

Clade I mpox vaccination: strategies for deployment and evaluation



Caitlin Pley,^a Jasmina Panovska-Griffiths,^{a,b,c} Robert Hinch,^a Chris Wymant,^a Lucie Abeler-Dörner,^a Deogratius Ssemwanga,^{d,e} Ronald Moses Galiwango,^f M. Kate Grabowski,^{f,g} Francesco Di Lauro,^a Luca Ferretti,^a James Hay,^a Marc Lipsitch,^h Jake Dunning,^{a,c} Joseph Kagaayi,^{f,i} Pontiano Kaleebu,^{d,e} and Christophe Fraser^{a,*}

^aPandemic Sciences Institute, Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom

^bThe Queen's College, University of Oxford, Oxford, United Kingdom

^cUK Health Security Agency, London, UK

^dMRC/UVRI & LSHTM Uganda Research Unit, Entebbe, Uganda

^eUganda Virus Research Institute, Entebbe, Uganda

^fRakai Health Sciences Program, Kalisizo and Entebbe, Uganda

^gDepartments of Pathology and Epidemiology, Johns Hopkins University, Baltimore, MD, USA

^hHarvard T.H. Chan School of Public Health, USA

ⁱSchool of Public Health, College of Health Sciences, Makerere University, Kampala, Uganda

Clade I mpox continues to spread in Central Africa with no sign of abating,¹ however very few doses of vaccine have been deployed. Mpox vaccination strategies using either of the licenced vaccines, MVA-BN and LC16m8, are being drawn up across 17 African countries and vaccination has begun in the Democratic Republic of Congo (DRC), Rwanda and Nigeria.² Clinical studies during the rollout could deliver much-needed data about the effectiveness of the vaccine against clade I mpox. Choosing the right study design is fundamental. In this piece, we advocate for the use of a cohort design where possible, with recommendations for alternative designs as appropriate to the setting.

Two main clades of monkeypox virus exist (I and II). Clade IIb, a sub-lineage of clade II, spread globally in 2022–2023. MVA-BN was deployed extensively in response,³ and its effectiveness against clade IIb disease after two doses was estimated to be 82% (95% confidence interval (CI) 72–92%).³ Since 2024, two sub-lineages of clade I (Ia and Ib) have spread in the DRC.¹ Neighbouring countries are also affected, with sporadic exportations elsewhere.¹ The extent of vaccine cross-reactivity, in addition to differences in virulence and different routes of exposure in the current outbreak, may change the vaccine effectiveness against clade I relative to that against clade IIb. Children are disproportionately affected in the ongoing clade I outbreak, and case-fatality rates are higher at younger ages, particularly in infants.⁴ Vaccine studies carried out during vaccine roll-out should therefore prioritise collecting additional effectiveness data in children, as well

as in other special populations like pregnant women and immunosuppressed individuals.

In settings with isolated or sporadic cases, ring vaccination could be deployed with the aim of containing further mpox spread. Because the vaccine is licenced, this policy would consist of ring vaccination with no control group, and a study would therefore be observational follow-up. Detailed follow-up data on cases, contacts, exposures, and timing of vaccination, aggregated over many rings, could be used in detailed transmission modelling to give statistical estimates of key vaccine effectiveness parameters (Table 1). Contact tracing data can be used to estimate vaccine effectiveness against becoming infected (VE_S) and against infecting others (VE_I), as well as against disease (VE_D).^{5,6} Understanding to what extent the vaccine protects against just disease or also against infection, especially in different age groups, can be crucial in the design of deployment strategies to maximise its public health impact.⁶

In high-transmission settings, vaccines are being deployed to high-risk individuals and communities.²

Although there is no estimate of vaccine effectiveness specifically against clade I, we believe a placebo-controlled trial of primary preventive vaccination would not be ethical given the strong evidence for pre-exposure effectiveness against clade II, and given the vaccines are licenced and already being deployed. A non-inferiority trial to compare the two vaccines, while at first glance attractive, would not provide an absolute estimate of vaccine protection, as there is no unvaccinated group for comparison. Study designs that compare vaccinated and unvaccinated communities, like stepped wedge trials, could have the advantage of delivering additional data on the overall vaccine effect, encompassing both direct and indirect effects. However, such studies would risk being underpowered,⁷ and randomising the order of vaccine roll-out, as required for a stepped-wedge trial, could again be considered

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*Corresponding author.

E-mail address: christophe.fraser@ndm.ox.ac.uk (C. Fraser).

