European Medical Agency*

Non-interventional registry-based Study – Study Report

Effectiveness and safety of Modified Vaccinia Ankara - Bavarian Nordic (MVA-BN) vaccination against monkeypox (mpox) in at-risk individuals in the United States (USMVAc)

Protocol: EUPAS104386

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DATE STUDY COMPLETED: Latest registry end date was 10 November 2023

PASS information

Title	**Effectiveness and safety of Modified Vaccinia Ankara - Bavarian Nordic (MVA-BN) vaccination against monkeypox (mpox) in at-risk individuals in the United States (USMVAc)**
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Marketing authorisation holder(s)	Bavarian Nordic
Framework contractor	Aetion Germany GmbH
Framework contractor contact person	**Nicolas Deltour** Vice president, Real World Strategy nicolas.deltour@aetion.com
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Research question and objectives	To assess the effectiveness and safety of MVA-BN vaccine against mpox disease among a population of men who have sex with men (MSM) and transgender women in the United States (U.S.) using secondary healthcare data? **Primary Objective:** To assess vaccine effectiveness of the MVA-BN vaccine against mpox disease from August 2022 to December 2022 in fully vaccinated MSM and transgender women compared to a comparator group of MSM and transgender women with no evidence of MVA-BN vaccination in a real-world setting. **Secondary Objective:** To describe the incidence of safety outcomes of interest from August 2022 to December 2022 among MSM and transgender women exposed to at least 1 dose of MVA-BN vaccination and comparator MSM and transgender women with no evidence of MVA-BN vaccination in a real-world setting.
Country(-ies) of study	U.S.

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MARKETING AUTHORIZATION HOLDER(S)

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List of abbreviations

Abbreviation	Definition
AESI	Adverse events of special interest
ASD	Absolute standardised mean difference
BHI	Blue Health Intelligence
CDC	Centres for Disease Control and Prevention
CEM	Coarsened exact matching
CI	Confidence interval
CPT	Current Procedural Terminology
DNA	Deoxyribonucleic acid
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FDA	U.S. Food and Drug Administration
GEP	Good Epidemiologic Practise
GPP	Good pharmacoepidemiology/pharmacovigilance practise
HCPCS	Healthcare Common Procedure Coding System
HIV	Human immunodeficiency virus
HR	Hazard ratios
HRSB	High Risk Sexual Behaviour
ICD-10-CM	ICD-10-CM International Classification of Diseases, Tenth Revision, Clinical Modification
ID	Index date
IDE	Index date of effectiveness outcomes
IDs	Index date of safety
IR	Incidence Rate
ISPE	International Society of Pharmacoepidemiology
LOINC	Logical Observation Identifier Names and Codes
Mpox	Monkeypox
MSM	Men who have sex with men
MVA-BN	Modified Vaccinia Ankara - Bavarian Nordic
NDC	National Drug Codes
PASS	Post-Authorisation Safety Study

Abbreviation	Definition
PCR	Polymerase chain reaction
PRAC	Pharmacovigilance Risk Assessment Committee
PrEP	Pre-exposure prophylaxis
PS	Propensity score
PS20	Private Source 20
RMP	Risk Management Plan
RNA	Ribonucleic acid
ROA	Route of Administration
RR	Risk ratio
SMR	Standardized mortality ratio
STD	Sexually transmitted disease
U.S.	United States
VIGIV	Intravenous vaccinia immune globulin
wRR	Weighted risk ratio
wRD	Weighted risk difference

1. Abstract

Title: Effectiveness and safety of MVA-BN vaccination against mpox in at-risk individuals in the United States (USMVAc study)

Background and Rationale: Mpox is an infectious disease caused by the human mpox virus (hMPXV) pertaining to the same genus (*Orthopox*) as the variola virus. An outbreak in April 2022 revealed epidemiological patterns in non-historical endemic countries in Europe and North America, associated with human-to-human viral transmission rather than contact with animal reservoirs (1–3). Notably, men who have sex with men (MSM) and transgender women between the ages of 18 and 50, are the population at highest risk of mpox disease (4).

In July 2022, the European Medicines Agency (EMA)'s Committee for Medicinal Products for Human Use (CHMP) recommended extending the indication of the third-generation smallpox vaccine MVA-BN to include protecting adults from mpox disease. EMA, in collaboration with the European Centre for Disease Prevention and Control (ECDC), is coordinating and supporting the conduct of post-authorisation pharmacoepidemiological studies on vaccine effectiveness and safety as part of the EU Vaccine Monitoring Platform (5). As part of this endeavour, this study aimed to generate further evidence on the benefit/risk profile of the MVA-BN vaccine.

Research Question and Objectives: To assess the effectiveness and safety of MVA-BN vaccine against mpox, among MSM and transgender women, in the United States (U.S.) through secondary use of healthcare data aggregated from HealthVerity between 1 April 2021 and 31 December 2022.

Study Design: A retrospective, non-interventional, observational comparative cohort study. To compare VE in the vaccinated compared to the unvaccinated groups, coarsened exact matching (CEM) was used to assign an index date (ID) for the unvaccinated group.

Variables: Baseline characteristics include sociodemographic characteristics, comorbidities (such as chronic and sexually transmitted infections), medical history (i.e., immunocompromised conditions), and medications (i.e., steroid use, immunosuppressives). The primary outcome of effectiveness is mpox captured by a diagnosis or a positive test record. The secondary outcomes of vaccine effectiveness comprised hospitalisation due to mpox (captured by a diagnosis or a positive test record), all potential mpox (captured by a diagnosis, a positive test record, or mpox treatment record), all-cause hospitalisation or death, and all hospitalisation due to any potential mpox (captured by a diagnosis, a positive test record, or mpox treatment record). Safety outcomes include pericarditis, myocarditis, myocarditis or pericarditis, encephalitis, and anaphylaxis.

Data Source: This study was conducted via secondary use of healthcare data, including anonymized U.S. nationwide hospital billing and medical and pharmacy claims from HealthVerity, a de-identified, patient-level dataset. The study period was from 1 April 2021 to 31 December 2022 and the inclusion period was from 1st August 2022 to 30th September 2022, to allow for follow-up observability of the outcome. MSM and transgender women were included in the data if they were assigned male at birth, aged ≥ 18 years old, and met at least one of the dataset inclusion criteria to be at risk for mpox: high sexual risk behaviour (HRSB), diagnosis of human

immunodeficiency virus (HIV), or evidence of pre-exposure prophylaxis (PrEP) therapy for HIV and no history of drug abuse.

Subjects and Study Size: Among those included in the high-risk data set created for the purpose of this study by HealthVerity, an at-risk population of MSM and transgender women was defined. Of the 68,381 MSM and transgender women in the HealthVerity dataset, there were 163 fully vaccinated patients (indexing on the 14th day enrolled after the 2nd dose ≥28 days after first dose between 1 August 2022 to 30 September 2022) after the application of inclusion and exclusion criteria. Each of these subjects were matched via CEM up to 5 subjects who were unvaccinated at the time of match yielding 815 comparator subjects for the vaccine effectiveness objective. Of the at-risk MSM and transgender population, there were 947 vaccinated patients receiving at least 1 dose (indexing on the first dose between 1 August 2022 to 31 December 2022) after the application of inclusion and exclusion criteria. Each of these subjects were matched via CEM up to 5 subjects who were unvaccinated at the time of match yielding 4,735 comparator subjects for the secondary safety objective.

Results: For the primary objective of vaccine effectiveness, 978 subjects met the study eligibility criteria, of which 163 subjects were fully vaccinated and initially matched to 815 comparator subjects. After subsequent standardised mortality ratio (SMR) weighting was applied, the effective sample size was 163 in the fully vaccinated group and a weighted pseudo-population of 159.85 with an effective sample size of 303 in the unvaccinated comparator group. For the primary objective of vaccine effectiveness, subjects who were fully vaccinated with the MVA-BN vaccine had vaccine effectiveness of 89% (95% CI 12%, 99%) against mpox disease, 7% (95% CI -1,402%, 94%) against hospitalisations related to mpox disease, and -1% (95% CI -72%, 41%) against risk of all-cause hospitalisation or death. For the secondary objective of vaccine safety, there were 5,682 total subjects who met the study eligibility criteria, of which 947 subjects were vaccinated and coarsened-exact matched to 4,735 comparator subjects. After the application of propensity-score (PS) matching, there were 915 subjects in each group. Using primary risk windows across all safety outcomes, there were no outcome events in either vaccinated or unvaccinated comparator group. When using sensitivity analysis considering risk windows of 28-days, 1 pericarditis event was identified in the vaccinated group using a 28-day risk window (IR of 3.90 cases per 100,000 person-days, 95% CI 0.55, 27.74).

Discussion: Our results were consistent with existing evaluation of vaccine effectiveness of MVA-BN vaccination against mpox in the United States and suggest that completing the second dose according to the MVA-BN vaccine schedule is associated with reduced risk of mpox disease among MSM and transgender women in the HealthVerity dataset within our study period. One safety event was identified within our study population when assessing a 28-day risk window. Additional studies with increased sample size to confirm the safety of MVA-BN vaccination among MSM and transgender women in the U.S. are warranted to ensure further pharmacovigilance of safety signals.

2. Milestones

Milestone	Planned Date	Actual Date	Comments
Start of data	1 July 2021	1 April 2021	

collection			
End of data collection	31 December 2022	31 December 2022	
Registration in the EU PAS register	N/A	17 April 2023, Updated 27 October 2023	
Study Report v1.0	10 November 2023		
Study Report v2.0	11 December 2023		
Study Report v3.0 (Final Version)	15 December 2023		

3. Summary of Figures and Tables

4. Rationale and background

Mpox outbreak 2022

Mpox disease is a viral infection caused by the human mpox virus (hMPXV) and pertains to the same genus (Orthopox) as the variola virus, though disease manifestations are less clinically severe and slightly less transmissible in the general population (6). Transmission of the virus typically occurs when humans come into close contact with animal hosts, however, human-to-human transmission is possible via close contact with another person's hMPXV-caused lesions, bodily fluids, respiratory secretions, or contaminated surfaces (7–9). Recently identified risk factors related to increased risk of infection include having multiple sexual partners or identifying as gay, bisexual, or men who have sex with men (MSM) (7). Although the disease is usually mild and self-limiting, immunocompromised are at increased risk for severe disease progression (7,9). As of September 2023, 31,277 cases and 55 deaths have been reported in the U.S, according to the Centers for Disease Control and Prevention (CDC) with cases disproportionately affecting the MSM population. Though rare, mpox disease can lead to adverse health outcomes for these populations such as severe dermatologic and mucosal manifestations, sepsis, or encephalitis (10). Given the vulnerabilities of this high-risk population, special attention to this mpox outbreak is warranted.

The April 2022 outbreak is also concerning due to the epidemiological patterns in non-endemic countries, namely regions in Europe and North America. Distinct from previous outbreaks, cases beginning in April 2022 were associated with human-to-human viral transmission, specifically in those with multiple sexual partners (2,3,7). As of September 2023, of the total cases worldwide (n=92,048) almost all (n=90,076) are entirely in non-endemic countries (11). The 2022 outbreak is also distinct from previous outbreaks in that the populations at risk of disease have evolved. Despite making up only 4% of the U.S. population, MSM were identified as being disproportionately affected by the outbreak (12). Of 2,891 U.S. cases reported in July 2022, 99% were men, and 94% of those were MSM; 41% of these cases also had concomitant HIV infection (13). MSM between the ages of 18 and 50 are currently the main population at risk possibly due to the high connectivity of sexual networks (2). Despite the decline in mpox cases reported to CDC since its peak in early August 2022, there is limited real-world data available on the effectiveness and safety of MVA-BN vaccines. The present study of MSM and transgender women provides insights adds to the totality of evidence for effectiveness and safety of the MVA-BN vaccine, demonstrating the value in continued and future use of MVA-BN vaccination against mpox..

Disease Management

Currently, no treatments are approved in the US for mpox disease. However, certain antiviral medications, such as tecovirimat, may be beneficial and are approved to treat mpox in the EU (14). Prognosis for mpox disease depends on a variety of factors including previous vaccination status, underlying health conditions such as an impaired immune system, comorbidities, or concurrent infections. Subjects who may be considered for treatment are those with or at high risk of acquiring severe disease (e.g. HIV, immunosuppression, sepsis), populations with a history of atopic dermatitis, persons with any secondary illness (e.g. complications such as bacterial skin infection), or subjects with mpox virus aberrant diseases involving eyes, mouth,

genital or anal area that might constitute a special hazard (15). Given this risk associated with the progression of mpox and that the MSM population is disproportionately affected by immunocompromising disease (e.g., HIV), disease management in this population poses a risk for long-term adverse health consequences.

Tecovirimat (brand name TPOXX in the U.S.) is indicated for the treatment of human smallpox and received an expanded access investigational new drug (EA-IND) on the 29th of May, 2022 for use in mpox diseases in the U.S. (15). It has been shown to reduce mortality from mpox disease in animal studies (15). Other antiviral treatments have received an expanded access for the treatment of mpox during the outbreak in the U.S., including vaccinia immune globulin intravenous (VIGIV; indicated for the treatment of complications related to vaccinia vaccine), Cidofovir (indicated for treatment of cytomegalovirus retinitis), or Brincidofovir (indicated for treatment of human smallpox disease) (16,17).

Symptoms of mpox disease, predominantly a mild rash, can be managed without special treatment. HIV infection or use of antiviral medications might influence disease prognosis, but further research is needed (2). Residual protection from previous smallpox vaccination may protect adults from infection or severe disease progression (18). Given that disease management of mpox may include prescription medications and/or care required in a hospital, secondary healthcare data provides an opportunity to study health outcomes associated with mpox disease. Additionally, immunocompromised are likely to have long term engagement with the healthcare system allowing for observability of populations who may have higher risk of infection.

Mpox Prophylaxis Vaccination

In July 2022, EMA's Committee for Medicinal Products for Human Use (CHMP) recommended extending the indication of the third generation smallpox vaccine MVA-BN to include protecting adults from mpox disease (19). The EMA, in collaboration with the ECDC, is coordinating and supporting the conduct of pharmacoepidemiological studies considering the pressing public health needs. In the European Union (EU), different scenarios have been considered to define priority groups for vaccination based on the identification of close contacts of confirmed cases (post-exposure prophylaxis/vaccination, PEP) and identification of individuals at high risk of acquisition of mpox (pre-exposure prophylaxis/vaccination, PrEP). The focus of the vaccination campaign in the U.S. is in those groups with risk factors for exposure to mpox virus and includes populations disproportionately affected by it (i.e., with high-risk sexual behaviour), similar to the scope of the campaign in Europe.

The U.S. national mpox vaccine strategy was first announced on 28 June 2022, and was updated on 22 August 2022 (20). As of 9 August 2022, the Food and Drug Administration (FDA) approved Emergency Use Authorization (EUA) for MVA-BN vaccine with brand names Jynneos (Imvanex in EU, and Imvamune in Canada), a third generation smallpox vaccine, to prevent Mpox disease in adults 18 years of age and older who are determined to be at high risk of disease, such as MSM and health workers as pre-exposure prophylaxis (PrEP) (21). In addition to PrEP, the mpox vaccine may be administered post-exposure (PEP) to persons who have come into contact with an infected person. CDC recommends that the vaccine be given within 4 days and up to 14 days from the date of exposure in order to prevent onset of the disease (22).

A full vaccination regimen includes 2 doses administered 4 weeks (28 days) apart (6). The

vaccination is considered effective 14 days after the second vaccine dose, though there is evidence that suggests some protection after the first dose (23). MVA-BN, may also be used as a booster vaccination (a single dose) in individuals previously vaccinated against smallpox, mpox, or vaccinia viruses, although there is inadequate data to determine the appropriate timing of booster doses (23,24). MVA-BN is contraindicated in individuals who experienced allergic reaction at the first dose administration or have a hypersensitivity to chicken protein, benzonase, gentamicin, and ciprofloxacin. According to the EU Risk Management Plan, myocarditis and pericarditis, as well as postvaccinal encephalitis, are important potential risks of this vaccine (25). The risk of these adverse events and vaccine use in several specific subpopulations, including clinically immunocompromised individuals, has been identified as important missing information.

Context of the current study - USMVAc:

In order to obtain effectiveness and safety data for pre-exposure vaccination with MVA-BN, the EMA has supported the current study which aims to generate further understanding of vaccination to prevent mpox disease across the U.S. population (26). This U.S. based study - USMVAc - provides complementary insights for an ongoing prospective German study- SEMVAc (EU PAS Register Number EUPAS50093) including a retrospective target trial emulation analysis, TEMVAc. Investigators expect that a combined approach of three studies will increase the robustness of the overall evidence obtained. The USMVAc study provides insights into the characteristics of the at-risk population in the U.S. leveraging a secondary healthcare database.

5. Research question and objectives

Research Question: To assess the effectiveness and safety profile of MVA-BN vaccine against mpox disease among a population of MSM and transgender women in the U.S. using secondary healthcare data?

Primary Objective (Effectiveness): To compare the incidence of mpox disease, hospitalisation, or death among the MVA-BN fully vaccinated population (two doses at least 28 days apart, 14 days prior to ID), vs. unvaccinated population (no evidence of any dose) in an at-risk population of MSM and transgender women, and HIV-specific subgroups (treated and untreated with antiretroviral treatments).

Secondary Objective (Safety): To compare the incidence of pre-specified adverse events of special interest (AESIs), pericarditis, myocarditis, pericarditis or myocarditis, encephalitis, and anaphylaxis among those who were vaccinated with at least 1 dose of MVA-BN vs. unvaccinated population (no evidence of any dose) in an at-risk population of MSM and transgender women.

6. Research methods

6.1. Study design

This non-interventional, retrospective, cohort study used closed claims data from the U.S. on MSM and transgender women (identified by proxy) and compared the incidence of mpox disease, hospitalisation, or death in the MVA-BN fully vaccinated population (two doses at least 28 days apart, 14 days prior to ID) with a matched unvaccinated population (no evidence of any dose) overall and among HIV (treated and untreated with antiretrovirals) subgroups. Secondly,

we compared the incidence of adverse events of special interest (AESIs) pericarditis, myocarditis, encephalitis, and anaphylaxis among those with at least 1 dose of MVA-BN matched to unvaccinated subjects. The study period spanned from 1 April 2021 to 31 December 2022.

Subjects were selected for inclusion in the study from 1 August 2022, when FDA emergency use authorization of the MVA-BN vaccine began, to 30 September 2022 to capture the peak of the outbreak in the US and allow for ample observation time of vaccine effectiveness outcomes. We defined two follow-up periods of interest appropriate for the primary objective of effectiveness and the secondary objectives of safety. For effectiveness, the index date (ID_E) for exposed subjects was the 14th day after the date of the second dose of MVA-BN 28 days apart from the first dose; for safety, the index date (ID_S) for exposed subjects was the date of the first MVA-BN administration. For both effectiveness and safety objectives, matched subjects in the comparator group were assigned the same ID. Follow-up concluded at the earliest occurrence of any of the following events: occurrence of mpox, disenrollment, death, end of AESI-specific risk window (for AESI outcome assessment), or the end of data (31 December 2022).

Figure 1: Study design schema for primary objective (vaccine effectiveness)

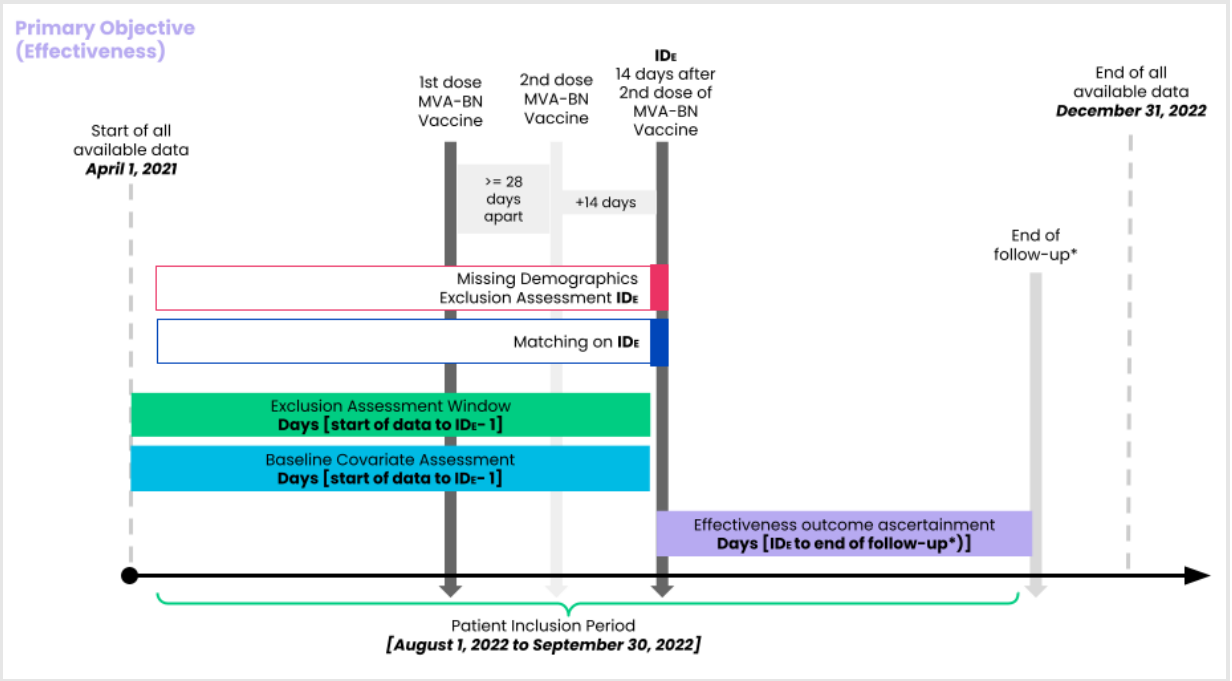
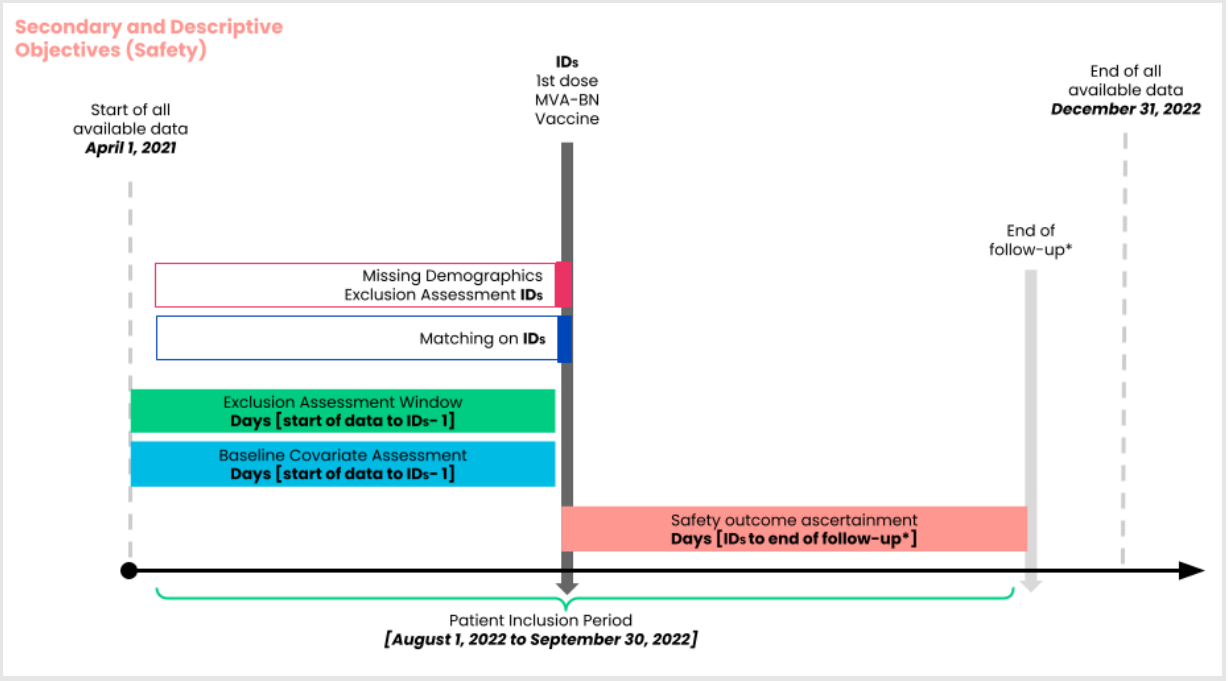


Figure 2: Study design schema for secondary objective (safety)



6.2. Setting

HealthVerity is a secondary, de-identified patient-level dataset that combines medical and pharmacy claims, hospital chargemaster data across more than 200 million individuals insured under commercial, Medicare, or Medicaid plans, and/or served by providers participating in several large U.S. medical and pharmacy insurance claims submission systems (27). Both primary and secondary objectives were addressed using the U.S. based HealthVerity closed claims and laboratory data source with available information on vaccination status and diagnosis of mpox. Inclusion criteria (specified in Section 6.3.3) were applied to limit the data abstracted from HealthVerity to a population of MSM and transgender women at risk for mpox.

