PNAS Nexus, 2023, 2, 1–4
https://doi.org/10.1093/pnasnexus/pgad095
Advance access publication 28 March 2023
Brief Report

Evaluation of mpox vaccine dose-sparing strategies

Dobromir Dimitrov [a,b,*], Blythe Adamson [c,d] and Laura Matrajt [a,b]

[a]Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Center, Seattle, WA 98109, USA
[b]Department of Applied Mathematics, University of Washington, Seattle, WA 98195, USA
[c]Infectious Economics, New York, NY 10025, USA
[d]Comparative Health Outcomes, Policy and Economics (CHOICE) Institute, School of Pharmacy, University of Washington, Seattle, WA 98195, USA
*To whom correspondence should be addressed: Email: ddimitro@scharp.org
Edited By: Bruce Levine

Abstract

The spring–summer 2022 mpox outbreak had over 50,000 cases globally, most of them in gay, bisexual, and other men who have sex with men (MSM). In response to vaccine shortages, several countries implemented dose-sparing vaccination strategies, stretching a full-dose vaccine vial into up to five fractional-dose vaccines. Recent studies have found mixed results regarding the effectiveness of the mpox vaccine, raising the question of the utility of dose-sparing strategies. We used an age- and risk-stratified mathematical model of an urban MSM population in the United States with ∼12% high-risk MSM to evaluate potential benefits from implementing dose-sparing vaccination strategies in which a full dose is divided into 3.5 fractional doses. We found that results strongly depend on the fractional-dose vaccine effectiveness (VE) and vaccine supply. With very limited vaccines available, enough to protect with a full dose approximately one-third of the high-risk population, dose-sparing strategies are more beneficial provided that fractional doses preserved at least 40% of full-dose effectiveness (34% absolute VE), projecting 13% (34% VE) to 70% (68% absolute VE) fewer infections than full-dose strategies. In contrast, if vaccine supply is enough to cover the majority of the high-risk population, dose-sparing strategies can be outperformed by full-dose strategies. Scenarios in which fractional dosing was 34% efficacious resulted in almost three times more infections than full dosing. Our analysis suggests that when mpox vaccine supply is limited and fractional-dose vaccination retains moderate effectiveness, there are meaningful health benefits from providing a smaller dose to a larger number of people in the high-risk population. These findings should inform the public-health response to future mpox outbreaks.

Keywords: mpox virus, mpox vaccine, fractional dosing, mathematical model

Introduction

The World Health Organization declared the mpox outbreak a public health emergency of international concern on 2022 July 23 (1). By September 2022, there were over 50,000 cases globally, and over 21,000 cases in the United States most of them occurring in gay, bisexual, and other men who have sex with men (MSM) (2). In the United States, two vaccines are approved for the prevention of mpox: the JYNNEOS vaccine (MVA vaccine) and the ACAM2000 vaccine. JYNNEOS is currently preferred and utilized as it has fewer side effects and contraindications. Due to the shortage of vaccine supply, regulatory agencies including the US Federal Drug Administration authorized a lower-than-standard dose regimen of two intradermal injections, allowing each vaccine vial to be divided into up to five fractional-dose vaccines (3–5). This dose-sparing strategy was based on a clinical study done in 2015 (6), but recent studies have found mixed results for effectiveness (7) raising the question of whether fractional dosing is the best use of the limited supply of MVA vaccine. In the present work, we use a mathematical model to explore different scenarios under which fractional dosing would be the optimal use of the available MVA vaccine.

Results

To compare the health outcomes from full-dose versus dose-sparing mpox vaccine strategies, we adapted a previously developed, calibrated, and published infectious disease dynamic transmission model of sexual activity patterns and HIV spread in a population of MSM in Seattle, WA (8). The population included 65,000 men stratified into age and risk groups, with ∼8,000 individuals in the group at high risk of mpox acquisition and greater need for vaccination. A model diagram (Fig. S1) and complete model description, including sexual mixing patterns (Table S1) and all parameters used in the analysis (Tables S3 and S4), can be found in the Supplement.

