Effectiveness of modified vaccinia Ankara-Bavarian Nordic vaccine against mpox infection: emulation of a target trial

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ABSTRACT

OBJECTIVE

To estimate the real world effectiveness of modified vaccinia Ankara-Bavarian Nordic (MVA-BN) vaccine against mpox infection.

DESIGN

Emulation of a target trial.

SETTING

Linked databases in Ontario, Canada.

PARTICIPANTS

9803 men aged ≥18 years with a history of being tested for syphilis and a laboratory confirmed bacterial sexually transmitted infection (STI) in the previous year, or who filled a prescription for HIV pre-exposure prophylaxis in the previous year. On each day between 12 June 2022 and 27 October 2022, those who had been vaccinated 15 days previously were matched 1:1 with unvaccinated men by age, geographical region, past HIV diagnosis, number of bacterial STI diagnoses in the previous three years, and receipt of any non-MVA-BN vaccine in the previous year.

MAIN OUTCOME MEASURE

The main outcome measure was vaccine effectiveness ((1−hazard ratio)×100) of one dose of subcutaneously administered MVA-BN against laboratory confirmed mpox infection. A Cox proportional hazards model was used to estimate hazard ratios to compare the rate of laboratory confirmed mpox between the two groups.

RESULTS

3204 men who received the vaccine were matched to 3204 unvaccinated controls. A total of 71 mpox infections were diagnosed, with 0.09 per 1000 person days (95% confidence interval (CI) 0.05 to 0.13) in the vaccinated group and 0.20 per 1000 person days (0.15 to 0.27) in the unvaccinated group over the study period of 153 days. Estimated vaccine effectiveness of one dose of MVA-BN against mpox infection was 58% (95% CI 31% to 75%).

CONCLUSION

The findings of this study, conducted in the context of a targeted vaccination programme and evolving outbreak of mpox, suggest that one dose of MVA-BN is moderately effective in preventing mpox infection.

Introduction

In May 2022, more than 20 countries where mpox had not been previously identified reported infections to the World Health Organization.[1] On 23 July 2022, the global mpox outbreak was declared a public health emergency of international concern, and targeted use of second or third generation smallpox vaccines was recommended for control of the outbreak.[2]

Modified vaccinia Ankara-Bavarian Nordic (MVA-BN) vaccine (trade names Imvamune, Jynneos, and Imvanex) is a third generation, live attenuated, non-replicating vaccine against smallpox.[3] In Ontario, Canada, MVA-BN was introduced in June 2022 as post-exposure prophylaxis for high risk contacts (but few doses were given in this context) and pre-exposure prophylaxis for gay, bisexual, and other men who have sex with men, and sex workers at high risk of exposure to mpox.[4] Although MVA-BN is approved in Canada as a series of two doses 28 days apart, Ontario initially employed a dose sparing strategy such that vaccine candidates could only receive one dose owing to concerns about limited vaccine supply. A two dose (0.5 mL each, subcutaneously) programme was subsequently implemented on 30 September 2022.

Before the global mpox outbreak, clinical or real world data on the use of MVA-BN to prevent mpox infection were limited.[5 6] Estimates of the effectiveness of a single dose of MVA-BN obtained using various observational study designs have since emerged in the literature, ranging from 36% to 86%.[7-15] As with all observational studies, each report discussed the potential for residual confounding and selection biases. Only one study to date emulated a target trial to address these biases, but it was restricted to HIV negative men who had used HIV pre-exposure prophylaxis.[10] In the current study we estimated the vaccine effectiveness of one dose of MVA-BN against laboratory confirmed mpox infection in a broader population through a target trial emulation to reduce biases.

Methods

Study design, setting, and population

We conducted a target trial emulation to answer the causal question of interest (see supplementary figure S1 and table S1) and to reduce biases, particularly from confounding.[16] Laboratory, vaccination, reportable diseases, and health administrative data were used from Ontario (population 15.1 million as of July 2022), which has a single payer healthcare system. All datasets included in the analysis (see supplementary methods) were linked using unique encoded identifiers and analysed at ICES.

The study period captured the beginning of the availability of pre-exposure vaccination (12 June 2022 to 26 November 2022, during which time mpox was

diagnosed in 691 people in Ontario; fig 1, also see supplementary table S2 for Ontario surveillance definitions of mpox).[17] The end date was chosen based on several indicators, including weekly percentage positivity <5% and the last individual with outbreak associated mpox reported on 10 November 2022.[18] Eligibility for single dose, pre-exposure vaccination comprised gay, bisexual, and other men who have sex with men reporting one or more of a diagnosis of bacterial sexually transmitted infection (STI) in the previous two months; currently engaging in or anticipating sex with two or more sexual partners; attending sex-on-premises venues; or engaging in anonymous sex. Eligibility for pre-exposure vaccination also included individuals engaged in sex work, immunocompromised individuals, or pregnant individuals if they were contacts of people at risk, as defined above.[19]

