currently taking antiretroviral therapy: [ ] Yes [ ] No
4. Do you have any other condition that could affect your immune system?
    [ ] Yes [ ] No
    a. If Yes: What is the condition? _____
    When were you diagnosed with this? ___/___/___ (dd/mo/yr)
    Are you currently taking medication to treat this? [ ] Yes [ ] No
    If yes, list your medications: _____
5. Do you take any medications that could affect your immune system? [ ] Yes [ ] No
    If yes, list your medications and when you started taking them:
    _____ Date: ___/___ (mo/yr)
    _____ Date: ___/___ (mo/yr)

CEM Reactogenicity Screening Questions (daily x 7 days after vaccination, then monthly x 3 months)

1. Systemic Reactogenicity: In the first week after vaccination have felt unwell? Did it affect your usual activities? Did you seek medical care?

2. Local Reactogenicity: Have you noticed any skin reaction at the site of vaccination? [ ] Yes [ ] No
    a. If Yes: complete the Dermatologic AESI form

CEM SAE Screening Questions (daily x 7 days after vaccination, then monthly x 3 months)

3. SAEs: Have you been hospitalized?
    a. Note: If lost to followup, seek family member to administer questions below [or verbal autopsy form]

CEM AESI Screening Questions by System (daily x 7 days after vaccination, then monthly x 3 months)

4. Anaphylaxis
    a. Have you had difficulty breathing, rash or hives, swelling of the skin, sick to your stomach, and feeling weak and faint starting within several hours after vaccination?

5. Cardiac
    a. Have you had chest pain, fluttering heart, or a fast heart rate during the six weeks after vaccination?
6. Dermatologic
    a. Have you had a rash around the vaccine site or elsewhere on your body that occurred within two weeks after vaccination ?
7. Ophthalmologic
    a. Have you had any change in your vision (blurry vision, painful eyes, double vision) in the 30 days after vaccination?
8. Neurologic
    a. Have you had severe headache, confusion, or limb movements you couldn't control in the three weeks after vaccination?

If “Yes” to any of the screening questions, trigger the relevant AESI questionnaire by body system

CEM AESI-specific Questionnaires (and associated Data Collection Forms)

1. General (Anaphylaxis)
2. Cardiac (Myocarditis/Pericarditis)
3. Dermatologic (Rash, robust take, generalized vaccinia, eczema vaccinatum, inadvertent autoinoculation)
4. Ophthalmologic (E.g. keratitis, blepharoconjunctivitis, EOM paresis)
5. Neurologic (Encephalitis, seizure)

For any possible in-person followup by study staff/focal point, review available records or registers at health post/center/hospital or arrange for evaluation by study staff to complete the Simplified Data Collection Forms (DCFs) as possible.

CEM AESI Questionnaire - Anaphylaxis

Anaphylaxis screening question: Have you had difficulty breathing, rash or hives, swelling of the skin, sick to your stomach, and feeling weak and faint starting within several hours after vaccination?

1. If yes, please specify which you had:

    a. Difficulty breathing? Y/N (if yes, answer below)
        i. When did it start? (date, approximate time)
        ii. When did it stop, or is it ongoing? (date/ongoing)

    b. Rash or hives, at a location other than where you got the vaccine? Y/N (if yes, answer below)
        i. When did it start? (date, approximate time)
        ii. When did it stop, or is it ongoing? (date/ongoing)

    c. Swelling of the skin at a location other than where you got the vaccine? Y/N (if yes, answer below)
        ii. Where did you have swelling of the skin?
        iii. When did it start? (date, approximate time)
        iii. When did it stop, or is it ongoing? (date/ongoing)

    d. Sick to your stomach, with new vomiting or diarrhea? Y/N (if yes, answer below)
        i. When did it start? (date, approximate time)
        ii. When did it stop, or is it ongoing? (date/ongoing)

    e. Feeling faint? Y/N (if yes, answer below)
        iv. When did it start? (date, approximate time)
        iv. When did it stop, or is it ongoing? (date/ongoing)