6.3. Subjects

The study population at risk was identified by proxy as adult MSM and transgender women. Among these participants, unexposed and matched comparator groups were identified to allow comparison of both effectiveness and safety outcomes.

6.3.3. Inclusion criteria

The following inclusion criteria has been applied by HealthVerity at the dataset level and applies to all patients in the at-risk population prior to assigning subjects to exposure or comparator groups:

1. Male according to sex assigned at birth (to include both cisgender men and transgender women)
2. Age 18 years or older between 1 April 2021 and 31 December 2022

3. Identify as MSM and transgender women according to the following proxy between 1 April 2021 and 31 December 2022 (2,29–31) if they met at least 1 of the following criteria:
    a. High Risk Sexual Behaviour (HRSB) as defined/referred by International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes, Z72.51, Z72.52, or Z72.53; OR
    b. Diagnosis of HIV disease by ICD-10 codes: B20 or Z21; OR
    c. Evidence of PrEP therapy for HIV with any of the following National Drug Codes (NDC); 6195807041, 6195807051, 6195807031, 6195807011, 6362975813, 6729612373, 6729612374, 6362975811, 6362975812, 6195820051, 6195820021, 6195820022, 4970226423, 4970224015, 4970225315, 4970224813; or Current Procedural Terminology (CPT); J0741, J0739 AND No history of substance use disorder within the study period identified by the following ICD-10-CM; F11*, F12*, F13*, F14*, F15*, F16*, F18, F19* (to accurately capture consistent users of PrEP and the population for whom PrEP is indicated to prevent HIV infection among MSM and transgender women)

These criteria are aligned to previous and ongoing studies of mpox disease in the MSM population (2,29,30,32).

6.3.4. Exclusion criteria

Subjects were excluded from the study if they:

- Had a missing value for age, region, or sex on $ID_{E/S}$.
- Did not have at least 1-year continuous enrollment (with 45 days of allowable gap) prior to and on $ID_{E/S}$; meaning that individuals were required to have medical or pharmacy enrollment during baseline period.
- Subjects with a prior positive result of an Orthopoxvirus PCR test or an mpox diagnosis code or with at least 1 prescription of tecovirimat, VIGIV, cidofovir, or brincidofovir prior to ID_E/ID_S (exclusive).

6.3.5. Exposure and Comparator Groups for Primary (Vaccine Effectiveness) Objective

Subjects were included in the **exposure** group if they:

- Had a first record of an MVA-BN vaccine administration.
- Had a second record of an MVA-BN vaccine administration occurring at least 28 days after the first administration.
- Were still continuously enrolled on day 14 after the second administration of an MVA-BN vaccine. This date is defined as ID_E.

Subjects were included in the comparator group if they:

- Had no record of MVA-BN vaccine administration before or on ID_E and matched with an exposed subject (see section 6.9.2 for details on matching process).

Subjects that had a record of a second dose <28 days since the first MVA-BN administration were not included in the fully vaccinated exposed group, nor the comparator group.

6.3.6. Exposure and Comparator Groups for Secondary (Safety)

Subjects were included in the **exposure** group if they:

- Had a record of an MVA-BN vaccine administration on a day where all inclusion and exclusion criteria were met. This date is defined as IDs.

Subjects were included in the comparator group if they:

- Had no record of MVA-BN vaccine administration on or before IDs and matched with an exposed subject (see section 6.9.2 for details on matching process).

6.4. Variables

Exposures, outcomes, and covariates were defined using International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes, Current Procedural Terminology (CPT) codes, Healthcare Common Procedure Coding System (HCPCS), Logical Observation Identifier Names and Codes (LOINC), National Drug Codes (NDC), generic drug names, and lab values (when available). The operational definitions of the analytic variables are described below.

6.4.1. Exposure

MVA-BN administration is defined as the occurrence of NDC codes 50632-0001-02 or 50632-0001-01, or the Medical HCPCS/CPT procedure code 90611 (mpox vaccine, attenuated vaccinia virus, live, non-replicating) on the patient's pharmacy or medical claims record.

For vaccine effectiveness outcomes, a patient is considered exposed if they were still continuously enrolled at day 14 (IDE) after having been fully vaccinated with MVA-BN (two doses at least 28 days apart).

For safety outcomes, a patient is considered exposed from the first administration of MVA-BN and for the duration of the AESI-specific risk window.

Table 1: Description of exposure to MVA-BN vaccination status

Variable	Operational Definition
First Dose	First occurrence of MVA-BN vaccination administration defined as either CPT code 90611 or NDC 50632-0001-02 or 50632-0001-01
Second Dose	Administration of a second dose of MVA-BN vaccination defined as the second of either CPT code 90611 or NDC 50632-0001-02 or 50632-0001-01 at least 28 days after the first occurrence of MVA-BN vaccine relevant NDC or CPT code

6.4.2. Outcomes

Primary Vaccine Effectiveness Outcomes: The primary outcome of vaccine effectiveness is mpox, defined as the occurrence of a positive orthopoxvirus PCR laboratory test result indicating

mpox or a diagnosis of mpox using ICD-10-CM diagnosis code B04 (any position, occurring in an inpatient or outpatient medical claim), as used in prior mpox RWE studies to identify mpox or PCR result of “Detected” (28).

Secondary Vaccine Effectiveness Outcomes: The secondary outcomes of vaccine effectiveness were:

- Hospitalisation related to mpox disease (mpox diagnosis in any position)
- All-cause hospitalisation or death
- All potential mpox
- All potential hospitalisation for mpox

Safety Outcomes (AESI’s): The safety outcomes comprised the occurrence (inpatient or outpatient) of pericarditis, myocarditis, encephalitis, and anaphylaxis.

In line with the outcomes classified as important potential risks for IMVANEX at the time of the initial EU Risk Management Plan (RMP) approval, the list of adverse events of special interest (AESI) in this study are myocarditis, pericarditis, encephalitis, anaphylaxis.

For the purpose of this study, and in light of the lack of commonly agreed upon definitions for encephalitis, a review of available event lists was performed (Brighton Collaboration, vACCine covid-19 monitoring readinESS (ACCESS) protocol, U.S. CDC’s preliminary list of AESI for Vaccine Adverse Event Reporting System (VAERS) surveillance, unpublished guidance from Medicines and Healthcare products Regulatory Agency (MHRA).

Events corresponding to encephalitis were defined using ICD-10-CM diagnosis codes from the Mpox Vaccine Safety Active Monitoring Master Protocol from the FDA Biologics Effectiveness and Safety (BEST) Initiative (30) and the Safety Platform for Emergency VACcines (SPEAC), a collaboration between Brighton Collaboration Group and the Coalition for Epidemic Preparedness Innovations’ (CEPI). The ICD-10-CM codes selected for each event were based on clinical relevance to increase the likelihood of case identification.

Table 2 describes each study outcome, the period for assessment, and any censoring criteria. The analytic approach for each outcome is described in Section 6.9.

The statistical analysis of these endpoints is further described in Section 6.9.2. Sensitivity risk windows are described in Section 6.9.5.

Table 2: Outcomes Definition

Objective	Main/ Secondary	Outcome(s)	Operational Definition	Assessment period

Primary Objective	**Primary Vaccine Effectiveness Outcome**	Mpox disease	At least 1 ICD-10-CM diagnosis code (any position, inpatient or outpatient) B04 or laboratory claims record of mpox polymerase chain reaction (PCR) test result of "DETECTED"	Index date (IDE) to end of follow-up (earliest occurrence of the outcome, disenrollment, death, end of data on 31 December 2022)
	Secondary Vaccine Effectiveness Outcomes	Hospitalisation related to mpox disease	An inpatient event recorded within 30 days after ICD-10-CM diagnosis code (any position, inpatient or outpatient) B04 or laboratory claims record of mpox PCR test result of "DETECTED"	
		All-cause hospitalisation or death	Any inpatient event or the record of death	
		All potential mpox cases	- A positive orthopoxvirus PCR test indicating mpox; OR - Mpox identified by at least 1 ICD-10 code B04; OR - At least 1 prescription of mpox treatments; tecovirimat, VIGIV, cidofovir, or brincidofovir	
		All potential hospitalisation for mpox	An inpatient hospitalisation event recorded within 30 days after: A positive orthopoxvirus PCR test indicating mpox; OR Mpox identified by at least 1 ICD-10 code B04 recorded in any position in the inpatient claim e; OR At least 1 prescription of mpox treatments; tecovirimat, VIGIV, cidofovir, or brincidofovir	
Secondary Objective	**Main Safety Outcomes** (Adverse events of special interest [AESIs])	Pericarditis	Any inpatient or outpatient claim of ICD-10-CM diagnosis code for pericarditis (please refer to Appendix B for codelist)	IDs to end of follow-up (earliest occurrence of the outcome, disenrollment, death, or end of 14-day follow-up)
		Myocarditis	Any inpatient or outpatient claim of ICD-10-CM diagnosis code for myocarditis (please refer to Appendix B for codelist)	IDs to end of follow-up (earliest occurrence of the outcome, disenrollment, death, or end of 14-day follow-up)
		Myocarditis/Pericarditis	Any inpatient or outpatient claim of ICD-10-CM diagnosis code for myocarditis or pericarditis (please refer to Appendix B for codelist)	IDs to end of follow-up (earliest occurrence of the outcome, disenrollment,

				death, or end of 14-day follow-up)
		Encephalitis	Any inpatient or outpatient claim of ICD-10-CM diagnosis code for encephalitis (please refer to Appendix B for codelist)	IDs to end of follow-up (earliest occurrence of the outcome, disenrollment, death, or end of 28-day follow-up)
		Anaphylaxis	Any inpatient or outpatient claim of ICD-10-CM diagnosis code for anaphylaxis (please refer to Appendix B for codelist)	IDs to end of follow-up (earliest occurrence of the outcome, disenrollment, death, or end of 1-day follow-up)

6.4.3. Covariates

Table 3 below lists covariate operational definitions and assessment periods. Covariate selection was performed *a priori* and informed by literature review and feasibility of information available in pharmacy and medical claims.

Table 3: Study covariates

Variable	Operational Definition	Assessment period
Age	Categorised: 18 - 25, 26 - 35, 36 - 45, > 45	$ID_{E/S}$
Region in the U.S.	Categorised: Northeast, Midwest, South and West	$ID_{E/S}$
Insurance Provider	Categorised: Commercial, Non-Commercial	$ID_{E/S}$
Race/Ethnicity	Categorised: White, Black, Hispanic, Asian, Other, Missing	$ID_{E/S}$
Human immunodeficiency virus (HIV) status	At least 1 outpatient or inpatient diagnosis (any position) using claims of any of the following ICD-10-CM codes: B20 or Z21	Baseline: start of data (1 April 2022) to 1 day before $ID_{E/S}$
Pre-exposure prophylaxis (PrEP) status	Any medical or pharmacy claim of the following medications identified by NDC codes (see Appendix B for codelist)	Baseline: start of data (1 April 2022) to 1 day before $ID_{E/S}$
History of Sexually transmitted disease (STD)	At least 1 outpatient or inpatient diagnosis (any position) using medical or pharmacy claims for any of the following (please refer to Appendix B for code list): chlamydia, gonorrhoea, syphilis, hepatitis B	Baseline: start of data (1 April 2022) to 1 day before $ID_{E/S}$
History of AESI (for secondary objective)	See definitions of AESI's in Table 2	Baseline: start of data (1 April 2022) to 1 day before ID_S

Variable	Operational Definition	Assessment period
Evidence of autoimmune condition or immunocompromised condition (non-HIV)	At least 1 outpatient or inpatient diagnosis (any position) using claims or of any of the following (please refer to Appendix B for codelist): autoimmune disease, immunodeficiency, inhaled/dermatological corticosteroid use, immunomodulating medication use, or immunotherapy	Baseline: start of data (1 April 2022) to 1 day before $ID_{E/S}$
Comorbidities	Any position outpatient or inpatient diagnosis of any of the following conditions (please refer to Appendix B for codelist): rheumatological disease, cancer, haematological disease, chronic cardiovascular disease (i.e., heart failure, coronary artery disease, cardiomyopathies), chronic lung disease, chronic kidney disease, chronic liver disease, type I or II diabetes, atopic dermatitis (neurodermatitis)	Baseline: start of data (1 April 2022) to 1 day before $ID_{E/S}$

6.5. Data sources and measurement

This study used de-identified HealthVerity laboratory and closed administrative claims data. The data license at the time of the study includes closed claims and laboratory records between 1 April 2021 and 31 December 2022.

HealthVerity is a secondary, de-identified patient-level dataset that combines medical and pharmacy claims across more than 200 million individuals insured under commercial, Medicare, or Medicaid plans, and/or served by providers participating in several large U.S. medical and pharmacy insurance claims submission systems (27).

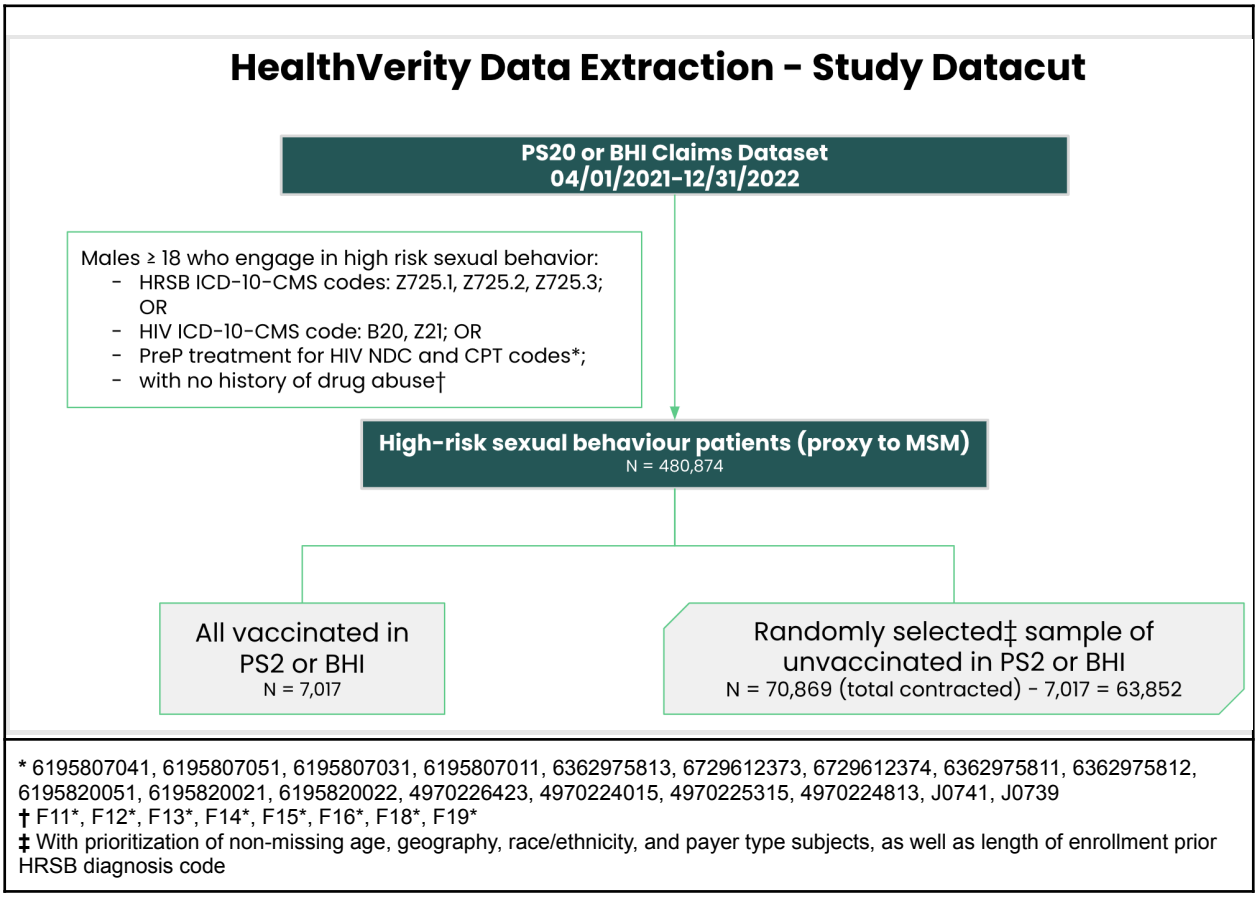
Across the selected data types (i.e., lab, medical and pharmacy claims) each HealthVerity data source qualifying as each data type were selected and evaluated for the study. Closed claims (i.e., claims that have been adjudicated and paid) and labs were retained for the analysis. There are 4 data sources in total: Blue Health Intelligence (BHI), Private Source 20 (PS20), Quest, and Labcorp. BHI contains all medical and pharmacy claims for up to 33,000 de-identified subjects for the data period covered. PS20 contributes all medical claims for up to 70,800 de-identified subjects for the data period covered. Quest comprises mpox lab test data for up to 8,500 de-identified subjects, and Labcorp comprises mpox lab test data for up to 8,500 de-identified subjects. Lab data from Quest and Labcorp allow access to the orthopox PCR testing for a subset of subjects in the overall data. It is noteworthy that during the proposed study period, Centres for Disease Control and Prevention (CDC) authorized 5 commercial lab providers to facilitate the orthopox PCR testing to broaden access: Aegis Science, Labcorp, Mayo Clinic, Quest, and Sonic (29). Labcorp additionally launched their own mpox test during the same timeframe (30).

Prior to the study, HealthVerity extracted male subjects (assigned at birth) who are ≥18 years of age who were considered to be part of the at-risk population of MSM and transgender women (2,28,31,32) if they met at least 1 of the following criteria between 1st April 2021 and 31st December 2022:

- HRSB as defined/referred by ICD-10-CM codes, Z72.51, Z72.52, or Z72.53; OR
- Diagnosis of HIV disease by ICD-10-CM codes: B20 or Z21); OR
- Evidence of PrEP therapy for HIV with any of the following NDC; 6195807041, 6195807051, 6195807031, 6195807011, 6362975813, 6729612373,

6729612374, 6362975811, 6362975812, 6195820051, 6195820021, 6195820022, 4970226423, 4970224015, 4970225315, 4970224813; or CPT; J0741, J0739 AND No history of substance use disorder within the study period identified by the following ICD-10-CM; F11*, F12*, F13*, F14*, F15*, F16*, F18, F19* (to accurately capture consistent users of PrEP and the population for whom PrEP is indicated to prevent HIV infection in the MSM population)

Figure 3: HealthVerity extraction of study datacut



6.6. Bias

As with any observational RWD/real-world evidence (RWE) study, there is potential for residual confounding. While best practices were applied to control for confounding, such as coarsened exact matching and PS matching, there is still potential for residual confounding due to lack of data availability and misclassification of measured variables:

- **Accuracy of MSM algorithm:** The main limitation is our ability to accurately identify MSM as well as major confounders that rely on subject-reported sexual practices, including unsafe sexual practice and number of sexual partners. However, several proxies were used to both identify this population and manage confounding. Unlike prospective studies, claims data are ascertained for insurance billing purposes, and information on sexual orientation and gender identity are not available within the HealthVerity data at the time of this study. This lack of information or potential miscoding

could lead to misclassification or mis-gendering of subjects in the study population. One of the possible criteria used to identify MSM or transgender women in the at-risk population is evidence of PrEP therapy and no history of drug abuse. This criterion was defined to include PrEP users who are likely to be adherent users of PrEP therapy for HIV due to unsafe sexual practice. A limitation of this criterion is that it may exclude MSM and transgender women who are at high risk of mpox, such as those who engage in chemsex if they do not otherwise have evidence of HRSB or HIV.

- **Specificity of the case definition for the safety outcomes:** Misclassification bias may arise from the ICD-10-CM codes selected for the safety outcomes. In particular, the additional codes selected for the broader definition of encephalitis in the sensitivity analysis are related to non-specific disseminated demyelinating conditions, which are related diagnoses that may be misdiagnosed, misclassified, or miscoded encephalitis. Results should then be interpreted with caution.

- **Underreporting of vaccination status:** The mpox vaccines are free or require a minimal administration fee (33). Vaccines are only available from the local health department or, in large cities, in public health clinics, hospitals, or at large social gatherings or venues (33). These facilities and services in the U.S. do not always bill or submit for reimbursement, and so vaccination status in RWD may be underreported and individuals may be misclassified as unvaccinated. Additionally, pre-exposure versus post-exposure prophylaxis is difficult to distinguish in secondary data. There is no accurate way to capture information around 'close contact' with someone infected with mpox in administrative claims data. If misclassification of vaccinated participants into the unvaccinated group occurred, the true risk of mpox infection would be lower for the unvaccinated group assuming that those who were vaccinated received some level of protection from the vaccination. Thus, we would expect that vaccine effectiveness would be underestimated (bias towards the null).