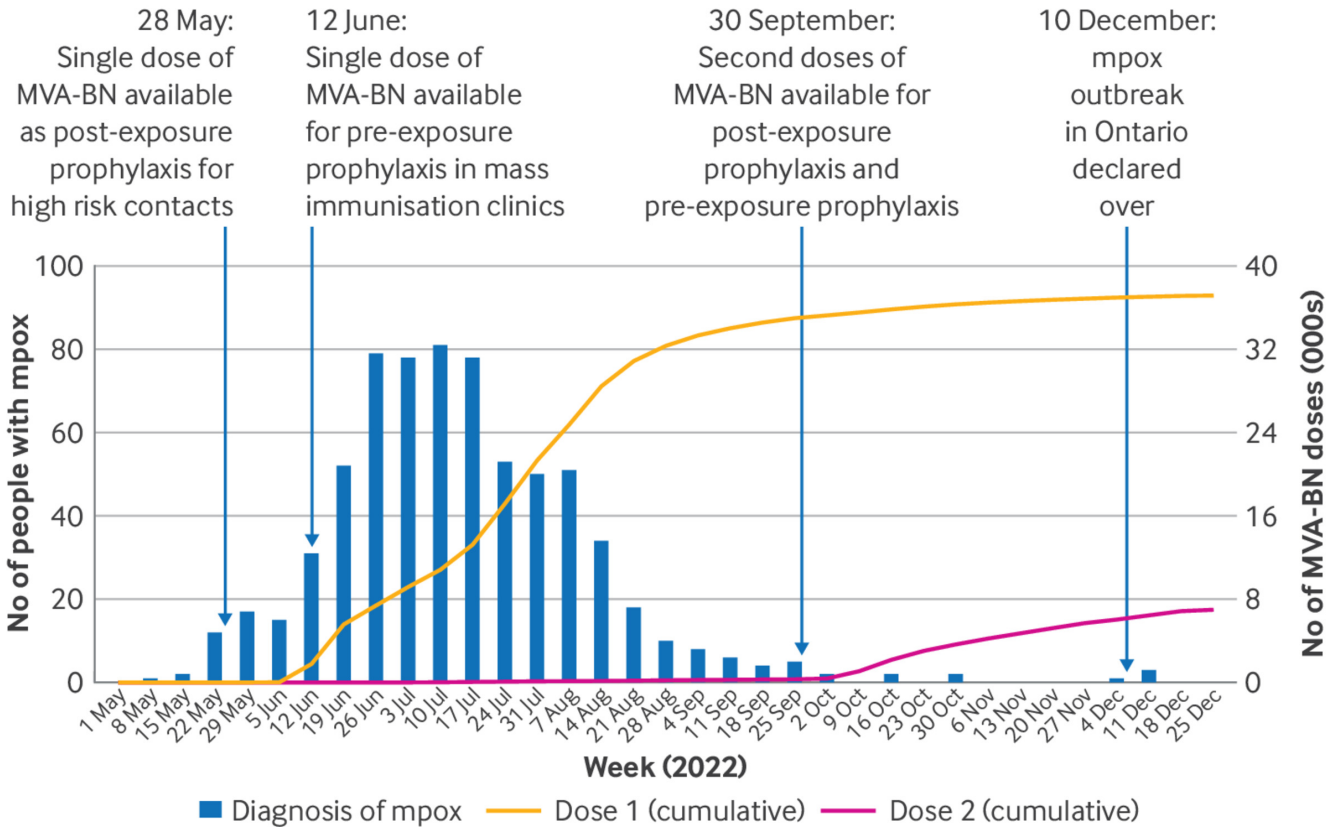


Fig 1 | Confirmed mpox infections and number of MVA-BN vaccine doses administered by week in Ontario, Canada, 1 May to 25 December 2022. MVA-BN= modified vaccinia Ankara-Bavarian Nordic

Because the administrative data do not include information on each of the specific criteria laid out by Ontario's MVA-BN vaccine programme, we used proxies for potential sexual exposure to mpox to define our eligible population for the trial specification. That is, if a randomised control trial were to be possible but was restricted to using variables available in the health administrative data, our approach to target trial specification would make use of these variables as proxies for sexual activity (see supplementary table S1). Eligibility criteria for the target trial were conceptualised to reduce confounding between vaccination status and risk of subsequent infection. The study population was restricted to men aged ≥18 years as of 12 June 2022 with at least one of the following proxies for risk of exposure to mpox as of the date of matching (ie, time zero, which could occur between 12 June 2022 and 27 October 2022, to ensure each person could have at least 30 days of observation): at least one syphilis test in the previous year and a new diagnosis of one bacterial STI or more (chlamydia, gonorrhoea, or syphilis) in the year before matching; or a filled prescription for HIV pre-exposure prophylaxis in the year before matching (see supplementary table S3 for definitions). We excluded individuals with a documented positive polymerase chain reaction test result for mpox before 12 June 2022.

