Effectiveness of one dose of MVA–BN smallpox vaccine against mpox in England using the case-coverage method: an observational study

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Summary

Background The UK experienced a national outbreak of mpox (formerly known as monkeypox) disease that started in May, 2022, as did many other countries worldwide, with case numbers rising rapidly, mainly among gay, bisexual, and other men who have sex with men (GBMSM). To control the outbreak, Modified Vaccinia Ankara–Bavaria Nordic (MVA–BN), an attenuated smallpox vaccine, was offered to at-risk GBMSM. We aimed to assess the effectiveness of a single MVA–BN dose against symptomatic mpox disease in at-risk GBMSM.

Methods In this case-coverage study, mpox cases in England were sent questionnaires collecting information on demographics, vaccination history, symptoms, and sexual orientation. Returned questionnaires were linked to laboratory data and a public health case management system (HP Zone) to obtain additional information on symptom onset and specimen date. Cases with a rash onset date (or alternative proxy) between July 4 and Oct 9, 2022, were included. Females, heterosexual men, and those with missing vaccination information were excluded. Vaccine effectiveness was calculated using the case-coverage method in which vaccine coverage among cases is compared with coverage in the eligible population, estimated from doses given to GBMSM and the estimated size of at-risk GBMSM. Sensitivity analyses included an increase and decrease of 20% differences in the estimated high-risk GBMSM population size.

Findings By Nov 3, 2022, 1102 people had responded to questionnaires, of which 739 were excluded (52 females or self-declared male heterosexuals, 590 with an index date outside of the study period, and 97 missing a vaccination date). 363 cases were included in the analyses. Vaccine uptake among eligible GBMSM increased steadily from July, 2022, reaching 47% by Oct 9, 2022. Of the 363 confirmed cases, eight cases either did occur or were likely to have occurred at least 14 days after vaccination, 32 within 0–13 days after vaccination, and the rest were unvaccinated. The estimated vaccine effectiveness against symptomatic mpox at least 14 days after a single dose was 78% (95% CI 54 to 89) ranging from 71 to 85 in sensitivity analyses. Vaccine effectiveness within 0–13 days after vaccination was –4% (95% CI –50 to 29).

Interpretation A single MVA–BN dose was highly protective against symptomatic mpox disease among at-risk GBMSM, making it a useful tool for mpox outbreak control when rapid protection is needed. For cases in which numbers at highest risk of infection exceed vaccine supply, there might be benefit in prioritising delivery of first doses.

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Introduction

In May, 2022, an mpox (formerly known as monkeypox) outbreak was identified in the UK, primarily among gay, bisexual, and other men who have sex with men (GBMSM). Similar outbreaks were subsequently identified across Europe and globally,[1,2] leading WHO to declare the outbreak a Public Health Emergency of International Concern on July 23, 2022.[3] As of Oct 11, 2022, more than 20 000 cases (including four deaths) have been confirmed in European Union and European Economic Area countries as part of this outbreak,[4] with 3500 cases in the UK.[5] Vaccination with a third generation smallpox vaccine (Modified Vaccinia Ankara–Bavaria Nordic [MVA–BN]) has been a crucial component of the outbreak control, yet before this outbreak there were no data on the clinical effectiveness of the vaccine against mpox in humans.

Following the first confirmed cases in England, the UK Health Security Agency (UKHSA) implemented extensive public health measures to control the outbreak, including isolation of cases and close contacts, surveillance of contacts, and raising awareness among

Research in context

Evidence before this study

We searched PubMed using the terms "monkeypox", "MVA", and "vaccine", with no date restrictions on Nov 23, 2022, and used the snowball process to identify additional relevant publications. The search was limited to articles published in English. We also searched websites of regulatory authorities (Food and Drug Administration and European Medicines Agency) for any data used during the regulatory approval processes. We also scoped preprint databases for vaccine effectiveness studies during the current mpox (formerly known as monkeypox) outbreak. Only publications related to the Modified Vaccinia Ankara–Bavaria Nordic (MVA–BN) vaccine were included. In the UK, MVA–BN was offered to at-risk gay, bisexual, and other men who have sex with men (GBMSM) to control a national outbreak which began in May, 2022. MVA–BN is now licensed against smallpox in the USA, Europe, and the UK; however, data on vaccine effectiveness against mpox are scarce. Preclinical studies indicated two vaccine doses were immunogenic and generated antibody concentrations considered protective against smallpox. Vaccine-induced antibodies are also cross-protective against the monkeypox virus in vitro and in animal models. A recent Israeli study done during the same outbreak estimated 79% vaccine effectiveness after one dose in at-risk GBMSM, while a US study also done during the same outbreak reported unvaccinated individuals to be 14 times more likely to develop mpox disease than were vaccinated individuals.