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VE estimate	Definition	Importance	Clade I	Clade II	Appropriate observational study designs
VE _{D, PPV}	Vaccine effect against disease when vaccinated before exposure.	- Reducing individuals' morbidity and mortality if infected. - Mitigating the overall health impact of a disease, e.g. on the health system.	No specific estimate for clade I but good prior for high efficacy given data from clade IIb.	Strong evidence: 82% (95% CI 72–92%) after two doses and 76% (95% CI 64–88%) after one dose. ³	Cohort study or TND
VE _{D, PEP}	Vaccine effect against disease when vaccinated post-exposure.		No specific estimate for clade I, but probably similar to the post-exposure efficacy against clade II.	From limited available data: point estimate 20% (95% CI –24 to 64%). ³ More studies needed.	
VE _s	Vaccine effect against susceptibility to infection if exposed.	- Reducing the incidence of new cases. - Curtailing the spread of disease and contributing to suppressing or containing the outbreak.	Knowledge gap, more data needed.	Knowledge gap, more data needed.	Cohort study (optimised to study sexually transmitted infections in networks) or contact tracing-based study design
VE _t	Vaccine effect against onward transmission if breakthrough infection occurs.		Knowledge gap, more data needed.	Knowledge gap, more data needed.	

Table 1: Different vaccine effect estimates, their importance, and the current state of knowledge for mpox clades I and II.

unethical. Given the lack of an accepted correlate of protection, immunobridging studies are also unfortunately not a possible alternative to an effectiveness study. We therefore propose two main possibilities for evaluating vaccine effectiveness in high-transmission contexts.

The first is the test-negative design (TND), which offers a convenient and practical way to estimate vaccine effectiveness against disease by comparing vaccination coverage between confirmed cases and controls, defined as people who present to healthcare with symptoms compatible with the disease and are tested as positive and negative respectively. TNDs control for healthcare-seeking behaviour but have known limitations.⁸ Like other observational studies, there is a risk of confounding if there are factors that are associated with both vaccination coverage and risk of exposure; for mpox this could be sex work. In the DRC, vaccination is targeted at high-risk groups. As a result, 16% of those vaccinated are sex workers, although they represent only 3% of the population.⁹ Not controlling for risk of exposure or not excluding individuals with past infection would likely introduce more bias in the VE estimate in test-negative studies than cohort studies.¹⁰ Another limitation that affects test-negative designs more than cohort studies is the impact of diagnostic inaccuracies. Notably, reductions in test specificity, for example due to contamination, will bias the effect estimate downward. Including matched community controls in addition to test-negative controls may mitigate some of this bias. Modelling studies can estimate the impact of the limitations of test-negative designs on bias and power and can guide clinical and laboratory protocols.

The second main possibility for mpox is a cohort study, which offers reduced selection bias and potentially better control of confounding than the TND.⁸ There could be cost and time savings in nesting an mpox cohort vaccine study within an existing cohort

followed for other reasons, since additional study procedures would only involve ascertaining vaccination status and adding mpox testing to the existing follow-up. The number of existing participants that would need to be recruited into the nested study would depend on the local mpox incidence and roll-out of vaccination. Prime candidates would be ongoing community cohort studies on risk of HIV infection and other sexually transmitted infections. These studies are often conducted in settings where female sex work is common, which would enable sufficient representation of the groups who are most at risk of mpox and are targeted by mpox vaccination programmes. These cohorts regularly follow-up people living with and without HIV, and there is both investigator experience and participant trust regarding the collection of data on sexual health and risk behaviours. Cohort studies also typically collect more contextual survey and demographic data than TNDs and ensure that the cohort is representative of the communities and risk groups of interest. This richness of collected information would allow for better adjustment of confounding in the estimation of mpox vaccine effectiveness. The diagnostic issues with test-negative designs, as mentioned above, do not affect cohort studies in the same way since all participants are screened for mpox symptoms and tested when clinically appropriate. Serology testing of all participants at fixed time points can further help to mitigate bias. An mpox study nested within an ongoing community cohort study could also be expanded to household members of participants, including children. Studying mpox vaccination in a pre-existing observational cohort would generate valuable data on vaccine effectiveness by comparing incidence in vaccinated and unvaccinated participants, on risk factors for mpox acquisition and transmission, as well as provide robust before- and after-data on vaccine safety.

Without intensified public health measures, the new mpox Ia and Ib clades will continue to spread. Optimal

vaccine deployment strategies depend on the setting, the public health aim, and the effectiveness of vaccination in preventing transmission and disease. We believe the immediate priority for vaccine research is the estimation of vaccine effectiveness against disease, particularly amongst children. In settings like the DRC, the test-negative design is a good option because of its convenience, efficiency, and feasibility. Despite its limitations, it may be able to deliver timely information in an evolving outbreak situation. In other settings like Uganda, where the necessary infrastructure is available, we recommend that existing ongoing cohort studies should be leveraged, as these will yield richer information.

Contributor

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