Intervention and outcome

The intervention of interest was vaccination with a single dose of MVA-BN. We were unable to estimate the effectiveness of a second dose because only a few individuals had received such a dose (13.7% of those who received one dose) by the end of the study period (26 November 2022) and few people received an mpox diagnosis in October and November. The outcome of interest was polymerase chain reaction confirmed mpox infection, based on the specimen collection date. Based on immunogenicity data, an individual was classified as vaccinated >14 days after the first dose.[20]

Specification and emulation of the target trial

On each day between 12 June 2022 and 27 October 2022, men who had been vaccinated with a single dose of MVA-BN 15 days previously were matched in a 1:1 ratio to unvaccinated controls. We followed individuals until the earliest date of any of the following events: outcome, death, 15 days after receipt of a first vaccine dose (for unvaccinated controls), 15 days after receipt of a second dose, or end of the study period. Individuals who initially contributed observation time as an unvaccinated control were censored (along with their matched vaccinated individual) 15 days after receipt of

MVA-BN and were re-matched as a vaccinated individual with a new unvaccinated control (see supplementary table S1).[21]

To balance the distribution of measured baseline covariates that are associated with the probability of vaccination and mpox infection between vaccine recipients and controls, we matched vaccine recipients and controls on age (within five years), geographical region (since the epidemic trajectory and vaccine uptake varied regionally), proxies for sexual exposures (number of bacterial STIs in the previous three years, HIV status), and a proxy for vaccine confidence (receipt of any non-MVA-BN vaccine in the previous year). These covariates were defined using 12 June 2022. The supplementary methods section provides details of the matching algorithm. For vaccinated individuals, time zero was 15 days after vaccination, whereas unvaccinated controls inherited the time zero of the vaccinated person to whom they were matched.

We conducted three sensitivity analyses. To explore the potential for residual confounding by risk of sexual exposures, we used two negative control outcomes that should not be directly affected by the receipt of MVA-BN but for which the effect of vaccination might be confounded.[22] Firstly, we measured the risk of mpox during the first 14 days after the first dose, when no difference between vaccinated and unvaccinated groups would be expected (the negative outcome period). Secondly, we used a negative tracer outcome by estimating vaccine effectiveness against bacterial STI >14 days after vaccination; MVA-BN vaccine presumably has no benefit against infection with chlamydia, gonorrhoea, or syphilis. However, an STI diagnosis could be influenced by differential rates of testing after vaccination. Thus we compared syphilis testing among vaccinated and unvaccinated groups over the study period to aid interpretation of the negative tracer outcome. Finally, we examined the potential for residual confounding related to socioeconomic status by adjusting for income at neighbourhood level, given that sexual networks and infection risks are shaped by systemic barriers to engagement in healthcare and access to vaccines.

Statistical analysis

We examined covariate balance after matching using standardised mean differences, and considered a difference of ≥0.1 as potentially clinically meaningful.[23] Cumulative incidence functions were estimated for the vaccinated and unvaccinated groups and we used a Cox proportional hazards model to estimate the hazard ratio comparing the hazard of mpox between the two groups, using a robust variance estimator to account for the matched design.[24] We calculated vaccine effectiveness as ((1−hazard ratio)×100). Analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC).

Patient and public involvement

This work was undertaken in response to questions about the effectiveness of MVA-BN by public health, clinical, and community members. Participants were not involved in the original design of this study. We shared study results with diverse community representatives interested in the mpox response.

Results

A total of 9803 men aged ≥18 years were eligible for the study, of whom 272 received a diagnosis of mpox during the study period, including 15 who required hospital admission with mpox. A total of 3204 men who received the vaccine were matched to 3204 unvaccinated controls (fig 2). The matched population was similar to the eligible population for baseline characteristics (see supplementary table S4). All measured variables were well balanced between the vaccinated and unvaccinated groups (table 1). The median age of matched participants was 35 years (interquartile range (IQR) 29-46 years) and more than half of the participants (66.1%) were residents of Toronto.