2. Did you see a medical person for help? Y/N
    a. If yes, which type and when did you see them?

Type	**Location**	**Date(s)**
Health post [ ]		
Health center [ ]		
Hospital [ ]		
Traditional healer [ ]		
Pharmacy [ ]		

    b. If yes, CEM nurse should complete the following from available records (ask patient for their take-home chart, check register for signs and symptoms, review hospital records)

3. If 1a. Difficulty breathing = yes, did you have or were you told by family or friends that you had:
    a. Faster breathing than your usual breathing rate?
    b. Skin turning blue or gray (e.g., your lips, fingertips)?
    c. Increased effort required to take a breath (e.g., big movements in the muscles of your chest in order to take a breath in)
    d. A rattling or high-pitched squeaking or whistling sound when you breathed in or out?
    e. Swelling of your tongue or inside your mouth or throat?
    f. Low oxygen level (e.g., on a health clinic's fingertip oxygen monitor)

CEM AESI Questionnaire - Cardiac

Myocarditis screening question: Have you had chest pain, shortness of breath, irregular or fast heartbeat, fatigue, sweating or fever since having vaccination?

2. If yes, please specify which you had:

    b. Chest Pain? Y/N (if yes, answer below)
        ii. When did it start? (date, approximate time)
        iii. How long did it last?
        iii. When did it stop, or is it ongoing? (date/ongoing)
        iv. Was it sharp, throbbing, dull or pounding?

    c. Shortness of Breath? Y/N (if yes, answer below)
        v. When did it start? (date, approximate time)
        v. When did it stop, or is it ongoing? (date/ongoing)
        vi. Was it made worse with exertion? (walking or climbing stairs)

    f. Irregular or fast heartbeat? Y/N (if yes, answer below)
        i. When did it start? (date, approximate time)
        vi. How long did it last?
        vii. When did it stop, or is it ongoing? (date/ongoing)
        viii. Have you had multiple episodes?

    g. Fatigue? Y/N (if yes, answer below)
        ii. When did it start? (date, approximate time)
        iii. When did it stop, or is it ongoing? (date/ongoing)

    h. Sweating? Y/N (if yes, answer below)
        i. When did it start? (date, approximate time)
        ii. When did it stop, or is it ongoing? (date/ongoing)

    f. Fever? Y/N (if yes, answer below)
        i. When did it start? (date, approximate time)
        ii. How long did it last?
        iii. How high was it?

3. Did you see a medical person for help? Y/N
    b. If yes, which type and when did you see them?

Type	**Location**	**Date(s)**
Health post [ ]		
Health center [ ]		
Hospital [ ]		

Traditional healer [ ]		
Pharmacy [ ]		

b. If yes, CEM nurse should complete the following from available records (ask patient for their take-home chart, check register for signs and symptoms, review hospital records)

4. If 1a. Chest Pain = yes, did you do any of the following?
    a. Have your blood pressure checked?
    b. Have an electrocardiogram?
    c. Have an echocardiogram?
    d. Take any medicines (e.g. aspirin, ibuprofen, paracetamol)

5. If 1a. Shortness of Breath = yes, did you have or were you told by family or friends that you had:
    g. Faster breathing than your usual breathing rate?
    h. Skin turning blue or gray (e.g., your lips, fingertips)?
    i. Increased effort required to take a breath (e.g., big movements in the muscles of your chest in order to take a breath in)
    j. A rattling or high-pitched squeaking or whistling sound when you breathed in or out?
    k. Swelling of your tongue or inside your mouth or throat?
    l. Low oxygen level (e.g., on a health clinic's fingertip oxygen monitor)

6. If 1f. Fever = yes, did you do any of the following?
    a. Take any medicines (aspirin, paracetamol, ibuprofen)?

7. Have you had any other recent illness in the last 4 weeks? Y/N
(if yes, answer below)

    What illness were you diagnosed with? List: _____

8. Were you taking any medicines, herbal medicines, or vaccines in the 4 weeks before this happened? Y/N (if yes, answer below)

    Which medicines, herbal medicines or vaccines? List: _____

CEM AESI Questionnaire - Dermatologic

Dermatologic screening question: Have you had a rash around the vaccine site or elsewhere on your body that occurred within two weeks after vaccination?

