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Prior Immunity Continues to Protect Against Severe Mpox in 2025 Despite Time Since Vaccination

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Introduction

- As the multinational mpox outbreak continues, ongoing transmission persists in the U.S. with recurrent clusters reported in 2025.
- Vaccination and prior infection were associated with reduced severity early in the outbreak, but the durability of this protection against severe disease remains uncertain.
- Other countries have issued recommendations on repeat (booster) mpox vaccination for certain groups, while U.S. guidance has continued to recommend no repeat doses highlighting ongoing uncertainty about if or when repeat dosing is warranted.
- We evaluated disease severity among mpox cases diagnosed in 2025, focusing on the impact of prior immunity and time since vaccination..

Methods

- Multicenter retrospective cohort study of PCR-confirmed mpox cases diagnosed between January 1 and October 31, 2025 across seven sites.
- Demographics, HIV status, prior immunity (≥14 days since mpox vaccination, all with prior infection were also vaccinated), and clinical outcomes were abstracted from medical records.
- Disease severity was assessed using the Mpox Severity Scoring System (MPOX-SSS); severe disease was defined a priori as MPOX-SSS ≥7, corresponding approximately to the upper quartile of observed severity.
- Multivariable logistic regression estimated adjusted odds of severe disease, adjusting for age, any concurrent STI, and HIV status.
- Secondary analyses among vaccinated individuals assessed associations between time since vaccination and severe disease.

Results

- Among 186 mpox cases, 92% occurred in cis-men, 75% in Black or LatinX, 39% were living with HIV, 118 (63.4%) had no prior evidence of immunity and 68 (36.6%) had prior evidence of immunity. (Table 1) Of 68 with prior immunity, 68 had received at least 1 prior mpox vaccine 5 of whom also had prior PCR-confirmed infections/
- Severe disease (24% vs 52%; p<0.001) and hospitalization (2.9% vs 17.8%, p=0.006) occurred less frequently among those with prior immunity. In adjusted analyses, prior immunity was associated with lower odds of severe disease (aOR 0.30, 95% CI 0.14–0.60) and lower odds of hospitalization (aOR 0.12 CI 0.02-0.48). (Table 2)
- Severity was lower in those with prior immunity (median MPOX-SSS 5 [IQR 3–6] vs 7 [5–8]; p<0.001). (Figure 1)
- Among 66 post-vaccination cases (median time since vaccination 36 months [IQR 34–38]), severity remained low across time-since-vaccination categories, though sample sizes in earlier intervals were limited. (Figure 2)

Table 1. Baseline characteristics by prior evidence of immunity, mpox cases (2025)

Characteristic	No prior evidence of immunity N = 118[1]	Prior evidence of immunity N = 68[1]	Overall N = 186[1]
Age, years	33 (28, 38)	36 (32, 43)	34 (30, 39)
Gender identity			
Cis man	112 (95%)	64 (94%)	176 (95%)
Race/ethnicity			
Asian	3 (2.6%)	4 (5.9%)	7 (3.8%)
Black	48 (42%)	9 (13%)	57 (31%)
First Nation, Inuit, Métis	1 (0.9%)	2 (2.9%)	3 (1.6%)
LatinX	40 (35%)	24 (35%)	64 (35%)
Mixed	3 (2.6%)	1 (1.5%)	4 (2.2%)
White	19 (17%)	28 (41%)	47 (26%)
HIV status			
HIV-negative	68 (58%)	49 (72%)	117 (63%)
HIV-positive	46 (39%)	19 (28%)	65 (35%)
PrEP use			
On PrEP	44 (37%)	43 (63%)	87 (47%)
Not on PrEP	27 (23%)	6 (8.8%)	33 (18%)
CD4 category (PWH)			
CD4 <200	6 (13%)	2 (11%)	8 (12%)
CD4 >200	30 (65%)	17 (89%)	47 (72%)
CD4 unknown	10 (22%)	0 (0%)	10 (15%)
Any concurrent STI	22 (19%)	13 (19%)	35 (19%)
Hospitalization / higher level of care			
Outpatient	97 (82%)	66 (97%)	163 (88%)
Hospitalized/ICU	21 (18%)	2 (2.9%)	23 (12%)
MPOX-SSS total score	7.00 (5.00, 8.00)	5.00 (3.00, 6.00)	5.00 (4.00, 8.00)

[1] Median (Q1, Q3); n (%)

Table 2. Adjusted odds ratios (95% CI) for severe mpox disease and hospitalization among mpox cases, 2025