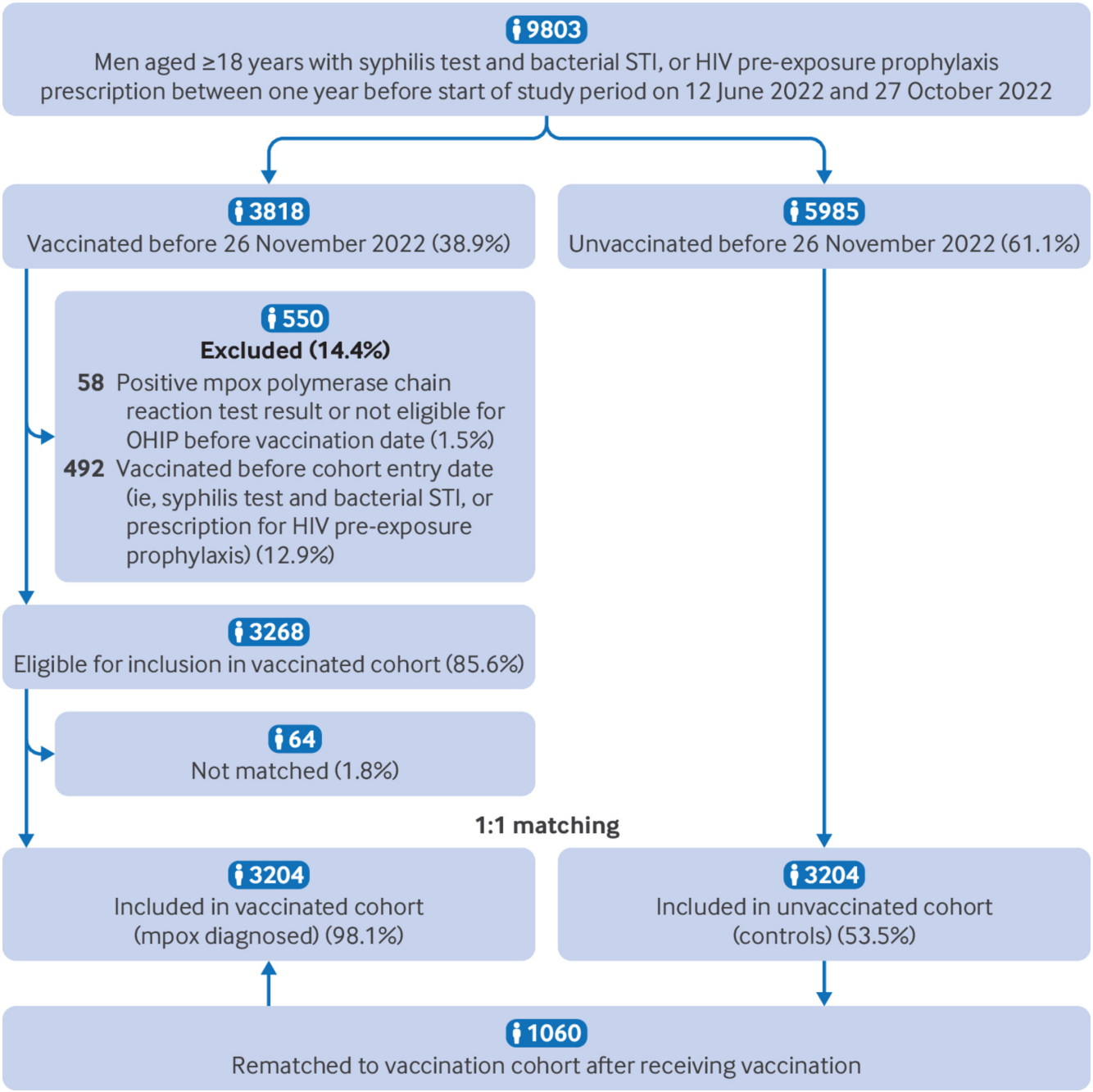


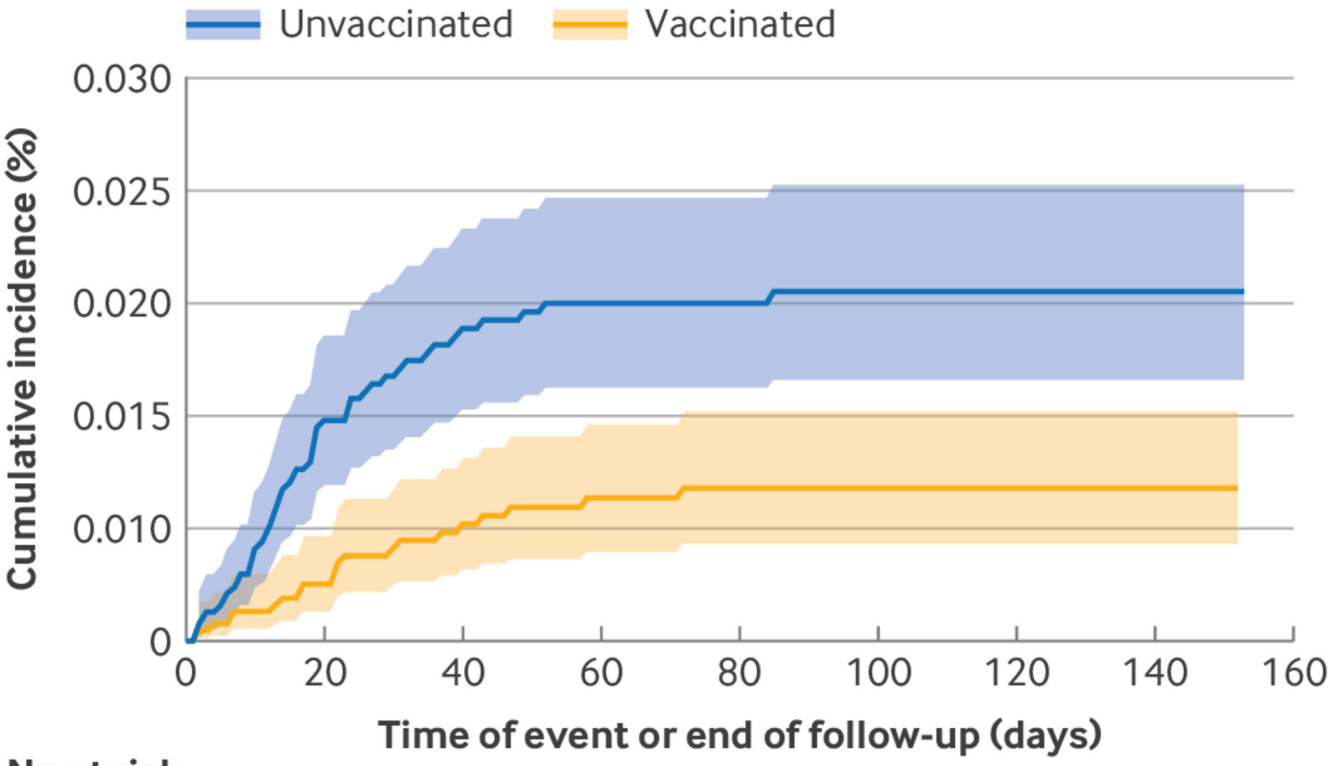
Fig 2 | Cohort enrolment process and selection of individuals for emulation of a target trial evaluating effectiveness of the modified vaccinia Ankara-Bavarian Nordic. OHIP=Ontario Health Insurance Plan; STI=sexually transmitted infection

Table 1 | Personal and sexual risk characteristics of the study population for the target trial emulation design. Values are number (percentage) unless stated otherwise

Characteristics	Vaccinated (n=3204)	Unvaccinated (n=3204)	Standardised difference
Median (IQR) age (years)	35 (29-46)	35 (29-46)	0.03
Age group (years):			
18-24	418 (13.0)	424 (13.2)	0.006
25-29	448 (14.0)	447 (14.9)	0.03
30-39	1122 (35.0)	1121 (35.0)	0.001
40-49	562 (17.5)	540 (16.9)	0.02
≥50	654 (20.4)	642 (20.0)	0.009
Geographical region, Ontario:			
Toronto	2117 (66.1)	2117 (66.1)	0
Peel, York, Durham, Halton	345 (10.8)	345 (10.8)	0
Hamilton, Niagara, London, Windsor	212 (6.6)	212 (6.6)	0
Ottawa	247 (7.7)	247 (7.7)	0
Rest of Ontario	283 (8.8)	283 (8.8)	0
Neighbourhood income fifth:			
1 (lowest)	794 (24.8)	938 (29.3)	0.10
2	742 (23.2)	753 (23.5)	0.008
3	604 (18.9)	572 (17.9)	0.03
4	508 (15.9)	475 (14.8)	0.03
5 (highest)	452 (14.1)	543 (16.9)	0.08
