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Center for Biologics Evaluation and Research
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CBER Surveillance Program

Safety Surveillance of Vaccines Used for Mpox Prevention: Active Monitoring Master Protocol

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VERSION CONTROL

Version	Description	Date
v1.0	Protocol to describe methods for descriptive safety monitoring of vaccines used to prevent mpox	12/16/2022

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1. Objectives

The objective of this protocol is to describe the methods for active descriptive monitoring of adverse events (AEs) following administration of vaccines used to prevent mpox infection. These AEs are health conditions identified to be potentially associated with this vaccination. Active monitoring allows us to assess vaccine exposures and potential adverse events, determine if more comprehensive analyses should be conducted, and provide timely information to support regulatory decision-making processes.

2. Background and Overview

Mpox infection is caused by the monkeypox virus. It is characterized primarily by a painful multi-staged rash that can last 2–4 weeks and develops 3–17 days after exposure to the monkeypox virus.[1] The monkeypox virus belongs to the *Orthopoxvirus* genus. This genus contains other viral species including variola virus (i.e., the virus that causes smallpox infection) and vaccinia virus (i.e., the virus used in some smallpox vaccines).[2] The monkeypox virus is endemic to parts of western and central Africa but, until recently, has not spread widely in other parts of the world.[3]

The 2022 mpox outbreak began in early May 2022 and has spread to more than 50 countries, including several which have not historically reported mpox cases.[4] The United States (U.S.) reported its first case of mpox in the 2022 outbreak in mid-May, 2022 and had over 29,000 reported cases and 20 deaths as of December 7, 2022.[5] As of the writing of this protocol, cases of mpox in this outbreak, in the U.S. and elsewhere, are largely concentrated among men who have sex with men.[6] In addition, almost 88% of all U.S. cases (as of December 7, 2022) have occurred in people 21–50 years of age.[7]

There are currently two orthopoxvirus vaccines available for the prevention of mpox. The JYNNEOS vaccine is a two-dose vaccine containing the Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN) strain—a live, attenuated, non-replicating orthopoxvirus.[8] It was licensed by the U.S. Food and Drug Administration (FDA) in 2019 for the prevention of mpox and smallpox in adults ≥18 years of age. Doses are 0.5 mL and are administered subcutaneously at least 4 weeks apart.[9] In addition, on August 9, 2022, FDA issued an emergency use authorization (EUA) which allowed the two-dose JYNNEOS series to be administered in 0.1 mL doses intradermally at least 4 weeks apart among adults ≥18 years of age. The EUA also allowed the two-dose JYNNEOS series to be administered in 0.5 mL doses subcutaneously to people <18 years of age.[9,10] The second orthopoxvirus vaccine, ACAM2000, contains a live, attenuated, replicating strain of the vaccinia virus and was licensed by FDA in 2007 for the prevention of smallpox infection in populations at risk of smallpox infection.[11] ACAM2000 is a single 0.3 mL dose vaccine and is administered percutaneously with 15 jabs using a bifurcated needle. Although JYNNEOS is the only vaccine licensed for prevention of mpox, ACAM2000 can be used to prevent mpox under the Expanded Access Investigational New Drug (IND), which requires informed consent and other requirements.

In response to the 2022 mpox outbreak, the U.S. government announced a national vaccine strategy, which included deployment of JYNNEOS vaccines from the U.S. Strategic National Stockpile (SNS) to prevent mpox infection for communities and individuals at highest risk of infection. Although ACAM2000 is available for use to prevent mpox infection through the Expanded Access IND mechanism, it has known severe adverse effects and is not recommended for use in all populations.[12] ACAM2000 has been

available from the SNS to jurisdictions only by special request. Consequently, the JYNNEOS vaccine is the primary vaccine used in the outbreak to date.