Added value of this study

Few countries have recommended or introduced large-scale vaccination programmes against the current global outbreak of mpox disease among GBMSM in non-endemic countries. The offer of MVA–BN to at-risk GBMSM through sexual health services in England provided a unique opportunity to rapidly assess vaccine effectiveness after a single dose using the case-coverage method, which involves comparing vaccine coverage in cases with vaccine coverage in the eligible population. Our vaccine effectiveness estimate of 78% at least 14 days after one MVA–BN dose is consistent with Israeli estimates and provided additional evidence of a lack of protection during the first 13 days after vaccination.

Implications of all the available evidence

A single dose of MVA–BN is highly protective against mpox disease and provides a useful tool for outbreak control when rapid protection might be needed. Given the lack of effectiveness in the first 13 days after the first dose and a median incubation period of 8–9 days after exposure to the virus, vaccination is likely to be most effective when offered as pre-exposure rather than prophylaxis. Because of the high vaccine effectiveness after one MVA–BN dose, in outbreaks for which numbers of at-risk individuals exceed vaccine supply of two doses, there might be benefit in prioritising delivery of first doses.

health-care professionals and at-risk groups.[6] Additionally, UKHSA recommended post-exposure vaccination for close contacts of cases, including health-care workers and laboratory staff, as well as pre-exposure vaccination for health-care staff who were likely to come into contact with patients with mpox disease or monkeypox virus samples.[7] From June, 2022, because of increasing case numbers, the Joint Committee on Vaccination and UKHSA also recommended pre-exposure vaccination for GBMSM considered at higher risk of mpox disease during this outbreak (at-risk GBMSM),[8] such as those with multiple partners, those participating in group sex, and those attending sex on premises venues. Proxy indicators, including recent bacterial sexually transmitted infection (in the past year) or eligibility for HIV pre-exposure prophylaxis were used to identify eligible groups [7] with roll-out for these groups starting at the end of June, 2022.[8]

MVA–BN is a third generation attenuated replication deficient smallpox vaccine licensed by the European Medicines Agency in 2013 for the prevention of smallpox.[9] In the USA, the Food and Drug Administration approved MVA–BN for smallpox and mpox prevention in 2019.[10] The vaccine was licensed based on immunogenicity studies; a two-dose schedule given 28 days apart was demonstrated to be immunogenic, generating antibody concentrations above protective thresholds for smallpox, which was also considered to confer protection against mpox.[11,12] Animal models have also shown rapid protection against mpox.[13–16]

Although data from studies in Africa suggested that previous generation smallpox vaccination also protected against mpox,[16,17] there were no real-world data on the effectiveness of MVA–BN vaccines against mpox disease in humans before the current outbreak.[16] A recent study involving people vaccinated during the current 2022 outbreak in the Netherlands found low levels of neutralising antibody titres against monkeypox virus after one dose with no increase in titres after two doses.[18] Early reports from Israel and the USA during the same outbreak indicate a high level of protection from vaccination against mpox disease.[19,20]

Following implementation of a large-scale national immunisation programme for at-risk GBMSM, we undertook an observational study which aimed to estimate the effectiveness of one dose of MVA–BN against symptomatic mpox in England.

Methods

Study design

We estimated vaccine effectiveness against laboratory-confirmed symptomatic mpox in the GBMSM cohort eligible for MVA–BN vaccination in England using the case-coverage method (also known as the screening

method), whereby vaccination rates among cases are compared with population coverage.[21]

The study was done in accordance with relevant guidelines and regulations under permissions granted to the UKHSA (formerly Public Health England) under Regulation 3 of The Health Service (Control of Patient Information) Regulations 2020 and under Section 251 of the NHS Act 2006 (UK legislation). All data were collected within the statutory approvals granted to the UKHSA for infectious disease surveillance and control and individual patient consent was not required. Questionnaire completion was voluntary. Information was held securely and in accordance with the Data Protection Act 2018 and Caldicott Principles.