History of HIV diagnosis	697 (21.8)	697 (21.8)	0
No of bacterial STIs in past 3 years:			
0	1158 (36.1)	1158 (36.1)	0
1	998 (31.1)	998 (31.1)	0
2	522 (16.3)	522 (16.3)	0
3	248 (7.7)	248 (7.7)	0
≥4	278 (8.7)	278 (8.7)	0
Received any non-MVA-BN vaccines in past year	3146 (98.2)	3146 (98.2)	0

IQR=interquartile range; MVA-BN=modified vaccinia Ankara-Bavarian Nordic; STI=sexually transmitted infection (chlamydia, gonorrhoea, or syphilis).

During a median follow-up of 85 days (IQR 32-110 days) after the first dose among vaccinated individuals and 86 (31-111) days among unvaccinated individuals, we observed a total of 71 infections, with 21 in the vaccinated group (0.09 per 1000 person days, 95% confidence interval (CI) 0.05 to 0.13) and 50 in the unvaccinated group (0.20 per 1000 person days, 0.15 to 0.27) over the study period of 153 days. We censored 293 (9.1%) individuals owing to receipt of a second dose. Figure 3 shows the cumulative incidence functions for the vaccinated and unvaccinated groups during the study period. The hazard ratio for infection in the vaccinated group compared with unvaccinated group was 0.42 (95% CI 0.25 to 0.69), thus the estimated vaccine effectiveness for a single dose of MVA-BN against mpox infection was 58% (95% CI 31% to 75%; fig 4).



