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# Mpox Vaccines and Natural Immunity Protect Against Severe Illness

People with repeat monkeypox infections and those who were vaccinated are less likely to develop severe symptoms.

September 20, 2023 By Liz Highleyman

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People with repeat mpox (monkeypox) infections and those who were infected after vaccination appear less likely to develop severe illness, according to a global case series described in The Lancet Infectious Diseases. A California study also showed that receiving at least one dose of the Jynneos vaccine reduced the risk of hospitalization.

These findings show that although people who had mpox can get it again, and vaccination does not always prevent infection, a past bout of mpox and vaccines confer partial immunity that reduces the risk of severe outcomes.

The global mpox outbreak that started in May 2022 has declined dramatically since it peaked late last summer, but sporadic clusters are still being reported. To date, the Centers for Disease Control and Prevention (CDC) has identified 30,767 mpox cases in the United States, while the World Health Organization has tallied nearly 90,500 cases worldwide, resulting in 157 deaths. Most cases outside of Africa have been among gay, bisexual and other men who have sex with men.

## Global Case Series

To learn more about the outbreak, Chloe Orkin, MD, of Queen Mary University of London, and a large team of colleagues formed an international collaboration known as the SHARE-net Clinical Group. The group previously published studies describing the spectrum of mpox symptoms, mpox cases among cisgender and transgender women and the severity of mpox among people with HIV.

In their latest report, the group analyzed epidemiological and clinical characteristics of mpox among people with past infections or vaccination in an effort to better understand the disease in the setting of previous immunity.

Mpox is an orthopoxvirus closely related to smallpox, and the same vaccines provide protection against both viruses. The modified vaccinia Ankara vaccine made by Bavarian Nordic (MVA-BN), known as Jynneos in the United States, Imvamune in Canada and Imvanex in Europe, was widely administered first as a subcutaneous injection and later—to stretch the limited supply—as an intradermal injection using one fifth of the original dose. Both methods require two doses given

about four weeks apart.

Previous infection or vaccination are thought to confer lifelong immunity against smallpox, the study authors noted as background. However, studies have yielded widely varying estimates of mpox vaccine effectiveness, and a substantial proportion of people in recent case clusters in the United States and Europe were partially or fully vaccinated.

For this case series, collaborators from nine countries provided data on people with PCR-confirmed mpox after a documented previous infection or more than 14 days after full vaccination between May 2022 and June 2023. People who were partially vaccinated or who had received doses prior to the global outbreak were excluded.

The series included 37 cases, all of them involving cisgender gay, bisexual or other men who have sex with men. Seven were reinfected, 29 were infected despite receiving two appropriately spaced Jynneos doses and one was both vaccinated and reinfected. Of the eight men with repeat infections, five were from the Americas and three were from Europe. Of the 30 men with infections after vaccination, 17 were from the United States and 13 were from Europe.

Looking at repeat infections and post-vaccine infections together, the median age was 36 years. About three quarters were white, 11% were Latino, 8% were Asian and 5% were Black. Consistent with prior studies, most men reported condomless sex with multiple male partners. Nearly a third had one or more other sexually transmitted infections at the time of their most recent mpox diagnosis.

Eight men (22%) were living with HIV, and 83% of HIV-negative men were taking pre-exposure prophylaxis (PrEP). Among those with HIV, all were on antiretroviral treatment with an undetectable viral load. The median CD4 T-cell count was 555 and the median nadir (lowest-ever) count was 355. As recently reported, people with HIV are not at greater risk for severe mpox unless they have advanced immune suppression.

Among men with repeat mpox infections, the median time between infections was 16 weeks. Among the 30 men who were vaccinated, 14 had received two subcutaneous Jynneos doses, eight received two intradermal doses and eight received one of each. The median time between the completion of vaccination and infection was 31 weeks. The HIV-negative man who was both vaccinated and reinfected was first infected just four days after his first vaccine dose and again 38 weeks later.

To describe the illness, the study authors used the Mpox Severity Score System (Mpox-SSS), which takes into account the number and extent of sores, the presence of confluent or combined lesions, bacterial superinfection, how much mucosal area is affected, the level of care required and the need for pain medication.

Men with repeat or post-vaccine infections had fewer and less severe sores that healed more rapidly. Two men with repeat infections (25%) and 12 who were vaccinated (40%) had only a single ulcer. Men who were reinfected had a median of 10 lesions during their first bout of mpox,

which fell to five during their second infection; vaccinated men had a median of two lesions. Most had sores on the chest or limbs, and anal-genital and oral lesions were common. Two vaccinated men required treatment with TPOXX (tecovirimat), including one who was hospitalized for a necrotizing neck lesion.

