"Cause of RASHes in the Emergency Department" – CRASHED Project
Subtitle: Examining the Prevalence, Clinical Characteristics, and Treatment of Mpox in U.S. Emergency Departments Participating in *EMERGE*ncy ID NET

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1.0 Protocol Summary

Project Purpose	We propose to conduct Mpox surveillance in the emergency department (ED) setting, which is unique in being broader-based and more likely to reach medically disadvantaged and socially vulnerable groups than surveillance for Mpox among recognized high-risk individuals presenting to sexually transmitted infections (STI), HIV, and LGBTQ+ clinics. This project may suggest that Mpox has been largely eradicated, or possibly resurged and/or that risk factors have evolved, which would impact ongoing public health efforts to control the spread of this infection. Our results will justify additional systematic efforts to conduct US ED surveillance through coordinated networks, such as *EMERGE*ncy ID NET.
Project Design	This will be a two-phase project with the first phase being a 1-month pilot project conducted at 3 Los Angeles EDs to develop, test, and refine data collection methods followed by a second phase that will be a 6-month large scale national surveillance project conducted at *EMERGE*ncy ID NET sites. Patients age >3 months presenting with a pustular, vesicular, crusted, or ulcerated skin rash will be enrolled and consented in the ED. During the ED visit, the site coordinator will record responses from the participant and their treating clinician about the participant's illness, and the participant will be asked to allow collection of specimens obtained by swabbing the rash(s) (i.e., 2 swabs). The site coordinator will also obtain two digital pictures of the rash sites that are swabbed. Participants ages ≥16 years of age will also be asked to complete a self-administered questionnaire about their sexual orientation, gender identity, and recent sexual behavior. After the ED visit, the site coordinator will review and abstract data from their medical record about their visit and outcomes. The site coordinator will contact the participant at 45 days to ask them about the outcome of their illness and healthcare utilization. For participants who test positive for Mpox during the project period, the site coordinator will conduct another medical record review at 45 days to capture additional healthcare utilization. Participants who test positive for Mpox and still have symptoms at 45 days will be called again at 90 days to ask about any additional healthcare utilization and the site team will conduct another medical record review at 90 days.

Participant Population	The project will enroll ED patients age >3 months who present for evaluation of a skin lesion that is pustular, vesicular, crusted, or ulcerated. This approach will allow the inclusion of populations that may have been underrepresented in Mpox surveillance, including women, children, homeless, immigrant, minorities, and individuals with low-income.
Duration of Participant's Participation	The duration of participation is 45 days for most participants but for those that test positive for Mpox and still have symptoms at 45 days, they will participate for 90 days, although the actual project-related time spent by the participant in those 90 days will be about one hour.
Duration of project enrollment	The first phase of the project will be initiated in March 2023 and will continue for one month. The second phase of the project involving the other sites will be initiated in April 2023 and will continue for six months in order to capture US community Mpox activity in the spring and summer months of 2023.

2.0 Background, Rationale

The Mpox outbreak of 2022 has implications for people in the U.S. and across the globe.[1] As of November 29, 2022, the U.S. has confirmed 29,325 cases,[2] and 2,387 of these were in LA County.[3] While most Mpox infections resolve without causing chronic morbidity or mortality, the CDC provided consultation for 57 hospitalized patients between August and October of 2022. Most of these patients were black men with Acquired Immune Deficiency Syndrome (AIDS). Twelve of the 57 patients died, and delayed diagnosis was cited as a contributing factor.[4]

Clinicians decide to test a patient for Mpox if the patient has risk factors and a compatible rash. CDC describes that risk factors for Mpox infection include: travel to a country with recent cases, close or intimate contact with someone with Mpox infection or suspicious rash, or close or intimate contact with someone in a social network experiencing Mpox infection or suspicious rash.[5] The vast majority (98%) of diagnosed cases have occurred among gay, bisexual, and other men who have sex with men (MSM),[6] and the CDC suggests that infected men are likely to have participated in specific sex activities (e.g., sex with someone they met on dating apps; sex with multiple partners at commercial sex venues or events where anonymous sex is common).[5] Signs and symptoms of Mpox include: (1) rash on any part of the body, which is often maculopapular, vesicular, and/or pustular; and (2) a viral syndrome, such as fever, headache, malaise, chills, and lymphadenopathy.[7] Patients with unknown or unsolicited risk factors are likely to experience missed or delayed diagnoses, which may lead to continued community spread.