No at risk

Unvaccinated	3204	2618	2243	2007	1747	1222	670	340
Vaccinated	3204	2644	2264	2010	1714	1184	617	281

Cumulative No of events

Unvaccinated	0	35	47	48-52*	48-52*	52	52	52
Vaccinated	0	9	18	19-23*	23	23	23	23

Fig 3 | Cumulative incidence functions of confirmed mpox infection in Ontario, Canada, 12 June 2022 to 26 November 2022. Shaded areas represent 95% confidence intervals. *Estimates that could lead to back calculation of small cells have been shown with a range of values instead of the exact value

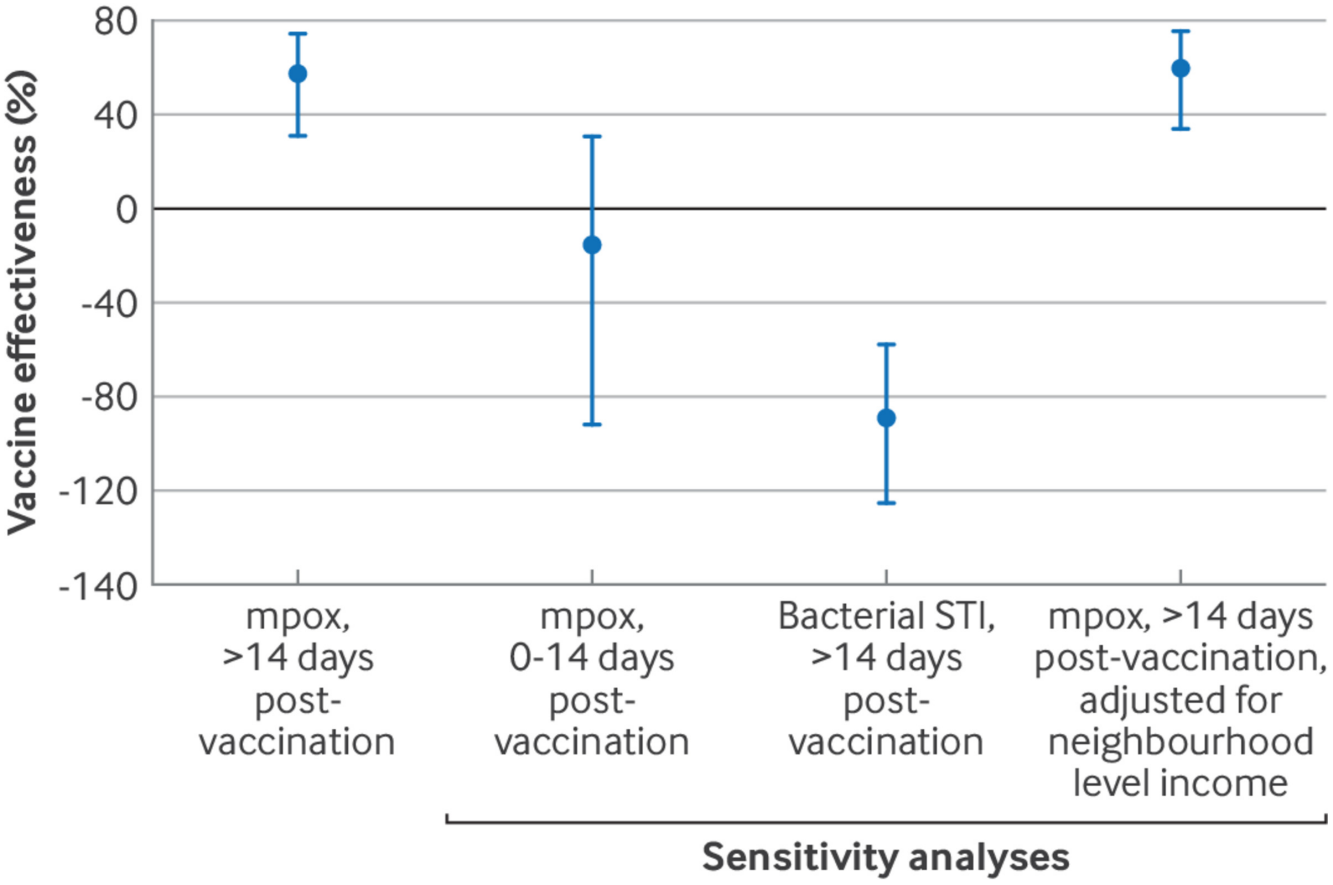


Fig 4 | Estimates of vaccine effectiveness of one dose of MVA-BN between 12 June 2022 and 26 November 2022 in Ontario, Canada, primary and sensitivity analyses. MVA-BN=modified vaccinia Ankara-Bavarian Nordic; STI=sexually transmitted infection

Examination for residual confounding using negative outcomes showed a vaccine effectiveness of −15% (−92% to 31%) during the first 14 days post-vaccination, and vaccine effectiveness of −89% (−125% to −58%) against bacterial STI (see cumulative incidence functions in supplementary figure S2). Rates of a first syphilis test post-vaccination were 0.05 per 1000 person days in the vaccinated group and 0.03 per 1000 person days in the unvaccinated group. Finally, we did not identify a meaningful change in vaccine effectiveness against mpox infection after additionally adjusting for neighbourhood level income (vaccine effectiveness 60%, 34% to 76%).

