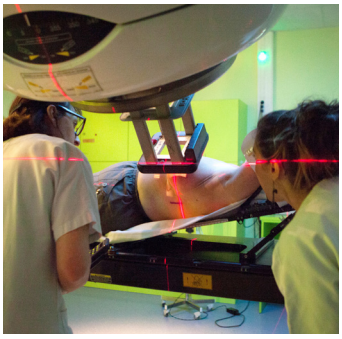
research

Effectiveness of MVA-BN mpox vaccine p 269



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ORIGINAL RESEARCH Emulation of a target trial

Effectiveness of modified vaccinia Ankara-Bavarian Nordic vaccine against mpox infection

Navarro C, Lau C, Buchan SA, et al; on behalf of the Canadian Immunization Research Network (CIRN) Provincial Collaborative Network Investigators

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Study question What is the real world effectiveness of modified vaccinia Ankara-Bavarian Nordic (MVA-BN) vaccine against mpox infection?

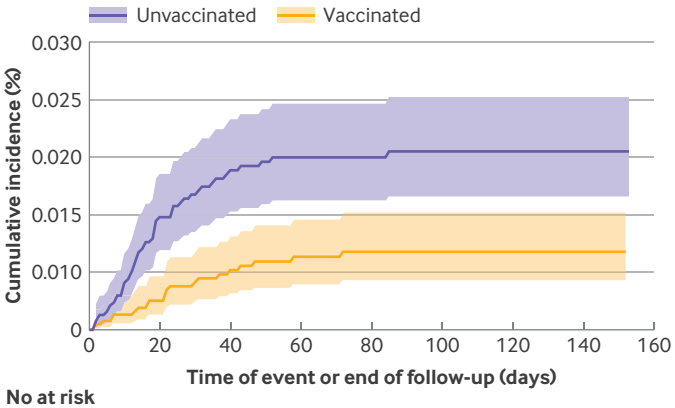
Methods This study emulated a target trial using linked databases in Ontario, Canada, to estimate the effectiveness of one dose of subcutaneously administered MVA-BN given as pre-exposure prophylaxis. Participants comprised men aged ≥18 years who had a history of being tested for syphilis and a laboratory confirmed bacterial sexually transmitted infection in the previous year; or filled a prescription for HIV pre-exposure prophylaxis in the previous year. On each day between 12 June 2022 and 27 October 2022, men who had been vaccinated 15 days previously were matched 1:1 with unvaccinated men on age, geographical region, previous HIV diagnosis, number of diagnosed bacterial sexually transmitted infections in the previous three years, and receipt of any non-MVA-BN vaccine in the previous year. A Cox proportional hazards model was used to estimate the hazard ratio comparing the rate of laboratory confirmed mpox infection between the two groups. Vaccine effectiveness was calculated as (1−hazard ratio)×100.