	Severe disease (MPOX-SSS =7)		Hospitalization / higher level of care	
Characteristic	**OR**	**95% CI**	**OR**	**95% CI**
Prior evidence of immunity				
No prior evidence of immunity	—	—	—	—
Prior evidence of immunity	0.30	0.14, 0.60	0.12	0.02, 0.48
Age (years)	1.02	0.98, 1.07	1.03	0.97, 1.10
Immunologic status				
HIV-negative	—	—	—	—
HIV+, CD4 >200	1.50	0.72, 3.13	2.89	0.98, 8.70
HIV+, CD4 unknown	1.86	0.49, 7.80	2.04	0.27, 10.4
HIV+, CD4 <200	2.40	0.51, 13.1	4.89	0.74, 28.7
Any concurrent STI				
No	—	—	—	—
Yes	1.25	0.55, 2.84	2.07	0.66, 6.15

Abbreviations: CI = Confidence Interval, OR = Odds Ratio

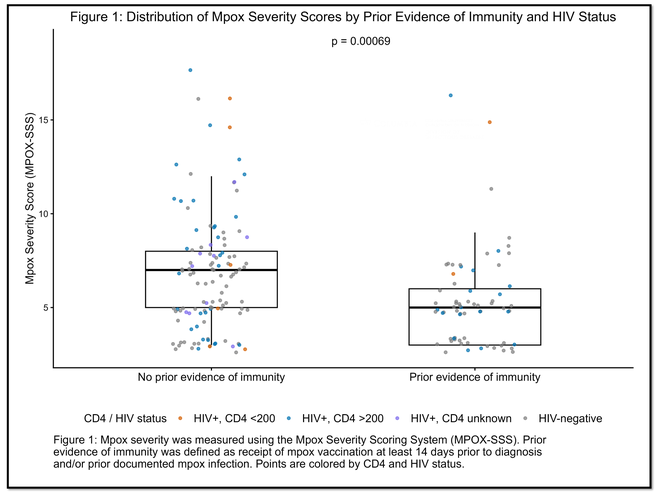


Figure 1: Distribution of Mpox Severity Scores by Prior Evidence of Immunity and HIV Status

Figure 1: Mpox severity was measured using the Mpox Severity Scoring System (MPOX-SSS). Prior evidence of immunity was defined as receipt of mpox vaccination at least 14 days prior to diagnosis and/or prior documented mpox infection. Points are colored by CD4 and HIV status.

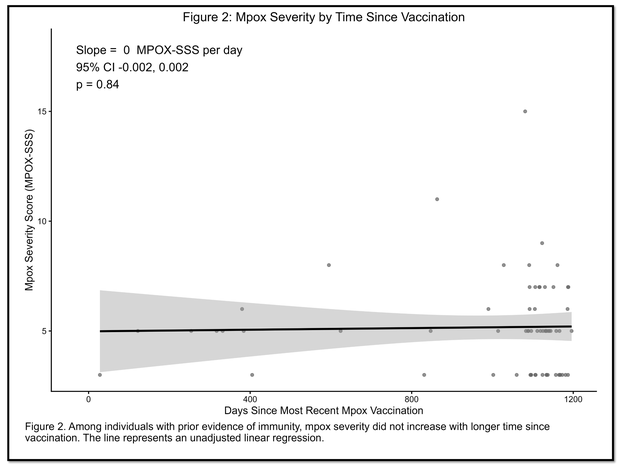


Figure 2: Mpox Severity by Time Since Vaccination

Figure 2. Among individuals with prior evidence of immunity, mpox severity did not increase with longer time since vaccination. The line represents an unadjusted linear regression.

Prior immunity was associated with lower risk of severe mpox or hospitalization in 2025. Our findings do not currently support routine booster vaccination for the general population. Continued surveillance is needed to guide future policy

Discussion

- In this multicenter cohort, immunity from vaccination and/or prior infection continued to mitigate mpox severity in 2025.
- Protection against severe disease appeared durable, with no increase in severity over time since vaccination.
- **These findings do not suggest a need for routine booster vaccination for the general population at this time.**
- Ongoing surveillance and periodic assessment of disease severity by time since vaccination will be critical to inform future vaccination strategies.

PLAIN LANGUAGE SUMMARY: In a seven-site study of 186 mpox cases in 2025, people with prior immunity (vaccination ± prior infection) had milder illness and were less likely to have severe disease or be hospitalized. Protection against severe mpox appeared to persist even years after vaccination.