Participants and procedures

Weekly vaccinations delivered to the at-risk GBMSM population along with an estimate of the GBMSM denominator was used to estimate coverage. The number of at-risk GBMSM had previously been estimated as 111 000 in the UK.[22] We used the same calculation to estimate a total in England of 89 240. This value is based on an estimated 48 500 at-risk GBMSM regular sexual health services attenders, 60% (29 100) non-regular attenders, and a further 15% (11 640) not in contact with sexual health services.[22,23] To account for uncertainty this denominator was increased and decreased by 20% in sensitivity analyses, corresponding to different coverage scenarios (primary, high, and low coverage).

An aggregated vaccination coverage reporting system was established at a vaccination site level at the start of the programme roll-out by NHS England.[24] Vaccination sites, primarily sexual health servies, reported daily number of vaccines delivered by cohort (ie, GBMSM, health-care workers, contacts of cases) and by dose (appendix p 2). We classified vaccine status as recent (vaccinated in the current or previous week) or one full dose (vaccinated with a first dose ≥2 weeks earlier). At the time of analyses, very few second doses had been delivered; therefore second dose vaccination was not assessed. During the study period, most vaccines administered were subcutaneous 0·5 ml doses of MVA–BN.

See Online for appendix

Confirmed (mpox positive) and highly probable (orthopox positive) cases were identified through laboratory reports.[25] Vaccine status was obtained from self-completed questionnaires sent to all cases via email or text message,[25] which included questions on vaccination status, symptoms, rash onset, age, gender, and sexual orientation. When available, personal identifiers such as name and date of birth were used to link cases to HP Zone (a public health case management system) and laboratory data to obtain missing and additional information, such as symptom onset date and laboratory specimen date (appendix p 2). We were unable to link vaccination data to clinical records as these data are anonymised and held within sexual health services and there is no vaccination register with identifiable data for this vaccination programme. The final dataset was extracted on Dec 21, 2022. Cases with available contact information that had not completed the questionnaire were sent a follow-up reminder to complete the questionnaire. No further follow-up was done as part of this study.

For each case an index date for mpox infection was defined in the following priority order depending on whether the previous information was available: (1) rash onset date (questionnaire); (2) symptom onset date (questionnaire); (3) symptom onset date (HP Zone); (4) test date (laboratory) minus 4 days; (5) test date (questionnaire) minus 4 days; and (6) questionnaire completion date minus 14 days. Dates (4) and (5) were based on median interval seen in those with a rash date and test or questionnaire date. Only cases with an index date from July 4, 2022, when GBMSM vaccination was scaled up, to Oct 9, 2022, were included. Females, self-reported heterosexual men, and those with missing vaccination information were excluded.

	Interval of vaccination before index date	Vaccination status	Younger than 50 years	Age 50 years and older	Unknown age
Not vaccinated	NA	Unvaccinated in 2022	217/260 (83%)	38/260 (15%)	5/260 (2%)
Before 1971	>50 years	Unvaccinated in 2022	3/33 (9%)	30/33 (91%)	0
1971–2021	6 months–50 years	Unvaccinated in 2022	24/29 (83%)	4/29 (14%)	1/29 (3%)
2022	0–13 days before rash	Recent vaccination (<14 days)	26/29 (90%)	3/29 (10%)	0
2022	0–13 before non-rash index date	Recent vaccination (<14 days)	3/3 (100%)	0	0
2022	≥14 days before rash	1 dose	4/4 (100%)	0	0
2022	≥14 days before non-rash index date	1 dose	3/4 (75%)	1/4 (25%)	0
2022	Vaccine date missing	Potential single dose (in sensitivity anaysis)	1/1 (100%)	0	0
Not known or prefer not to say	NA	Unknown (excluded)	67/97 (69%)	25/97 (26%)	5/97 (5%)

Data are n/N (%). NA=not applicable.

Table 1: **Vaccination status of gay, bisexual, and other men who have sex with men, with confirmed mpox, by age group and classifications for analyses**

Vaccination status was categorised as pre-1971, 1971–2022, in 2022 (with dates given), or not known or missing. Cases vaccinated after the index date were included as unvaccinated. Cases reporting vaccination in 2022 but without a date were only included in a sensitivity analysis because they might have been vaccinated after disease. Cases vaccinated before 2022 were considered unvaccinated—genuine vaccinations before 2022 were most likely to include childhood smallpox vaccinations. Smallpox vaccination ended in the UK in 1971 and globally by 1980, once smallpox eradication was declared.[26]

To estimate the proportion of cases with completed questionnaires, we used a numerator of returned questionnaires for which the sample date was between July 11 and Sept 25, 2022. For the denominator we used the number of cases sent a questionnaire via text message during this period (appendix p 2). Note that cases with a sample date from July 4 were not eligible for the study (as they probably had a symptom onset date before July 4) and cases since Sept 26, 2022 had not had sufficient time for all questionnaires to be returned. An exact return rate could not be calculated as it was not always possible to link questionnaires sent and returned because some questionnaires were completed anonymously.