The Centers for Disease Control and Prevention (CDC) has recommended vaccination for those with known or presumed exposure to mpox (i.e., post-exposure prophylaxis or expanded post-exposure prophylaxis). At the end of September 2022, the agency expanded vaccination recommendations to pre-exposure prophylaxis for those at highest risk.[13] As of December 9, 2022, the Administration for Strategic Preparedness and Response (ASPR) reported 857,393 doses of the JYNNEOS vaccine have been shipped to jurisdictions.[14]

To monitor JYNNEOS vaccine safety, we will conduct active monitoring in large healthcare commercial insurance claims databases. We will generate descriptive statistics of vaccination and outcome counts monthly for the AEs following vaccination. If vaccine uptake increases or a possible safety concern is identified, we may complete additional activities and amend this protocol to conduct signal detection and/or evaluation activities. Such activities could include rapid cycle analysis or other epidemiologic studies. Currently, ACAM2000 is only deployed in limited capacity. As such, only descriptive counts of ACAM2000 will be included. If ACAM2000 uptake increases, we will descriptively monitor adverse events in a similar framework as the JYNNEOS vaccine.

3. Data Sources

The current study will include the following commercial insurance databases: CVS Health Clinical Trial Services (CVS Health), Optum, and HealthCore, Inc. (HCI). Table 1 below briefly outlines currently available administrative claims data sources and displays how often each data source is updated.

Table 1. Data Source Characteristics

Data Source	Claims Type	Update Frequency	Data Lag*	Population Enrolled Ages 18-64 Years**
CVS Health	Fully Adjudicated	Monthly	Approximately 80% data completeness in 3-4 months for inpatient claims, 2-3 months for outpatient claims, and 1-2 months for professional claims	18-25 years: > 2.7 million 26-35 years: > 3.2 million 36-45 years: > 2.9 million 46-55 years: > 2.8 million 56-64 years: > 2.5 million
Optum	Pre-Adjudicated	Bi-Weekly	Approximately 80% data completeness in 1-2 months for inpatient, outpatient, and professional claims	18-25 years: > 1.6 million 26-35 years: > 2.5 million 36-45 years: > 2.5 million 46-55 years: > 2.4 million 56-64 years: > 2.0 million

Data Source	Claims Type	Update Frequency	Data Lag*	Population Enrolled Ages 18-64 Years**
HCI	Fully Adjudicated	Monthly	Approximately 80% data completeness in 2-3 months for inpatient claims and 1-2 months for outpatient and professional claims	18-25 years: > 3.2 million 26-35 years: > 3.7 million 36-45 years: > 3.6 million 46-55 years: > 3.6 million 56-64 years: > 3.2 million

** Data lag can vary by outcome; we will produce outcome- and setting-specific delay profiles.*

*** Enrollment numbers for CVS Health and HCI from 2021; enrollment numbers from Optum from 2020*

CVS Health data includes enrollment, demographic, and medical and drug claims data, for individuals enrolled in Aetna commercial and Medicare Advantage health plans. The CVS Health data contains, on average, about 22 million individuals annually and is updated monthly with a data lag of approximately 1 week for drug, 6 weeks for outpatient, and 12 weeks for inpatient claims for over 80% of claims.

HCI data includes medical and pharmacy claims drawn from commercially insured individuals enrolled in Anthem health plans. On average, the HCI data contains approximately 20-25 million unique individuals annually, with approximately 80% data completeness within 2-3 months for inpatient claims and 1-2 months for outpatient and professional claims.

Optum data includes enrollment, prescription drug and pre-adjudicated hospital and physician health insurance claims for commercially insured and Medicare Advantage enrollees. The pre-adjudicated claims have an approximately two-month delay for 90% completeness for inpatient claims and over 70% completeness at one-month for outpatient claims.

Vaccines that are administered during a public health emergency, such as the JYNNEOS vaccine, may be administered by public health agencies in health departments or other public venues and may not be captured in commercial insurance claims databases. To ensure more complete capture of vaccines, insurance databases may include both administrative claims data as well as data linked to Immunization Information System (IIS) vaccination data. IISs are population-based vaccine registries that are operated by local and state public health agencies to record vaccinations administered in various settings. The FDA Biologics Effectiveness and Safety (BEST) Initiative, through its data sharing network, facilitated linkage of claims data with several local and state IISs to enhance capture of vaccinations in commercially insured populations for vaccine surveillance studies.[15]

4. Safety Monitoring in Claims Databases

To provide characterization of the patterns of vaccine utilization and incidence of adverse events following JYNNEOS doses, we will conduct active monitoring in available commercial insurance claims data sources.