EDs act as the front line of defense for emerging infectious diseases, and Mpox is no exception, since early evidence suggests that 20% of all cases are diagnosed in EDs.[6] However, routine surveillance for emerging infectious diseases is rarely conducted in EDs.[8]

The mandate to use surveillance in EDs to identify public health threats and protect our communities is more apparent than ever before, since emerging infectious diseases disproportionately affect vulnerable patients such as persons with HIV (PWH) and historically under-represented groups.[9-11] Furthermore, the risk factors for Mpox infection are not well-delineated, especially since this extra-African outbreak has different features than what has historically been described.[12]

We are proposing to conduct a surveillance project to test as many patients as possible who have rashes that could be due to Mpox infection based on rash appearance alone. We suspect that despite decreasing rates of diagnosis of Mpox nationwide, we will continue to identify cases, and some of these cases will be among patients with yet to be identified risk factors.

The primary objectives of this project are to determine the prevalence of Mpox in the ED population, describe presenting symptoms and signs, characterize community risk factors for infection, and describe patients' health outcomes.

3.0 Project Population

3.1 Inclusion Criteria

- The project will enroll ED patients age ≥3 months who present for evaluation of one or more skin lesions that appears pustular, vesicular, crusted or ulcerated.

3.2 Exclusion Criteria

- Prior enrollment in the same project
- Any records flagged "break the glass" or "opt out."
- Speak a language other than English or Spanish
- Unable to provide consent

3.3 Participant Identification, Recruitment, and Consent

Eligible participants will be identified by treating ED clinicians who will notify the site team that a patient meets inclusion criteria and by site coordinators periodically checking the ED tracking board. Participants will be recruited in-person by site staff. There will be posters in ED clinician work rooms to remind staff to notify the site team of possible eligible participants.

3.3.1 Consent Description

Participation in the project is strictly voluntary. The site coordinator will approach patients to determine eligibility in the site ED. If the patient is interested, the site coordinator will present the informed consent (and assent, if applicable) form to them. If the patient qualifies and is willing to participate, the site coordinator will obtain written informed consent. For children, the parent or legal guardian will provide parental permission by signing the informed consent. For children ages 8-17, they will provide assent. All consent/assent documents will be kept at each site in a secure location in project offices.

4.0 Project Design and Procedures

4.1 Schedule of Events

Patients will be enrolled in the ED during the index visit. At the index visit, a baseline/enrollment form will be completed, two rash swabs will be obtained, and two images of the rash will be obtained. For participants age ≥16 years, they will complete a self-administered survey about their gender identify and recent social and sexual behavior. Approximately 3-4 days after their index visit, site coordinators will access the participant's electronic medical record (EMR) and abstract information about their index visit, relevant lab results, and care. Approximately 45 days after enrollment, the site team will contact the participant by phone or video call to obtain information about outcomes of their illness, and if they tested positive for Mpox, any subsequent healthcare utilization. Participants who tested positive for Mpox and report symptoms at 45 days will be called again at 90 days to collect information on further health care utilization. For participants who had a positive Mpox test at any time through 90 days, an EMR review will be performed to obtain data on subsequent healthcare utilization for their initial illness.

Every 2 weeks, the site team will ship rash swabs to the central laboratory at UCLA for Mpox testing. For participants who have a positive test and did not receive a standard of care test in the ED, they will be notified of their positive result by the site team.

4.2 Project Design and Duration

This is a two-phase project: in the first one-month phase, we will conduct a pilot investigation to develop, test, and refine data collection methods, including recruitment, questionnaires, swab specimen shipping and processing methods. The pilot will involve review of data collection materials and processes by community patient representatives and experts in STI/HIV, LGBTQ health, and Mpox research and surveillance.

In the second phase, we will use the refined methods from the first phase and conduct a national surveillance investigation that consists of a Mpox test swab(s), a questionnaire administered in the ED, a self-administered questionnaire for participants age ≥16 years, medical record reviews of the initial ED visit, phone follow-up at 45 days, and for participants who test positive for Mpox another medical record review to collect information on healthcare utilization at 45 and 90 days, if still symptomatic. Most participants will participate for 45 days, but the actual time spent participating in the project will be approximately 45-60 minutes total over the 45 days.

