Research shows that over the last 20 years, MPX outbreaks in Africa have been expanding geographically and becoming more frequent as cohorts of people who were vaccinated for smallpox age out, leaving more susceptible unvaccinated, younger people. Moreover, the MPX virus itself has mutated at least 50 times since 2018, culminating in the current variant, which behaves differently (fewer lesions and sexually transmitted) compared to the MPX virus circulating in Africa.

Opportunities exist for immediate and longer term clinical, epidemiological, behavioral, and social research studies to better understand MPX prevention and care; how and when to deliver vaccines; how to deliver preventive services and treatments to garner maximum individual and population impacts; and identify (if any) long-term sequelae. These studies are critical in supporting the communities impacted by this outbreak. Furthermore, since MPX is just one of many growing infectious disease threats, new knowledge gained about MPX, social and structural drivers of MPX, and programmatic responses in the U.S. and around the world can play a critical role in advancing more comprehensive and effective programs to prevent and treat a variety of infectious diseases.
RESEARCH GAPS

Although the MPX virus was identified fifty years ago, not enough is known about the latest variant. There are several critical epidemiological, clinical, and behavioral research questions that must be addressed to extinguish the current outbreak and to prevent a future resurgence of MPX community transmission in the U.S. Chief among the epidemiological research questions is understanding the trajectory of the U.S. MPX epidemic; determining whether the decline in diagnoses reflects a true decline in transmission; measuring the likelihood that MPX may become endemic in specific racial and geographic communities in the U.S.; and assessing whether MPX diagnoses will gain a foothold in other communities (e.g., transgender/gender diverse populations, people who are homeless, and women).

Essential clinical research questions include estimating the real-world effectiveness of the JYNNEOS vaccine, including the durability of the immune response, and whether the immune response is worse among younger people without legacy smallpox vaccination or among immunocompromised individuals (e.g., people living with HIV who are not virally suppressed). Additionally, the effectiveness of tecovirimat (TPOXX) therapy must be thoroughly investigated, as well as whether other effective therapies are available in the event of tecovirimat resistance.

Important social/behavioral research questions include understanding the characteristics of sexual networks that protect against or facilitate MPX transmission; whether MSM are less likely to return for a second dose in localities that adopted and released messaging around a one-dose strategy; and whether there is an understanding of the protective level from the first or second dose of the vaccine over time that comports with appropriate reductions in specific behaviors.

Equally pressing, the global outbreak caused by this MPX variant highlights the need to tackle longstanding infectious disease threats around the world. This includes addressing access to vaccines, prevention, and treatment in countries where MPX has been endemic. An analogous research agenda is needed to evaluate whether MPX vaccine effectiveness is similar or different with the ancestral virus, as well as operational research to anticipate and circumvent possible obstacles in vaccine distribution and administration in resource constrained settings.

FEDERAL RESPONSE

In late July, the White House Office of Science and Technology Policy (OSTP) released an outline of federal MPX research priorities in seven key areas, covering topics such as epidemiological, immunological, and clinical characteristics of the MPX virus; safety and equitable distribution of...
## EPIDEMIOLOGICAL GAPS
- Does the decline in diagnoses reflect a true decline in transmission?
  - Is this due to behavior, maxing out susceptible individuals, or vaccine coverage?
- To what extent is asymptomatic transmission taking place?
- Why are HIV+ MSM a large proportion of MPX outbreaks?
  - Networks? Greater interaction with healthcare?
- Why are MSM not returning for a second MPX dose?
  - Are there differences by region or race/ethnicity?
  - What are the implications of mutations on outbreak control?
- Are HIV+ MSM more or less likely to complete two-dose MPX vaccinations than HIV-MSM?
- Are behaviors similar, reduced, or the same?
  - Immediately after the first dose?
  - Outside two weeks of the first dose?
  - Immediately after the second dose (4 weeks) or fully vaxxed at 6 weeks?
- What issues place Latinx/Black MSM at greater risk for MPX?
  - Are there differences by ethnicity, language, immigration status?
- What is the secondary attack rate of MPX?
  - How often is transmission in households without sexual contact?
- Will the MPX outbreak extend into other communities?
- What is the role of wastewater or animal reservoir surveillance in detecting MPX outbreaks?
- What is the role of genomic tracking to anticipate and assess viral resistance?
- How do overlapping infectious disease threats impact MPX prevention and treatment for MSM?

