Mpox vaccines attenuate disease – but evidence and equity gaps remain

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MPOX, an infection closely related to smallpox, has traditionally been associated with zoonotic outbreaks and limited human to human transmission in West and Central Africa[1]. In 2022, a global pandemic of MPOX occurred with more than 100,000 confirmed cases reported across every inhabited continent. Transmission was predominantly associated with close physical and sexual contact, disproportionately affecting gay, bisexual, and other men who have sex with men (GBMSM)[2].

Initial responses focused on isolation of cases and behavioural guidance for at risk populations. Biomedical interventions quickly followed, particularly targeted vaccination of individuals at highest risk, such as health care workers and GBMSM.

At the time of the pandemic, no specific MPOX vaccines had been developed or evaluated. Instead, attention turned to the Modified Vaccinia Ankara vaccine (MVA-BN, marketed as JYNNEOS), previously licensed for smallpox. Notably, this vaccine had been shown to protect non-human primates in an MPOX challenge model and to be immunogenic and safe in studies in healthy volunteers[3,4]. Many countries worldwide ultimately rolled out either single or two-dose vaccination schedules of the MVA-BN vaccine

In this issue of *The Lancet Infectious Diseases*, Granskog and colleagues[5] conducted a case control study involving 4,609 cisgender males, employing detailed public health surveillance data from California. Whilst previous studies mainly focused on infection prevention, the current study provides valuable insights into the disease modifying impact of vaccination. The authors estimate a vaccine effectiveness against progression (VEP) to disease involving disseminated lesions of 58.8% (95%CI: 50.3-65.9%), and VEP for hospitalization of 85.4% (54.3-95.3%), suggesting the vaccine mitigates disease severity. Consistent with other studies they demonstrate that overall protection was markedly higher for pre-exposure vaccination than post-exposure. Protection against severe disease was higher than against any infection demonstrating that this effect was not solely mediated by preventing infection in the first place. The study also shows reduced VEP among people living with HIV (44.8% [27.5-58.0%]) – particularly in those with low CD4 counts yet still shows a clear role in preventing severe outcomes.

Strengths of the study include the prospective nature of data collection and the use ofstandardised tools to assess clinicals severity and outcomes. Although the study is focused on cis-gender males it would appear reasonable to assume that similar reduction in disease severity would also be expected in other groups who receive vaccination.

A number of points warrant particular consideration. The study by Granskog and colleagues[5] adds to a number of other non-randomised studies which have evaluated the protective effectiveness of the MVA-BN vaccine[6]. Collectively, these suggest high levels of protection when used pre-exposure and a modest protection when used post-exposure. Whilst there was clearly an urgent need to deploy vaccination as a potential public health intervention, it is disappointing that no randomised trial data was generated globally on vaccine efficacy of the MVA-BN vaccine. Experience from the West African Ebola outbreak has clearly demonstrated that such trials can be conducted rapidly and ethically, even in pandemic emergency settings. At a time when vaccinations are under increasing scrutiny, we must be certain that we do not lower the standards of evidence that are required to licence and ultimately adopt novel vaccines.

An additional concern is the durability of vaccine-induced protection. The study[5]gr time period covers May 2022 to December 2023, with vaccination beginning mid-2022. While follow-up could extend up to 16 months, the median time from vaccination to illness onset was 47 days (IQR: 28–318), so most infections occurred within a few months—limiting evaluation of long-term protection. Accumulating immunological evidence suggest waning immunity within months of exposure[7], which may affect not only infection risk but also effectiveness against progression to severe disease. Moreover, subcutaneous or intramuscular administration induce limited mucosal immunity, potentially insufficient to prevent viral entry at genital or rectal sites, and possibly dissemination. These limitations underscore the need for longer-term follow up studies.

Secondly, the fact remains that the overwhelming burden of severe outcomes associated with MPOX is in Africa. Over the last 18 months major outbreaks of Clade I MPOX have occurred in both West and Eastern regions of the Democratic Republic of Congo with cross-border transmission occurring to neighbouring countries in the region[8,9]. Compared to the global north, access to vaccination in populations most at need remains limited undoubtedly contributing to ongoing transmission, morbidity,and mortality amongst some of the most at risk populations in the world. Vaccine efficacy data to date has been almost exclusively derived from observational studies and in the context of Clade II MPOX. There is an urgent need to generate robust, prospective, and ideally randomised data on vaccine effectiveness against Clade I infection in order to guide public health responses. Vaccines remain one of the most powerful tools we have in the fight against infectious diseases and it is vital that we support and advocate to ensure they reach those most in need.

Declarations of Interest

MM declares no competing interests. OM reports that the Fight Infectious Diseases Foundation received research funding from Bavarian Nordic to conduct studies on vaccine effectiveness.

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