- **Vaccine Administration Route for Safety Outcomes:** The NDC-associated dose administered for the MVA-BN vaccine contained the entire 0.5mL vial for subcutaneous injection and was captured as such in claims and pharmacy data. On the 9th of August 2022 the FDA authorised a dose saving strategy of 0.1 mL for intradermal administration using the same NDC code. Due to the nature of administrative claims data, we do not have sufficient clinical documentation to determine if the practitioner administering the vaccine made the decision to administer via the intradermal route rather than the subcutaneous route as instructed in the package insert. Therefore, it is difficult to fully assess its influence on related safety outcomes such as allergic urticaria. Previous studies have assessed the reactogenicity of different ROA of the MVA-BN vaccine (23).

- **Mpox diagnosis:** Outcome ascertainment was determined based on the presence of either a positive orthopoxvirus PCR test or ICD-10 diagnostic code. There is a risk of misclassification by using such approaches given the nature of the data and lack of studies providing validated algorithms to identify mpox diagnosis in secondary data. Misclassification/misattribution of the hospitalizations due to mpox events may also exist because of the time frames linked to their capture, however, causal association is not guaranteed. Furthermore, lab data may not be available for all subjects in this study and the absence of lab data is not indicative of true absence of orthopox PCR testing or lab

result. Missing lab data can lead to misclassification of subjects in the comparator group.

- **Lack of indicators of socio-economic status (SES):** The data leveraged for this study does not include direct measures of SES. Proxies through area-level data were evaluated by leveraging the patient's state/location. The patient's geographic region was also used for matching exposed and comparator groups as the vaccine was allocated to jurisdictions based on cases reported and the at-risk population in each jurisdiction.

- **Representativeness of the at-risk population:** This study is limited in that only those who are insured are captured within the closed claims HealthVerity data sources. A large portion of the study cohort was excluded from the analysis due to missing information regarding insurance providers. It is possible that the MSM community has less insurance coverage than the general population and could therefore be under-represented in the data (34). Additionally, it is plausible that information regarding occurrence of mpox disease in the at-risk population was lost in the case that patients sought care outside of insurance networks or in public health clinics. Data sources that contribute to the HealthVerity network are exclusively U.S.-based, therefore results from these analyses may not be representative of non-U.S. populations. Lastly, this study includes data starting from 1 April 2022. There may be misclassification due to subjects experiencing baseline covariate events prior to start of data. However, it is expected that misclassification of baseline covariates to be non-differential between treatment groups.

6.7. Study size

To estimate the expected study sample and number of MVA-BN-exposed persons that could be observed in the U.S. population, we used public data available from the CDC regarding cases of mpox, vaccine availability by U.S. jurisdiction, and the expected proportion of the U.S. population determined as high-risk for mpox. At the peak of the mpox outbreak in August 2022 the 7-day average of new mpox cases reached 450. As of the 8th June 2023, approximately 1.2 million doses of MVA-BN mpox vaccine have been administered across the U.S. to persons identified as high risk (33). Early in the U.S. outbreak, the population most at-risk for mpox were identified as MSM and transgender women who have sex with men. In an estimation based on data from the National Health and Nutrition Examination Survey (NHANES), approximately 3.9% of the U.S. population reported having had sex with a male partner in the last five years and being part of the MSM community (35). The specific datacut used in this study results were among MSM and transgender women and may be under-representative of the whole U.S. MSM and transgender women population given that selection was based on criteria such as non-missing data, insurance type, sex assigned at birth, and differences between regions of the U.S. (i.e., urbanicity). Power calculations were performed prior to the beginning of the study as a function of a fixed sample size and the expected outcome rates (36,37).

Initially, approximately 7,000 vaccinated individuals from a total of approximately 70,800 subjects, were identified in the entire HealthVerity data source. From these subjects, we examined preliminary estimates of the potential study sample size and identified approximately 5,000 MSM and transgender women who received at least 1 dose of the MVA-BN vaccine and around 27,000 matched unvaccinated comparator subjects using initially a 1:5 matching ratio (subject to be reduced upon implementation) at the cohort matching step.

For the comparative objectives, it was expected that our analytic cohort would be reduced via the propensity-score matching step (details outlined in Section (6.9.2) below) to select a 1:1 ratio of matched population of unvaccinated comparator subjects.

Precision calculations were calculated as a function of expected sample size, the expected outcome risk in the unexposed population, and varying ratios of the unexposed to exposed. Precision of the effect estimate is presented below in Table 4 as the probability of the upper limit of the 95% confidence interval of the incidence rate ratio (IRR) being below 1.00 under various assumptions.

Table 4: Example Study Size Precision Estimates

Expected Vaccine Effectiveness (VE) (VE = 1 - Incidence Rate Ratio [IRR])	Ratio of Vaccine Unexposed to Exposed	Sample Size (Unexposed + Exposed)	Expected Risk in the Unexposed*	Probability of the Upper Limit of the 95% CI to be Below 1.00
50% (IRR = 0.50)	1:1	2,000	0.005	0.12
50% (IRR = 0.50)	5:1	6,000	0.005	0.14
50% (IRR = 0.50)	1:1	10,000	0.005	0.40
50% (IRR = 0.50)	5:1	30,000	0.005	0.51
50% (IRR = 0.50)	5:1	30,000	0.002	0.24
50% (IRR = 0.50)	5:1	30,000	0.001	0.14
50% (IRR = 0.50)	5:1	60,000	0.0005	0.14
80% (IRR = 0.20)	1:1	10,000	0.005	0.87
80% (IRR = 0.20)	5:1	30,000	0.005	0.91
80% (IRR = 0.20)	5:1	30,000	0.002	0.55
80% (IRR = 0.20)	5:1	30,000	0.001	0.31
80% (IRR = 0.20)	5:1	60,000	0.0005	0.31
90% (IRR = 0.10)	1:1	10,000	0.005	0.91
90% (IRR = 0.10)	5:1	30,000	0.005	0.93
90% (IRR = 0.10)	5:1	30,000	0.002	0.59
90% (IRR = 0.10)	5:1	30,000	0.001	0.34
90% (IRR = 0.10)	5:1	60,000	0.0005	0.34

**Cases per person.*

6.8. Data transformation

As part of the data ingestion process to Aetion® Substantiate, raw data review is conducted to

understand contents of the database and scientific integrity checks are performed to ensure the contents of the data are consistent with the expected data as laid out in the applicable data usage agreement. Data checks are also performed to assess data quality. Some of the key characteristics explored in this process include:

- Table structure (number of rows, columns, column names etc.)
- Summary counts per table (i.e., non-missing counts, unique counts)
- Variable distribution (e.g., min, mean, median, max for numeric variables; top frequencies for categorical variables)
- Date range (min, max, and distribution over a time period)
- Missingness percentage of attributes

Raw data files as well as transformed data files are retained on the platform; rows are dropped if they do not contain dates or have start dates that are earlier than end dates. Aetion performs an additional deidentification step to map the raw data unique patient identifier to an Aetion patient ID.

Aetion performs a two-step process to validate all database connections: Data Engineers build the connector based on a validated specification document as developed by Aetion data scientists. In parallel, an Aetion Data Science/Integration team develops validation code that serves as a quality check (e.g., event, patient, etc. counts match up with the raw data). Substantiate enables the preservation of the robustness of the raw data and has been validated against other analytic softwares (38–40).

6.9. Statistical methods

Analyses were performed within Aetion® Substantiate and R version 3.4.2.

6.9.1. Main summary measures

The baseline characteristics of individuals listed in Section 6.4.3 were reviewed and described prior to PS matching in the at-risk study population of adult MSM and transgender women in the fully vaccinated and comparator groups for the primary vaccine effectiveness objective, and the vaccinated and comparator groups for the safety objective. Categorical variables were reported as the count and percentage of individuals within each category. Subjects with missing values were retained in the analytic cohort and missing values were quantified and reported.

6.9.2. Main statistical methods

6.9.2.1. Primary Objective - Vaccine Effectiveness

Step 1. Coarsened Exact Matching

Given the absence of an active comparator, coarsened exact matching (CEM) was used to identify ID_E in the comparator group. Each eligible vaccinated subject was matched with 5 similar unvaccinated subjects. Subjects were matched on calendar date as well as on the following variables:

- Age (categorised; 18 - 25, 26 - 35, 36 - 45, > 45)
- Region in the U.S. (Northeast, Midwest, South and West)
- Insurance provider (Commercial, Non-Commercial (Medicare/Medicaid))

Step 2. Propensity Score Adjustment

Of the exposed and comparator populations, confounder control was first attempted using PS matching (with a ratio of 1:1). The PS is defined as the probability of MVA-BN exposure conditional on the below covariates and was estimated using multivariable logistic regression.

The following covariates were considered for inclusion in the PS model:

- Coarsened-exact matching variables listed in Step 1 (categorised age, region, and insurance provider) on ID_E
- Race/ethnicity (white, black, hispanic, asian, other, missing) on ID_E
- Evidence of any autoimmune or immunocompromised condition including autoimmune disease, immunodeficiency, inhaled or dermatological corticosteroid use, immunomodulating medication use, or immunotherapy during the baseline period
- Diagnosis of HIV during the baseline period
- PrEP use during the baseline period
- Time from first PrEP prescription fill to $ID_{E/S}$
- History of STD including chlamydia, gonorrhoea, syphilis, or hepatitis B during the baseline period
- History of comorbidities including rheumatological disease, cancer, haematological disease, chronic cardiovascular disease (i.e., heart failure, coronary artery disease, cardiomyopathies), chronic lung disease, chronic kidney disease, chronic liver disease, type I or II diabetes, atopic dermatitis during the baseline period

Since PS matching led to depletion of the analytic cohort (>10%) due to exclusion of unmatched subjects, standardized mortality/morbidity ratio (SMR) weighting was applied as an alternative confounding control method to preserve the results within the vaccinated group. This method assigns vaccinated patients a weight of 1 and referent patients a weight of PS / (1 - PS), creating a pseudo-population that is representative of the vaccinated group (41). Any extreme weights above the 99th percentile of the weight distribution were truncated.

Balance of covariates were assessed by comparing absolute standardised mean difference (ASD) pre- and post-PS matching for each covariate. Groups were considered to be balanced if more than 90% of the covariates have an ASD < 0.10 (+/- 0.04). Since balance was achieved, it was not necessary to include any confounders in the outcome model as covariates.

Step 3. Estimation of vaccine effectiveness endpoints

For the primary analysis of vaccine effectiveness, weighted rates, weighted incidence rate ratios (IRR) reported per 100,000 person-days, weighted risk ratios (wRR) reported per 100,000 persons, weighted risk differences (wRD), and corresponding 95% confidence interval (CI) limits for each outcome (as described in Section 3.4.2), overall and in subgroups, were estimated using a Poisson regression model.

Vaccine effectiveness of MVA-BN was defined as (1 - wRR)*100.

6.9.2.2. Secondary Objective - Safety

Step 1. Coarsened Exact Matching

Similar to the primary objective, CEM was used to identify ID_s in the comparator group. Each eligible vaccinated subject was matched with up to 5 similar unvaccinated subjects. Subjects were matched on calendar date as well as on the following variables:

- Age (categorised; 18 - 25, 26 - 35, 36 - 45, > 45)
- Region in the U.S. (Northeast, Midwest, South and West)
- Insurance provider (Commercial, Non-Commercial (Medicare/Medicaid))

Step 2. Propensity Score Adjustment

Of the exposed and comparator populations, confounder control was conducted using PS matching (with a ratio of 1:1). The PS is defined as the probability of MVA-BN exposure conditional on the below covariates and was estimated using multivariable logistic regression. The following covariates were considered for inclusion in the PS model:

- Coarsened-exact matching variables listed in Step 1 (categorised age, region, and insurance provider) on ID_E
- Race/ethnicity (white, black, hispanic, asian, other, missing) on ID_E
- Evidence of any autoimmune or immunocompromised condition including autoimmune disease, immunodeficiency, inhaled or dermatological corticosteroid use, immunomodulating medication use, or immunotherapy during the baseline period
- Diagnosis of HIV during the baseline period
- PrEP use during the baseline period
- Time from first PrEP prescription fill to ID_E
- History of STD including chlamydia, gonorrhoea, syphilis, or hepatitis B during the baseline period
- History of comorbidities including rheumatological disease, cancer, haematological disease, chronic cardiovascular disease (i.e., heart failure, coronary artery disease, cardiomyopathies), chronic lung disease, chronic kidney disease, chronic liver disease, type I or II diabetes, atopic dermatitis during the baseline period
- History of myocarditis during the baseline period
- History of pericarditis during the baseline period
- History of encephalitis during the baseline period
- History of anaphylaxis during the baseline period

Balance of covariates were assessed by comparing ASD pre- and post-PS matching for each covariate. Groups were considered to be balanced if more than 90% of the covariates have an ASD < 0.10 (+/- 0.04). Since balance was achieved, it was not necessary to include any confounders in the outcome model as covariates. Since PS matching excluded less than 10% of vaccinated subjects, alternative confounding control methods (e.g., SMR weighting) were not considered.

Step 3. Estimation of safety endpoints

For the secondary analysis of safety, the following were reported in the overall cohort after PS adjustment as appropriate:

Rates, rate ratios (reported per 100,000 person-days), risk ratios (reported per 100,000 persons), risk differences, and corresponding 95% confidence interval (CI) limits for each outcome (as described in Section 3.4.2), were estimated using a Poisson regression model.

The safety of MVA-BN was defined as risk ratio and as the reduction in risk of myocarditis, pericarditis, myocarditis/pericarditis, encephalitis, or anaphylaxis in the vaccinated group versus unvaccinated subjects.

6.9.3. Missing values

Multiple imputation was not used to impute missing data. The number and proportion of patients with missing values for covariates listed in Section 6.4.3 is reported for each group in the descriptive analysis in Section 7.2. During the statistical analysis, all steps and decisions made are documented within Substantiate using automatic audit logs that cannot be deleted. All variables, cohorts and analysis were reviewed throughout the implementation process by multiple scientists to ensure validity. Claims databases are primarily collected for reimbursement and therefore definitions are based on the presence or absence of a claim observed in the data. Therefore, missingness will not be considered for variables where absence of a value implies absence of a condition.

6.9.4. Subgroup analyses

Primary Vaccine Effectiveness (mpox disease) Subgroup Analyses:

For a better understanding of the vaccination strategy as actually applied, primary vaccine effectiveness outcome (mpox disease) were assessed in the following subgroups:

- Evidence of HIV (defined via ICD-10-CM code) and treatment with antiretrovirals after HIV diagnosis during baseline
- Evidence of HIV and no treatment with antiretrovirals during baseline
- No evidence of HIV during baseline and treatment with antiretrovirals (PrEP) during baseline
- No evidence of HIV during baseline and no treatment with antiretrovirals (PrEP) during baseline

6.9.5. Sensitivity analyses

The following sensitivity analyses below were planned during the protocol development phase and executed after completion of the primary and secondary objectives.

1. The risk of mpox disease was assessed in the overall cohort of MSM and transgender women who met inclusion criteria during the study period.
2. Primary and secondary vaccine effectiveness outcomes were assessed among the coarsened-exact matched subjects in the exposed group of the safety cohort. Outcomes were assessed among the following:
    a. Exposed subjects who received at least 1 MVA-BN dose
    b. Exposed subjects who received 1 MVA-BN dose only
    c. Exposed subjects with previous smallpox vaccination, inferred by subjects >50 years old who received 1 MVA-BN dose only.

3. Assess vaccine effectiveness among the fully vaccinated cohort using a different mpox outcome definition: Orthopoxvirus PCR test done regardless of the results (all subjects with CPT code 87593 - Infectious agent detection by nucleic acid (DNA or RNA); orthopoxvirus (e.g., mpox virus, cowpox virus, vaccinia virus) amplified probe technique, each). Considering the low attack rate at the time of writing this report, we may hypothesise that the vast majority of individuals with evidence of an orthopoxvirus PCR were tested for mpox (42).
4. Assess the safety outcome of encephalitis using a broader sensitivity definition by adding non-specific ICD-10-CM codes for encephalitis (i.e., G36.9, G37.3, and G37.9). The rationale for including these codes in the broader definition is related to the potential inclusion of subjects who present for unspecified acute disseminated demyelinating disease or broader codes that may capture other diseases relating to the central nervous system. These codes are more general and may capture medical conditions that have no clear, causal association with the current study vaccine, providing context for the primary safety outcome definition. This sensitivity definition of encephalitis was assessed within the safety cohort from ID_S to the end of follow-up (earliest occurrence of the outcome, disenrollment, death, or end of 28-day follow-up).
5. Assess different risk windows for safety outcome assessment: The assessment of all safety outcomes in the secondary objective were assessed using secondary risk windows to ensure the robustness of the results:
    a. Myocarditis: 28 days
    b. Pericarditis: 28 days
    c. Myocarditis/Pericarditis: 28 days
    d. Encephalitis (primary definition and broader sensitivity definition): 42 days
    e. Anaphylaxis: 3 days

6.10. Quality control

Aetion built measures for cohort identification, outcomes and covariates based on codes and algorithms described in the protocol. All measures created have undergone independent quality control review by at least 1 additional analyst or scientist under the supervision of the Study Lead.

This protocol was strictly followed when conducting the analysis of this study. The Study Lead has reviewed all results tables and other final deliverables to confirm accuracy, logical flow, and appropriate format.

This study involves secondary use of data and follows the Guidelines for Good Epidemiologic Practise (GEP) practices laid out in 2005 U.S. Food and Drug Administration (FDA) Good Pharmacoepidemiology/Pharmacovigilance Practise (GPP) (FDA 2005), Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets (FDA 2013), the 2015 International Society of Pharmacoepidemiology (ISPE) Good Pharmacoepidemiology Practices (GPP) (ISPE 2015) and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology (43).

Substantiate maintains a date/time-stamped record of all analytic cohorts and corresponding analyses.

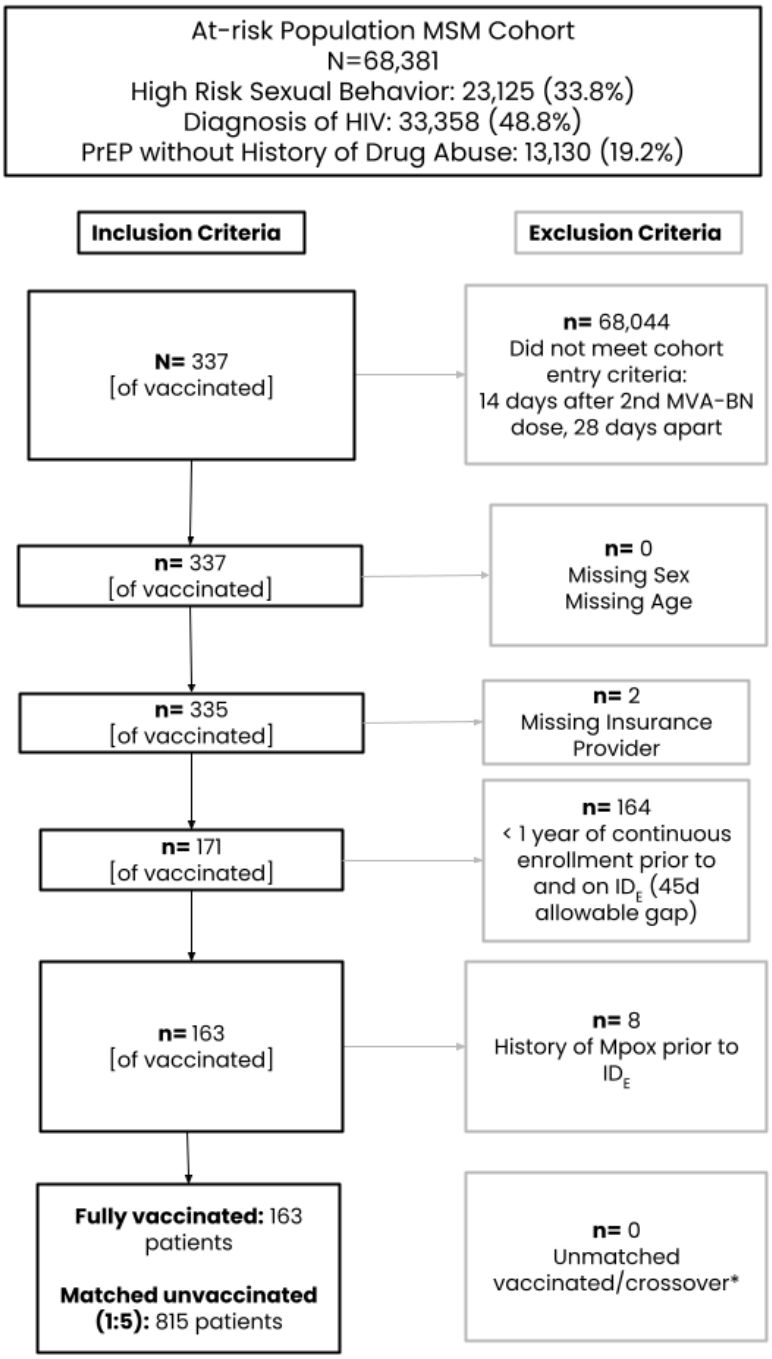
7. Results

7.1. Participants

7.1.2. Vaccine Effectiveness Cohort

After the application of inclusion/exclusion criteria and matching via CEM, the vaccine effectiveness cohort included 163 fully vaccinated subjects (receiving 2 doses at least 28 days apart, 14 days prior to ID_E) and 815 matched unvaccinated subjects using a CEM ratio of 1:5.