The pilot will be conducted at 3 sites: Ronald Reagan UCLA, Olive View-UCLA, and Cedars-Sinai Medical Centers. The larger surveillance project will be conducted at 13 sites, including the 3 listed above and the following additional 10 *EMERGE*ncy ID NET sites:

1. Brigham and Women's Hospital; G Jambaulikar
2. Hennepin County Medical Center; J. Moore;
3. Johns Hopkins Medical Center; R. Rothman;
4. Lewis Katz School of Medicine at Temple University; D. Isenberg;
5. Valleywise Medical Center; F. Lovecchio;
6. Oregon Health Sciences University, Portland: J. Jui

7. University of Iowa, Iowa City; B. Faine;
8. University of New Mexico Health Sciences Center, Albuquerque: J. Femling;
9. University of Mississippi Medical Center, Jackson, MS: U. Nandi;
10. University of Missouri–Kansas City, Missouri: M. T. Steele;

All sites are academically affiliated institutions with well-established and experienced surveillance infrastructure led by a site principal investigator in their ED and have participated successfully as *EMERGE*ncy ID NET sites on various projects for many years.

4.3 Description of Project Procedures

Below is an overview of project procedures. More detailed procedures will be drafted and distributed to all site teams in a Manual of Procedures (MOP) prior to project start up and updated regularly throughout the project.

Questionnaires/surveys:
This project involves the administration of questionnaires (see appendix A). The first questionnaire(s) will be administered during the index visit. Immediately after obtaining consent, the site coordinator will complete an initial questionnaire by interviewing the clinician and the participant (and/or their parent). This questionnaire will collect information about the participant's demographics, social and medical history, and the history and symptoms of their current illness. For participants age ≥16 years, the site coordinator will access a REDCap link, enter in the participant's ID which will initiate a self-administered questionnaire that the participant can complete on a tablet. If the participant prefers to complete this additional questionnaire by paper, this will be facilitated. This questionnaire will ask more sensitive questions about the participant's gender identity and recent sexual history. All the information obtained in the questionnaires is routinely collected as part of clinical care. The participant's name or medical record number will NOT be entered into the REDCap database. The initial baseline questionnaires should take about 20 minutes to complete.

At 45 (+/-10) days after their initial ED visit, a site coordinator will call the participant to conduct a telephone survey. The survey will take approximately 10 minutes and collect information about symptoms, recurrence, healthcare utilization, Mpox testing after initial ED visit, and infections in household or other contacts. Although rarely expected, if a participant who test positive for Mpox reports they are still having symptoms at the 45 telephone follow-up we will call them again at 90 days (+/-10 days) to ask them again about further healthcare utilization related to their Mpox illness.

Medical Record/Clinical Record Review:
This project involves EMR reviews. Data will be abstracted from the medical record 3-4 days after the ED visit to abstract data about the baseline/enrollment visit, and for participants with a positive Mpox test, again at the end of the 45-day follow-up period. If a participant with a positive Mpox test reports symptoms at the 45 day follow-up period, we will conduct another EMR review at 90 days. The data points to be abstracted are hospital laboratory testing results, including for Mpox and sexually transmitted infections, ED treatment received,

including medications, and their disposition. At 45 days (and 90 days, if applicable), data about any hospitalizations or additional care received will be abstracted. If the participant sought care at an outside facility for their rash/illness, the project team will obtain permission from the participant to request their medical records from that facility and abstract information about their care received and any Mpox or STI lab results, if obtained.

Specimen Collection:
This project will collect two Mpox lesion swab specimens for testing at enrollment. If there is one lesion, two swabs will be obtained from the one lesion. If there is more than one lesion, two swabs will be obtained, but from two different lesion sites. The project coordinator will note the locations of the lesion(s) that were obtained on the swab label and on the enrollment form. The collection will be done during the index visit. The tests to be performed on the specimens include orthopoxviridae PCR. The testing will be performed at the University of California, Los Angeles Microbiology Research Laboratory (Los Angeles, CA) under the direction of Dr. Omai Garner. Specimens will stored at -70 degrees Celsius, and then will be shipped on dry ice from sites to the UCLA-based lab approximately every 2 weeks. Specimens will be labeled with a project ID and date of collection only. Detailed specimen collection, processing, and shipping procedures will be drafted in the project's Manual of Procedures.