If yes:

1. Where on your body did the rash occur? _____
2. When did it start? (date)
3. When did it stop, or is it ongoing? (date/ongoing)
4. What does it look like? _____
5. Could you send a photo?
    i. If yes, refer to expected vaccine takes and complications to classify OR apply a program such as VisualDx to classify and complete Derm AESI-specific questions below, and associated DCFs
    ii. If no, ask participant to come for an in-person visit to assess them or have a CHW visit them to assess the rash, and complete Derm AESI-specific questions below, and associated DCFs]
6. Did you see a medical person for help? Y/N
7. If yes, which type and when did you see them?

Type	Location	Date(s)
Health post [ ]		
Health center [ ]		
Hospital [ ]		
Traditional healer [ ]		
Pharmacy [ ]		

Derm AESI-specific questions:

Re Robust Take

Re Generalized vaccinia, Inadvertent inoculation and eczema vaccinatum – general question for all 3

- Did any lesions, similar to the one at the vaccination site, develop in other skin areas beyond the vaccination site?
    - If Yes, what body areas were involved. (face, trunk, R/L arm, R/L leg, buttocks
- In the week before or since vaccination, were you in contact with anyone with an infectious rash (such as chickenpox, scabies…..list the commonly known vesicular-pustular diseases in the area)?

Follow up question relevant for inadvertent inoculation

- Did any lesions occur inside your mouth, in your nose, in your eyes or private parts (vagina, glans penis, anus)?
- Did you scratch any of the skin areas or rub your eyes, nose or inside your mouth prior to the lesions appearing?

Follow up question relevant to eczema vaccinatum

- At the time of vaccination did you have any skin rash due to eczema or other skin problem?
- If yes did the skin lesions following vaccination occur in the involved areas of skin?

Re Progressive vaccinia [ONLY if immunocompromised host = yes]

- Briefly describe the expected evolution of vaccination site – e.g.: About a week after vaccination a small red bump (papule) or 'blister' (vesicle) appears at the site; over the next several days blister may look like a p ustule, and then a scab forms which should drop off leaving a small depressed area in the skin (scar) by the end of the 3rd week.,
    - Does this match what you experienced? If not how was it different?
    - How big did the reaction at the vaccine site get? – could compare to known things (common fruit, coins, width of local currency notes etc). – would focus on lesions that persist beyond two weeks
    - Did the centre of the lesion look black (necrosis).
    - [1 month and after] Did the scab fall off, leaving a sore area underneath?

For study staff: Consider obtaining photo by text or in person, or refer to poster guide of usual vaccine take progression to complete the simplified DCFs

CEM AESI Questionnaire – Neurologic

Neurologic screening question: Have you had severe headache, confusion, or limb movements you couldn't control in the three weeks after vaccination?

1. If yes, please specify which you had:
    1. Fever? Y/N (if yes, answer below)
        i. When did it start? (date)
        ii. When did it stop, or is it ongoing? (date/ongoing)

    2. Headache? Y/N (if yes, answer below)
        i. When did it start? (date)
        ii. When did it stop, or is it ongoing? (date/ongoing)

    3. Confusion? Y/N (if yes, answer below)
        i. When did it start? (date)
        ii. When did it stop, or is it ongoing? (date/ongoing)

    4. Limb movements you couldn't control Y/N (if yes, answer below)
        i. When did it start? (date)
        ii. When did it stop, or is it ongoing? (date/ongoing)

2. Did you see a medical person for help? Y/N
    1. If yes, which type and when did you see them?

Type	Location	Date(s)
Health post [ ]		
Health center [ ]		
Hospital [ ]		
Traditional healer [ ]		
Pharmacy [ ]		

3. If 1b. Confusion = yes, did you have or were you told by family or friends that you had:
    1. Lethargy for more than 1 day?
    2. Change in your personality for more than one day?

4. Were you taking any medicines, herbal medicines, or vaccines in the 3 weeks before this happened? Y/N (if yes, answer below)
    1. Which medicines, herbal medicines, or vaccines? List: _____

If 2. Sought medical care = yes, CEM nurse should complete the Neuro Data Collection Form (or adapted version) from available records (ask participant for their take-home chart, check register for signs and symptoms, review hospital records), and/or evaluate participant in person.