Figure 4: Cohort attrition of primary objective cohort (vaccine effectiveness)

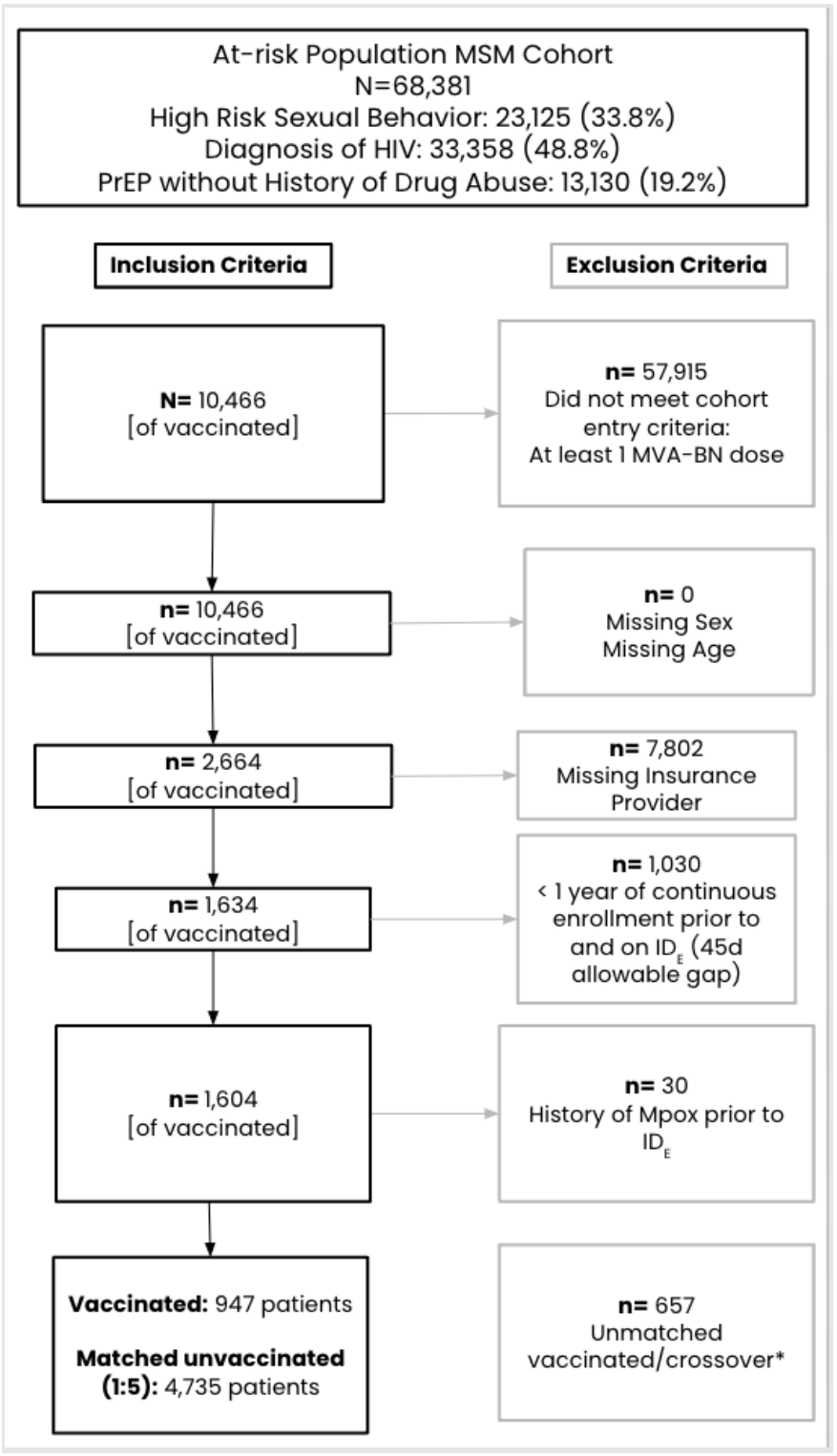


*Exposed subjects are matched to unexposed subjects on calendar date, age, region, and insurance provider in chronological order The matching was done without replacement (each patient can only be sampled once and contribute to the treated or untreated group, depending on whichever group that they are selected to first, therefore some patients may be “crossover” patients, or patients who were selected as referent unexposed patients at the time of selection before they could be selected as exposed patients.

7.1.3. Safety Cohort

After the application of inclusion/exclusion criteria and matching via CEM, the safety cohort included 947 vaccinated subjects (receiving at least 1 dose) and 4,735 matched unvaccinated subjects using a CEM ratio of 1:5.

Figure 5: Cohort attrition of secondary objective cohort (safety)



*Exposed subjects are matched to unexposed subjects on calendar date, age, region, and insurance provider in chronological order The matching was done without replacement (each patient can only be sampled once and contribute to the treated or untreated group, depending on whichever group that they are selected to first, therefore some patients may be “crossover” patients, or patients who were selected as referent unexposed patients at the time of selection before they could be selected as exposed patients.

7.2. Descriptive data

7.2.1. Covariate balance and propensity score application

Vaccine Effectiveness

In evaluating initial covariate balance across the fully vaccinated and unvaccinated groups, there were 163 fully vaccinated subjects in the exposed group and 815 matched unvaccinated subjects in the comparator group for analysis. The covariates in Table 5 were considered for inclusion in the PS model. Table 5 below describes the baseline characteristics of fully vaccinated and unvaccinated adult men who have sex with men (MSM) and transgender women, prior to and after SMR weighting. Of these covariates, race/ethnicity, HIV diagnosis, time from first use of PrEP, comorbidities at baseline, and PrEP use during baseline were imbalanced (ASD > 0.10) during baseline.

In the final 1:1 matching PS model, age categories 18-25 and 26-35 years were combined, and race categories were combined to create a binary ‘White’ and ‘Non-White’ variable to reduce the number of covariates in the model and to avoid overfit. Although balance was achieved in the PS model using 1:1 matching, 18 fully vaccinated subjects were dropped (>10% of the exposed group); thus SMR weighting was applied as an alternative to the PS modelling approach which resulted in an effective sample size of 163 for the fully vaccinated group and weighted pseudo-population of 159.85 for the unvaccinated comparator group with an effective sample size of 303. Age was assessed using the more granular categorization, race/ethnicity was combined as a binary variable due to having 1 patient in the Asian race/ethnicity category, and time from first PrEP in baseline to ID_E was assessed in 6 month increments for the SMR weighting model. Table 6 shows the balance across the two groups after weighting was applied; all covariates included in the PS model were determined to be effectively balanced according to the a priori standards specified in the protocol. All intermediary tables produced during the propensity score method identification process are available upon request.

Table 5: Baseline characteristics of fully vaccinated and unvaccinated adult men who have sex with men (MSM) and transgender women, prior to and after SMR weighting

	Prior to SMR Weighting			After SMR Weighting		
Variable	Fully Vaccinated	Comparator Unvaccinated**	ASD (Unweighted)	Fully Vaccinated	Comparator Unvaccinated**	ASD (Weighted)
Number of subjects	163	815	-	163	303	-
Sum of weights	N/A	N/A	-	**163**	**159.85**	-
Age on index date*						
...18-25 years	10 (6.1%)	50 (6.1%)	0.000	10.0 (6.1%)	9.5 (5.9%)	0.009
...26-35 years	52 (31.9%)	260 (31.9%)	0.000	52.0 (31.9%)	53.9 (33.7%)	0.039
...36-45 years	44 (27.0%)	220 (27.0%)	0.000	44.0 (27.0%)	40.4 (25.3%)	0.040
...>45 years	57 (35.0%)	285 (35.0%)	0.000	57.0 (35.0%)	56.1 (35.1%)	0.002
Region in the US on index date*						
...Northeast	26 (16.0%)	130 (16.0%)	0.000	26.0 (16.0%)	24.1 (15.0%)	0.025
...Midwest	25 (15.3%)	125 (15.3%)	0.000	25.0 (15.3%)	22.7 (14.2%)	0.033
...South	39 (23.9%)	195 (23.9%)	0.000	39.0 (23.9%)	35.9 (22.4%)	0.035
...West	73 (44.8%)	365 (44.8%)	0.000	73.0 (44.8%)	77.3 (48.3%)	0.071
Insurance Provider on index date*						
...Commercial	94 (57.7%)	470 (57.7%)	0.000	94.0 (57.7%)	87.1 (54.5%)	0.065
...Non-Commercial	69 (42.3%)	345 (42.3%)	0.000	69.0 (42.3%)	72.8 (45.5%)	0.065
Race/Ethnicity on index date*						
...White	50 (30.7%)	373 (45.8%)	**0.314**	50.0 (30.7%)	49.7 (31.1%)	0.010
...Non-White	47 (28.8%)	382 (46.9%)	**0.379**	47.0 (28.8%)	47.0 (29.4%)	0.012
...Missing	66 (40.5%)	60 (7.4%)	**0.843**	66.0 (40.5%)	63.1 (39.5%)	0.020
HIV+ diagnosis during baseline	106 (65.0%)	460 (56.4%)	**0.177**	106.0 (65.0%)	107.0 (67.0%)	0.041
PrEP use during baseline	48 (29.4%)	179 (22.0%)	**0.172**	48.0 (29.5%)	45.8 (28.6%)	0.018

Time from first PrEP in baseline to index date*						
...0-6 months	19 (11.7%)	52 (6.4%)	**0.185**	19.0 (11.7%)	15.0 (9.4%)	0.073
...6 months - 1 year	12 (7.4%)	57 (7.0%)	0.014	12.0 (7.4%)	12.5 (7.8%)	0.017
...≥ 1 year	17 (10.4%)	70 (8.6%)	0.063	17.0 (10.4%)	18.2 (11.4%)	0.031
...No PrEP in baseline	115 (70.6%)	636 (78.0%)	**0.172**	115.0 (70.6%)	114.1 (71.4%)	0.018
History of STD† during baseline	8 (4.9%)	40 (4.9%)	0.000	8.0 (4.9%)	9.5 (5.9%)	0.046
Evidence of autoimmune disorders or immunocompromised conditions (non-HIV)‡ during baseline	46 (28.2%)	212 (26.0%)	0.050	46.0 (28.2%)	44.3 (27.7%)	0.011
Comorbidities§ during baseline	45 (27.6%)	264 (32.4%)	**0.105**	45.0 (27.6%)	44.7 (28.0%)	0.009

ASD = absolute standardised differences; HIV = human immunodeficiency virus; IQR = interquartile range; MSM = men who have sex with men; PrEP = pre-exposure prophylaxis; SD = standard deviation; STD = sexually transmitted diseases; U.S. = United States
Baseline period = Start of data (1 April 2022) to 1 day before Index Date.
*Index date for the fully vaccinated group is the 14th day after the date of the second dose of MVA-BN between 1 August 2022 and 30 September 2022.
**Subjects in the fully vaccinated group (N=163) were coarsened-exact matched with up to 5 unvaccinated comparator subjects on calendar date, age, region, and insurance provider N=815). Comparator unvaccinated subjects were subsequently SMR-weighted using the calculated propensity score of those who received a vaccination, assigning a weight of PS / (1 - PS) to create a pseudo-population of weighted unvaccinated comparator subjects. Weights were truncated at the 99th percentile of the weight distribution.
†History of STD includes the following conditions: chlamydia, gonorrhoea, syphilis, hepatitis B.
‡Evidence of autoimmune disorders or immunocompromised conditions (Non-HIV) includes the following conditions: autoimmune disease, immunodeficiency, inhaled/dermatological corticosteroid use, immunomodulating medication use, and immunotherapy.
§Comorbidities include the following conditions: rheumatological disease, cancer, haematological disease, chronic cardiovascular disease (i.e., heart failure, coronary artery disease, cardiomyopathies), chronic lung disease, chronic kidney disease, chronic liver disease, type I or II diabetes, and atopic dermatitis (neurodermatitis).
Note: ASDs ≥0.10 have been depicted in bold text.

For a better understanding of the mpox outbreak and of the vaccination strategy, subgroups of the fully vaccinated and unvaccinated comparator subjects were defined by HIV and antiretroviral treatment use. Baseline characteristics of adult men who have sex with men (MSM) and transgender women prior to and after SMR weighting are described in Tables 6 and 7 below.

Table 6: Baseline characteristics of fully vaccinated and unvaccinated adult men who have sex with men (MSM) and transgender women, prior to SMR weighting, by HIV and treatment status

	Prior to SMR Weighting											
	HIV+ and Antiretroviral Use			HIV+ and No Antiretroviral Use			HIV- and PrEP Use			HIV- and No PrEP Use		
Variable	Fully Vaccinated	Comparator Unvaccinated**	ASD (not weighted)	Fully Vaccinated	Comparator Unvaccinated**	ASD (not weighted)	Fully Vaccinated	Comparator Unvaccinated**	ASD (not weighted)	Fully Vaccinated	Comparator Unvaccinated**	ASD (not weighted)
Number of subjects	104	316	-	0	139	-	37	146	-	20	209	-
Age on index date*												
...18-25 years	7 (6.7%)	9 (2.8%)	**0.183**	0 (0.0%)	3 (2.2%)	-	1 (2.7%)	6 (4.1%)	0.078	2 (10.0%)	32 (15.3%)	**0.160**
...26-35 years	28 (26.9%)	69 (21.8%)	**0.119**	0 (0.0%)	29 (20.9%)	-	15 (40.5%)	66 (45.2%)	0.094	9 (45.0%)	95 (45.5%)	0.009
...36-45 years	28 (26.9%)	99 (31.3%)	0.097	0 (0.0%)	43 (30.9%)	-	11 (29.7%)	35 (24.0%)	**0.130**	5 (25.0%)	43 (20.6%)	**0.106**
...>45 years	41 (39.4%)	139 (44.0%)	0.093	0 (0.0%)	64 (46.0%)	-	10 (27.0%)	39 (26.7%)	0.007	4 (20.0%)	39 (18.7%)	0.034
Region in the US on index date*												
...Northeast	15 (14.4%)	45 (14.2%)	0.005	0 (0.0%)	32 (23.0%)	-	3 (8.1%)	18 (12.3%)	**0.140**	7 (35.0%)	35 (16.7%)	**0.426**
...Midwest	9 (8.7%)	42 (13.3%)	**0.149**	0 (0.0%)	18 (12.9%)	-	9 (24.3%)	19 (13.0%)	**0.293**	7 (35.0%)	46 (22.0%)	**0.291**
...South	32 (30.8%)	79 (25.0%)	**0.129**	0 (0.0%)	30 (21.6%)	-	7 (18.9%)	26 (17.8%)	0.029	0 (0.0%)	58 (27.8%)	**0.877**
...West	48 (46.2%)	150 (47.5%)	0.026	0 (0.0%)	59 (42.4%)	-	18 (48.6%)	83 (56.8%)	**0.165**	6 (30.0%)	70 (33.5%)	0.075
Insurance Provider on index date*												
...Commercial	53 (51.0%)	181 (57.3%)	**0.127**	0 (0.0%)	52 (37.4%)	-	25 (67.6%)	111 (76.0%)	**0.189**	14 (70.0%)	123 (58.9%)	**0.235**
...Non-Commercial	51 (49.0%)	135 (42.7%)	**0.127**	0 (0.0%)	87 (62.6%)	-	12 (32.4%)	35 (24.0%)	**0.189**	6 (30.0%)	86 (41.1%)	**0.235**
Race/Ethnicity on index date*												

...White	26 (25.0%)	133 (42.1%)	**0.368**	0 (0.0%)	54 (38.8%)	-	14 (37.8%)	82 (56.2%)	**0.374**	9 (45.0%)	102 (48.8%)	0.076
...Non-White	36 (34.6%)	149 (47.2%)	**0.257**	0 (0.0%)	78 (56.1%)	-	9 (24.3%)	54 (37.0%)	**0.277**	2 (10.0%)	100 (47.8%)	**0.919**
...Missing	42 (40.4%)	34 (10.8%)	**0.722**	0 (0.0%)	7 (5.0%)	-	14 (37.8%)	10 (6.8%)	**0.801**	9 (45.0%)	7 (3.3%)	**1.113**
HIV+ diagnosis during baseline	104 (100.0%)	316 (100.0%)	-	0 (0.0%)	139 (100.0%)	-	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	-
PrEP use during baseline	11 (10.6%)	32 (10.1%)	0.015	0 (0.0%)	0 (0.0%)	-	37 (100.0%)	146 (100.0%)	-	0 (0.0%)	0 (0.0%)	-
Time from first PrEP in baseline to index date*												
...0-6 months	4 (3.8%)	9 (2.8%)	0.056	0 (0.0%)	0 (0.0%)	-	15 (40.5%)	42 (28.8%)	**0.249**	0 (0.0%)	0 (0.0%)	-
...6 months - 1 year	3 (2.9%)	7 (2.2%)	0.043	0 (0.0%)	0 (0.0%)	-	9 (24.3%)	50 (34.2%)	**0.219**	0 (0.0%)	0 (0.0%)	-
...≥ 1 year	4 (3.8%)	16 (5.1%)	0.059	0 (0.0%)	0 (0.0%)	-	13 (35.1%)	54 (37.0%)	0.039	0 (0.0%)	0 (0.0%)	-
...No PrEP in baseline	93 (89.4%)	284 (89.9%)	0.015	0 (0.0%)	139 (100.0%)	-	0 (0.0%)	0 (0.0%)	-	20 (100.0%)	209 (100.0%)	-
History of STD† during baseline	7 (6.7%)	15 (4.7%)	0.085	0 (0.0%)	9 (6.5%)	-	0 (0.0%)	9 (6.2%)	**0.363**	1 (5.0%)	7 (3.3%)	0.083
Evidence of autoimmune disorders or immunocompromised conditions (non-HIV)‡ during baseline	35 (33.7%)	105 (33.2%)	0.009	0 (0.0%)	19 (13.7%)	-	9 (24.3%)	46 (31.5%)	**0.161**	2 (10.0%)	42 (20.1%)	**0.285**
Comorbidities§ during baseline	34 (32.7%)	117 (37.0%)	0.091	0 (0.0%)	67 (48.2%)	-	5 (13.5%)	35 (24.0%)	**0.270**	5 (25.0%)	45 (21.5%)	0.082

ASD = absolute standardised differences; HIV = human immunodeficiency virus; IQR = interquartile range; MSM = men who have sex with men; PrEP = pre-exposure prophylaxis; SD = standard deviation; STD = sexually transmitted diseases; U.S. = United States
Baseline period = Start of data (1 April 2022) to 1 day before Index Date.
*Index date for the fully vaccinated group is the 14th day after the date of the second dose of MVA-BN between 1 August 2022 and 30 September 2022.
**Subjects in the vaccinated group (N=163) were coarsened-exact matched with 5 unvaccinated comparator subjects who were unvaccinated at the time of match on calendar date, age, region, and insurance provider (N=815).
†History of STD includes the following conditions: chlamydia, gonorrhoea, syphilis, hepatitis B.
‡Evidence of autoimmune disorders or immunocompromised conditions (Non-HIV) includes the following conditions: autoimmune disease, immunodeficiency, inhaled/dermatological corticosteroid use, immunomodulating medication use, and immunotherapy.
§Comorbidities include the following conditions: rheumatological disease, cancer, haematological disease, chronic cardiovascular disease (i.e., heart failure, coronary artery disease, cardiomyopathies), chronic lung disease, chronic kidney disease, chronic liver disease, type I or II diabetes, and atopic dermatitis (neurodermatitis).

Table 7: Baseline characteristics of fully vaccinated and unvaccinated adult men who have sex with men (MSM) and transgender women, after SMR weighting, by HIV and treatment status

	After SMR Weighting											
	HIV+ and Antiretroviral Use			HIV+ and No Antiretroviral Use			HIV- and PrEP Use			HIV- and No PrEP Use		
Variable	Fully Vaccinated	Comparator Unvaccinated**	ASD (Weighted)	Fully Vaccinated	Comparator Unvaccinated**	ASD (Weighted)	Fully Vaccinated	Comparator Unvaccinated**	ASD (Weighted)	Fully Vaccinated	Comparator Unvaccinated**	ASD (Weighted)
Effective sample size	104	134	-	0	139	-	37	51	-	20	26	-
Sum of weights	**104**	**107.52**	**-**	**0**	**0.00**	**-**	**37**	**32.98**	**-**	**20**	**19.14**	**-**
Age on index date*												
...18-35 years	35.0 (33.7%)	41.8 (38.9%)	**0.109**	0.0 (-%)	0.0 (23.0%)	-	16.0 (43.2%)	14.2 (43.1%)	0.004	11.0 (55.0%)	9.3 (48.5%)	**0.131**
...36-45 years	28.0 (26.9%)	24.2 (22.6%)	**0.102**	0.0 (-%)	0.0 (30.9%)	-	11.0 (29.7%)	9.2 (28.0%)	0.037	5.0 (25.0%)	5.1 (26.8%)	0.042
...>45 years	41.0 (39.4%)	41.5 (38.6%)	0.017	0.0 (-%)	0.0 (46.0%)	-	10.0 (27.0%)	9.5 (28.9%)	0.042	4.0 (20.0%)	4.7 (24.7%)	**0.113**
Region in the US on index date*												
...Northeast	15.0 (14.4%)	16.6 (15.5%)	0.029	0.0 (-%)	0.0 (23.0%)	-	3.0 (8.1%)	2.1 (6.4%)	0.067	7.0 (35.0%)	6.4 (33.2%)	0.037
...Midwest	9.0 (8.6%)	9.4 (8.7%)	0.003	0.0 (-%)	0.0 (13.0%)	-	9.0 (24.3%)	5.7 (17.4%)	**0.171**	7.0 (35.0%)	5.7 (30.0%)	**0.108**
...South	32.0 (30.8%)	27.4 (25.5%)	**0.119**	0.0 (-%)	0.0 (21.6%)	-	7.0 (18.9%)	10.1 (30.8%)	**0.277**	0.0 (0.0%)	0.0 (0.0%)	0.000
...West	48.0 (46.2%)	54.1 (50.4%)	0.084	0.0 (-%)	0.0 (42.4%)	-	18.0 (48.7%)	15.0 (45.5%)	0.064	6.0 (30.0%)	7.0 (36.8%)	**0.145**
Insurance Provider on index date*												
...Commercial	53.0 (51.0%)	48.6 (45.2%)	**0.116**	0.0 (-%)	0.0 (37.4%)	-	25.0 (67.6%)	22.5 (68.2%)	0.013	14.0 (70.0%)	13.6 (71.3%)	0.029
...Non-Commercial	51.0 (49.0%)	59.0 (54.8%)	**0.116**	0.0 (-%)	0.0 (62.6%)	-	12.0 (32.4%)	10.5 (31.8%)	0.013	6.0 (30.0%)	5.5 (28.7%)	0.029
Race/Ethnicity on index date*												
...White	26.0 (25.0%)	25.0 (23.3%)	0.040	0.0 (-%)	0.0 (38.9%)	-	14.0 (37.8%)	13.8 (41.9%)	0.084	9.0 (45.0%)	9.3 (48.4%)	0.068
...Non-White	36.0 (34.6%)	36.3 (33.8%)	0.018	0.0 (-%)	0.0 (56.1%)	-	9.0 (24.3%)	8.6 (26.0%)	0.038	2.0 (10.0%)	2.0 (10.5%)	0.016
...Missing	42.0 (40.4%)	46.2 (43.0%)	0.052	0.0 (-%)	0.0 (5.0%)	-	14.0 (37.8%)	10.6 (32.1%)	**0.121**	9.0 (45.0%)	7.9 (41.1%)	0.078
HIV+ diagnosis during baseline	104.0 (100.0%)	107.5 (100.0%)	-	0.0 (-%)	0.0 (100.0%)	-	0.0 (0.0%)	0.0 (0.0%)	-	0.0 (0.0%)	0.0 (0.0%)	-