Rash image capture:
At enrollment, the site coordinator will obtain two images of the swabbed lesion sites. If there is one lesion, two images will be obtained of the one lesion. If there is more than one lesion, two images will be obtained, but from the two different lesion sites. The project coordinator will include the assigned project ID label in the image if possible. All personal identifiers will be removed prior to image capture and the image will be obtained in a manner that does not allow the participant to be recognized.

Participant Compensation:
Participants will be compensated for their time spent to complete surveys. They will receive $25 for each visit they complete (i.e., enrollment, 45-day call, and if applicable, the 90-day call). Compensation will be disbursed by each site team to the participants they enroll by gift card, cash, or check, depending on site capability.

Clinician Compensation:
Some participating sites may decide to compensate clinicians for the time they take to help screen for potential eligible patients and answer questions required for data collection. Sites must follow their institutional requirements regarding clinician compensation for public health surveillance projects and obtain necessary approvals prior to launch.

5.0 Data Collection and Management

The Data Coordinating Center (DCC) is located at the main site, UCLA. The Clinical Coordinating Center (CCC) is located at the Olive View-UCLA site. The DCC and CCC will oversee data collection and management and will be specifically responsible for the following:

1) Creating, testing, and maintaining the project REDCap,
2) Overseeing data collection activities at all sites and ensuring sites are collecting complete, accurate, and logical data,
3) Getting all site team members access to the REDCap and training staff on how to access and enter data, and
4) Creating and implementing project quality control and quality assurance activities.

Data collection will occur on paper at the site and electronically on a secure and HIPAA-compliant REDCap database accessed through the UCLA CTSI. Trained site coordinators will record all personal identifying information necessary for EMR review (i.e., first name, last name, date of ED visit, and medical record number) and telephone follow-up (i.e., phone number, alternate phone number, email, alternate contact information) on a paper form. All paper forms (including consent materials) will be kept in a secure locked cabinet in their project offices where access is limited to approved personnel. The records will not be removed from each participating site's premises.

Site coordinators will also enter data collected from the participant, treating clinician, and participant's EMR onto the REDCap database. Aside from the date of ED visit (in case of data entry error of the project ID), no other personal identifying information will be recorded on the REDCap database that will only be accessible by trained and approved project staff.

Each participant will be assigned a unique project ID number. The linking list will be kept secure at each site. Direct identifiers will be separated from the project materials (data and/or specimens) as soon as possible. After data abstraction is complete and data have been verified, the identifiers and the linking lists will be destroyed as soon as scientifically possible. Specimens will be maintained for this project at a secure location at the UCLA microbiology laboratory where access is limited to approved personnel and specimens are labeled with a project ID, lesion location, and date of collection only. Specimens will be retained at the UCLA microbiology lab for future use (e.g., research or public health surveillance). Project investigators will seek guidance from CDC and participant institutions regarding keeping and destroying project materials and specimens, and ensure applicable policies are followed by all sites.

6.0 Human subjects

6.1 Non-research determination

This project is exempt from human subjects review because it is considered public health surveillance. This determination will come from the CDC human subjects advisor review. This project is considered "surveillance" because the project data and specimen collection are intended to provide timely information to inform public health action. All results will be reported promptly to CDC investigators involved in the Mpox response. The project is supported by Dr. Peggy Honein who led the CDC Mpox response team and will be funded as a supplement to

an existing cooperative agreement with CDC (U01CK000643-01) that funds the *EMERGE*ncy ID NET core infrastructure. Finally, all project activities will be limited to those that are necessary to achieve the public health objective. All site teams will submit the protocol to their IRB to notify them of the project and obtain their agreement with CDC's determination.

6.2 Risks to project participants

The risks to participants are minimal and include 1) the time required to complete survey interviews, 2) pain and discomfort associated with rash swabs, 3) discomfort in answering questions about gender identity and sexual behavior, and 4) inadvertent release of protected health care information and sensitive gender identity and sexual behavior information.