Discussion

Using a target trial emulation, we estimated the effectiveness of a single dose of MVA-BN vaccine to be moderate (58%, 31% to 75%) for preventing mpox infection in the context of a targeted vaccination programme in Ontario, Canada. To confirm the specificity of this association, we determined that MVA-BN was not associated with a reduced rate of mpox infection during the first 14 days post-vaccination (before developing an adequate antibody response) nor bacterial STI diagnoses (against which no protection would be expected).

Comparison with other studies

Our estimate of vaccine effectiveness falls within the range observed across previous studies conducted in jurisdictions with similar epidemic dynamics and targeted vaccination programmes. Our findings are most consistent with studies that restricted the study population to those at greatest risk of exposure to mpox and that reduced time based and risk based confounding.[8 10 11 14 15] In the Canadian province of Quebec, a test negative study that used health administrative data and adjusted for exposure risks based on similar proxies as in our study (ie, previous bacterial STI), estimated vaccine effectiveness against mpox infection to be 35% (95% CI 2% to 59%).[14] After further adjusting for self-reported measures of exposure risks (restricting analyses to those who completed a detailed questionnaire), vaccine effectiveness was estimated to be 65% (1% to 87%), similar to our estimate. Our estimate is lower than (but still compatible with) an estimate of 86% (95% CI 59% to 95%) from a retrospective cohort study in Israel that used more restrictive study eligibility criteria (ie, living with HIV and a recent diagnosis of bacterial STI, or receipt of HIV pre-exposure prophylaxis),[8] and an estimate of 79% (95% CI 33% to 100%) from a target trial emulation conducted in Spain with even more restrictive study eligibility (ie, enrolment restricted to men receiving HIV pre-exposure prophylaxis).[10]

Strengths and limitations of this study

Our study has several strengths. Firstly, we used linked population based databases within a publicly funded healthcare system to identify all MVA-BN vaccination events and all mpox related laboratory tests in Ontario. Secondly, to address the risks of residual confounding present in any observational study, we conducted rigorous matching across key potential confounders of the causal effect of vaccination on mpox infection. Risk confounding is particularly important when estimating vaccine effectiveness

because Ontario, like other jurisdictions, specifically targeted vaccination to individuals at greatest risk of infection. Evidence of exchangeability includes the similarity between groups for proxies of sexual exposure risks, and similar outcomes during the negative control period before the vaccine was expected to confer protection. We examined this negative control period based on immunogenicity data, recognising that some protection may have been conferred in the first 14 days, if the dose was administered deliberately or inadvertently within the window for post-exposure prophylaxis.[25 26] The negative tracer outcome analysis involving bacterial STI suggests that the observed vaccine effect is unlikely to be explained by differential reductions in sexual activity among gay, bisexual, and other men who have sex with men over the study period. In contrast, our finding of higher rates of newly diagnosed bacterial STIs among vaccinated men suggests that the vaccination programme successfully reached those most at risk of mpox and/or vaccinated men engaged in increased sexual activity post-vaccination. This means that vaccinated individuals may have engaged in more sexual activity than their unvaccinated counterparts after vaccination. Indeed, given the focus of vaccine campaign messaging on preventing future exposure risks, individual decisions about the vaccine could be shaped by anticipating future sexual partnerships, irrespective of the past. The higher rates of bacterial STIs post-vaccination could also stem from additional STI testing opportunities and detection after engagement in preventive care with vaccination, as evidenced by higher syphilis testing rates during the post-vaccination period. However, the negative tracer findings suggest that residual confounding could be present due to differential increases in sexual activity, and thus our estimate of vaccine effectiveness may be underestimated. Finally, the study period included a rapidly evolving outbreak, with risks of exposure to mpox declining quickly before a large fraction of the study eligible population was vaccinated, thus the risk for time varying confounding due to differential exposure risks was substantial, which we reduced by emulating a target trial.