Statistical analysis

The primary outcome of this study was laboratory-confirmed (mpox or orthopox positive) clinical mpox disease, assessed in GBMSM eligible for vaccination who completed a case questionnaire and provided vaccination information.

Vaccine effectiveness against laboratory-confirmed clinical disease is calculated as 1−odds of vaccination in cases/odds of vaccination in the population.[21,27] This was done using the weekly aggregated cases matched to the appropriate vaccine coverage and analysed using a logistic regression model with an offset for the log-odds of the coverage and a fitted constant. Vaccine effectiveness is 1−the exponent of the estimated parameter.[27] When calculating vaccine effectiveness in those vaccinated at least 14 days earlier, those vaccinated within 0–13 days were not included. 14 days was chosen as the cutoff because this is the typical period in other first dose vaccinations before a clear vaccine effect is seen.[28,29] Consequently, vaccine coverage for this cohort was calculated as: (proportion of the cohort vaccinated at least 14 days previously)/(1−proportion vaccinated within 0–13 days). A similar adjustment was made when calculating corrected coverage for those vaccinated within 0–13 days (ie, subtracting the ≥14 days coverage). Vaccine effectiveness for 0–13 days is used as a comparator in the analyses and expected to be low. To account for the impact that previous smallpox vaccination might have in individuals vaccinated against smallpox during childhood, vaccine effectiveness was also calculated for cases younger than 50 years. However, we used the overall population coverage in these analyses as these data were not available by age. Analyses were done with Stata version 17.0.

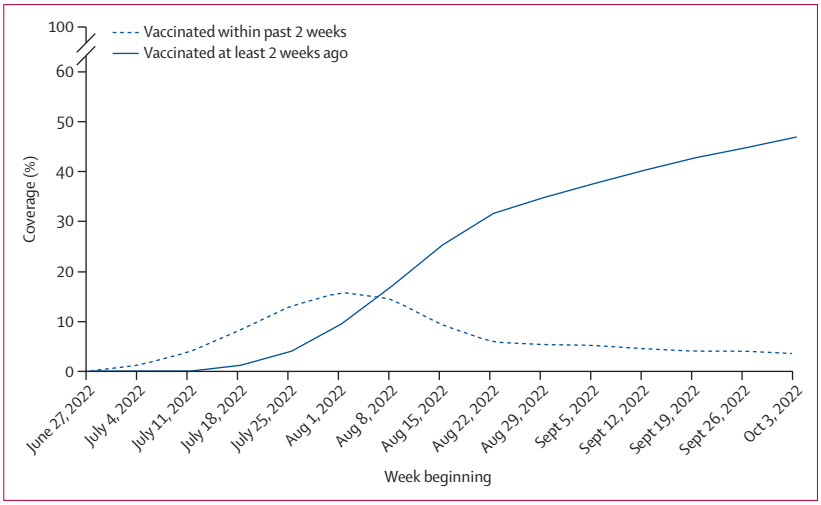

Figure 1: **Estimated first dose coverage by week for recent Modified Vaccinia Ankara–Bavaria Nordic vaccinations and vaccinations at least 2 weeks before in at-risk gay, bisexual, and other men who have sex with men in England, from June 27 to Oct 9, 2022 (weeks 26–40)**

Role of the funding source

All authors are employed by the funder and they contributed to study design, data collection, data analysis, data interpretation, and writing of the report.

Results

A total of 1102 cases had responded to questionnaires by Nov 3, 2022; 52 were female or self-declared male heterosexuals and excluded from the analyses. Only one of these 52 reported to have been vaccinated with an unknown date in 2022, and onset for this participant was before our study period. Overall, 460 cases had an index date from July 4, 2022, based on rash onset date (n=412), other symptoms (n=32), test date minus 4 days (n=4), and questionnaire completion date minus 14 days (n=12). The vaccination status for these participants is summarised in table 1.