Personal identifying data will not be entered into the UCLA REDCap database. All PHI will be maintained at the site and not shared with the main site. Each participant will be assigned a unique project ID and along with their REDCap assigned ID, these two IDs will be used to link back to their identifying information maintained at the site. More sensitive data collected from participant's ages 16 and over will be kept in a separate database from the rest of their collected information with no personal identifying information and a unique project ID assigned, so that at the time of data analysis, we can link the information to the rest of their data. After data analysis and reporting, all personal identifying information will be removed from all databases.

7.0 Sample Size and Data analysis

7.1 Sample Size

The sample size of the project is 1,000 participants across the 13 sites. A sample size justification is not required for this project since it is considered surveillance and is based on funding availability.

7.2 Data analysis

This project will obtain estimates of the following parameters: prevalence of Mpox and prevalence by age category, race, ethnicity, sexual and gender identity, vaccine status, and other known risk factors.

Data analysis will be completed by the DCC led by project statistician, Dr. William Mower. We will present data as frequencies and percentages or means and standard deviations. We will also compare responses to survey questions across the subgroups of participants described above.

8.0 References

1. Multi-country monkeypox outbreak in non-endemic countries: Update. World Health Organization. 16 Sep 2022. Updated 29 May 2022. https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON388
2. Monkeypox: 2022 Outbreak Cases and Data. Centers for Disease Control and Prevention. 10 Nov 2022. https://www.cdc.gov/poxvirus/monkeypox/response/2022/index.html

3. Los Angeles County Monkeypox Daily Case Update. Los Angeles County Department of Public Health. 10 Nov 2022. Updated 10 Nov 2022. http://publichealth.lacounty.gov/media/monkeypox/data/index.htm
4. Miller MJ, S C-G, Marx G, et al. Severe Monkeypox in Hospitalized Patients—United States, August 10–October 10, 2022. *MMWR Morbidity and mortality weekly report*. 2022;71:1412-1417.
5. Monkeypox: What to do if you suspect Monkeypox. Centers for Disease Control and Prevention, US Department of Health and Human Services. Accessed 16 Sep 2022, https://www.cdc.gov/poxvirus/monkeypox/pdf/mpx-clinician-what-to-do.pdf
6. Thornhill JP, Barkati S, Walmsley S, et al. Monkeypox Virus Infection in Humans across 16 Countries - April-June 2022. *The New England journal of medicine*. Aug 25 2022;387(8):679-691. doi:10.1056/NEJMoa2207323
7. Clinical Recognition: Key Characteristics for Identifying Monkeypox. Centers for Disease Control and Prevention, US Department of Health and Human Services. https://www.cdc.gov/poxvirus/monkeypox/clinicians/clinical-recognition.html. Published 2022. Updated 23 Aug 2022. Accessed 16 Sep 2022, https://www.cdc.gov/poxvirus/monkeypox/clinicians/clinical-recognition.html
8. Talan DA, Moran GJ, Mower WR, et al. EMERGEncy ID NET: an emergency department-based emerging infections sentinel network. The EMERGEncy ID NET Study Group. *Annals of emergency medicine*. Dec 1998;32(6):703-11. doi:10.1016/s0196-0644(98)70071-x
9. Rodriguez-Diaz CE, Crowley JS, Santiago-Rivera Y, Millett GA. From COVID-19 to Monkeypox: Unlearned Lessons for Black, Latino, and Other Men With HIV Who Have Sex With Men. *American journal of public health*. Nov 2022;112(11):1567-1571. doi:10.2105/AJPH.2022.307093
10. Tai DBG, Shah A, Doubeni CA, Sia IG, Wieland ML. The disproportionate impact of COVID-19 on racial and ethnic minorities in the United States. *Clinical Infectious Diseases*. 2021;72(4):703-706.
11. Evans MK. Covid's color line—infectious disease, inequity, and racial justice. *New England Journal of Medicine*. 2020;383(5):408-410.
12. Patel A, Bilinska J, Tam JCH, et al. Clinical features and novel presentations of human monkeypox in a central London centre during the 2022 outbreak: descriptive case series. *BMJ*. Jul 28 2022;378:e072410. doi:10.1136/bmj-2022-072410