4.1 Study Population

The study population will be people 18–64 years of age who received at least one dose of JYNNEOS or ACAM2000 vaccines during the study period who were also enrolled in a commercial health insurance

plan covered in one of the three claims databases previously described (i.e., CVS Health, Optum, and HCI). Participants will enter the study cohort at the first vaccine dose. For inclusion in the adverse event-specific analysis population, continuous enrollment in a medical insurance plan is required from the start date of the clean window (i.e., vaccination date minus the length of the clean window) through the date of vaccination. People in the study population are also required to have birth date information.

4.2 Study Period

The study period will be from May 10, 2022, the date of the first known U.S. case of mpox, until it is deemed no longer necessary by FDA.[16]

4.3 Exposure

Vaccine exposure is defined as receipt of any dose of the JYNNEOS or ACAM2000 vaccines, as identified by product codes such as Current Procedural Terminology (CPT)/Healthcare Common Procedure Coding System (HCPCS) codes, National Drug Codes (NDCs), and CVX codes, in all settings. If additional vaccines are approved or authorized for use, they will be included in analyses. The list of valid codes will be continuously reviewed and updated if new codes are added (code list posted as supplemental materials).

4.4 Outcomes

A list of pre-specified potential AEs following JYNNEOS administration (Table 2) will be used for active monitoring. Considerations in the selection of these potential AEs included serious events that have followed other immunizations and events known or possibly related to smallpox vaccination or the vaccine platform.

AEs were defined using claims-based algorithms based on literature reviews, consultations with clinical experts, and previous studies. The care settings in which each AE will be evaluated, as well as the clean (i.e., washout), and risk windows for each are described in Table 2. The first qualifying occurrence of the event in the observation period is defined as an incident AE only if no event of the same type was recorded during the preceding pre-defined clean window. Persons with an event in the clean window will be excluded from the relevant outcome analysis, because subsequent outcomes captured post-vaccination may be prevalent rather than incident outcomes. The risk window is defined as an interval post-vaccination during which occurrence of the AE may be associated with the vaccine exposure and thus considered a qualifying outcome. Clean and risk windows were selected based on the literature review and consultation with subject matter experts.

Table 2. Potential AEs, age groups, healthcare settings, clean windows, and risk windows

AE	Age Group of Interest	Healthcare Setting	Clean Window	Risk Window
Acute Myocardial Infarction	All	IP	365 days*	1-28 days[17,18]
Anaphylaxis	All	IP, OP-ED	30 days*	0-1 day[19,20]

AE	Age Group of Interest	Healthcare Setting	Clean Window	Risk Window
Bell's Palsy	All	IP, OP/PB	183 days*	1-42 days[21]
Cardiomyopathy	All	IP, OP-ED	365 days	1-42 days
Deep Vein Thrombosis (DVT)	All	IP, OP/PB	365 days*	1-28 days[22-24]
Encephalitis/Myelitis /Encephalomyelitis	All	IP	183 days*	1-42 days[25]
Guillain-Barré Syndrome	All	IP- primary position only	365 days*	1-42 days[26,27]
Myocarditis/Pericarditis	All	IP, OP-ED	365 days*	1-21 days 1-42 days[28]
Non-hemorrhagic Stroke	All	IP	365 days*	1-28 days[17,18]
Pulmonary Embolism[#] (PE)	All	IP	365 days*	1-28 days[22-24]
Transverse Myelitis	All	IP, OP-ED	365 days*	1-42 days[29]

Definitions: Clean Window is an interval used to define incident outcomes where an incident outcome is counted only if the AE did not occur during the defined pre-vaccination interval. Risk Window is an interval during which occurrence of the incident AE will be included in the analysis.
Setting Definitions: IP refers to inpatient facility claims. OP-ED refers to a subset of outpatient facility claims occurring in the emergency department. OP/PB refers to all outpatient facility claims, and professional/provider claims except those professional/provider claims with a laboratory place of service.
** References for the duration of these windows could not be located in the literature and are instead based on input from clinicians.*
[#] If an individual has both DVT and PE (i.e., the DVT progressed to PE), the case will be de-duplicated in analyses and assigned only PE. The PE onset date is determined by the date the PE code is reported in the database.