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



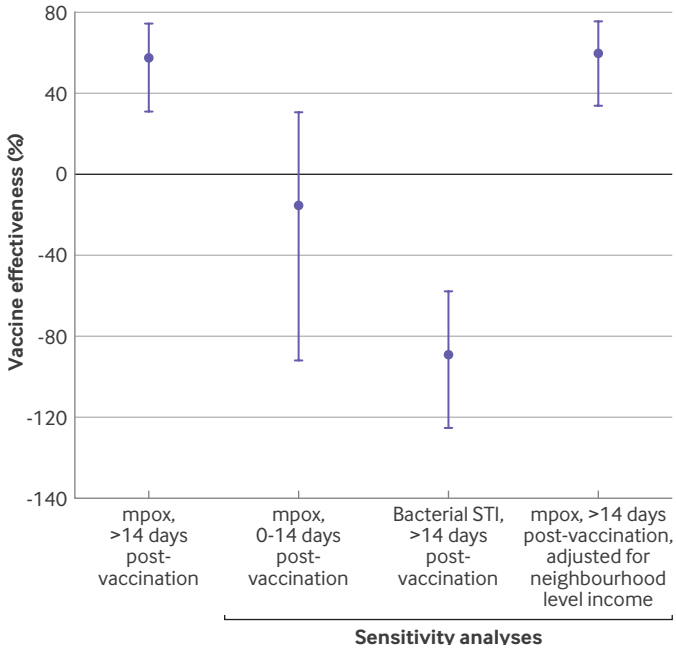
No at risk

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

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



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

Study answer and limitations 3204 men who received the vaccine were matched to 3204 unvaccinated men (controls). During a median follow-up after the first dose of 85 days (interquartile range 32-110 days) among vaccinated individuals, and 86 (interquartile range 31-111) days among unvaccinated individuals, a total of 71 mpox infections were observed, with 21 in the vaccinated group (0.09 per 1000 person days, 95% confidence interval 0.05 to 0.13 per 1000 person days) and 50 in the unvaccinated group (0.20 per 1000 person days, 0.15 to 0.27 per 1000 person days) over the study period of 153 days. Estimated vaccine effectiveness of one dose of MVA-BN against mpox infection was 58% (95% confidence interval 31% to 75%). Sensitivity analyses confirmed the specificity of the association, as MVA-BN was not associated with a reduced rate of mpox infection during the first 14 days after vaccination (before the development of an adequate antibody response) nor diagnoses of bacterial sexually transmitted infections (against which no protection would be expected) and suggested no residual confounding by level of neighbourhood income. Although rigorous matching reduces bias due to confounding, this came at the price of decreased sample size and precision of the estimate. Limitations of the sample size precluded subgroup analyses and estimation of vaccine effectiveness against severe outcomes, and the two dose regimen could not be evaluated because of low second dose coverage during the study period.

What this study adds The findings of this study, conducted in the context of a targeted vaccination programme and evolving outbreak, suggested that one dose of MVA-BN is moderately effective in preventing mpox infection and should be made available and accessible to communities at risk.

Funding, competing interests, and data sharing Support from ICES and the Canadian Immunization Research Network. No competing interests declared. The full dataset creation plan and underlying analytical code are available from the authors upon request, on the 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.

Randomised controlled trials on radiation dose fractionation in breast cancer

Lee SF, Kennedy SKF, Caini S, et al

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Study question How do different fractionation schedules (moderate hypofractionation, conventional fractionation, and ultra-hypofractionation) in breast cancer radiation therapy affect side effects, cosmesis, quality of life, recurrence risks, and survival outcomes?

Methods This systematic review and meta-analysis (with searches of Ovid Medline, Embase, and the Cochrane Central Register of Controlled Trials for data up to 23 October 2023) focused on randomised controlled trials comparing different fractionation schedules. Grade ≥2 acute radiation dermatitis and late radiation therapy related side effects (primary outcomes) were analysed using a random effects model for pooled risk ratios and hazard ratios. Risk of bias and quality assessment were evaluated using the Cochrane Collaboration's tool and the GRADE (grading of recommendations, assessment, development and evaluation) approach, respectively. A network meta-analysis integrated the evidence.

Study answer and limitations Moderate hypofractionation significantly reduced the risk of grade ≥2 acute radiation dermatitis compared with conventional fractionation (eg, 207/777 *v* 390/831 in one trial), with risk ratios of 0.54 (95% confidence interval 0.49 to 0.61) and 0.68 (0.49 to 0.93) in patients having breast conserving therapy and mastectomy, respectively. Additionally, moderate hypofractionation reduced hyperpigmentation and breast shrinkage in the combined breast conserving therapy and mastectomy population, enhancing cosmesis and quality of life relative to conventional fractionation. Data on ultra-hypofractionation, although promising, were less definitive. Survival and recurrence were similar across moderate hypofractionation, conventional fractionation, and ultra-hypofractionation. Study limitations include potential biases due to the lack of blinding and incomplete outcome reporting.

What this study adds Moderate hypofractionation and ultra-hypofractionation effectively reduced the risk of grade ≥2 acute radiation dermatitis compared with conventional fractionation. Moderate hypofractionation improved safety, cosmesis, and quality of life and provided similar outcomes in cancer control to conventional fractionation. Fewer studies have evaluated ultra-hypofractionation, but its safety and efficacy seem to be comparable to the other fractionation schedules with short term follow-up.