PrEP use during baseline	11.0 (10.6%)	11.2 (10.4%)	0.006	0.0 (-%)	0.0 (0.0%)	-	37.0 (100.0%)	33.0 (100.0%)	-	0.0 (0.0%)	0.0 (0.0%)	-
Time from first PrEP in baseline to index date*												
...0-6 months	4.0 (3.9%)	4.4 (4.1%)	0.010	0.0 (-%)	0.0 (0.0%)	-	15.0 (40.5%)	11.1 (33.6%)	**0.145**	0.0 (0.0%)	0.0 (0.0%)	-
...6 months - 1 year	3.0 (2.9%)	2.7 (2.5%)	0.024	0.0 (-%)	0.0 (0.0%)	-	9.0 (24.3%)	9.0 (27.4%)	0.070	0.0 (0.0%)	0.0 (0.0%)	-
...≥ 1 year	4.0 (3.9%)	4.2 (3.9%)	0.001	0.0 (-%)	0.0 (0.0%)	-	13.0 (35.1%)	12.9 (39.1%)	0.081	0.0 (0.0%)	0.0 (0.0%)	-
...No PrEP in baseline	93.0 (89.4%)	96.3 (89.6%)	0.006	0.0 (-%)	0.0 (100.0%)	-	0.0 (0.0%)	0.0 (0.0%)	-	20.0 (100.0%)	19.1 (100.0%)	-
History of STD† during baseline	7.0 (6.7%)	8.3 (7.8%)	0.039	0.0 (-%)	0.0 (6.5%)	-	0.0 (0.0%)	0.0 (0.0%)	0.000	1.0 (5.0%)	0.5 (2.6%)	**0.124**
Evidence of autoimmune disorders or immunocompromised conditions (non-HIV)‡ during baseline	35.0 (33.7%)	32.3 (30.0%)	0.078	0.0 (-%)	0.0 (13.7%)	-	9.0 (24.3%)	10.6 (32.2%)	**0.175**	2.0 (10.0%)	1.5 (7.9%)	0.073
Comorbidities§ during baseline	34.0 (32.7%)	33.2 (30.9%)	0.038	0.0 (-%)	0.0 (48.2%)	-	5.0 (13.5%)	5.5 (16.6%)	0.087	5.0 (25.0%)	5.2 (27.0%)	0.046

ASD = absolute standardised differences; HIV = human immunodeficiency virus; IQR = interquartile range; MSM = men who have sex with men; PrEP = pre-exposure prophylaxis; SD = standard deviation; STD = sexually transmitted diseases; U.S. = United States
Baseline period = Start of data (1 April 2022) to 1 day before Index Date.
*Index date for the fully vaccinated group is the 14th day after the date of the second dose of MVA-BN between 1 August 2022 and 30 September 2022.
**Subjects in the vaccinated group (N=163) were coarsened-exact matched with 5 unvaccinated comparator subjects who were unvaccinated at the time of match on calendar date, age, region, and insurance provider (N=815). Comparator unvaccinated subjects were subsequently SMR-weighted using the calculated propensity score of those who received a vaccination, assigning a weight of PS / (1 - PS) to create a pseudo-population of weighted unvaccinated comparator subjects.
†History of STD includes the following conditions: chlamydia, gonorrhoea, syphilis, hepatitis B.
‡Evidence of autoimmune disorders or immunocompromised conditions (Non-HIV) includes the following conditions: autoimmune disease, immunodeficiency, inhaled/dermatological corticosteroid use, immunomodulating medication use, and immunotherapy.
§Comorbidities include the following conditions: rheumatological disease, cancer, haematological disease, chronic cardiovascular disease (i.e., heart failure, coronary artery disease, cardiomyopathies), chronic lung disease, chronic kidney disease, chronic liver disease, type I or II diabetes, and atopic dermatitis (neurodermatitis).
Note: Weights were truncated at the 99th percentile of the weight distribution.

In the final SMR weighting model, age categories 18-25 and 26-35 years were combined due to the larger representation of younger patients in the non-HIV subgroups, and race categories were combined to create a binary ‘White’ and ‘Non-White’ variable due to the small number of patients in each group. All subgroups were determined to be sufficiently balanced according to the a priori standards specified in the protocol, with the exception of the HIV- and PrEP use subgroup which remained imbalanced on region (i.e., Midwest, South) and evidence of autoimmune disorders or non-HIV immunocompromised conditions. Balance was unable to be determined for the HIV+ and no antiretroviral use subgroup given there were 0 exposed (i.e., fully vaccinated) subjects in this subgroup.

Safety

There were 947 vaccinated subjects in the exposed group and 4,735 matched unvaccinated subjects in the comparator group prior to PS matching in the safety analysis. All covariates in Table 8 were considered for inclusion in the PS model, including history of AESIs: myocarditis, pericarditis, encephalitis, and anaphylaxis. The results for the full set of baseline characteristics assessed for the secondary safety objective can be found in Appendix B Tables C11-C13. Of these covariates, race/ethnicity, PrEP use, and comorbidities during baseline were imbalanced (ASD > 0.10) during baseline.

Using 1:1 PS matching process, the final PS model including all covariates except for history of myocarditis and history of encephalitis were selected. History of myocarditis and history of encephalitis were removed due to having 0 patients in the exposed or comparator group, leading to a violation of positivity (e.g., covariates in the model must have non-zero values) for those covariates. Table 8 shows the balance across the two groups after 1:1 PS matching was applied; all covariates included in the PS model were determined to be effectively balanced according to the a priori standards specified in the protocol.

Table 8: Baseline characteristics of vaccinated and unvaccinated adult men who have sex with men (MSM) and transgender women, prior to and after propensity score adjustment, 1:1 matching

	Prior to PS Matching			After PS Matching		
Variable	Vaccinated	Comparator Unvaccinated	ASD (not matched)	Vaccinated	Comparator Unvaccinated	ASD (matched)
Number of subjects	947	4,735	-	915	915	-
Age on index date*			0.000			0.032
...18-25 years	70 (7.4%)	350 (7.4%)	-	65 (7.1%)	60 (6.6%)	-
...26-35 years	309 (32.6%)	1,545 (32.6%)	-	296 (32.3%)	288 (31.5%)	-
...36-45 years	247 (26.1%)	1,235 (26.1%)	-	239 (26.1%)	246 (26.9%)	-
...>45 years	321 (33.9%)	1,605 (33.9%)	-	315 (34.4%)	321 (35.1%)	-
Region in the US on index date*			0.000			0.037
...Northeast	153 (16.2%)	765 (16.2%)	-	148 (16.2%)	157 (17.2%)	-
...Midwest	143 (15.1%)	715 (15.1%)	-	135 (14.8%)	126 (13.8%)	-

...South	262 (27.7%)	1,310 (27.7%)	-	260 (28.4%)	256 (28.0%)	-
...West	389 (41.1%)	1,945 (41.1%)	-	372 (40.7%)	376 (41.1%)	-
Insurance Provider on index date*			0.000			0.009
...Commercial	546 (57.7%)	2,730 (57.7%)	-	521 (56.9%)	517 (56.5%)	-
...Non-Commercial	401 (42.3%)	2,005 (42.3%)	-	394 (43.1%)	398 (43.5%)	-
Race/Ethnicity on index date*			0.130			0.075
...White	240 (25.3%)	1,998 (42.2%)	-	240 (26.2%)	223 (24.4%)	-
...Black	140 (14.8%)	940 (19.9%)	-	140 (15.3%)	150 (16.4%)	-
...Hispanic	113 (11.9%)	775 (16.4%)	-	113 (12.3%)	123 (13.4%)	-
...Asian	18 (1.9%)	165 (3.5%)	-	18 (2.0%)	16 (1.7%)	-
...Other	36 (3.8%)	367 (7.8%)	-	36 (3.9%)	35 (3.8%)	-
...Missing	400 (42.2%)	490 (10.3%)	-	368 (40.2%)	368 (40.2%)	-
HIV+ diagnosis during baseline	564 (59.6%)	2,690 (56.8%)	0.056	554 (60.5%)	587 (64.2%)	0.074
PrEP use during baseline	281 (29.7%)	1,052 (22.2%)	**0.171**	264 (28.9%)	239 (26.1%)	0.061
Time from first PrEP in baseline to index date in days*			0.044			0.097
...mean (sd)	263.96 (161.87)	271.14 (162.59)		270.44 (161.59)	254.46 (166.94)	
...median (IQR)	233.00 [136.00, 442.00]	255.00 [137.00, 427.75]		240.50 [139.00, 450.25]	225.00 [104.00, 421.00]	
History of STD† during baseline	45 (4.8%)	227 (4.8%)	0.002	43 (4.7%)	38 (4.2%)	0.027
Evidence of autoimmune disorders or immunocompromised conditions (non-HIV)‡ during baseline	211 (22.3%)	1,051 (22.2%)	0.002	205 (22.4%)	216 (23.6%)	0.029
Comorbidities§ during baseline	260 (27.5%)	1,525 (32.2%)	**0.104**	253 (27.7%)	260 (28.4%)	0.017
History of AESI during baseline						

...Myocarditis	0 (0.0%)	2 (0.0%)	0.029	0 (0.0%)	1 (0.1%)	0.047
...Pericarditis	2 (0.2%)	6 (0.1%)	0.021	2 (0.2%)	3 (0.3%)	0.021
...Encephalitis	0 (0.0%)	4 (0.1%)	0.041	0 (0.0%)	0 (0.0%)	-
...Anaphylaxis	1 (0.1%)	3 (0.1%)	0.015	1 (0.1%)	1 (0.1%)	0.000

AESIs = adverse events of special interest; ASD = absolute standardised differences; HIV = human immunodeficiency virus; IQR = interquartile range; MSM = men who have sex with men; PrEP = pre-exposure prophylaxis; SD = standard deviation; STD = sexually transmitted diseases; U.S. = United States
Baseline period = Start of data to 1 day before Index Date
*Index date for the vaccinated group is the date of the first MVA-BN administration for exposed subjects between 1 August 2022 and 30 September 2022.
**Subjects in the vaccinated group (N=947) were coarsened-exact matched with 5 unvaccinated comparator subjects who were unvaccinated at the time of match on calendar date, age, region, and insurance provider (N=4,735). Vaccinated subjects were subsequently 1:1 propensity score matched to unvaccinated comparator subjects to select a comparable matched sample of the analytic cohort.
†History of STD includes the following conditions: chlamydia, gonorrhoea, syphilis, hepatitis B.
‡Evidence of autoimmune disorders or immunocompromised conditions (Non-HIV) includes the following conditions: autoimmune disease, immunodeficiency, inhaled/dermatological corticosteroid use, immunomodulating medication use, and immunotherapy.
§Comorbidities include the following conditions: rheumatological disease, cancer, haematological disease, chronic cardiovascular disease (i.e., heart failure, coronary artery disease, cardiomyopathies), chronic lung disease, chronic kidney disease, chronic liver disease, type I or II diabetes, and atopic dermatitis (neurodermatitis).
Note: ASDs ≥0.10 have been depicted in bold text.

7.3. Outcome data

7.3.1. Vaccine Effectiveness

In the fully vaccinated group (sum of weights =163), there was 1 subject with the primary outcome of mpox disease, 1 subject with hospitalisation related to mpox disease, 18 subjects with all-cause hospitalisation or death, 1 subject with all potential mpox infection, and 0 subjects with all potential hospitalisation for mpox infection.

In the SMR weighted unvaccinated comparator group (sum of weights = 159.85), there were 12 subjects with the primary outcome of mpox disease, 1 subject with hospitalisation related to mpox disease, 92 subjects with all-cause hospitalisation or death, 12 subjects with all potential mpox infections, and 0 subjects with all potential hospitalisation for mpox infection.

7.3.2. Safety

In both vaccinated (N=915) and unvaccinated (N=915) groups, there were 0 subjects with a myocarditis or pericarditis event within 14 days of ID_S. There were 0 subjects with an encephalitis event within 28 days of ID_S and 0 subjects with an anaphylaxis event within 1 day of ID_S.

7.4. Main results

7.4.1. Vaccine Effectiveness

As shown in Table 9, subjects who were fully vaccinated with 2 doses with the MVA-BN vaccine 14 days prior to ID_E were associated with decreased risk of mpox disease (wRR 0.11, 95% CI 0.01-0.88) and all potential mpox infections (wRR 0.11, 95% CI 0.01, 0.88) compared to the weighted unvaccinated comparator subjects (crude and adjusted results provided). This corresponded to adjusted vaccine effectiveness for 2 doses in preventing diagnosis of mpox disease of 89% (95% CI 12%, 99%). No difference was found in the risk of hospitalisations related to mpox disease (wRR 0.93, 95% CI 0.06, 15.02) and increased risk of all-cause hospitalisation (wRR 1.01 95% CI 0.59, 1.72) between the 2 groups .

Table 9: Vaccine effectiveness among fully vaccinated and unvaccinated adult men who have sex with men (MSM) and transgender women

Variable	Vaccinated	Comparator Unvaccinated*
Number of subjects prior to SMR weighting	163	815
Effective sample size	163	303
Sum of weights	**163**	**159.85**
Mpox disease **(At least one ICD-10-CM diagnosis code or laboratory record of mpox PCR test result of "DETECTED")**		
Number of events	1	12
Number of person-days (unweighted)**	16,436.25	80,355.00
Weighted rate per 100,000 person-days (95% CI)	6.12 (0.86, 43.71)	58.47 (29.29, 116.75)
Weighted risk per 100,000 persons (95% CI)	613.50 (85.90, 4,381.64)	5,545.14 (2,839.90, 10,827.36)
Weighted Rate Ratio (vs. comparator; 95% CI)	0.11 (0.01, 0.85)	-
Weighted Risk Ratio (vs. comparator; 95% CI)	0.11 (0.01, 0.88)	-
Weighted Rate Difference per 100,000 person-days (95% CI)	-52.35 (-94.54, -10.17)	
Weighted Risk Difference per 100,000 persons (95% CI)	-4,931.64 (-8,833.30, -1,029.98)	
Weighted Vaccine Effectiveness (%)	**89% (12%, 99%)**	**-**
Crude Rate Ratio (vs. comparator; 95% CI)	0.41 (0.05, 3.16)	-

Crude Risk Ratio (vs. comparator; 95% CI)	0.42 (0.05, 3.22)	-
Crude Rate Difference per 100,000 person-days (95% CI)	-3,209.92 (-21,066.14, 14,646.30)	
Crude Risk Difference per 100,000 persons (95% CI)	-858.90 (-2321.85, 604.06)	
Crude Vaccine Effectiveness (%)	58% (-222%, 95%)	-
Hospitalisation related to mpox disease **(An inpatient event recorded within 30 days after any ICD-10-CM diagnosis code or laboratory record of mpox PCR test result of "DETECTED")**		
Number of events	1	1
Number of person-days (unweighted)**	16,436.25	81,450.75
Weighted rate per 100,000 person-days (95% CI)	6.12 (0.86, 43.70)	6.67 (0.94, 47.53)
Weighted risk per 100,000 persons (95% CI)	613.50 (85.90, 4,381.64)	657.16 (92.27, 4,680.27)
Weighted Rate Ratio (vs. comparator; 95% CI)	0.92 (0.06, 14.72)	-
Weighted Risk Ratio (vs. comparator; 95% CI)	0.93 (0.06, 15.02)	-
Weighted Rate Difference per 100,000 person-days (95% CI)	-0.56 (-18.34, 17.23)	
Weighted Risk Difference per 100,000 persons (95% CI)	-43.66 (-1,809.79, 1,722.46)	
Weighted Vaccine Effectiveness (%)	**7% (94%, 1,402%)**	**-**
Crude Rate Ratio (vs. comparator; 95% CI)	4.97 (0.31, 79.51)	-
Crude Risk Ratio (vs. comparator; 95% CI)	5.00 (0.31, 80.35)	
Crude Rate Difference per 100,000 person-days (95% CI)	1,784.38 (-2,763.25, 6,332.02)	
Crude Risk Difference per 100,000 persons (95% CI)	490.80 (-739.11, 1720.70)	
Crude Vaccine Effectiveness (%)	-400% (-7,935%, 69%)	
All-cause hospitalisation or death **(Any inpatient event or the record of death)**		
Number of events	18	92
Number of person-days (unweighted)**	15,340.50	75,972.00
Weighted rate per 100,000 person-days (95% CI)	117.27 (73.48, 187.16)	118.85 (85.70, 164.81)

Weighted risk per 100,000 persons (95% CI)	11,042.94 (7,123.42, 17,119.12)	10,977.49 (8,092.63, 14,890.73)
Weighted Rate Ratio (vs. comparator; 95% CI)	0.99 (0.56, 1.74)	-
Weighted Risk Ratio (vs. comparator; 95% CI)	1.01 (0.59, 1.72)	-
Weighted Rate Difference per 100,000 person-days (95% CI)	-1.58 (-68.77, 65.62)	
Weighted Risk Difference per 100,000 persons (95% CI)	65.46 (-5,820.12, 5,951.03)	
Weighted Vaccine Effectiveness (%)	**-1% (-72%, 41%)**	**-**
Crude Rate Ratio (vs. comparator; 95% CI)	0.97 (0.58, 1.60)	-
Crude Risk Ratio (vs. comparator; 95% CI)	0.98 (0.61, 1.58)	
Crude Rate Difference per 100,000 person-days (95% CI)	-1,477.42 (-72,058.00, 69,103.15)	
Crude Risk Difference per 100,000 persons (95% CI)	-245.40 (-5552.90, 5062.11)	
Crude Vaccine Effectiveness Risk (%)	2% (-58%, 39%)	-
All potential mpox infections **(A positive orthopox PCR test indicating mpox, mpox defined by at least ICD-10-CM diagnosis code, or at least one prescription of mpox treatments; tecovirimat, VIGIV, cidofovir, or brincidofovir)**		
Number of events	1	12
Number of person-days (unweighted)**	16,436.25	80,355.00
Weighted rate per 100,000 person-days (95% CI)	6.12 (0.86, 43.71)	58.47 (29.29, 116.75)
Weighted risk per 100,000 persons (95% CI)	613.50 (85.90, 4,381.64)	5,545.14 (2,839.90, 10,827.36)
Weighted Rate Ratio (vs. comparator; 95% CI)	0.11 (0.01, 0.85)	-
Weighted Risk Ratio (vs. comparator; 95% CI)	0.11 (0.01, 0.88)	-
Weighted Rate Difference per 100,000 person-days (95% CI)	-52.35 (-94.54, -10.17)	
Weighted Risk Difference per 100,000 persons (95% CI)	-4,931.64 (-8,833.30, -1,029.98)	
Weighted Vaccine Effectiveness (%)	**89% (12%, 99%)**	**-**
Crude Rate Ratio (vs. comparator; 95% CI)	0.41 (0.05, 3.16)	-
Crude Risk Ratio (vs. comparator; 95% CI)	0.42 (0.05, 3.22)	
Crude Rate Difference per 100,000 person-days (95% CI)	-3,209.92 (-21,066.14, 14,646.30)	

Crude Risk Difference per 100,000 persons (95% CI)	-858.90 (-2321.85, 604.06)	
Crude Vaccine Effectiveness (%)	58% (-222%, 95%)	
All potential hospitalisation for mpox infections **(An inpatient hospitalisation event recorded within 30 days after a positive orthopox PCR test indicating mpox, mpox defined by an inpatient ICD-10-CM diagnosis code in any position, or at least one prescription of mpox treatments; tecovirimat, VIGIV, cidofovir, or brincidofovir)**		
Number of events	0	0
Number of person-days (unweighted)**	16,436.25	81,450.75
Weighted rate per 100,000 person-days (95% CI)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
Weighted risk per 100,000 persons (95% CI)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
Weighted Rate Ratio (vs. comparator; 95% CI)	-	-
Weighted Risk Ratio (vs. comparator; 95% CI)	1.00 (0.83, 1.21)	-
Weighted Rate Difference per 100,000 person-days (95% CI)	0.00 (-, -)	
Weighted Risk Difference per 100,000 persons (95% CI)	0.00 (-, -)	
Weighted Vaccine Effectiveness (%)	**0% (-21%, 17%)**	**-**
Crude Rate Ratio (vs. comparator; 95% CI)	0.99 (0, ∞)	-
Crude Risk Ratio (vs. comparator; 95% CI)	1.00 (0.84, 1.18)	
Crude Rate Difference per 100,000 person-days (95% CI)	0.00 (-, -)	
Crude Risk Difference per 100,000 persons (95% CI)	0.00 (-, -)	
Crude Vaccine Effectiveness (%)	0% (-18%, 16%)	-

*Subjects in the vaccinated group (N=163) were coarsened-exact matched with 5 unvaccinated comparator subjects who were unvaccinated at the time of match on calendar date, age, region, and insurance provider (N=815). Comparator unvaccinated subjects were subsequently SMR-weighted using the calculated propensity score of those who received a vaccination, assigning a weight of PS / (1 - PS) to create a pseudo-population of weighted unvaccinated comparator subjects.

**Follow-up began on index date (14th day after the date of the second dose of MVA-BN between 1 August 2022 and 30 September 2022) and ended on the earliest occurrence of the outcome of interest, disenrollment, death, or end of data availability. Additionally, unvaccinated subjects were censored upon cross-over to the vaccinated group upon receiving the first dose of MVA-BN vaccination.

HIV and treatment subgroups were defined among the fully vaccinated and unvaccinated comparator subjects, as shown in Table 10 below. Majority of fully vaccinated subjects are HIV+ and antiretroviral users. Among this subgroup, vaccine effectiveness was broadly consistent with the

overall results. There were no fully vaccinated subjects who were HIV+ with no antiretroviral use. There were no reportable differences in vaccine effectiveness with respect to mpox between HIV- PrEP users and HIV-PrEP non-users.