Vaccine coverage by week for first doses increased to 47% by early October (week 40), with most vaccinations being given by Aug 22, 2022 (week 34). Analysis of protection within 2 weeks of vaccination included the cohort that was mostly vaccinated during July and August, 2022 (figure 1). The number of doses given and estimated coverage by week are included in the appendix (p 3). Cases were matched to coverage based on their index week—for example, a case with index week 33 matches to recent vaccination coverage of 9·4% and vaccination of at least 2 weeks ago of 25·4%. The coverage for one dose at the end of the study period was 50%. For the sensitivity analyses, reducing the denominator by 20% increased coverage at the end of the study period to 63% and increasing it by 20% reduced coverage to 42%.

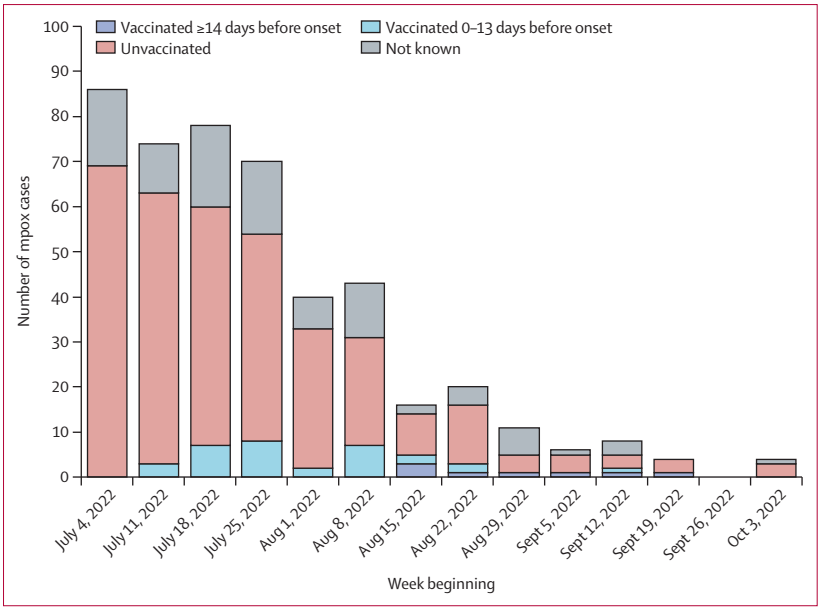

Figure 2: **Number of mpox cases by week and vaccination status from July 4 (week 27) to Oct 9, 2022 (week 40) in England**

	Vaccination status unknown	Vaccination status known
15–19	1/5 (20%)	4/5 (80%)
20–24	6/24 (25%)	18/24 (75%)
25–29	10/55 (18%)	45/55 (82%)
30–34	11/71 (15%)	60/71 (85%)
35–39	9/65 (14%)	56/65 (86%)
40–44	18/77 (23%)	59/77 (77%)
45–49	12/51 (24%)	39/51 (76%)
50–54	17/46 (37%)	29/46 (63%)
55–59	6/25 (24%)	19/25 (76%)
60 and older	2/30 (7%)	28/30 (93%)
Unknown	5/11 (45%)	6/11 (55%)

Data are n/N (%).

Table 2: **Age distribution in years of cases of gay, bisexual, and other men who have sex with men, by vaccination status**

After excluding cases with an unknown vaccination date (n=97), 363 cases were included in the analyses. Four cases were vaccinated at least 14 days before rash onset and a further four cases were likely to have been vaccinated at least 14 days before infection. For these four cases, the index date was based on symptom onset date for two cases and test date minus 4 days for the other two cases. The time interval between vaccination and mpox disease was longer than 3 weeks for these four cases. The case with vaccination date missing was included in a sensitivity analysis (table 1). No cases reported receiving two vaccine doses. The number of cases by week and vaccination status within those who returned a questionnaire are shown in figure 2. Lower numbers in the most recent weeks reflect declining incidence and a lower questionnaire return rate.

The age of the 460 cases returning the questionnaire and their vaccine status is shown in table 2. Individuals older than 50 years were potentially eligible for smallpox vaccination as an infant. This age group accounts for 21% of cases (table 2), compared with 14% of all cases of men in England (data not shown). As expected, proportionally more of those older than 50 years reported vaccination before 2022 than those younger than 50 years (table 1). There was only one vaccine failure (a case occurring at least 14 days after vaccination) in this age group.

For context, between July 11 and Sept 25, 2022, a total of 2018 cases were reported in England of whom 1545 (76·6%) had questionnaires sent by text. A total of 508 questionnaires were returned in this period giving an estimated return rate of 33%.