Our base-case scenario without vaccination resulted on average in 11, 330 cumulative infections over 6 months with a maximum of 1,126 infections weekly. In the main vaccination scenario, we simulated vaccination campaigns over 5 weeks with either 2,500 or 7,500 full-dose vaccine vials available (31 and 94% of the high-risk population). For dose-sparing strategies, we assumed that each vaccine vial could be divided into 3.5 fractional doses (9), so that there was enough vaccine to cover 8,750 or

Competing Interest: The authors declare no competing interest.
Received: November 21, 2022. **Accepted:** March 8, 2023

Table 1. Comparison of full-dose with dose-sparing mpox vaccination strategies for our main scenarios.

	Full-dose vaccination strategy	Dose-sparing vaccination strategy (% incremental difference compared with full dose)	
Population size of men who have sex with men (number high risk)		**65,000 [7,924]**	
Number of high-risk people vaccinated	**2,500**	**8,750** (+250%)	
Vaccine effectiveness (VE)	**85%**	Low VE **34%**	High VE **68%**
Peak weekly number of new MPX infections over 6 months	745	736 (−1.2%)	170 (−77.1%)
Cumulative number of new MPX infections over 6 months	5,424	4,743 (−12.6%)	1,679 (−69.0%)
Number of people vaccinated	**7,500**	**26,250** (+250%)	
Vaccine effectiveness (VE)	**85%**	Low VE **34%**	High VE **68%**
Peak weekly number of new MPX infections over 6 months	115	655 (+465%)	122 (+5.3%)
Cumulative number of new MPX infections over 6 months	1,420	4,147 (+193%)	1,358 (−4.3%)

26,250 people (corresponding to 2,500 and 7,500 vaccine vials, respectively). We assumed that a full dose of MVA vaccine had a vaccine effectiveness (VE) of 85% against mpox infection (10). We simulated low (34% absolute VE) and high (68% absolute VE) fractional-dose VE scenarios, corresponding to retaining 40 or 80% of the effectiveness of the full-dose vaccine (Table 1). We ran additional scenarios (see Fig. 1 and Table S2) with 5,000 or 10,000 full doses available, delaying the vaccination campaigns by 5 or 10 weeks, and exploring fractional-dose VE ranging from 17% (20% of the full-dose VE) to 85% (100% of the full-dose VE). In all scenarios, the high-risk population was vaccinated first, and additional doses (if available) were then offered to the low-risk population.

When a limited number of vaccine vials were available (2,500 vaccine vials), sufficient to vaccinate 31% of the high-risk population, a dose-sparing strategy prevented more infections compared with full-dose vaccination as long as the fractional-dose VE was >34%, retaining 40% of the effectiveness of a full dose. In that scenario, we projected 13% fewer infections when the dose-sparing strategy was implemented instead of the full-dose strategy with 1% less infections at the peak recorded over 6 months (Table 1), and it averted 6% more infections than full-dose vaccination when comparing both strategies to a base-case scenario without vaccination (Fig. 1A). In contrast, if 7,500 vaccine vials were available (enough to cover 94% of the high-risk population), then full-dose campaigns were projected to outperform dose-sparing campaigns with low fractional-dose VE (34%). In that scenario, dose-sparing strategies would generate almost three times more infections than full-dose campaigns (Table 1), averting 21% fewer cumulative base-case infections (Fig. 1C).

Assuming high-fractional-dose VE (68%, retaining 80% of the full-dose VE), dose-sparing strategies always outperformed or were similar to full-dose campaigns. With limited vaccine supply (2,500 vials), dose-sparing strategies resulted in 69% fewer cumulative infections and 77% less infections at the peak compared with full-dose strategies, averting an additional 30% in cumulative base-case infections (Fig. 1A, magenta vs. black). With more vaccine supply, the number of base-case infections averted by the full-dose (86.7%) and fractional-dose (87.4%) strategies were similar with slightly more infections at the peak (+5.3%) projected with dose-sparing strategies.

In the most optimistic scenario in which fractional dosing is as effective as full dosing with limited number of vaccine vials available (2,500 vials), the fractional-dose strategy is expected to prevent >30% more infections (compared with no vaccination) over 6-month period. However, in simulations with large number of vaccine vials available (at least 7,500 vials), the projected increase in the infections averted by using fractional-dose compared with full-dose strategies was ∼5% when both strategies were implemented without delay. This difference grew to 13% if vaccination was initiated after 10-week delay (Fig. 1C). In contrast, in the more pessimistic scenario, if fractional dosing had very low VE (17%), then dose-sparing strategies would result in more infections than full-dose vaccination across all scenarios considered. The projected difference between these two strategies in proportion infection averted was projected to be between 13 and 20% with limited vaccine availability (2,500 vials, Fig. 1A) but increased to >40% if >7,500 vaccine vials were available (Fig. 1C and D).