Funding, competing interests, and data sharing No external funding received. No competing interests declared. Data used in the analysis are available on reasonable request from the corresponding author.

Systematic review registration PROSPERO CRD42023460249.

AMELIE-BENOIST/BSIP/ALAMY

Summary of findings for primary outcomes

Outcomes	Risk ratio (95% CI)
Moderate hypofractionation *v* conventional fractionation	
Grade ≥2 acute radiation dermatitis	0.59 (0.51 to 0.69)*
Grade ≥2 telangiectasia	0.84 (0.66 to 1.06)
Any hyperpigmentation	0.77 (0.62 to 0.95)*
Grade ≥2 breast or chest wall induration/fibrosis	0.92 (0.80 to 1.06)
Grade ≥2 breast shrinkage	0.92 (0.85 to 0.99*
Grade ≥2 breast oedema	0.82 (0.62 to 1.09)
Grade ≥2 breast pain	0.94 (0.43 to 2.06)
Grade ≥2 lymphoedema	1.00 (0.78 to 1.29)
Grade ≥2 pneumonitis/symptomatic lung fibrosis	1.57 (0.81 to 3.02)
Ischaemic heart disease	0.95 (0.56 to 1.58)
Moderate/marked shoulder stiffness/dysfunction	1.14 (0.69 to 1.89)
Symptomatic rib fracture	2.82 (0.87 to 9.14)
Ultra-hypofractionation *v* moderate hypofractionation	
Grade ≥2 acute radiation dermatitis	0.85 (0.47 to 1.55)
Grade ≥2 telangiectasia	1.42 (0.88 to 2.30)
Grade ≥2 breast or chest wall induration/fibrosis	1.86 (1.19 to 2.92)*
Grade ≥2 breast shrinkage	1.38 (1.07 to 1.76)*
Grade ≥2 breast oedema	2.44 (1.32 to 4.52)*
Grade ≥2 lymphoedema	0.84 (0.61 to 1.16)
Grade ≥2 pneumonitis/symptomatic lung fibrosis	1.33 (0.63 to 2.80)
Ischaemic heart disease	0.87 (0.49 to 1.56)
Moderate/marked shoulder stiffness/dysfunction	0.89 (0.64 to 1.23)
Symptomatic rib fracture	2.07 (1.04 to 4.12)*
Ultra-hypofractionation *v* conventional fractionation	
Grade ≥2 acute radiation dermatitis	0.27 (0.19 to 0.40)*
Grade ≥2 telangiectasia	1.86 (0.11 to 30.23)
Grade ≥2 breast or chest wall induration/fibrosis	1.97 (0.58 to 6.71)
Grade ≥2 breast shrinkage	1.83 (1.09 to 3.07)*
Grade ≥2 breast oedema	3.05 (0.13 to 74.09)
Grade ≥2 pneumonitis/symptomatic lung fibrosis	0.82 (0.25 to 2.70)
Ischaemic heart disease	0.82 (0.25 to 2.70)
Symptomatic rib fracture	0.87 (0.31 to 2.45)

CI=confidence interval.
*Statistically significant.

Effect of laughter exercise versus 0.1% sodium hyaluronic acid on ocular surface discomfort in dry eye disease

Li J, Liao Y, Zhang S-Y, et al

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Study question Is laughter exercise as effective as artificial tears in relieving the symptoms of symptomatic dry eye disease?