Among the men with repeat infections, the median Mpox-SSS score decreased from 7.0 during their first infection to 5.5 during the second, while vaccinated men had a median score of 5.0. For comparison, the median score was 8.0 among the first 172 retrospectively analyzed mpox cases in New York City. The lower score was primarily driven by less need for pain medication.

The study authors noted that the clinical presentation of repeat and post-vaccine mpox appeared to differ from initial infections reported in 2022. Those cases were often characterized by severe painful anal mucosal lesions or debilitating mouth or throat lesions. There were no deaths in the new cohort, and all but one were managed as outpatients. In contrast, around 10% of cases reported in 2022 required hospitalization, often for more intensive pain management or treatment of bacterial superinfections.

“Clinical features and outcomes of repeat infection and infection after vaccination appear to be less clinically severe than those described in 2022 case literature,” they wrote. “Natural immunity and vaccine-induced immunity are not fully protective against mpox infection. However, in this small series, both disease duration and severity appear to be reduced.”

As limitations of this analysis, the authors noted that this series included only PCR-confirmed symptomatic cases, so people with minimally symptomatic or asymptomatic repeat or post-vaccine infections might have been missed. What’s more, the men were not tested for antibodies to see whether they had actually developed immunity, nor was their virus sequenced to determine if presumed repeat infections might have been relapses.

“Consistent and clear interventions developed with and for affected communities to improve vaccination uptake are vital, as is further research to better understand vaccine effectiveness in preventing infection,” the authors concluded. “Above all, ensuring equity of access to vaccines and treatments, specifically to geographical areas historically affected by mpox, must be prioritized if we aim to end this global outbreak and ensure elimination of human-to-human mpox transmission.”

## Mpox in California

Samuel Schildhauer, MPH, of the California Department of Public Health, and colleagues looked at the effect of Jynneos vaccination on hospitalization risk, especially among people with HIV, who are at higher risk for severe disease. Previous CDC reports found that more than 80% of people hospitalized with severe mpox in the United States were living with HIV, and most of those who died were Black gay men with AIDS.

As described in the CDC’s Morbidity and Mortality Weekly Report, Schildhauer’s team analyzed

surveillance data collected by the California Department of Public Health. The analysis included all 5,765 people with mpox reported in California between May 2022 and May 2023. Of these, 1,154 were excluded due to missing hospitalization data, leaving 4,611 cases.

The median age was 35 years. Most (94%) were cisgender men, just under 3% were cisgender women and about 1.5% were transgender. More than three quarters identified as gay, bisexual or same-gender loving. About 45% were Latino, 29% were white, 13% were Black and 5% were Asian. Consistent with prior U.S. studies, 41% were living with HIV.

As a limitation of the analysis, the authors noted that there were some differences between included cases and those excluded due to missing hospitalization data in terms of race/ethnicity, sexual orientation and HIV prevalence. What's more, people with diagnosed mpox might represent a population with better access to health care than those with unreported mpox.

Within this group, 230 received a single Jynneos vaccine dose at least 14 days prior to symptom onset, specimen collection or a positive lab test (whichever was earlier). People who received two doses less than 24 days apart or who got their second shot less than two weeks before developing mpox were counted as having had a single dose. Another 79 people received two correctly spaced Jynneos doses at least two weeks before an mpox episode. A larger number, 457, received the vaccine as post-exposure prophylaxis after a known or suspected exposure. This left 3,845 people unvaccinated.

A total of 250 people with mpox were hospitalized, including 140 people living with HIV. Most (233) were unvaccinated, four had received a single pre-exposure vaccine dose and one had received two pre-exposure doses, while 12 had received the vaccine as post-exposure prophylaxis. Although people with HIV made up 41% of the mpox cases, they accounted for 56% of hospitalizations.

The researchers found that the odds of hospitalization were lower for people who received one or two pre-exposure Jynneos doses. Overall, vaccine effectiveness was 73% for a single dose and 80% for two doses compared with being unvaccinated. Among people with HIV, one dose was 72% effective; no HIV-positive people who received two doses were hospitalized. Post-exposure vaccination was somewhat less effective, at 58%.

"To optimize durable immunity, all eligible persons at risk for mpox, especially those infected with HIV, should complete the two-dose Jynneos series," the study authors concluded. Messaging to people at higher risk for mpox and those living with HIV "should encourage completion of the two-dose Jynneos vaccination series to limit virus transmission and mitigate disease severity."

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