APPENDIX 3: ADULT INFORMED CONSENT FORM

[The adult ICF template and process should be adapted for special populations (e.g., minors, pregnant women, elderly patients lacking full capacity, migrants, prisoners) that require a tailored approach to consent, including possible surrogate decision-makers (e.g., parents, adult children) or study advocates (e.g., for inclusion of prisoners, orphans) and additional forms (e.g., assent forms), as well as tailoring to the details provided to participants during consent].

Participant information sheet

You are visiting this vaccination centre to receive the first dose of MPOX vaccine as part of routine care. This vaccination centre is participating in observational research to monitor the safety of COVID- 19 vaccines in [POPULATION OF INTEREST]. This study is taking place in [NUMBER] vaccination centres in [COUNTRY]. Around 10,000 persons vaccinated with mpox vaccine will be included in the study and followed up for 6 months after the last dose of mpox vaccine for specific health events of interest.

The study sponsor is [STUDY SPONSOR], and the principal investigators are [PRINCIPAL INVESTIGATORS].

If you participate in the study, data will be collected from you by interview at the time of enrolment and through regular questionnaires throughout the study period. By participating in the study you agree:

- to complete the study questionnaires [THOUGH MOBILE/WEBLINK/TELEPHONE] (weekly after each mpox vaccine dose, until 3 months after the second MPOX vaccine dose) (or more frequently if selected for the reactogenicity subset);
- to be contacted by phone in case of non-response, if no answer is received, your next of kin can be contacted;
- that the [NATIONAL AEFI FOCAL POINT/NATIONAL PHARMACOVIGILANCE CENTER, to be detailed in the protocol] may contact your healthcare provider if further investigation is required;
- that, in the event you learn you are pregnant during the study, the [NATIONAL AEFI FOCAL POINT/NATIONAL PHARMACOVIGILANCE CENTER, to be detailed in the protocol] may follow you until the time of delivery, to monitor the safety of mpox vaccines administered during pregnancy.

This study will not lead to any changes in your routine care. You will not be receiving any intervention (vaccine, drug, other) as part of the study. So, there will be no direct benefit to you from this research. However, information gathered from individuals vaccinated with MPOX vaccines will contribute to the safety surveillance of mpox vaccines.

Your individual identity will be protected because the final information used for the research study will not bear your name, contact details or any other personal information about you that will allow

you to be identified. The vaccination centre will assign a responsible person to use and store the research data in a safe place.

The key-coded data obtained from this study will be stored in a secured database located in [COUNTRY]. Your personal data will always be handled in accordance with all applicable data protection and privacy laws. All information about you as an individual is confidentially and will be protected and only communicated to authorized persons. Any information collected from other physicians will be handled in the same confidential manner as those collected by the study doctor. Data will be archived for [XXX] years, as per national regulations, and will then be destroyed. Should you decide to withdraw from the study, data collected up until the time of the time of withdrawal will be used in the analyses.

If you are willing to participate in this study that will monitor the safety of MPOX vaccines, please sign and date this form. You are free to contact [XXX] to understand how your information will be used. If at any time you do not wish to share your information, you are free to contact [XXX] and withdraw from this study.

You also have the choice to say no and opt out of this research. Not participating, or withdrawing from this study, will not impact your access to healthcare.

I have read the above information, or it has been read to me. I have had the opportunity to ask questions about it and all questions have been answered to my satisfaction. I consent voluntarily to be a participant in this study.

Print name of participant

_____

Signature of participant

Date _____

Day/month/year

Statement by the researcher/person taking consent:

I have accurately read out the information sheet to the potential participant. I confirm that the participant was given every opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this informed consent form has been provided to the participant.