Our study also has limitations. Firstly, the rigorous matching meant that our final cohort comprised only 65% of the eligible population, with 71 outcomes for analysis. Thus, the final cohort comprised 8.8% of the 36 312 first dose vaccinations and 10% of all mpox diagnoses in Ontario during the study period. Although the characteristics of included and eligible participants were similar, a reduction in confounding came at the price of decreased sample size and precision. It also meant that subgroup analyses, such as among individuals aged >50 years, who may have received earlier generation smallpox vaccines, were not possible. Secondly, we were limited to routinely collected data, and information on previous smallpox vaccination, sexual exposures, and individual level measures of social determinants of health were not available. Information on neighbourhood level income was available but was not used for matching to limit further loss of sample size, and because area level median income may not capture the ways in which individual level income, or other individual level social determinants, might influence sexual networks.[27] Furthermore, comparison across groups and the third sensitivity analysis suggested no residual confounding by neighbourhood level income. Thirdly, although we included men with a history of bacterial STIs, our study eligibility population could be missing men who are at risk of mpox infection but have negligible access to healthcare and/or healthcare engagement (thus leading to a selection bias). Fourthly, although data from other studies showed added protective benefit of two vaccine doses,[9 11 12] we could not evaluate the two dose regimen because of low second dose coverage during the study period, nor could we evaluate duration of protection. Finally, vaccination could also reduce symptoms and signs of mpox and thus result in less testing,[28] which would mean a higher chance of under-ascertainment of people with subclinical infection among the vaccinated group, which would lead to overestimation of vaccine effectiveness against infection.

Conclusions

Vaccination with a single dose of MVA-BN vaccine was found to be moderately effective against laboratory confirmed mpox infection in this population based study of an evolving outbreak and using a target trial emulation to reduce biases. One implication of our finding is that single dose vaccination may have been a contributing factor in helping to slow transmission in Ontario in 2022. Mpox infections in Canada and across the globe are rising again in 2024, with most diagnoses among individuals who have not yet been vaccinated or have received only a single dose of vaccine.[29 30] Given the moderate effectiveness of a single dose, achieving high coverage with a full course could be important to prevent and manage ongoing transmission globally and prevent a large resurgence.[31 32] In the absence of randomised clinical trials, our findings strengthen the evidence that MVA-BN is effective at preventing mpox infection and should be made available and accessible to communities at risk.

What is already known on this topic

- No randomised clinical trials of vaccination against mpox have been conducted
- Estimates of vaccine effectiveness of a single dose of vaccination range from 36% to 86%, but these observational designs noted residual confounding as a major concern given vaccine implementation was appropriately prioritised to individuals most at risk of infection
- Estimates of vaccine effectiveness, using approaches to minimise biases, are needed

What this study adds

- In an emulated target trial to reduce biases, the effectiveness of a single dose of modified vaccinia Ankara-Bavarian Nordic (MVA-BN) vaccine against mpox infection was 58% (95% confidence interval 31% to 75%)—a finding that was robust to further sensitivity analysis for residual confounding
- In the absence of data from randomised controlled trials, the study findings strengthen the evidence that MVA-BN is effective at preventing mpox infection and should be made available and accessible to communities at risk

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Contributors: JCK and SM designed the study and analysis plan and are joint senior authors with equal contribution. SAB, CN, JCK, and LF acquired the data for the work. CL designed the data extraction and assembly workflow. CL analysed the data. All authors made substantial contributions to the analysis plan and the interpretation of the data. JCK and SM vouch for the data analysis. CN, SM, and JCK wrote the first draft of the manuscript. All authors critically reviewed the manuscript and decided to proceed with publication. SM and JCK are responsible for the overall content as guarantors and accept full responsibility for the work and conduct of the study and had access to the data and controlled the decision to publish. The corresponding authors attest that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at https://www.icmje.org/disclosure-of-interest/ and declare: support from ICES and the Canadian Immunization Research Network; no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Transparency: The corresponding author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: Preliminary results of this study have been made available to the public on a preprint server and have been shared with the Ministry of Health and ICES. After peer review publication, they will be further disseminated by ICES through news media and social media. It is not possible to send study results to participants because all personal identifying information has been removed from the dataset.

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Ethical approval: ICES is a prescribed entity under Ontario's Personal Health Information Protection Act (PHIPA). Section 45 of PHIPA authorises ICES to collect personal health information, without consent, for the purpose of analysis or compiling statistical information with respect to the management of, evaluation or monitoring of, the allocation of resources to or planning for all or part of the health system. Projects that use data collected by ICES under section 45 of PHIPA, and use no other data, are exempt from REB review. The use of the data in this project is authorised under section 45 and approved by ICES' Privacy and Legal Office. Ethical approval for this study was obtained from Public Health Ontario's Ethics Review Board.

Data sharing: The dataset from this study is held securely in coded form at ICES. While legal data sharing agreements between ICES and data providers (eg, healthcare organisations and government) prohibit ICES from making the dataset publicly available, access may be granted to those who meet prespecified criteria for confidential access, available at https://www.ices.on.ca/DAS (email das@ices.on.ca). The full dataset creation plan and underlying analytical code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification. Correspondence and requests for materials should be addressed to JCK or SM.

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Supplementary information: Figures S1 and S2, supplementary methods, tables S1-S4, and references