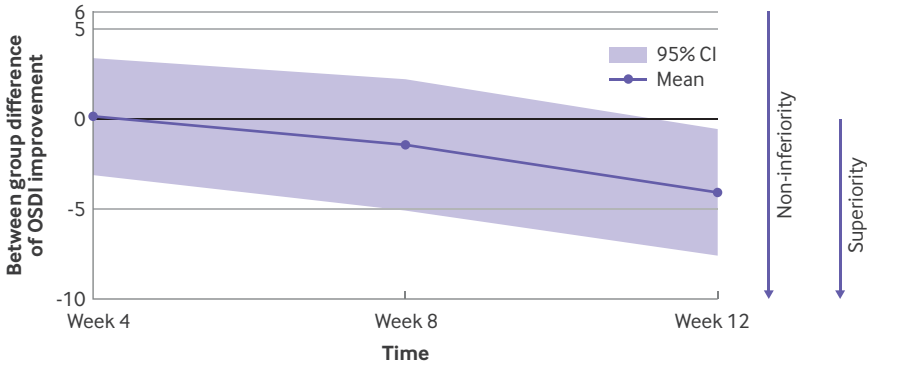
Methods This non-inferiority randomised controlled trial was conducted at the largest ophthalmic centre in China. Patients aged 18-45 years with ocular surface disease index scores ranging from 18 to 80 and tear film break-up time of eight seconds or less were randomly assigned to receive either laughter exercise or 0.1% sodium hyaluronic acid eye drops (control group) four times a day for eight weeks. The primary outcome was mean change from baseline in the ocular surface disease index at eight weeks; the non-inferiority margin was 6 points. The laughter exercise group viewed an instructional video and were requested to vocalise the phrases "Hee hee hee, hah hah hah, cheese cheese cheese, cheek cheek cheek, hah hah hah hah hah hah" 30 times per five minute session. Investigators assessing study outcomes were masked to group assignment, but participants were unmasked for practical reasons.

Study answer and limitations Between 18 June 2020 and 8 January 2021, 299 participants (mean age 28.9 years; 74% female) were randomly assigned to receive either laughter exercise (n=149) or 0.1% sodium hyaluronic acid (n=150). 283 (95%) completed the trial. Laughter exercise was non-inferior to 0.1% sodium hyaluronic acid in relieving subjective symptoms in patients with dry eye disease and limited corneal staining after eight weeks: mean difference was −1.45 points (95% confidence interval −5.08 to 2.19), of which the upper bound was less than the non-inferiority margin of 6. The limitation of this trial is that a double blinded study design was not practical because a sham laughter exercise would be needed, for which a validated approach is presently lacking.

What this study adds Laughter exercise was non-inferior to artificial tears (0.1% sodium hyaluronic acid) in improving symptoms of dry eye disease at eight weeks. Laughter exercise could be a safe, environmentally friendly, and low cost intervention for patients with symptomatic dry eye disease and limited corneal staining.

Funding, competing interests, and data sharing
Funded by the National Natural Science Foundation of China and the high level hospital construction project. No competing interests declared. All data requests should be submitted to lianglingyi@gzzoc.com for consideration. Access to anonymised data might be granted after review.

Study registration ClinicalTrials.gov NCT04421300.



Results of the non-inferiority comparison between laughter exercise group and 0.1% sodium hyaluronic acid group. CI=confidence interval; OSDI=ocular surface disease index

Adjusted effect of laughter exercise on primary outcome of OSDI score at eight weeks

	Baseline*		Follow-up		Change in OSDI†		Baseline adjusted between group difference in change in OSDI‡
Outcomes	No	Mean (SD)	No	Mean (SD)	No	Mean (95% CI)	Mean (95% CI)
Per protocol analysis							
Laughter exercise group	136	35.6 (12.9)	136	25.1 (15.3)	136	−10.5 (−13.1 to −7.82)***	−1.45 (−5.08 to 2.19)
0.1% hyaluronic acid group	147	36.7 (14.5)	147	27.9 (17.7)	147	−8.83 (−11.7 to −6.02)***	P=0.43
Intention to treat analysis							
Laughter exercise group	149	35.9 (13.6)	149	25.9 (15.9)	149	−10.0 (−12.8 to −7.29)***	−1.32 (−4.90 to 2.26)
0.1% hyaluronic acid group	150	36.8 (14.4)	150	28.0 (17.6)	150	−8.79 (−11.6 to −6.03)***	P=0.47

CI=confidence interval; OSDI=ocular surface disease index; SD=standard deviation.
*No statistically significant differences between two groups for all baseline comparisons by two sample *t* test.
†Paired *t* test.
‡Linear regression with adjustment for OSDI grade at baseline.
***P<0.001.