Print name of researcher/person taking the consent_____

Signature of researcher/person taking the consent

Date _____

Day/month/year

APPENDIX 4: KEY ELEMENTS FOR DATA COLLECTION FOR PREGNANT WOMEN AND NEWBORNS

<table>
<tr><td colspan="5">A. GENERAL INFORMATION</td></tr>
<tr><td colspan="5">• Date of initial report
• Source of information (e.g. pregnant woman, primary care physician, obstetrician, pediatrician, other)</td></tr>
<tr><td colspan="5">B. MATERNAL INFORMATION</td></tr>
<tr><td colspan="2">• Identification of patient</td><td>Study ID</td><td colspan="2">Site</td></tr>
<tr><td colspan="2">• Date of enrollment in trial</td><td>Vaccine administered: Name of vaccine administered (brand and lot number), dose(s) given, and the gestational timing of vaccine administration</td><td colspan="2">Study group assignment (if pertinent)</td></tr>
<tr><td>• Demographics:</td><td>Date of birth (or age)</td><td>Occupation</td><td colspan="2">Education level</td></tr>
<tr><td colspan="5">• Obstetrical history: Parity, number of previous pregnancies and outcome (live birth, miscarriage, elective termination, with specification of gestational length and context, late fetal death, ectopic pregnancy, molar pregnancy); Previous maternal pregnancy complications; Previous fetal/neonatal abnormalities and type</td></tr>
<tr><td colspan="5">• Maternal medical history:Risk factors for adverse pregnancy outcomes including environmental or occupational exposures e.g. hypertension, diabetes, seizure disorder, thyroid disorder, asthma, allergic disease, heart disease, depression or other psychiatric disorders, sexual transmitted disorders, hepatitis, AIDS (specify viral load, CD4 count), other.</td></tr>
<tr><td colspan="5">• Family history: History of congenital abnormality, psychomotor conditions in the family (specify paternal/maternal and relationship); Consanguinity between parents (specify degree)</td></tr>
</table>

- Current pregnancy
  - Date of last menstrual period (LMP); Gestational age at the time of IP exposure, preferably given as gestational week+days, based on ultrasound (specify if based on ultrasound or LMP); Estimated date of delivery
  - Exposure to products subject to medical prescription, OTC products, pregnancy supplements such as folic acid, multivitamins (include name, Dosage & route, Date of first use, date of end of treatment, duration, Indication)
  - Recreational drug use, e.g. tobacco, alcohol, illicit drugs (specify amount and if stopped during pregnancy)
  - Antenatal check-up (specify dates and results), e.g. fetal ultrasound, serum markers (AFP, other), chorionic villi biopsy (CVS), amniocentesis, results of antenatal care tests including serology tests, e.g. rubella, toxoplasmosis etc.
  - Complications during pregnancy and date (including any adverse drug reactions)
  - Disease course(s) during pregnancy and any complications

- End of Pregnancy Event or Delivery
  - End of pregnancy event: Ectopic pregnancy, Molar pregnancy; Elective termination, SAB, Stillbirth, Delivery
  - Date of event
  - GA at event, interval from IP administration to event
  - Mode of delivery

- Labour / Delivery complications (fetal distress, amniotic fluid abnormal, abnormal placenta, etc)

C. FETAL INFORMATION in case of elective termination, spontaneous abortion and late foetal death

- Date of receipt of information and Source of information
- End of pregnancy event: SAB, Stillbirth, other
- Gestational age at end of event
- Results of physical examination (gender, external anomalies)
- Results of laboratory testing and pathology (if available)

- Reason for or factors contributing to end of pregnancy event (if known)
- Other specific testing relevant to IP

D. NEONATAL INFORMATION

- Initial -
    - Source of information -
    - Date of receipt of information -
    - Outcome of pregnancy and date (live birth, miscarriage, late foetal death, elective termination, ectopic pregnancy, molar pregnancy) -
    - Date of birth
    - Gestational age at birth -
    - Gender of neonate -
    - Results of neonatal physical examination including: ⇒
    - Weight at birth ⇒
    - Length, head circumference at birth -
    - Malformation/anomalies diagnosed at birth -
    - Conditions at birth (including Apgar scores at 1 and 5 minutes, need for resuscitation, admission to intensive care unit)
    - Dysmaturity

- Follow-up -
    - Source and date of information -
    - Malformation/anomalies diagnosed since initial report -
    - Developmental assessment -
    - Infant illnesses, hospitalisations, drug therapies, breastfeeding

E. INFANT INFORMATION

• Follow up
  • Infant weight: baseline at 3, 6, 9, and 12 months
  • Infant developmental milestones: baseline at 6, 9, and 12 months
  • Infant height: baseline at 6, 9, and 12 months