Table 10: Vaccine effectiveness among fully vaccinated and matched unvaccinated adult men who have sex with men (MSM) and transgender women, by HIV and treatment status

	HIV+ and Antiretroviral Use		HIV+ and No Antiretroviral Use		HIV- and PrEP Use		HIV- and No PrEP Use	
Variable	Vaccinated	Comparator Unvaccinated*	Vaccinated	Comparator Unvaccinated*	Vaccinated	Comparator Unvaccinated*	Vaccinated	Comparator Unvaccinated*
Number of subjects prior to SMR weighting	104	316	0	139	37	146	20	209
Effective sample size	104	134	-	139	37	51	20	26
Sum of weights	**104**	**107.52**	**0**	**0**	**37**	**32.98**	**20**	**19.14**
Mpox disease **(At least one ICD-10-CM diagnosis code or laboratory record of mpox PCR test result of "DETECTED")**								
Number of events	1	7	0	2	0	3	0	0
Number of person-days (unweighted)**	10,227.00	31,046.25	0.00	13,879.50	3,652.50	14,610.00	2,191.50	20,819.25
Weighted rate per 100,000 person-days	9.61 (1.34, 68.92)	34.30 (13.09, 89.90)	-	14.48 (3.60, 58.15)	0.00 (0.00, 0.00)	170.58 (56.08, 518.83)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
Weighted risk per 100,000 persons	961.54 (134.17, 6,891.13)	3,265.30 (1,270.67, 8,391.00)	-	1,438.85 (359.87, 5,752.94)	0.00 (0.00, 0.00)	15,721.02 (5,471.94, 45,166.87)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
Weighted Rate Ratio (vs. comparator; 95% CI)	0.28 (0.03, 2.50)	-	-	-	-	-	-	-
Weighted Risk Ratio (vs. comparator; 95% CI)	0.29 (0.03, 2.62)	-	-	-	0.00 (0.00, 0.00)	-	1.00 (0.54, 1.85)	-
Weighted Rate Difference per 100,000 person-days (95% CI)	-24.69 (-62.78, 13.40)		-		-170.58 (-360.32, 19.17)		0.00 (-, -)	
Weighted Risk Difference per 100,000 persons (95% CI)	-2,303.76 (-5,920.90, 1,313.38)		-		-15,721.02 (-32,312.44, 870.40)		0.00 (-, -)	
Weighted Vaccine Effectiveness (%)	**71% (-162%, 97%)**	**-**	**-**	**-**	**N/R**	**-**	**0% (-85%, 46%)**	**-**

Crude Rate Ratio (vs. comparator; 95% CI)	0.42 (0.05, 3.45)	-	-	-	<0.001 (0, ∞)	-	0.97 (0, ∞)	-
Crude Risk Ratio (vs. comparator; 95% CI)	0.43 (0.05, 3.55)	-	-	-	0.00 (0.00, 0.00)	-	1.00 (0.62, 1.62)	-
Crude Rate Difference per 100,000 person-days (95% CI)	-4,749.71 (-37,754.00, 28,254.58)		-	-	-7,555.89 (-36,764.37, 21,652.59)		0.00 (-, -)	
Crude Risk Difference per 100,000 persons (95% CI)	-1,253.65 (-3,750.87, 1,243.57)		-	-	-2,054.79 (-4,371.83, 262.24)		0.00 (-, -)	
Crude Vaccine Effectiveness (%)	57% (-255%, 95%)	-	-	-	N/R	-	0% (-62%, 38%)	-
Hospitalisation related to mpox disease **(An inpatient event recorded within 30 days after any ICD-10-CM diagnosis code or laboratory record of mpox PCR test result of "DETECTED")**								
Number of events	1	0	0	1	0	0	0	0
Number of person-days (unweighted)**	10,227.00	31,411.50	0.00	13,879.50	3,652.50	14,610.00	2,191.50	20,819.25
Weighted rate per 100,000 person-days	9.61 (1.34, 68.91)	0.00 (0.00, 0.00)	-	7.22 (1.01, 51.61)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
Weighted risk per 100,000 persons	961.54 (134.17, 6891.13)	0.00 (0.00, 0.00)	-	719.42 (100.62, 5,143.58)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
Weighted Rate Ratio (vs. comparator; 95% CI)	>999.999 (>999.999, >999.999)	-	-	-	-	-	-	-
Weighted Risk Ratio (vs. comparator; 95% CI)	>999.999 (>999.999, >999.999)	-	-	-	1.00 (0.65, 1.55)	-	1.00 (0.54, 1.85)	-
Weighted Rate Difference per 100,000 person-days (95% CI)	9.61 (-9.32, 28.55)		-		0.00 (-, -)		0.00 (-, -)	
Weighted Risk Difference per 100,000 persons (95% CI)	961.54 (-932.17, 2,855.25)		-		0.00 (-, -)		0.00 (-, -)	
Weighted Vaccine Effectiveness (%)	**N/R**	**-**	**-**	**-**	**0% (-55%, 35%)**	**-**	**0% (-85%, 46%)**	**-**
Crude Rate Ratio (vs. comparator; 95% CI)	>999.999 (0, ∞)	-	-	-	1.00 (0, ∞)	-	0.97 (0, ∞)	-
Crude Risk Ratio (vs. comparator; 95% CI)	>999.999 (>999.999, >999.999)	-	-	-	1.00 (0.69, 1.45)		1.00 (0.62, 1.62)	-
Crude Rate Difference per 100,000 person-days (95% CI)	3,508.94 (-3,703.15, 10,721.03)		-		0.00 (-, -)		0.00 (-, -)	

Crude Risk Difference per 100,000 persons (95% CI)	961.54 (-932.17, 2,855.25)		-		0.00 (-, -)		0.00 (-, -)	
Crude Vaccine Effectiveness (%)	N/R	-	-	-	0% (-45%, 31%)	-	0% (-62%, 38%)	-
All-cause hospitalisation or death **(Any inpatient event or the record of death)**								
Number of events	11	41	0	13	5	19	2	19
Number of person-days (unweighted)**	9,861.75	28,854.75	0.00	13,149.00	3,287.25	13,514.25	1,826.25	19,723.50
Weighted rate per 100,000 person-days	111.83 (61.55, 203.20)	113.79 (68.68, 188.53)	-	98.28 (56.87, 169.83)	150.20 (59.87, 376.80)	93.92 (49.09, 179.71)	100.15 (24.55, 408.62)	225.21 (75.21, 674.36)
Weighted risk per 100,000 persons	10,576.92 (6,016.00, 18,595.62)	10,345.73 (6,477.67, 16,523.55)	-	9,352.52 (5,553.03, 15,751.70)	13,513.51 (5,846.82, 31,233.23)	8,910.62 (4,820.49, 16,471.19)	10,000.00 (2,505.79, 39,907.65)	19,692.46 (7,396.77, 52,427.34)
Weighted Rate Ratio (vs. comparator; 95% CI)	0.98 (0.45, 2.14)	-	-	-	1.61 (0.52, 4.99)	-	0.46 (0.09, 2.44)	-
Weighted Risk Ratio (vs. comparator; 95% CI)	1.02 (0.49, 2.13)	-	-	-	1.52 (0.54, 4.29)	-	0.51 (0.09, 2.77)	-
Weighted Rate Difference per 100,000 person-days (95% CI)	-1.95 (-90.05, 86.14)		-		56.27 (-94.72, 207.26)		-125.06 (-409.37, 159.26)	
Weighted Risk Difference per 100,000 persons (95% CI)	231.19 (-7,455.29, 7,917.67)		-		4,602.89 (-7,972.72, 17,178.50)		-9,692.46 (-33,427.74, 14,042.83)	
Weighted Vaccine Effectiveness (%)	**-2% (-113%, 51%)**	**-**	**-**	**-**	**-52% (-329%, 46%)**	**-**	**49% (-177%, 91%)**	**-**
Crude Rate Ratio (vs. comparator; 95% CI)	0.78 (0.40, 1.53)	-	-	-	1.08 (0.40, 2.89)	-	1.04 (0.24, 4.46)	-
Crude Risk Ratio (vs. comparator; 95% CI)	0.82 (0.43, 1.53)	-	-	-	1.04 (0.41, 2.65)	-	1.10 (0.26, 4.69)	-
Crude Rate Difference per 100,000 person-days (95% CI)	-11,225.49 (-123,024.09, 100,573.10)		-		4,048.88 (-152,180.96, 160,278.73)		1,387.49 (-136,261.59, 139,036.57)	
Crude Risk Difference per 100,000 persons (95% CI)	-2,397.76 (-9,428.48, 4,632.96)		-		499.81 (-12,084.85, 13,084.48)		909.09 (-13,474.15, 15,292.33)	
Crude Vaccine Effectiveness (%)	18% (-53%, 57%)	-	-	-	-4% (-165%, 59%)	-	-10% (-369%, 74%)	-
All potential mpox infections **(A positive orthopox PCR test indicating mpox, mpox defined by at least ICD-10-CM diagnosis code, or at least one prescription of mpox treatments; tecovirimat, VIGIV, cidofovir, or brincidofovir)**								

Number of events	1	7	0	2	0	3	0	0
Number of person-days (unweighted)**	10,227.00	31,046.25	0.00	13,879.50	3,652.50	14,610.00	2,191.50	20,819.25
Weighted rate per 100,000 person-days	9.61 (1.34, 68.92)	34.30 (13.09, 89.90)	-	14.48 (3.60, 58.15)	0.00 (0.00, 0.00)	170.58 (56.08, 518.83)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
Weighted risk per 100,000 persons	961.54 (134.17, 6,891.13)	3,265.30 (1,270.67, 8,391.00)	-	1,438.85 (359.87, 5,752.94)	0.00 (0.00, 0.00)	15,721.02 (5,471.94, 45,166.87)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
Weighted Rate Ratio (vs. comparator; 95% CI)	0.28 (0.03, 2.50)	-	-	-	-	-	-	-
Weighted Risk Ratio (vs. comparator; 95% CI)	0.29 (0.03, 2.62)	-	-	-	0.00 (0.00, 0.00)	-	1.00 (0.54, 1.85)	-
Weighted Rate Difference per 100,000 person-days (95% CI)	-24.69 (-62.78, 13.40)		-		-170.58 (-360.32, 19.17)		0.00 (-, -)	
Weighted Risk Difference per 100,000 persons (95% CI)	-2,303.76 (-5,920.90, 1,313.38)		-		-15,721.02 (-32,312.44, 870.40)		0.00 (-, -)	
Weighted Vaccine Effectiveness (%)	**71% (-162%, 97%)**	**-**	**-**	**-**	**N/R**	**-**	**0% (-85%, 46%)**	**-**
Crude Rate Ratio (vs. comparator; 95% CI)	0.42 (0.05, 3.45)	-	-	-	<0.001 (0, ∞)	-	0.97 (0, ∞)	-
Crude Risk Ratio (vs. comparator; 95% CI)	0.43 (0.05, 3.55)	-	-	-	0.00 (0.00, 0.00)		1.00 (0.62, 1.62)	-
Crude Rate Difference per 100,000 person-days (95% CI)	-4,749.71 (-37,754.00, 28,254.58)		-		-7,555.89 (-36,764.37, 21,652.59)		0.00 (-, -)	
Crude Risk Difference per 100,000 persons (95% CI)	-1,253.65 (-3,750.87, 1,243.57)		-		-2,054.79 (-4,371.83, 262.24)		0.00 (-, -)	
Crude Vaccine Effectiveness (%)	57% (-255%, 95%)	-	-	-	100% (-,-)	-	0% (-62%, 38%)	-
All potential hospitalisation for mpox infections **(An inpatient hospitalisation event recorded within 30 days after a positive orthopox PCR test indicating mpox, mpox defined by an inpatient ICD-10-CM diagnosis code in any position, or at least one prescription of mpox treatments; tecovirimat, VIGIV, cidofovir, or brincidofovir)**								
Number of events	0	0	0	0	0	0	0	0
Number of person-days (unweighted)**	10,592.25	31,411.50	0.00	13,879.50	3,652.50	14,610.00	2,191.50	20,819.25
Weighted rate per 100,000 person-days	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	-	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
Weighted risk per 100,000 persons	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	-	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)

Weighted Rate Ratio (vs. comparator; 95% CI)	107.52	-	-	-	-	-	-	-
Weighted Risk Ratio (vs. comparator; 95% CI)	1.00 (0.77, 1.30)	-	-	-	1.00 (0.65, 1.55)		1.00 (0.54, 1.85)	-
Weighted Rate Difference per 100,000 person-days (95% CI)	0.00 (-, -)		-		0.00 (-, -)		0.00 (-, -)	
Weighted Risk Difference per 100,000 persons (95% CI)	0.00 (-, -)		-		0.00 (-, -)		0.00 (-, -)	
Weighted Vaccine Effectiveness (%)	**0% (-30, 23%)**	**-**	**-**	**-**	**0% (-55%, 35%)**	**-**	**0% (-85%, 46%)**	**-**
Crude Rate Ratio (vs. comparator; 95% CI)	0.99 (0, ∞)	-	-	-	1.00 (0, ∞)	-	0.97 (0, ∞)	-
Crude Risk Ratio (vs. comparator; 95% CI)	1.00 (0.80, 1.25)	-	-	-	1.00 (0.69, 1.45)		1.00 (0.62, 1.62)	-
Crude Rate Difference per 100,000 person-days (95% CI)	0.00 (-, -)		-		0.00 (-, -)		0.00 (-, -)	
Crude Risk Difference per 100,000 persons (95% CI)	0.00 (-, -)		-		0.00 (-, -)		0.00 (-, -)	
Crude Vaccine Effectiveness (%)	0% (-25%, 20%)	-	-	-	0% (-45%, 31%)	-	100% (-62%, 38%)	-

CI = confidence interval; MSM = men who have sex with men; mpox = monkeypox; PrEP = Pre-exposure Exposure Prophylaxis
*Subjects in the vaccinated group (N=163) were coarsened-exact matched with 5 unvaccinated comparator subjects who were unvaccinated at the time of match on calendar date, age, region, and insurance provider (N=815). Comparator unvaccinated subjects were subsequently SMR-weighted using the calculated propensity score of those who received a vaccination, assigning a weight of PS / (1 - PS) to create a pseudo-population of weighted unvaccinated comparator subjects.
**Follow-up began on index date (14th day after the date of the second dose of MVA-BN between 1 August 2022 and 30 September 2022) and ended on the earliest occurrence of the outcome of interest, disenrollment, death, or end of data availability. Additionally, unvaccinated subjects were censored upon cross-over to the vaccinated group upon receiving the first dose of MVA-BN vaccination.
Note: Subgroups definitions do not include those with HIV+ status and antiretroviral use prior to HIV diagnosis, thus subgroups are not mutually exclusive.

7.4.2. Safety

As shown in Table 11, there were no events among MSM and transgender women who received at least 1 dose of the MVA-BN vaccine and their matched comparator subjects within the specified risk windows for each safety outcome.

Table 11: Vaccine AESIs among vaccinated and matched unvaccinated MSM and transgender women using primary risk windows

Variable	Vaccinated	Comparator Unvaccinated
Number of PS matched subjects*	915	915

Myocarditis, 14-day risk window		
Number of events	0	0
Number of person-days**	12,783.75	12,418.50
Rate per 100,000 person-days	0.00	0.00
Risk per 100,000 persons	0.00	0.00
Rate Ratio (vs. comparator; 95% CI)	0.91 (0, ∞)	
Risk Ratio (vs. comparator; 95% CI)	1.00 (0.91, 1.10)	
Rate Difference per 100,000 person-days (95% CI)	0.00 (-, -)	
Risk Difference per 100,000 persons (95% CI)	0.00 (-, -)	
Crude Rate Ratio (vs. comparator; 95% CI)	0.96 (0, ∞)	-
Crude Risk Ratio (vs. comparator; 95% CI)	1.00 (0.93, 1.07)	-
Crude Rate Difference per 100,000 person-days (95% CI)	0.00 (-, -)	
Crude Risk Difference per 100,000 persons (95% CI)	0.00 (-, -)	
Pericarditis, 14-day risk window		
Number of events	0	0
Number of person-days**	12,783.75	12,418.50
Rate per 100,000 person-days	0.00	0.00
Risk per 100,000 persons	0.00	0.00
Rate Ratio (vs. comparator; 95% CI)	0.91 (0, ∞)	-
Risk Ratio (vs. comparator; 95% CI)	1.00 (0.91, 1.10)	-
Rate Difference per 100,000 person-days (95% CI)	0.00 (-, -)	
Risk Difference per 100,000 persons (95% CI)	0.00 (-, -)	
Crude Rate Ratio (vs. comparator; 95% CI)	0.96 (0, ∞)	-
Crude Risk Ratio (vs. comparator; 95% CI)	1.00 (0.93, 1.07)	-
Crude Rate Difference per 100,000 person-days (95% CI)	0.00 (-, -)	

Crude Risk Difference per 100,000 persons (95% CI)	0.00 (-, -)	
Myocarditis or Pericarditis, 14-day risk window		
Number of events	0	0
Number of person-days**	12,783.75	12,418.50
Rate per 100,000 person-days	0.00	0.00
Risk per 100,000 persons	0.00	0.00
Rate Ratio (vs. comparator; 95% CI)	0.91 (0, ∞)	-
Risk Ratio (vs. comparator; 95% CI)	1.00 (0.91, 1.10)	-
Rate Difference per 100,000 person-days (95% CI)	0.00 (-, -)	
Risk Difference per 100,000 persons (95% CI)	0.00 (-, -)	
Crude Rate Ratio (vs. comparator; 95% CI)	0.96 (0, ∞)	-
Crude Risk Ratio (vs. comparator; 95% CI)	1.00 (0.93, 1.07)	-
Crude Rate Difference per 100,000 person-days (95% CI)	0.00 (-, -)	
Crude Risk Difference per 100,000 persons (95% CI)	0.00 (-, -)	
Encephalitis (Primary Definition), 28-day risk window		
Number of events	0	0
Number of person-days**	25,567.50	23,376.00
Rate per 100,000 person-days	0.00	0.00
Risk per 100,000 persons	0.00	0.00
Rate Ratio (vs. comparator; 95% CI)	0.84 (0, ∞)	-
Risk Ratio (vs. comparator; 95% CI)	1.00 (0.91, 1.10)	-
Rate Difference per 100,000 person-days (95% CI)	0.00 (-, -)	
Risk Difference per 100,000 persons (95% CI)	0.00 (-, -)	
Crude Rate Ratio (vs. comparator; 95% CI)	0.92 (0, ∞)	-

Crude Risk Ratio (vs. comparator; 95% CI)	1.00 (0.93, 1.07)	-
Crude Rate Difference per 100,000 person-days (95% CI)	0.00 (-, -)	
Crude Risk Difference per 100,000 persons (95% CI)	0.00 (-, -)	
Anaphylaxis, 1-day risk window		
Number of events	0	0
Number of person-days**	1,095.75	730.50
Rate per 100,000 person-days	0.00	0.00
Risk per 100,000 persons	0.00	0.00
Rate Ratio (vs. comparator; 95% CI)	0.99 (0, ∞)	-
Risk Ratio (vs. comparator; 95% CI)	1.00 (0.91, 1.10)	-
Rate Difference per 100,000 person-days (95% CI)	0.00 (-, -)	
Risk Difference per 100,000 persons (95% CI)	0.00 (-, -)	
Crude Rate Ratio (vs. comparator; 95% CI)	1.00 (0, ∞)	-
Crude Risk Ratio (vs. comparator; 95% CI)	1.00 (0.93, 1.07)	-
Crude Rate Difference per 100,000 person-days (95% CI)	0.00 (-, -)	
Crude Risk Difference per 100,000 persons (95% CI)	0.00 (-, -)	

CI = confidence interval; MSM = men who have sex with men; mpox = monkeypox

*Subjects in the vaccinated group were coarsened-exact matched with 5 unvaccinated comparator subjects who were unvaccinated at the time of match on calendar date, age, region, and insurance provider. Vaccinated subjects were subsequently 1:1 propensity score matched to unvaccinated comparator subjects to select a comparable matched sample of the analytic cohort. Prior to PS adjustment, there were 947 subjects in the vaccinated group and 4,735 subjects in the comparator unvaccinated group.

**Follow-up began on index date (first MVA-BN dose after meeting eligibility criteria between 1 August 2022 and 30 September 2022) and ended on the earliest occurrence of the outcome of interest, disenrollment, death, end of data availability, or end of the AESI-specific risk window. Additionally, unvaccinated subjects were censored upon cross-over to the vaccinated group upon receiving the first dose of MVA-BN vaccination.

7.5. Sensitivity analyses

7.5.1. Sensitivity analysis 1. Background risk of mpox disease among overall MSM and transgender women prior to selection of vaccinated and matched unvaccinated subjects

Among 68,381 MSM and transgender women, there were 4,708 subjects with an mpox disease event from index date (diagnosis code indicating HRSB, HIV+ diagnosis, or PrEP therapy for HIV among those with no prior diagnosis code for substance use disorder) until end of follow-up (first occurrence of mpox disease, disenrollment, death, end of data, or 31 December 2022). The risk of mpox disease was 6,884.95 per 100,000 persons (95% CI 6,695.18, 7,074.73) in those who met the MSM and transgender women criteria during the study period. Given that all subjects in the overall MSM and transgender women cohort index on the date they met the MSM and transgender women criteria independent of vaccination status, sensitivity analysis using an analytical cohort of vaccinated versus unvaccinated participants was not performed given that the unvaccinated group could not be assigned a comparable index date prior to coarsened-exact matching. Assignment of an index date for unvaccinated participants was not feasible without the introduction of immortal time bias in the comparison of person-time in relation to vaccination status. Given a comparable index date was not able to be identified among the unvaccinated subjects in this cohort, comparative estimates were not calculated for this sensitivity analysis. Furthermore, rates were not reported given the index date for the overall MSM and transgender women cohort represents the date in which subjects met the MSM and transgender women criteria in our dataset and is not representative of an exposure or clinical event. Under these circumstances, the background risk of mpox among all MSM and transgender women in the HealthVerity dataset was estimated as opposed to risk ratios or rate ratios.

Table 12: Sensitivity analysis of mpox disease among adult men who have sex with men (MSM) and transgender women

Variable	MSM and transgender women cohort
Number of subjects	68,381
Mpox disease	
Number of events	4,708
Risk per 100,000 persons (95% CI)	6,884.95 (6,695.18, 7,074.73)

CI = confidence interval; MSM = men who have sex with men; mpox = monkeypox
Follow-up began on index date (day the subject met the MSM criteria) and ended on the earliest occurrence of the outcome of interest, disenrollment, death, or end of data availability.

7.5.2. Sensitivity analysis 2. Vaccine effectiveness among coarsened-exact matched subjects in the exposed group of the safety cohort

Among 947 subjects in the exposed group of the safety cohort (i.e., subjects who had a record of a MVA-BN vaccine administration), there were 947 (100.00%) subjects who received at least 1 dose of the MVA-BN vaccine, 788 (83.21%) subjects who received 1 MVA-BN dose only, and 215 (22.70%) subjects age >50 years who received 1 MVA-BN dose only (i.e., proxy for smallpox vaccination). After propensity score matching, there were 908 subjects who received at least 1 dose of the MVA-BN vaccine, 751 subjects who received 1 MVA-BN dose only, and 195 subjects age >50 years who received 1 MVA-BN dose only.

Single dose vaccination was 64% and 70% effective against mpox disease among those with at least one MVA-BN dose and among those receiving only one MVA-BN dose, respectively. Single dose vaccination was less effective among aged >50 years who received only one MVA-BN dose, with a vaccine effectiveness of 0% (95% CI -242%, 71%).