Our findings suggest that when there is limited availability of mpox vaccine supply, there is a threshold in the fractional dose VE above which it is expected to prevent more infections than full-dose vaccination. As a greater supply of vaccine becomes available, the threshold for fractional-dose VE needed to outperform full-dose vaccination increases: with 2,500 vials the threshold is below 34% as our main results showed; at 5,000 vials, fractional-dose vaccines need to be at least 51% efficacious (approximately same proportion of cumulative infections averted over 6 months when compared with no vaccination: 80 vs. 79.5%, respectively; Fig. 1B). If at least 7,500 vials were available, the fractional-dose vaccines needed to be at least 68% efficacious to avert as many infections as the full-dose campaign (Fig. 1, C and D). There was little gain in the number of infections averted once the available vaccine doses exceeded the size of the high-risk group (Fig. 1, C vs. D).

Discussion

Several regulatory agencies have approved the use of fractional dosing for the MVA vaccine, allowing each vaccine vial of the MVA vaccine to be divided into up to five intradermal fractional-dose vaccines. However, a recent study has raised concerns about the effectiveness of the fractional-dose vaccines (7). In the present work, we used a previously validated model of the network of an urban MSM population in the United States and adapted it to the summer of 2022 US mpox outbreak. Our analysis projected better population health outcomes with a dose-sparing compared with full-dose vaccine strategy in times when there is shortage in mpox vaccine supply. Considering that as of the summer of 2022, the United States had secured 1.1 million of MVA vaccines and that there are an estimated 1.7 million people at high risk (11), our results suggest that dose-sparing strategies would outperform full-dose vaccination provided that the fractional dose retains at least 60% effectiveness of the full dose. These results are consistent with previous studies for other infectious diseases, such as cholera (12, 13), influenza (14, 15), and COVID-19 (16), which