4.5 Descriptive Analyses

We will use descriptive statistics to summarize the observed vaccinations for both ACAM2000 and JYNNEOS vaccination in the study population. We will additionally monitor incident outcomes occurring during the risk window following JYNNEOS vaccination. Monitoring of AEs for the ACAM2000 vaccine will not be conducted at this time due to the very low utilization of the vaccine in the U.S. We will present the following statistics:

- The number of observed JYNNEOS and ACAM2000 doses, and the overall number of doses over time (by month). Vaccines observed from IIS data will be summarized by jurisdiction;
- The number of observed incident adverse events in the risk window following JYNNEOS doses (but not ACAM2000 doses);
- The observed proportion of incident AEs, calculated as the number of incident outcomes per JYNNEOS vaccinated persons; and
- The observed rate of adverse events following JYNNEOS doses, calculated as the number of incident outcomes per 100,000 person-years, where person-time is defined as the summation of

time all participants were at risk of the outcome during the post-vaccination risk window. Participants stop contributing dose-specific person-time to an AE analysis when they experience an AE, death, disenrollment, a subsequent JYNNEOS or ACAM2000 dose, or the end of the risk window.

Given analyses will be conducted using partially accrued data, the entirety of a risk window may not have elapsed by the time a subsequent vaccination claim is observed. Multiple doses observed within 0-3 days of one another will be grouped into a single dose.

Separate analyses will be conducted for all, first, and second doses. If a person receives a second dose during their first dose risk window, the first dose risk window will be truncated on the day of second dose receipt. For example, the risk window of a person who received a first dose on day 0 and a second dose on day 28 would be truncated after 27 days for all outcomes with a pre-specified risk windows ≥28 days.

These statistics will be additionally stratified by sex, age, age and sex, U.S. Department of Health & Human Services (HHS) region, health care setting, and data source. Descriptive statistics will be updated monthly. An example table representing the proposed descriptive statistics can be found below in Tables 3 and 4.

Table 3. Example table of vaccine counts stratified by brand, age, and dose

	Brand					
Characteristic	**All Doses**	**All Doses**	**First Dose**	**First Dose**	**Second Dose**	**Second Dose**
	#	**%**	**#**	**%**	**#**	**%**
Total						
Sex						
Female						
Male						
Age						
18-25						
…						
56-64						
Age*sex						
18-25						
…						
56-64						

Note: Separate tables will be provided for each Data Partner.

Table 4. Example table of JYNNEOS descriptive statistics stratified by outcome and dose

Characteristic	Outcome [1]			
	JYNNEOS Dose [#]			
	# of JYNNEOS doses	Person-Years	# Observed Outcome	Rate per Person-Year
Age*sex				
18-25				
…				
56-64				
HHS Region				
[Region 1]				
[Region 2]				
…				
[Region N]				
Urban/Rural				
Urban				
Rural				
Missing				
Facility/Provider Type				
Hospice				
Office				
Pharmacy				
Skilled Nursing Facility				
Home Health Agency				
Mass Immunization Center				
Other				
Missing				

Note: Separate tables will be provided for each Data Partner.

5. Quality Assurance

The study will be conducted using well-characterized databases, in which the study team members have conducted numerous epidemiologic studies. The study team has assessed these databases for quality and suitability for epidemiologic studies by executing checks examining the validity of claims data variables, stability of enrollment and health event trends, and consistency with population selection criteria for the database, if any.

During active monitoring, data quality will be continuously monitored with every update from the study databases in order to ensure that insurance claims representing vaccinations and AEs are captured accurately. As an overall check, the total number of claims newly observed in each data cut will be

counted and stratified by care setting and HHS region. If substantial increases or decreases in the rate of claims accrual relative to previous cuts are observed, we will implement steps to trace the potential causes of the discrepancy.

Well-established and validated software such as SAS version 9.4 and R will be used for statistical analyses. Programs will be developed under version control and changes to programs or other specifications will be tracked (e.g., updates to code lists due to new diagnosis codes). Procedures such as regular code reviews will be used to ensure integrity of statistical analyses.

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