Table 13: Sensitivity analysis of vaccine effectiveness among vaccinated MSM and transgender women and matched unvaccinated MSM and transgender women

Variable	Safety Cohort - At least one MVA-BN dose		Safety Cohort - One MVA-BN dose only		Safety Cohort - One MVA-BN dose only and age > 50 years	
	Vaccinated	Comparator Unvaccinated	Vaccinated	Comparator Unvaccinated	Vaccinated	Comparator Unvaccinated
Number of PS matched subjects*	908	908	751	751	195	195
Mpox disease (At least one ICD-10-CM diagnosis code or laboratory record of mpox PCR test result of "DETECTED")						
Number of events	20	55	13	43	5	5
Number of person-days**	111,036.00	79,259.25	87,660.00	75,606.75	22,280.25	20,088.75
Rate per 100,000 person-days (95% CI)	18.02 (11.60, 28.00)	69.33 (52.96, 90.76)	14.83 (8.59, 25.58)	56.80 (41.90, 77.00)	22.36 (9.25, 54.07)	24.87 (10.27, 60.25)
Risk per 100,000 persons (95% CI)	2,202.64 (1,427.28, 3,399.21)	6,057.27 (4,687.15, 7,827.90)	1,731.03 (1,009.17, 2,969.23)	5,725.70 (4,281.78, 7,656.54)	2,564.10 (1,074.59, 6,118.28)	2,564.10 (1,074.59, 6,118.28)
Rate Ratio (vs. comparator; 95% CI)	0.26 (0.16, 0.43)	-	0.26 (0.14, 0.49)	-	0.90 (0.26, 3.11)	-

Risk Ratio (vs. comparator; 95% CI)	0.36 (0.22, 0.60)	-	0.30 (0.16, 0.56)	-	1.00 (0.29, 3.42)	-
Rate Difference per 100,000 person-days (95% CI)	-51.31 (-71.60, -31.01)		-41.97 (-61.06, -22.89)		-2.51 (-32.07, 27.05)	
Risk Difference per 100,000 persons (95% CI)	-3,854.63 (-5,678.38, -2,030.87)		-3,994.67 (-5,902.78, -2,086.57)		0.00 (-3,153.59, 3,153.59)	
Adjusted Vaccine Effectiveness (%)	**64% (40%, 78%)**	**-**	**70% (44%, 84%)**	**-**	**0% (-242%, 71%)**	**-**
Crude Rate Ratio (vs. comparator; 95% CI)	0.74 (0.47, 1.18)	-	0.72 (0.42, 1.24)	-	1.81 (0.64, 5.07)	-
Crude Risk Ratio (vs. comparator; 95% CI)	0.86 (0.54, 1.36)		0.77 (0.45, 1.32)		1.91 (0.69, 5.32)	
Crude Rate Difference per 100,000 person-days (95% CI)	-6.22 (-15.17, 2.73)		-6.31 (-15.77, 3.15)		9.03 (-9.84, 27.90)	
Crude Risk Difference per 100,000 persons (95% CI)	-368.31 (-1,410.73, 674.10)		-564.64 (-1,636.11, 506.83)		1,108.35 (-1,019.99, 3,236.70)	
Crude Vaccine Effectiveness (%)	14% (-36%, 46%)	-	23% (-32%, 55%)	-	-91% (-432%, 31%)	-
Hospitalisation related to mpox disease **(An inpatient event recorded within 30 days after any ICD-10-CM diagnosis code or laboratory record of mpox PCR test result of "DETECTED")**						
Number of events	7	6	7	7	2	1
Number of person-days**	112,131.75	84,372.75	88,390.50	79,259.25	22,645.50	20,454.00
Rate per 100,000 person-days (95% CI)	6.24 (2.97, 13.10)	7.13 (3.20, 15.90)	7.94 (3.78, 16.69)	8.82 (4.20, 18.56)	8.87 (2.20, 35.70)	4.89 (0.68, 34.90)
Risk per 100,000 persons (95% CI)	770.93 (368.28, 1,613.79)	660.79 (297.39, 1,468.25)	932.09 (445.46, 1,950.32)	932.09 (445.46, 1,950.32)	1025.64 (256.52, 4,100.89)	512.82 (71.87, 3,658.96)
Rate Ratio (vs. comparator; 95% CI)	0.87 (0.29, 2.60)	-	0.90 (0.32, 2.57)	-	1.81 (0.16, 20.01)	-
Risk Ratio (vs. comparator; 95% CI)	1.17 (0.39, 3.46)	-	1.00 (0.35, 2.84)	-	2.00 (0.18, 22.15)	-
Rate Difference per 100,000 person-days (95% CI)	-0.89 (-8.25, 6.47)		-0.88 (-9.71, 7.94)		3.98 (-11.67, 19.63)	
Risk Difference per 100,000 persons (95% CI)	110.13 (-666.19, 886.46)		0.00 (-973.23, 973.23)		512.82 (-1,229.56, 2,255.20)	
Adjusted Vaccine Effectiveness (%)	**-17% (-246%, 61%)**	**-**	**0% (-184%, 65%)**	**-**	**-100% (-2,115%, 82%)**	**-**
Crude Rate Ratio (vs. comparator; 95% CI)	1.80 (0.75, 4.34)	-	1.83 (0.77, 4.39)	-	3.13 (0.52, 18.74)	-

Crude Risk Ratio (vs. comparator; 95% CI)	2.05 (0.85, 4.94)	-	1.94 (0.81, 4.63)	-	3.31 (0.55, 19.81)	-
Crude Rate Difference per 100,000 person-days (95% CI)	2.66 (-2.06, 7.37)		3.44 (-2.50, 9.38)		5.47 (-6.09, 17.02)	
Crude Risk Difference per 100,000 persons (95% CI)	378.85 (-193.42, 951.13)		430.31 (-258.81, 1,119.43)		649.33 (-678.44, 1,977.10)	
Crude Vaccine Effectiveness (%)	-105% (-394%, 15%)	-	-94% (-363%, 19%)	-	-231% (-1,881%, 45%)	-
All-cause hospitalisation or death (Any inpatient event or the record of death)						
Number of events	138	106	97	94	28	27
Number of person-days**	101,174.25	77,798.25	81,085.50	73,780.50	20,819.25	18,627.75
Rate per 100,000 person-days (95% CI)	136.37 (114.96, 161.76)	136.17 (112.20, 165.28)	119.60 (97.67, 146.44)	127.50 (104.00, 156.31)	135.42 (92.88, 197.46)	145.89 (99.14, 214.70)
Risk per 100,000 persons (95% CI)	15,198.24 (13,031.48, 17,725.27)	11,674.01 (9,759.64, 13,963.88)	12,916.11 (10,724.38, 15,555.77)	12,516.64 (10,357.66, 15,125.65)	14,358.97 (10,173.97, 20,265.45)	13,846.15 (9,738.56, 19,686.27)
Rate Ratio (vs. comparator; 95% CI)	1.00 (0.78, 1.29)	-	0.94 (0.71, 1.25)	-	0.93 (0.55, 1.57)	-
Risk Ratio (vs. comparator; 95% CI)	1.30 (1.03, 1.65)	-	1.03 (0.79, 1.35)	-	1.04 (0.63, 1.70)	-
Rate Difference per 100,000 person-days (95% CI)	0.19 (-34.99, 35.38)		-7.90 (-43.41, 27.61)		-10.47 (-86.53, 65.59)	
Risk Difference per 100,000 persons (95% CI)	3,524.23 (387.89, 6,660.57)		399.47 (-2,974.66, 3,773.60)		512.82 (-6,431.12, 7,456.76)	
Adjusted Vaccine Effectiveness (%)	**-30% (-65%, -3%)**	**-**	**-3% (-35%, 21%)**	**-**	**-4% (-70%, 37%)**	**-**
Crude Rate Ratio (vs. comparator; 95% CI)	1.07 (0.89, 1.29)	-	0.99 (0.80, 1.23)	-	0.95 (0.65, 1.38)	-
Crude Risk Ratio (vs. comparator; 95% CI)	1.20 (1.01, 1.42)	-	1.04 (0.86, 1.28)	-	1.01 (0.71, 1.42)	-
Crude Rate Difference per 100,000 person-days (95% CI)	9.29 (-15.63, 34.21)		-0.73 (-26.74, 25.28)		-7.51 (-63.63, 48.61)	
Crude Risk Difference per 100,000 persons (95% CI)	2,531.43 (60.29, 5,002.57)		552.30 (-2,010.72, 3,115.33)		86.66 (-5,213.60, 5,386.93)	
Crude Vaccine Effectiveness (%)	-20% (-42%, -1%)	-	-4% (-28%, 14%)	-	-1% (-42%, 29%)	-

All potential mpox infections **(A positive orthopox PCR test indicating mpox, mpox defined by at least ICD-10-CM diagnosis code, or at least one prescription of mpox treatments; tecovirimat, VIGIV, cidofovir, or brincidofovir)**						
Number of events	20	55	13	43	5	5
Number of person-days**	111,036.00	79,259.25	87,660.00	75,606.75	22,280.25	20,088.75
Rate per 100,000 person-days (95% CI)	18.02 (11.60, 28.00)	69.33 (52.96, 90.76)	14.83 (8.59, 25.58)	56.80 (41.90, 77.00)	22.36 (9.25, 54.07)	24.87 (10.27, 60.25)
Risk per 100,000 persons (95% CI)	2,202.64 (1,427.28, 3,399.21)	6,057.27 (4,687.15, 7,827.90)	1731.03 (1,009.17, 2,969.23)	5,725.70 (4,281.78, 7,656.54)	2,564.10 (1,074.59, 6,118.28)	2,564.10 (1,074.59, 6,118.28)
Rate Ratio (vs. comparator; 95% CI)	0.26 (0.16, 0.43)	-	0.26 (0.14, 0.49)	-	0.90 (0.26, 3.11)	-
Risk Ratio (vs. comparator; 95% CI)	0.36 (0.22, 0.60)	-	0.30 (0.16, 0.56)	-	1.00 (0.29, 3.42)	-
Rate Difference per 100,000 person-days (95% CI)	-51.31 (-71.60, -31.01)		-41.97 (-61.06, -22.89)		-2.51 (-32.07, 27.05)	
Risk Difference per 100,000 persons (95% CI)	-3,854.63 (-5,678.38, -2,030.87)		-3,994.67 (-5,902.78, -2,086.57)		0.00 (-3,153.59, 3,153.59)	
Adjusted Vaccine Effectiveness (%)	**64% (40%, 78%)**	**-**	**70% (44%, 84%)**	**-**	**0% (-242%, 71%)**	**-**
Crude Rate Ratio (vs. comparator; 95% CI)	0.74 (0.47, 1.18)	-	0.72 (0.42, 1.24)	-	1.81 (0.64, 5.07)	-
Crude Risk Ratio (vs. comparator; 95% CI)	0.86 (0.54, 1.36)	-	0.77 (0.45, 1.32)	-	1.91 (0.69, 5.32)	-
Crude Rate Difference per 100,000 person-days (95% CI)	-6.22 (-15.17, 2.73)		-6.31 (-15.77, 3.15)		9.03 (-9.84, 27.90)	
Crude Risk Difference per 100,000 persons (95% CI)	-368.31 (-1,410.73, 674.10)		-564.64 (-1,636.11, 506.83)		1108.35 (-1,019.99, 3236.70)	
Crude Vaccine Effectiveness (%)	14% (-36%, 46%)	-	23% (-32%, 55%)	-	-91% (-432%, 31%)	-
All potential hospitalisation for mpox infections **(An inpatient hospitalisation event recorded within 30 days after a positive orthopox PCR test indicating mpox, mpox defined by an inpatient ICD-10-CM diagnosis code in any position, or at least one prescription of mpox treatments; tecovirimat, VIGIV, cidofovir, or brincidofovir)**						
Number of events	2	6	3	6	0	1
Number of person-days**	112,862.25	84,372.75	88,755.75	79,624.50	22,645.50	20,454.00
Rate per 100,000 person-days (95% CI)	1.78 (0.44, 7.11)	7.13 (3.20, 15.90)	3.39 (1.09, 10.51)	7.55 (3.39, 16.85)	0.00 (0.00, 0.00)	4.89 (0.68, 34.90)

Risk per 100,000 persons (95% CI)	220.26 (55.09, 880.71)	660.79 (297.39, 1,468.25)	399.47 (128.93, 1,237.64)	798.93 (359.70, 1,774.53)	0.00 (0.00, 0.00)	512.82 (71.87, 3,658.96)
Rate Ratio (vs. comparator; 95% CI)	0.25 (0.05, 1.23)	-	0.45 (0.11, 1.79)	-	<0.001 (0, ∞)	-
Risk Ratio (vs. comparator; 95% CI)	0.33 (0.07, 1.65)	-	0.50 (0.13, 2.00)	-	0.00 (0.00, 0.00)	-
Rate Difference per 100,000 person-days (95% CI)	-5.35 (-11.58, 0.87)		-4.17 (-11.34, 3.01)		-4.89 (-14.50, 4.72)	
Risk Difference per 100,000 persons (95% CI)	-440.53 (-1,050.05, 168.99)		-399.47 (-1,180.84, 381.90)		-512.82 (-1,520.52, 494.88)	
Adjusted Vaccine Effectiveness (%)	**67% (-65%, 93%)**	**-**	**50% (-100%, 87%)**	**-**	**N/R**	**-**
Crude Rate Ratio (vs. comparator; 95% CI)	0.54 (0.13, 2.37)	-	0.88 (0.26, 3.02)	-	<0.001 (0, ∞)	-
Crude Risk Ratio (vs. comparator; 95% CI)	0.62 (0.14, 2.71)	-	0.94 (0.27, 3.21)	-	0.00 (0.00, 0.00)	-
Crude Rate Difference per 100,000 person-days (95% CI)	-1.43 (-4.25, 1.39)		-0.44 (-4.52, 3.64)		-2.57 (-5.47, 0.34)	
Crude Risk Difference per 100,000 persons (95% CI)	-127.93 (-464.38, 208.52)		-26.41 (-500.77, 447.94)		-280.90 (-598.61, 36.81)	
Crude Vaccine Effectiveness (%)	38% (-171%, 86%)	-	6% (-221%, 73%)	-	100% (-,-)	-

*Subjects in the vaccinated group were selected for entry into the cohort if they met the cohort entry requirements for the exposed group and were coarsened-exact matched with at least one (up to 5) unvaccinated comparator subjects on calendar date, age, region, and insurance provider. Vaccinated subjects were subsequently 1:1 propensity score matched to unvaccinated comparator subjects to select a comparable matched sample of the analytic cohort. Prior to propensity score matching, there were 947 subjects who received at least 1 dose of the MVA-BN vaccine, 788 subjects who received at least 1 dose of the MVA-BN vaccine, and 215 subjects age >50 years who received 1 MVA-BN vaccine only.
**Follow-up began 1 day after index date (first MVA-BN dose after meeting eligibility criteria between 1 August 2022 and 30 September 2022) and ended on the earliest occurrence of the outcome of interest, disenrollment, death, end of data availability, or end of the AESI-specific risk window. Additionally, unvaccinated subjects were censored upon cross-over to the vaccinated group upon receiving the first dose of MVA-BN vaccination.

7.5.3. Sensitivity analysis 3. Vaccine effectiveness among the fully vaccinated and unvaccinated MSM and transgender women using a different mpox outcome definition

The primary vaccine effectiveness outcome was assessed among the fully vaccinated exposed subjects and unvaccinated comparator subjects using the orthopox PCR test CPT code 87593 to define mpox disease. In the unvaccinated comparator group, there were 6 subjects with an mpox event defined by orthopox PCR test. Among the fully vaccinated group, there was 1 subject with an mpox event defined by orthopox PCR test and 2-dose vaccination was 53% (95% CI -397%, 96%) effective against mpox using the sensitivity definition, although the 95% confidence intervals were wide.

Table 14: Sensitivity analysis of vaccine effectiveness using a different mpox outcome definition (orthopox PCR test) among fully vaccinated and unvaccinated adult men who have sex with men (MSM) and transgender women

Variable	Vaccinated	Comparator Unvaccinated*
Number of subjects prior to SMR weighting	163	815
Effective sample size	163	303
Sum of weights	**163**	**159.85**
Orthopoxvirus PCR test (CPT code 87593)		
Number of events	1	6
Number of person-days (unweighted)**	16,436.25	81,085.50
Weighted rate per 100,000 person-days	6.11 (0.86, 43.68)	13.23 (3.62, 48.33)
Weighted risk per 100,000 persons	613.50 (85.90, 4,381.64)	1,297.92 (356.03, 4,731.66)
Weighted Rate Ratio (vs. comparator; 95% CI)	0.46 (0.04, 4.83)	-
Weighted Risk Ratio (vs. comparator; 95% CI)	0.47 (0.04, 4.97)	-
Weighted Rate Difference per 100,000 person-days (95% CI)	-7.11 (-28.05, 13.82)	
Weighted Risk Difference per 100,000 persons (95% CI)	-684.43 (-2,751.65, 1,382.79)	
Vaccine Effectiveness (%)	**53% (-397%, 96%)**	**-**
Crude Rate Ratio (vs. comparator; 95% CI)	0.82 (0.10, 6.85)	-
Crude Risk Ratio (vs. comparator; 95% CI)	0.83 (0.10, 6.96)	-
Crude Rate Difference per 100,000 person-days (95% CI)	-475.28 (-21,962.97, 21,012.41)	
Crude Risk Difference per 100,000 persons (95% CI)	-122.70 (-1,464.36, 1,218.96)	
Crude Vaccine Effectiveness (%)	17% (-596%, 90%)	-

CI = confidence interval; CPT = Current Procedural Terminology; MSM = men who have sex with men; PCR = polymerase chain reaction; SMR = standardized mortality/morbidity ratio
*Subjects in the vaccinated group (N=163) were coarsened-exact matched with 5 unvaccinated comparator subjects who were unvaccinated at the time of match on calendar date, age, region, and insurance provider (N=815). Comparator unvaccinated subjects were subsequently SMR-weighted using the calculated propensity score of those who received a vaccination, assigning a weight of PS / (1 - PS) to create a pseudo-population of weighted unvaccinated comparator subjects.
**Follow-up began on index date (14th day after the date of the second dose of MVA-BN between 1 August 2022 and 30 September 2022) and ended on the earliest occurrence of the outcome of interest, disenrollment, death, or end of data availability. Additionally, unvaccinated subjects were censored upon cross-over to the vaccinated group upon receiving the first dose of MVA-BN vaccination.

7.5.4. Sensitivity analysis 4. Vaccine safety using a broader definition for encephalitis

In the 1:1 PS matched cohort, encephalitis was assessed using a broader definition by adding non-specific ICD-10-CM codes for encephalitis (i.e., G36.9, G37.3, and G37.9). As shown in Table 15, 1 encephalitis event was identified in the unvaccinated group using the broader definition (4.27 per 100,000 person-days), however there were no events in the vaccinated group.

Table 15: Sensitivity analysis of encephalitis safety outcome using a broader definition among vaccinated and unvaccinated MSM and transgender women

Variable	Vaccinated	Comparator Unvaccinated
Number of PS matched subjects*	915	915
Encephalitis (Primary Definition), 28-day risk window		
Number of events	0	0
Number of person-days**	25,567.50	23,376.00
Rate per 100,000 person-days	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
Risk per 100,000 persons	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
Rate Ratio (vs. comparator; 95% CI)	0.84 (0, ∞)	-
Risk Ratio (vs. comparator; 95% CI)	1.00 (0.91, 1.10)	-
Rate Difference per 100,000 person-days (95% CI)	0.00 (-, -)	
Risk Difference per 100,000 persons (95% CI)	0.00 (-, -)	
Crude Rate Ratio (vs. comparator; 95% CI)	0.92 (0, ∞)	-
Crude Risk Ratio (vs. comparator; 95% CI)	1.00 (0.93, 1.07)	-
Crude Rate Difference per 100,000 person-days (95% CI)	0.00 (-, -)	
Crude Risk Difference per 100,000 persons (95% CI)	0.00 (-, -)	

Encephalitis (Broader Definition), 28-day risk window		
Number of events	0	1
Number of person-days**	25,567.50	23,376.00
Rate per 100,000 person-days	0.00 (0.00, 0.00)	4.27 (0.60, 30.37)
Risk per 100,000 persons	0.00 (0.00, 0.00)	109.29 (15.38, 776.69)
Rate Ratio (vs. comparator; 95% CI)	<0.001 (0, ∞)	-
Risk Ratio (vs. comparator; 95% CI)	0.00 (0.00, 0.00)	-
Crude Rate Ratio (vs. comparator; 95% CI)	<0.001 (0, ∞)	-
Crude Risk Ratio (vs. comparator; 95% CI)	0.00 (0.00, 0.00)	
Crude Rate Difference per 100,000 person-days (95% CI)	-287.31 (-2,553.08, 1,978.47)	
Crude Risk Difference per 100,000 persons (95% CI)	-21.12 (-62.52, 20.28)	

CI = confidence interval; MSM = men who have sex with men
*Subjects in the vaccinated group were coarsened-exact matched with 5 unvaccinated comparator subjects who were unvaccinated at the time of match on calendar date, age, region, and insurance provider. Vaccinated subjects were subsequently 1:1 propensity score matched to unvaccinated comparator subjects to select a comparable matched sample of the analytic cohort. Prior to PS adjustment, there were 947 subjects in the vaccinated group and 4,735 subjects in the comparator unvaccinated group.
**Follow-up began on index date (first MVA-BN dose after meeting eligibility criteria between 1 August 2022 and 30 September 2022) and ended on the earliest occurrence of the outcome of interest, disenrollment, death, end of data availability, or end of the AESI-specific risk window. Additionally, unvaccinated subjects were censored upon cross-over to the vaccinated group upon receiving the first dose of MVA-BN vaccination.

7.5.5. Sensitivity analysis 5. Using different risk windows for safety outcome assessment.

In the 1:1 propensity score matched cohort, safety outcomes were assessed using broader risk windows to ensure the robustness of the results. As shown in Table 16, 1 pericarditis event was identified among the vaccinated group when a 28-day risk window was applied (3.90 per 100,000 person-days). Using a 42-day risk window, an encephalitis event was identified in the unvaccinated group (2.96 per 100,000 person-days), however there were no events in the vaccinated group.