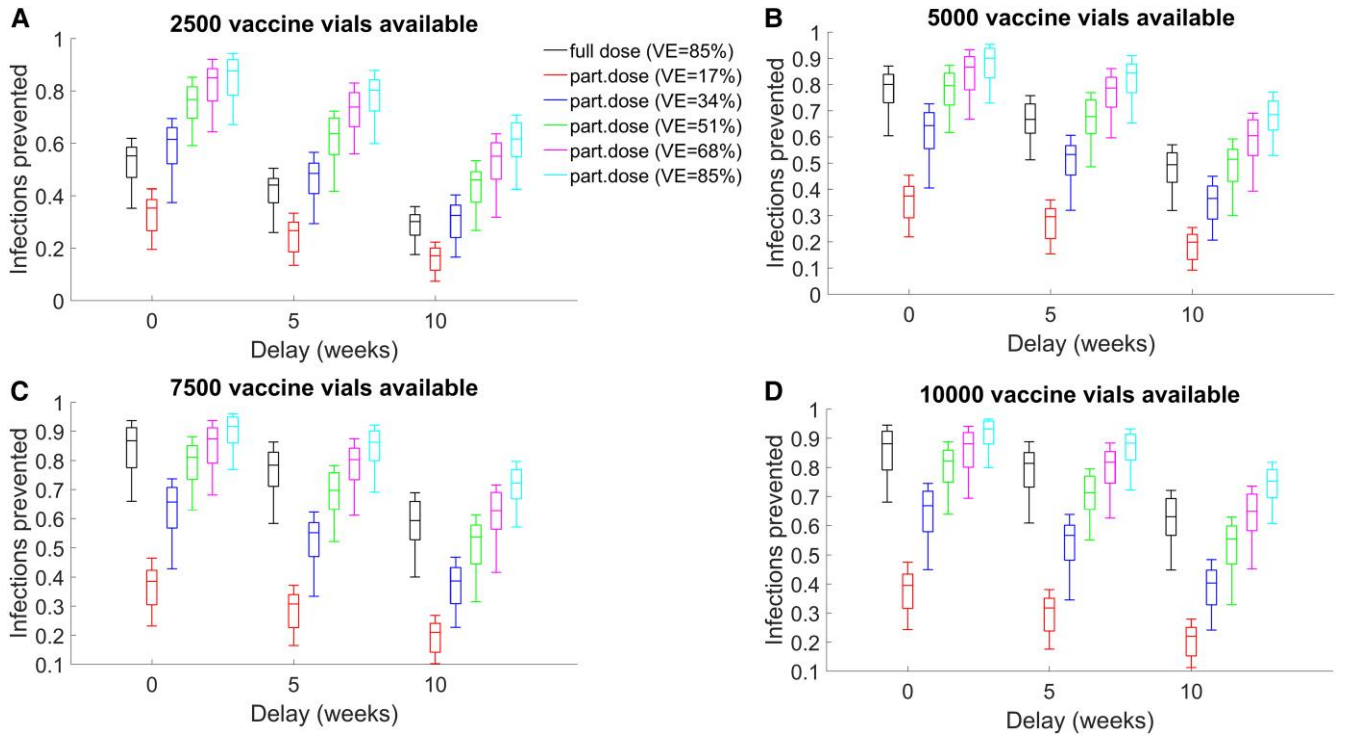

Fig. 1. Proportion of infections prevented for (A) 2,500, (B) 5,000, (C) 7,500, or (D) 10,000 vaccine vials available compared with base-case scenario without vaccination. For each panel, we compared vaccination with full-dose (VE = 85%) and fractional-dose VE, ranging from 17 to 85%. We compared immediate vaccination (0-week delay) to delayed vaccination starting 5 or 10 weeks after the first infection was identified.

have found that dose-sparing strategies are optimal when the fractional-dose VE is around half as effective as the full dosage. The fewer the doses of MVA vaccine available, the projected payoff from using dose-sparing strategies increases. Finally, we demonstrated that delaying the vaccination even by a few weeks may lead to a substantial reduction of the expected benefits from the vaccination campaign in terms of prevented infections. We have reported similar results when COVID vaccines were rolled out in early 2021 (17).

Our model, like any mathematical model, is subject to some limitations. We assumed that the MVA vaccine is highly efficacious in preventing infection, but more data are needed to evaluate the effectiveness of the MVA vaccine in this outbreak. If the vaccine only prevents disease but not transmission, vaccinated individuals could continue to spread the mpox virus to others (2, 18). We simulated an MSM population with relatively small proportion of high-risk individuals. If this proportion was bigger, then dose-sparing strategies would be more effective when compared with full-dose vaccination for low vaccine supply, provided that the fractional dose VE remained moderately high. We assumed that mpox virus would transmit only in the MSM population, but spillovers to other populations are likely to happen. Reports of people getting infected without sexual exposure are starting to emerge (19), but continue to be rare. Although we use vaccine supply as limiting factor, vaccination coverage may also be affected by vaccine accessibility and hesitancy which may vary by risk group and render some vaccination strategies more difficult to achieve. In the present work, we focused only on dose-sparing strategies as a way to stretch vaccine supply. However, other strategies, like delaying the second dose, could also be considered.

Taken together, our results suggest that when mpox vaccine supply is limited and fractional dosing retains at least moderate effectiveness, there can be meaningful health benefits from providing a smaller dose to a larger number of people in the high-risk population.

It is then imperative to evaluate the effectiveness of a fractional dose of the MVA vaccine in the context of the current outbreak.

Supplementary material

Supplementary material is available at *PNAS Nexus* online.

Funding

This work was partially supported by grants from the National Institute of Allergy and Infectious Diseases of the National Institutes of Health (UM1AI068635 and UM1AI068617). This material is also based upon work supported by the National Science Foundation under grant no. 2210382.

Author contributions

L.M. and D.D. conceptualized the work and wrote the first draft. D.D. and B.A. developed and calibrated the original HIV model. D.D. performed the analysis. All authors contributed to manuscript writing.

Data availability

All data needed to reproduce this analysis are included in the manuscript and/or supporting information.