## CLINICAL GAPS
- How effective is the vaccination in preventing MPX?
  - Is the JYNNEOS vaccine immune response more robust among those with legacy smallpox vaccine?
  - How durable is the response?
- Are there effectiveness differences in subcutaneous, intradermal vaccinations, or a mix of each? Does effectiveness differ for severely immunocompromised individuals?
- How different is the current mutated virus compared to ancestral virus in endemic countries?
  - Are clinical manifestations different as preliminary data suggest (e.g., fewer lesions, earlier clinical manifestation, less fever/ headaches)?
  - Are asymptomatic infections a possibility?
  - Have non-lesion-based methods of MPX diagnosis been validated?
  - Is MPX infectiousness greatest and more enduring in lesions than blood, semen, or oral fluids (as preliminary data suggests)?
  - Can MSM correctly distinguish MPX lesions from pimples, mosquito bites, or other conditions?
  - What are MPX susceptibility and outcomes among undiagnosed or newly HIV-positive MSM?
- What long-term consequences arise from MPX and COVID-19 infection among people living with HIV?
  - Heart disease?
  - Other conditions?
- How effective is tecovirimat as treatment? Is tecovirimat effective as PrEP? Is tecovirimat resistance a possibility and what other antivirals are available?

## SOCIAL/BEHAVIORAL GAPS
- What sexual network characteristics protect or facilitate MPX transmission?
- What are specific activities and interactions that contribute directly to MPX transmission?
- What is the effect of behavior change on MPX rates among specific populations (+/- vaccination)?
- Is taking a COVID-19 vaccine associated with a greater likelihood to be vaccinated for MPX?
- Has COVID-19 isolation created greater fatigue and lower likelihood of isolation among MSM with MPX?
- What is the role of stigma on behavior or accessing MPX testing or vaccine among MSM?
- Will stigma and discrimination hide emergent outbreaks among MSM and other sexual minorities?
- Do isolation requirements for people with confirmed MPX diagnoses deter MPX testing?
- What is the acceptability of home-based MPX testing?
- What are effective MPX prevention strategies in countries that do not have access to MPX vaccines or tecovirimat?
- What operational research can be implemented to help improve our nation’s outbreak response?
- How are social institutions (e.g., CBOs, social media, colleges & universities, etc.) responding to MPX?
- What models of community-engaged research are most effective?
ADDITIONAL RESEARCH MUST PLAY A CRITICAL ROLE IN HELPING THE IMMEDIATE RESPONSE IN THE U.S., AS WELL AS STEMING MPX OUTBREAKS IN ENDEMIC COUNTRIES.

vaccines and therapeutics; prevention of secondary transmission in congregate settings; addressing and reducing stigma; and other priority areas. NIH also has allocated $140 million for MPX research, and they have begun a Phase 3 clinical trial evaluating tecovirimat in adults and children with MPX in the U.S. Additionally, NIH is initiating a separate clinical trial of tecovirimat in adults and children with MPX in the Democratic Republic of the Congo.

NEEDED ACTIONS

These are good first steps, but more is needed, including new investments. Federal research priorities were developed through an internal interagency process and they are notably devoid of discussion of gay and bisexual male communities who comprise the overwhelming majority of MPX cases. Additional public consultations are needed with frontline clinical providers and affected communities. The Administration has requested supplemental MPX funding, but it appears unlikely that Congress will make such funds available, at least in the immediate future. HIV research advocates have met with federal research leaders and were told that existing resource constraints and the limited ability to transfer earmarked dollars reduce the capacity to initiate many valuable research activities.

MPX will not go away on its own, and unless we answer critical questions, it could return. We also remain at risk of other infectious diseases. Additional research must play a critical role in helping the immediate response in the U.S., as well as stemming MPX outbreaks in endemic countries.

TO LEARN MORE

For additional background information, please read our MPX materials available at the link in the box below. Also see:


QUICK TAKE: MPX RESEARCH GAPS: WHAT REMAINS UNKNOWN

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