Table 16: Sensitivity Analysis - Vaccine AESIs among vaccinated and matched unvaccinated MSM and transgender women using sensitivity risk windows

Variable	Vaccinated	Comparator Unvaccinated
Number of PS matched subjects*	915	915
Myocarditis, 28-day risk window		
Number of events	0	0
Number of person-days**	25,567.50	23,376.00
Rate per 100,000 person-days	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
Risk per 100,000 persons	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
Rate Ratio (vs. comparator; 95% CI)	0.84 (0, ∞)	-
Risk Ratio (vs. comparator; 95% CI)	1.00 (0.91, 1.10)	-
Risk Difference per 100,000 person-days (95% CI)	0.00 (-, -)	
Risk Difference per 100,000 persons (95% CI)	0.00 (-, -)	
Crude Rate Ratio (vs. comparator; 95% CI)	0.92 (0, ∞)	-
Crude Risk Ratio (vs. comparator; 95% CI)	1.00 (0.93, 1.07)	-
Crude Rate Difference per 100,000 person-days (95% CI)	0.00 (-, -)	
Crude Risk Difference per 100,000 persons (95% CI)	0.00 (-, -)	
Pericarditis, 28-day risk window		
Number of events	1	0
Number of person-days**	25,567.50	23,376.00
Rate per 100,000 person-days	3.90 (0.55, 27.74)	0.00 (0.00, 0.00)
Risk per 100,000 persons	109.29 (15.38, 776.69)	0.00 (0.00, 0.00)
Rate Ratio (vs. comparator; 95% CI)	>999.999 (0, ∞)	-

Risk Ratio (vs. comparator; 95% CI)	>999.999 (0, ∞)	-
Risk Difference per 100,000 person-days (95% CI)	3.90 (-3.75, 11.56)	
Risk Difference per 100,000 persons (95% CI)	109.29 (-105.03, 323.61)	
Crude Rate Ratio (vs. comparator; 95% CI)	>999.999 (0, ∞)	-
Crude Risk Ratio (vs. comparator; 95% CI)	>999.999 (0, ∞)	-
Crude Rate Difference per 100,000 person-days (95% CI)	1,376.63 (120.36, 2,632.90)	
Crude Risk Difference per 100,000 persons (95% CI)	105.60 (-101.48, 312.67)	
Myocarditis or Pericarditis, 28-day risk window		
Number of events	1	0
Number of person-days**	25,567.50	23,376.00
Rate per 100,000 person-days	3.90 (0.55, 27.74)	0.00 (0.00, 0.00)
Risk per 100,000 persons	109.29 (15.38, 776.69)	0.00 (0.00, 0.00)
Rate Ratio (vs. comparator; 95% CI)	>999.999 (0, ∞)	-
Risk Ratio (vs. comparator; 95% CI)	>999.999 (0, ∞)	-
Risk Difference per 100,000 person-days (95% CI)	3.90 (-3.75, 11.56)	
Risk Difference per 100,000 persons (95% CI)	109.29 (-105.03, 323.61)	
Crude Rate Ratio (vs. comparator; 95% CI)	>999.999 (0, ∞)	-
Crude Risk Ratio (vs. comparator; 95% CI)	>999.999 (0, ∞)	-
Crude Rate Difference per 100,000 person-days (95% CI)	1,376.63 (120.36, 2,632.90)	
Crude Risk Difference per 100,000 persons (95% CI)	105.60 (-101.48, 312.67)	
Encephalitis (Primary Definition), 42-day risk window		
Number of events	0	0
Number of person-days**	38,351.25	33,603.00
Rate per 100,000 person-days	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)

Risk per 100,000 persons	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
Rate Ratio (vs. comparator; 95% CI)	0.77 (0, ∞)	-
Risk Ratio (vs. comparator; 95% CI)	1.00 (0.91, 1.10)	-
Risk Difference per 100,000 person-days (95% CI)	0.00 (-, -)	
Risk Difference per 100,000 persons (95% CI)	0.00 (-, -)	
Crude Rate Ratio (vs. comparator; 95% CI)	0.88 (0, ∞)	-
Crude Risk Ratio (vs. comparator; 95% CI)	1.00 (0.93, 1.07)	-
Crude Rate Difference per 100,000 person-days (95% CI)	0.00 (0.00, 0.00)	
Crude Risk Difference per 100,000 persons (95% CI)	0.00 (-, -)	
Encephalitis (Broader Definition), 42-day risk window		
Number of events	0	1
Number of person-days**	38,351.25	33,603.00
Rate per 100,000 person-days	0.00 (0.00, 0.00)	2.96 (0.42, 21.07)
Risk per 100,000 persons	0.00 (0.00, 0.00)	109.29 (15.38, 776.69)
Rate Ratio (vs. comparator; 95% CI)	<0.001 (0, ∞)	-
Risk Ratio (vs. comparator; 95% CI)	0.00 (0.00, 0.00)	-
Risk Difference per 100,000 person-days (95% CI)	-2.96 (-8.78, 2.85)	
Risk Difference per 100,000 persons (95% CI)	-109.29 (-323.61, 105.03)	
Crude Rate Ratio (vs. comparator; 95% CI)	<0.001 (0, ∞)	-
Crude Risk Ratio (vs. comparator; 95% CI)	0.00 (0.00, 0.00)	-
Crude Rate Difference per 100,000 person-days (95% CI)	-195.36 (-2,048.55, 1,657.84)	
Crude Risk Difference per 100,000 persons (95% CI)	-21.12 (-62.52, 20.28)	
Anaphylaxis, 3-day risk window		
Number of events	0	0

Number of person-days**	2,922.00	2,556.75
Rate per 100,000 person-days	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
Risk per 100,000 persons	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
Rate Ratio (vs. comparator; 95% CI)	0.98 (0, ∞)	-
Risk Ratio (vs. comparator; 95% CI)	1.00 (0.91, 1.10)	-
Risk Difference per 100,000 person-days (95% CI)	0.00 (-, -)	
Risk Difference per 100,000 persons (95% CI)	0.00 (-, -)	
Crude Rate Ratio (vs. comparator; 95% CI)	0.99 (0, ∞)	-
Crude Risk Ratio (vs. comparator; 95% CI)	1.00 (0.93, 1.07)	
Crude Rate Difference per 100,000 person-days (95% CI)	0.00 (-, -)	
Crude Risk Difference per 100,000 persons (95% CI)	0.00 (-, -)	

CI = confidence interval; MSM = men who have sex with men
*Subjects in the vaccinated group were coarsened-exact matched with 5 unvaccinated comparator subjects who were unvaccinated at the time of match on calendar date, age, region, and insurance provider. Vaccinated subjects were subsequently 1:1 propensity score matched to unvaccinated comparator subjects to select a comparable matched sample of the analytic cohort. Prior to PS adjustment, there were 947 subjects in the vaccinated group and 4,735 subjects in the comparator unvaccinated group.
**Follow-up began on index date (first MVA-BN dose after meeting eligibility criteria between 1 August 2022 and 30 September 2022) and ended on the earliest occurrence of the outcome of interest, disenrollment, death, end of data availability, or end of the AESI-specific risk window. Additionally, unvaccinated subjects were censored upon cross-over to the vaccinated group upon receiving the first dose of MVA-BN vaccination.

8. Discussion

8.1. Key Results

8.1.1. Vaccine Effectiveness

Overall, 978 subjects met the study eligibility criteria, of which 163 subjects were fully vaccinated (received 2 doses at least 28 days apart, 14 days prior to ID_E) and coarsened-exact matched to 815 comparator subjects. SMR weighting was applied to weight the unvaccinated comparator group to be similar to the fully vaccinated group, creating a comparable pseudo-population for the assessment of vaccine effectiveness outcomes. After SMR weighting was applied, a vaccination group of 163 subjects and a weighted pseudo-population of 159.85 with an effective sample size of 303 remained for analysis. The population was majority <45 years old, commercially insured, and largely represented the Western region of the United States. Majority of subjects had HIV diagnosis during baseline (65.0% in the fully vaccinated group and 67.0% in the unvaccinated comparator

group). Approximately ⅓ of subjects in the fully vaccinated and unvaccinated comparator group used PrEP (29.5% and 28.6%), had evidence of autoimmune disease or non-HIV immunocompromised conditions (28.2% and 27.7%), and comorbidities (27.6% and 27.7%) during baseline. Fewer than 10% of subjects in both groups had a history of STD during baseline.

In the fully vaccinated group (2 doses 14 days prior to ID_E), MVA-BN vaccination was 89% (95% CI 12%, 99%) effective against mpox disease . Similarly, full MVA-BN vaccination was 89% (95% CI 12%, 99%) effective against all potential mpox infections. This demonstrates vaccine effectiveness with respect to mpox disease among our study population. A sensitivity analysis using an alternative definition of mpox disease (using the orthopox PCR test CPT code) was conducted to evaluate the robustness of the vaccine effectiveness results. Results using sensitivity definition of mpox disease show that 2-dose vaccination was 53% (95% CI -397%, 96%) effective, however the precision of vaccine effectiveness estimates were improved when using the primary definition more so than when using the sensitivity definition.

Full MVA-BN vaccination was 7% (95% CI -1,402%, 94%) effective against hospitalisations related to mpox disease and was -1% (95% CI -72%, 41%) effective against all-cause hospitalisations or death among the fully vaccinated group compared to the unvaccinated group, however, 95% confidence interval ranges were wide.

Vaccine effectiveness outcomes were assessed among HIV status and treatment subgroups of the fully vaccinated and unvaccinated comparator cohort. Majority of the fully vaccinated group were HIV+ and antiretroviral users (63.8%). Among the fully vaccinated HIV+ antiretroviral users, 2-dose vaccination was 71% (95% CI -162%, 97%) effective against mpox disease, although confidence levels were wide. The HIV+ and no antiretroviral use subgroup may comprise immunosuppressed subjects at highest risk of mpox disease. Events among the unvaccinated comparator subjects within this subgroup have the potential to bias vaccine effectiveness estimates in the overall group, as there were 0 vaccinated subjects in this high-risk subgroup. However, among the 139 unvaccinated subjects within the HIV+ untreated subgroup, there were 2 (16.8%) mpox events which contributed to the total of 12 events in the overall comparator unvaccinated group. For secondary outcomes, the HIV+ untreated subgroup had the only hospitalisation related to mpox disease event of the overall comparator unvaccinated group, 13 all-cause hospitalisation or death events out of the total 92 events in the overall comparator unvaccinated group, and 0 potential hospitalisations for mpox infection.

8.1.2. Safety

There were 5,682 total subjects who met the study eligibility criteria for the safety cohort, of which 947 subjects were vaccinated (had at least 1 record of an MVA-BN vaccine administration) and coarsened-exact matched to 4,735 comparator subjects. After the application of PS matching, there were 915 subjects in each group. In the PS matched cohort, subjects were majority <45 years old, commercially insured, and largely

representative of the Western region of the United States. A large proportion of subjects had missing race information (40.2%). Most subjects had an HIV diagnosis during baseline (60.5% in the vaccinated group and 64.2% in the unvaccinated group). Almost ⅓ of subjects in both groups had PrEP use during baseline (28.9% in the vaccinated group and 26.1% in the unvaccinated group). Among those with PrEP use during baseline, average time from first PrEP treatment in baseline to ID_S was approximately 9 months. There were 22.4% and 23.6% subjects with evidence of autoimmune conditions or non-HIV immunocompromised conditions in the vaccinated and unvaccinated comparator group, respectively. Approximately ⅓ of subjects in both groups had comorbidities during baseline (27.7% in the vaccinated group and 28.4% in the unvaccinated group). Overall, there were <5 subjects with history of myocarditis, pericarditis, encephalitis, or anaphylaxis during the baseline period in either group.

Using primary risk windows across all safety outcomes, there were no outcome events in either vaccinated or unvaccinated comparator group. When using sensitivity risk windows, 1 pericarditis event was identified in the vaccinated group using a 28-day risk window (3.90 cases per 100,000 person-days). A broader ICD-10-CM definition was used to define encephalitis as a sensitivity analysis, which identified 1 outcome event among the unvaccinated comparator group (28-day risk window: 4.27 cases per 100,000 person-days, 42-day risk window: 2.96 cases per 100,000 person-days), but no events among the vaccinated group.

8.2. Interpretation

In a previous study of persons aged 15-64 years old in the U.S. between 10 May 2022 and 31 December 2022, the overall incidence of mpox was reported to be 13.5 per 100,000 persons. Among 2,391 cases reported through 2022 of July, 94% of cases of mpox in the U.S. reported recent male-to-male sexual or close intimate contact (44,45). In our study, the incidence of mpox among the at-risk population of MSM and transgender women was much higher than the reported overall incidence of U.S. adults at 6,885 cases per 100,000 persons. While these findings demonstrate that the outbreak has disproportionately impacted the MSM and transgender women population, it is also possible that the MSM algorithm used to define the at-risk population in our study identified those who are likely to be at high risk for mpox, such as those with a diagnosis for HRSB and HIV.

Our primary results are consistent with existing real-world evaluation of vaccine effectiveness of MVA-BN vaccination against mpox in the United States. A multijurisdictional case-control study found vaccine effectiveness of 86% among fully vaccinated MSM and transgender adults (46). A study conducted using U.S. electronic health record (EHR) data reported vaccine effectiveness of 66% among fully vaccinated and unvaccinated comparator subjects (47). Another study conducted in New York State among men diagnosed with mpox compared to negative controls with rectal gonorrhoea or primary syphilis found 2-dose vaccine effectiveness of 76% (48). MSM or transgender women in our study had 2-dose vaccine

effectiveness of 89%, although our sample size was smaller compared to these studies and It is also important to note that our study population was defined differently, using specific criteria (see Section 6.3.3), however our findings support existing evidence that completing the second dose according to the MVA-BN vaccine schedule is associated with reduced risk of mpox disease among MSM and transgender women in the HealthVerity dataset within our study period.

Sensitivity analyses of vaccine effectiveness among recipients of a single dose of the MVA-BN vaccine was consistent with existing knowledge of single dose vaccine efficacy of the MVA-BN vaccine. Previous studies have shown that a single dose of the MVA-BN vaccine yields strong protection against mpox infection 14 days after the first dose, with vaccine effectiveness ranging from 78-86% among high risk populations (23,49). A key difference in our analyses is that our sensitivity analyses of vaccine effectiveness of single-dose MVA-BN vaccination began follow-up starting 1 day after vaccination, which means outcome events observed in our analyses could have occurred prior to reaching the maximum protective effect of the vaccine which occurs 14 days after vaccination.

Safety outcomes pericarditis, myocarditis, encephalitis, and anaphylaxis were identified as potential risks for the MVA-BN vaccine at the time of the initial EU Risk Management Plan approval, and outcomes were assessed among those receiving 1 dose of the MVA-BN vaccine and matched comparator subjects identified between 1 August 2022 and 30 September 2022. In our study, there were no safety events associated with the MVA-BN vaccine, with the exception of 1 pericarditis event in the 28-day risk window following vaccination (109 cases per 100,000 persons). Although there were no confirmed cases of myocarditis or pericarditis in completed clinical trials for IMVANEX, smallpox vaccines are associated with a rare risk of myocarditis and pericarditis among healthy adult vaccines (573 per 100,000 primary vaccines) (25).

Vaccination is not recommended for those with a history of anaphylaxis or severe allergic reactions to any component of the MVA-BN vaccine. Those with prior history of anaphylaxis or severe allergic reactions were excluded from pivotal and supporting clinical trials (25). In our study, those with anaphylaxis during baseline were not excluded, and there was 1 subject in the vaccinated group with history of anaphylaxis during baseline. It is possible that MSM and transgender women who are at high risk of anaphylaxis postponed their vaccination per CDC guidelines or did not receive a vaccination (50). In either vaccinated or unvaccinated comparator groups, there were no anaphylaxis events during follow-up when assessed using a 1-day and 3-days risk window.

Lastly, although there were no cases of encephalitis observed with IMVANEX in the clinical trials, the safety outcome was included in this study given the risk of encephalitis among smallpox vaccine recipients (12.3 per 1 million vaccinations) (44). Using a specific definition of encephalitis did not capture subjects with an outcome event, however, when using a broader definition of encephalitis that includes non-specific ICD-10-CM codes for encephalitis (i.e., G36.9, G37.3, and G37.9), there was 1 subject identified in the unvaccinated comparator group with an event in the 28 days

after ID_S. These additional codes may have potentially captured an event that is non-specific to encephalitis, such as unspecified acute disseminated demyelinating disease or broader codes that may capture other diseases relating to the central nervous system.

8.3. Limitations

The following limitations and their potential impact have been considered when interpreting the study results:

Accuracy of the MSM algorithm:

Unlike prospective studies, claims data are ascertained for insurance billing purposes, and information on sexual orientation and gender identity were not available within the HealthVerity data at the time of this study. Due to the unavailability of information, a claims-based proxy was used to identify MSM and could lead to the potential misclassification or mis-gendering of subjects in the study population. MSM who are at risk of mpox may not have a medical or pharmacy claim during the study period that qualifies for the claims-based proxy definition, and are therefore excluded from this study, which may bias our study population towards those who are more likely to encounter the healthcare system. Furthermore, it is possible that the criteria used to identify MSM and transgender women in the HealthVerity dataset is too exclusive - one of the criteria used to define MSM or transgender women in the at-risk population is the evidence of PrEP therapy and no history of substance use disorder. This criterion was included as part of the clinical indications for PrEP given that substance use disorder may affect sexual risk behaviours as well as medication adherence, and possibly modifies the risk of acquiring STDs (including HIV). An unintended limitation of this criterion is that this may exclude MSM and transgender women who are at high risk of mpox, such as those who engage in chemsex. It is unclear how well the algorithm used in this study captures the intended MSM and transgender women population in the U.S. In particular, ICD-10-CM code for “high risk heterosexual behaviour” (Z72.51) was used to capture the indication of high risk sexual behaviour and qualified subjects for entry into the overall MSM and transgender women cohort. While there is differential potential to misclassify subjects who are not truly MSM or transgender women for inclusion in the overall cohort thereby limiting the generalizability of findings, the potential for misclassification is mitigated in the analytic sub-cohort. Misclassification of subjects who are vaccinated is unlikely given the assumption that they were indicated to receive the vaccine, however it is more likely that misclassification occurred in the unvaccinated group. The two-step process to select the analytic cohort by first performing coarsened-exact matching to match subjects with similar demographics who are unvaccinated on the same calendar day as their vaccinated match and then performing PS adjustment to ensure that the unvaccinated subjects are comparable to the vaccinated subjects mitigates the potential for misclassification in the analytic cohort. Prospective studies that use survey data regarding gender identity and high-risk sexual behaviours should also be considered when evaluating the evidence generated from claims data studies. HealthVerity is a de-identified claims-based data source and in addition to a lack of information on sexual orientation and gender identity, there is no clinical notes or other documentation that could be utilised to validate the MSM and transgender algorithm used for this study.

Small sample size:

There were fewer eligible vaccinated MSM and transgender women identified in the HealthVerity dataset than anticipated during preliminary stages of this study. For the assessment of vaccine effectiveness, a large proportion of subjects (99.5%) in the HealthVerity data did not meet the entry criteria of having a second MVA-BN dose ≥ 28 days apart and continuously enrolled ≥14 days after the second dose during the study period. 84.7% of subjects in the dataset did not meet the entry criteria of having 1 dose of MVA-BN vaccination during the study period. In the US, the mpox vaccines are available at no or minimal cost to the vaccine recipient and are only available from the local health department or, in large cities, in public health clinics, hospitals, or at large social gatherings or venues (33). These facilities and services in the U.S. do not always bill or submit for reimbursement, thus vaccination status in RWD may be underreported and individuals misclassified as unvaccinated. The sample size required to adequately power the comparative analyses was limited by the number of MSM and transgender women vaccines we were able to identify who met the cohort eligibility requirements during the study period and had complete data captured on their covariates in the HealthVerity dataset. At the time of protocol development, sample size calculations were performed based on projections of potential spread and were limited by the ability to capture the underlying rate given the lack of understanding about the disease due to its novelty and recency of the outbreak. Despite being underpowered, these results provide important information that contributes to the totality of evidence of the vaccine effectiveness and safety of MVA-BN vaccine (50).

Specificity of the case definition for outcomes:

Claims databases are primarily collected for reimbursement purposes rather than research, and therefore are prone to incomplete or inaccurate coding of diagnoses (including comorbidities and outcomes), leading to potential misclassification. For instance, the presence of a diagnosis code may not indicate the presence of a disease, but rather a rule out diagnosis. Absence of a diagnosis code may not be indicative of absence of disease. The presence of a claim for a filled prescription does not provide any information on adherence or persistence to treatment. The claim does not indicate that the medication was consumed or that it was taken as prescribed, and any medications filled over the counter or provided as samples by the physician cannot be observed in the claims data. Misclassification of the exposure may have occurred if any subjects in the unvaccinated group received the MVA-BN vaccination in a setting that was unable to be captured in our dataset, which could have underestimated mpox cases among the unvaccinated group and thus the underestimation of vaccine effectiveness in our study. There is a risk of misclassification by using such approaches that may exist given the nature of the data and lack of studies providing validated algorithms to identify mpox diagnosis in secondary data. There could also be misclassification/misattribution of the hospitalisations due to mpox events, as they are required to happen in a period around this hospitalisation but might not necessarily be the cause of it.

Safety outcomes were defined using available algorithms that have been validated in prior vaccine studies, however, ICD-10-CM codes used to define safety outcome events may have potentially captured an event that is non-specific to the safety event of interest, such as broader codes that may capture other diseases relating to the condition. Results from prospective studies or registry data in which safety signals are reported to the pharmacovigilance authorities should be considered in tandem with the results of secondary healthcare data studies to fully evaluate the public health impact of vaccinations.

Cohort attrition due to insurance provider

Claims data are sourced from healthcare insurance providers and primarily collected for reimbursement purposes rather than research. Therefore, there are limitations when applying exclusion criteria based on enrollment. Only patients who were enrolled during the study period and had information regarding insurance providers were included. This inclusion criteria implies that some information regarding vaccination status or mpox occurrence may be unattainable based on the study selection criteria. Observability may be reduced given these criteria. Generalizability of results beyond patients who have continuous insurance coverage in the United States may be potentially limited.

Potential for residual confounding

Although best practices were applied to control for confounding, the potential for residual confounding still exists in observational cohort analyses. However, coarsened-exact matching was used to control for time-related biases, which are assumed to be strong given the evolving healthcare landscape of the mpox epidemic. Furthermore, we additionally used propensity score adjustment to control for confounding due to measured covariates. Although factors causing residual confounding may manifest after index if there are changes in a subject's behaviour (e.g., sudden increase in sexual partners indicated by an increase in STDs during follow-up), this study does not account for factors after index date to avoid potential bias that may be induced by conditioning on mediating variables in the causal pathway, or on colliders.

8.4. Generalizability

Studies using data from insurance claims are subject to some common limitations. As with all claims database studies, this study relies on the accuracy of diagnosis codes and NDC codes contained in the claims data. In the absence of verification via chart review, these data are subject to misclassification of diagnosis, comorbidities, or study outcomes. Study inclusion was based on a large, non-random sample of MSM or transgender women in the U.S. identified by a claims-based algorithm, which may be prone to biases or lack generalizability to other populations. Furthermore, as with all claims-based analyses, study results may not be generalizable to the overall population or patients without health insurance. Subjects are required to meet pre-index enrolment criteria, and therefore, results from this study may not be generalizable to patients with no coverage or

shorter coverage. Additionally, results may not be generalizable to the overall MSM and transgender population in the U.S due to the limited sample size.

9. Conclusions

Results from this retrospective, comparative real-world study were consistent with existing evaluation of vaccine effectiveness of MVA-BN vaccination against mpox in the United States and suggest that completing the second dose according to the MVA-BN vaccine schedule is associated with reduced risk of mpox disease among MSM and transgender women in the HealthVerity dataset within our study period. One pericarditis event was identified within our study population in a sensitivity analysis using an alternate risk window (28 days). Further studies with increased sample size are warranted to ensure further pharmacovigilance of safety signals.

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Appendix A: Code List Definitions

See attachment.