References

1 WHO. 2022. WHO director-general declares the ongoing monkeypox outbreak a Public Health Emergency of International

Concern [accessed 2022 Nov 20]. https://www.who.int/europe/news/item/23-07-2022-who-director-general-declares-the-ongoing-monkeypox-outbreak-a-public-health-event-of-international-concern.
2 CDC. 2022. Interim clinical considerations for use of JYNNEOS and ACAM2000 vaccines during the 2022 U.S. monkeypox outbreak [accessed 2022 Nov 20]. https://www.cdc.gov/poxvirus/monkeypox/health-departments/vaccine-considerations.html.
3 FDA. 2022. Monkeypox update: FDA authorizes emergency use of JYNNEOS vaccine to increase vaccine supply [accessed 2022 Nov 20]. https://www.fda.gov/news-events/press-announcements/monkeypox-update-fda-authorizes-emergency-use-jynneos-vaccine-increase-vaccine-supply.
4 European Medicines Agency. 2022. EMA's emergency task force advises on intradermal use of Imvanex/Jynneos against monkeypox [accessed 2022 Nov 20]. https://www.ema.europa.eu/en/news/emas-emergency-task-force-advises-intradermal-use-imvanex-jynneos-against-monkeypox.
5 UK Health Security Agency. 2022. Monkeypox vaccines to be piloted in smaller but equally effective doses [accessed 2022 Nov 20]. https://www.gov.uk/government/news/monkeypox-vaccines-to-be-piloted-in-smaller-but-equally-effective-doses.
6 Frey SE, *et al.* 2015. Comparison of lyophilized versus liquid modified vaccinia Ankara (MVA) formulations and subcutaneous versus intradermal routes of administration in healthy vaccinia-naïve subjects. *Vaccine*. 33:5225–5234.
7 Zaeck LM, *et al.* 2023. Low levels of monkeypox virus neutralizing antibodies after MVA-BN vaccination in healthy individuals. *Nat Med*. 29:270–278.
8 Adamson B, *et al.* 2019. Competing biomedical HIV prevention strategies: potential cost-effectiveness of HIV vaccines and PrEP in Seattle, WA. *J Int AIDS Soc*. 22:e25373.
9 Branswell H, Gaffney T. 2022. U.S. plan to stretch monkeypox vaccine supply already hitting hurdles [accessed 2022 Nov 20]. https://www.statnews.com/2022/08/23/u-s-plan-to-stretch-monkeypox-vaccine-supply-runs-into-problems/.
10 Jezek Z, Grab B, Szczeniowski MV, Paluku KM, Mutombo M. 1988. Human monkeypox: secondary attack rates. *Bull World Health Organ*. 66:465–470.
11 CNBC. 2022. CDC estimates 1.7 million gay and bisexual men face highest risk from monkeypox [accessed 2022 Nov 20]. https://www.cnbc.com/2022/08/04/cdc-estimates-1point7-million-gay-and-bisexual-men-face-highest-risk-from-monkeypox-.html.
12 Azman AS, *et al.* 2015. The impact of a one-dose versus two-dose oral cholera vaccine regimen in outbreak settings: a modeling study. *PLoS Med*. 12:e1001867.
13 Leung T, Eaton J, Matrajt L. 2022. Optimizing one-dose and two-dose cholera vaccine allocation in outbreak settings: a modeling study. *PLoS Negl Trop Dis*. 16:e0010358.
14 Riley S, Wu JT, Leung GM. 2007. Optimizing the dose of pre-pandemic influenza vaccines to reduce the infection attack rate. *PLoS Med*. 4:e218.
15 Matrajt L, Britton T, Halloran ME, Longini IM Jr. 2015. One versus two doses: what is the best use of vaccine in an influenza pandemic? *Epidemics*. 13:17–27.
16 Matrajt L, *et al.* 2021. Optimizing vaccine allocation for COVID-19 vaccines shows the potential role of single-dose vaccination. *Nat Commun*. 12:3449.
17 Swan DA, *et al.* 2021. COVID-19 vaccines that reduce symptoms but do not block infection need higher coverage and faster rollout to achieve population impact. *Sci Rep*. 11:15531.
18 Kupferschmidt K. 2022. Scientists scramble to set up monkeypox vaccine trials. *Science*. 377(6607):696–697.
19 CIDRAP. 2022. Florida infant, New Hampshire child contract monkeypox [accessed 2022 Nov 20]. https://www.cidrap.umn.edu/news-perspective/2022/09/florida-infant-new-hampshire-child-contract-monkeypox.