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Letter to the Editor

Humoral and T-cell responses following MVA-BN booster vaccination against mpox virus clades Ib and IIb

Dear Editor,

In this Journal, Matusali et al. reported that immunity elicited by the primary course of MVA-BN vaccination against mpox virus (MPXV) wanes over time, especially in individuals without a history of smallpox vaccination.[1]

This decline has been described in other reports, highlighting the potential usefulness of a booster dose,[2–4] especially in the context of ongoing circulation of mpox virus (MPXV) worldwide.[5] The emergence of Clade Ib in Africa, followed by imported cases in non-endemic countries, and the ongoing transmission of Clade IIb worldwide, led the WHO to renew the Public Health Emergency of International Concern.[6]

Previously, Ilchmann et al. investigated the humoral response to an MVA-BN booster using a vaccinia virus-based assay, showing a rapid and robust VACV-neutralizing antibody (nAb) response after the booster,[7] but no data are available on the specific antibody response against MPXV (let alone against different clades) or on the T-cell response after the booster dose. In this scenario, booster administration remains controversial,[8] and it is recommended only by a few countries.[9,10]

We assessed both humoral and T-cell responses elicited by an MVA-BN booster dose administered at least two years after the primary two-dose course in 37 individuals at risk for mpox who had not been historically vaccinated against smallpox. Participants were sampled on the day of the booster (baseline) and one month later. We measured anti-MPXV IgG antibody titers, clades Ib and IIb, nAb titers against clade IIb, and MVA-BN-specific T-cell responses. (*methods in supplements*).

Details of the study population are reported in Table 1.

One month after booster vaccination, IgG titers significantly increased from baseline for both clades Ib and IIb ($p < 0.0001$), and the proportion of reactive individuals reached 100% in both groups ($p < 0.0001$). However, a difference of less than one dilution was observed between the two clade groups ($p=0.0148$) (Fig. 1A-B). Likewise, nAb titers against clade IIb significantly increased from baseline to one month after the booster ($p < 0.0001$), with the reactivity rate rising from 8% to 76% ($p < 0.0001$) (Fig. 1C). Similarly, one month after the booster dose, the MVA-BN T-specific response was higher than before ($p=0.0001$), with 78% of people above the cut-off compared to 37% before the booster (Fig. 1D). People with HIV showed the same response trend (Fig. 1, red dots), although the small sample size prevented a powered analysis.

Our study demonstrates that an MVA-BN booster administered two years after the primary vaccination series effectively restores and enhances both humoral and cellular immunity in individuals at ongoing risk for mpox. We observed a significant increase in IgG titers against both circulating MPXV clades, suggesting potential cross-clade protection, alongside marked improvements in neutralizing antibody levels and T-cell responses.

These findings are relevant in the context of MPXV still circulating and of the debate on booster recommendations. The US CDC currently limits booster administration to individuals with persistent high-risk exposures, reflecting uncertainties regarding the duration of protection and lack of defined correlates of immunity.[8] In contrast, in other countries (e.g. France), health authorities endorsed broader booster use, citing the important waning of nAbs over time, and concerns over the emergence of Clade Ib and its potential clinical and epidemiological implications.[9]

Our findings may help reconcile these divergent positions. We previously demonstrated that, after the primary MVA-BN vaccination, humoral immunity, particularly neutralizing immunity, wanes over time, with less than one-third of vaccinees maintaining detectable neutralizing antibodies one year after vaccination[1] and a poor residual response two years after.[2] Conversely, cellular immunity appears more durable despite being substantially diminished two years after vaccination.[2]

In this context, our results showed that a booster administered two years after the primary course significantly enhances both arms

Table 1
Characteristics of the study population.

Characteristic	N = 37[a]
Sexual orientation	
Bisexual	1 (2.7%)
Transgender	1 (2.7%)
MSM	35 (95%)
Age	39.9 (34.5, 46.3)
PrEP use	
No	8 (22%)
Yes	3 (8.1%)
Not reported	26 (70%)
>=1 STI over previous year	7 (19%)
PLWH	5 (14%)
PLWH on effective ART	5 (100%)
CD4 cell count, cells/mm3	
<200	0 (0%)
200–500	2 (40%)
>500	3 (60%)
Route of administration of first dose	
Intradermal	33 (89%)
Subcutaneous	4 (11%)
Subcutaneous	0 (0%)
Route of administration of booster dose	
Intradermal	4 (11%)
Subcutaneous	33 (89%)
Time between second dose and booster dose, months	25.70 (25.03, 26.58)

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

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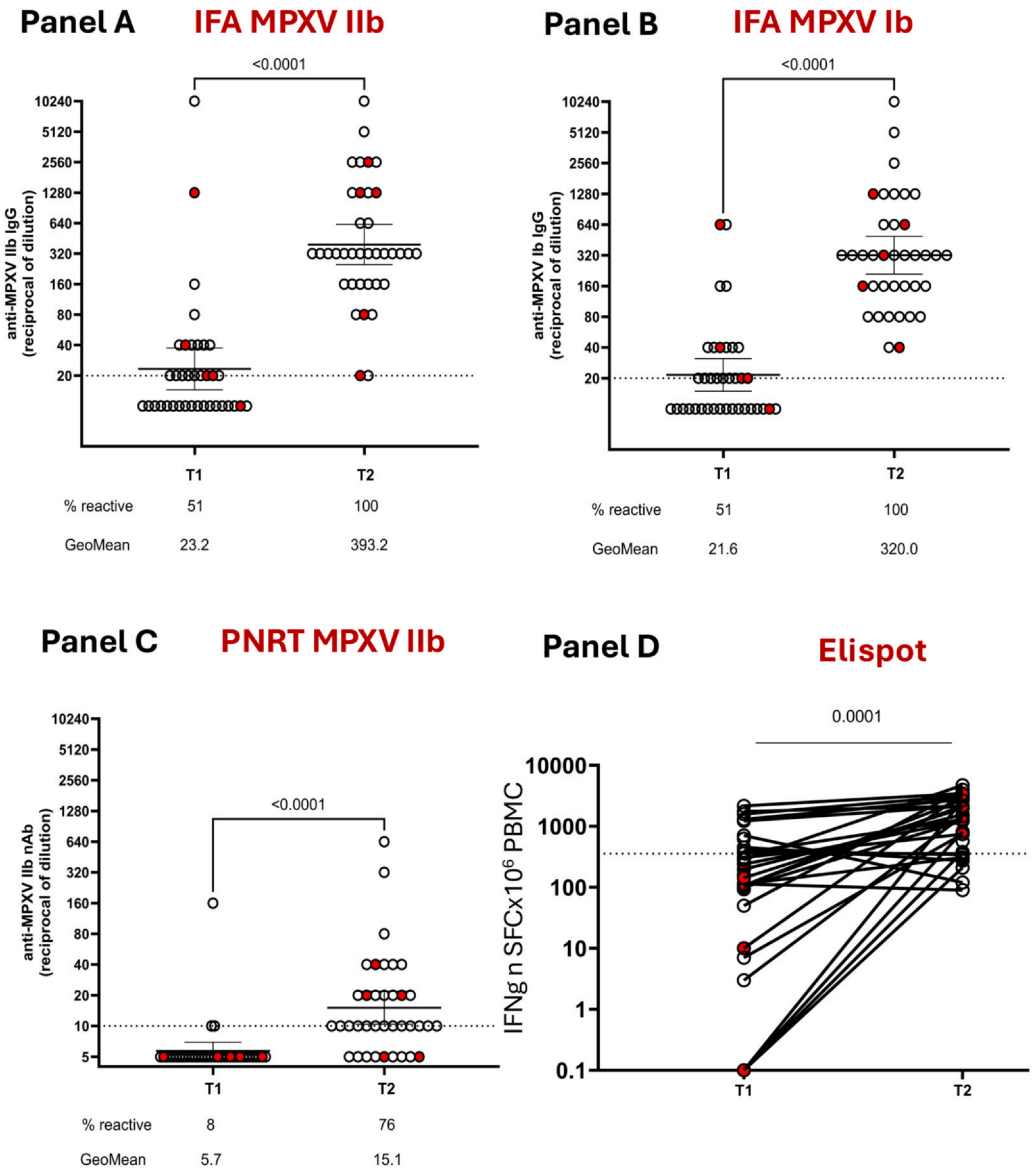

Fig. 1. Immune response after an MVA-BN booster dose. MPXV-IgG titers against clade IIb (panel A) and Ib (panel B), MPXV-neutralizing antibodies (nAbs) titers (clade IIb) (panel C) and MVA-BN T-cell specific response expressed as number of Spot Forming Cells (SFC)x10^6 PBMC (panel D). Red spots = PWH (people living with HIV). Antibody titers are expressed as Geometric Mean Titers (GMT) of the reciprocal serum dilution. Dashed line: limit of assay detection (1:20 for IgG, 1:10 for nAbs, and a home-made cut-off based on results from 10 healthy donors for T-cell response). Error bars refer to the 95% confidence interval of GMT. T1=baseline, T2=1 month after booster.

of the immune response. Notably, we observed increased IgG titers (reaching 100% seroreactivity) against both clades (IIb and Ib), supporting cross-protection and the usefulness of MVA-BN also against Clade Ib.

The question of booster needs in specific subgroups, such as PWH, remains poorly clarified. While MVA-BN is generally safe and immunogenic in PWH,[11] more recent data suggest a suboptimal neutralizing response early after a primary single-dose cycle, supporting the recommendation for a full two-dose regimen regardless of prior smallpox vaccination history.[12]

In our study, the immunological response trend after the booster dose seemed similar in PWH and people without HIV (PWoH), although the small sample size prevents definitive conclusions. To date, no validated immunological correlates of protection against mpox have been identified, making it challenging to translate laboratory findings into clear policy decisions, and data on efficacy are mainly derived through emulation trials from observational data.[13] In this uncertain landscape, immunogenicity data are crucial for supporting evidence-based vaccination strategies.

Limitations of our study include the small sample size and the lack of a control group of unboosted individuals, which precludes direct assessment of clinical protection or waning in the absence of boosting. The short follow-up period limits conclusions on the durability of the booster-elicited immune response. Finally, the study was not powered to detect subgroup differences, particularly among PWH.

Nonetheless, these data provide essential immunological evidence supporting booster dose administration in individuals at ongoing risk for mpox, contributing to the refinement of vaccination policies in the evolving epidemiological scenario.

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Disclosures

No potential conflict of interest reported.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2025.106602.

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