The primary estimate of vaccine effectiveness after a single dose of smallpox vaccine against symptomatic mpox disease was 78% (95% CI 54 to 89; table 3). In the sensitivity analyses, the high-coverage scenario resulted in a vaccine effectiveness of 85% (95% CI 69 to 93), while the low-coverage scenario reduced vaccine effectiveness to 71% (40 to 86; table 3). When the extra case with unknown vaccine date was added to those vaccinated at least 14 days before onset, vaccine effectiveness dropped to 75% (95% CI 50 to 87). Single-dose vaccine effectiveness within 0–13 days was –4% (95% CI –50 to 29) for the central estimate and ranged from –30% (–89 to 10) to 23% (–11 to 47), with no evidence of a vaccine effect in any scenario (table 3). Five cases with onset in the 0–13-day period were vaccinated within 14 days after a known exposure, which might have been post-exposure vaccination. If these cases are removed then single-dose vaccine effectiveness within 0–13 days was 13% (95% CI –30 to 42). In the analysis including only individuals younger than 50 years, vaccine effectiveness at least 14 days after vaccination was 74% (95% CI 43 to 88; table 3).

Discussion

We estimated MVA–BN vaccine effectiveness against symptomatic mpox at least 14 days after a single dose to be 78% (range from 71% to 85% in sensitivity analyses), with no evidence of protection in the first 13 days after vaccination.

Our estimates are consistent with a recent Israeli study during the same 2022 outbreak, which estimated a vaccine effectiveness of 79% (95% CI 24 to 94) after a single dose of MVA–BN in a similar cohort of at-risk GBMSM aged 18–42 years using an electronic health-care system that covers around 52% of the Israeli population.[19] The eligible cohort in this study was similar to the cohort in our study: male participants at high risk of mpox infection, defined by similar criteria to those in England.[19] Only participants aged 18–42 years were included, excluding those who might have received childhood smallpox vaccinations, which would be

comparable to our analyses in those younger than 50 years. The analysis did not report vaccine effectiveness within and after 14 days, with a follow-up interval of 25 days after vaccination. Similarly, a US study during the same outbreak reported a 14-fold higher incidence of mpox disease in unvaccinated individuals eligible for MVA–BN compared with those receiving at least one vaccine dose in 32 jurisdictions, covering 56% of the US population eligible for vaccination, with similar trends observed in a sensitivity analysis but lower relative incidence rates.[20] This risk is equivalent to a vaccine effectiveness of about 93%. Similar to our study, the authors used aggregate data provided by public health jurisdictions, which obtained vaccination date from case interviews or linkage to vaccine registries.[30] They restricted their analysis by age to exclude anyone who might have received childhood smallpox vaccinations (those aged 50 years and older), as we did in our secondary analyses. We also focused on vaccine effectiveness at least 14 days after vaccination to allow time for an immune response to develop after vaccination. The higher vaccine effectiveness in the US study might in part be explained by the fact that they excluded those with possible previous smallpox vaccination (which we cannot exclude from our population comparator), and they also included a small number who had received second doses. Another study done in France focused on participants who received post-exposure vaccination and researchers reported that 12 (4%) of 276 had a confirmed mpox breakthrough infection.[30] Of these 12 cases, ten developed within 1–5 days of vaccination. This result highlights the importance of analysing the period soon after vaccination separately in our study.

Our effectiveness results after one dose are also consistent with preclinical studies based on immunogenicity responses and animal models.[12,14] One of these studies assessed the response after one single dose of MVA–BN in animal models challenged with monkeypox virus.[14] Full protection against the virus was shown after 30 days, but antibody response and protection against severe disease (and death) was shown as soon as 4 days after vaccination, although the sample size was small.[14] During this outbreak, Zaeck and colleagues[18] showed low concentrations of monkeypox virus neutralising antibodies after one vaccine dose in a small sample of human patients. Notably, there was a difference between individuals born before or after 1974, with 63% of the younger group eliciting neutralising antibodies compared with 100% of those born before 1974,[18] who were likely to have received previous smallpox vaccination, showing additional protection against mpox. These individuals also showed higher levels of neutralising antibodies than those born after 1974 who were unlikely to have received any previous smallpox vaccination.[18] To our knowledge, no studies have examined correlates of protection for mpox and further studies are required that include serology and clinical outcomes. However, this study by Zaeck and colleagues suggests the need to differentiate between participants previously vaccinated during childhood and unvaccinated individuals. This strategy is in line with reports from surveillance data from Africa suggesting a protective effect of previous smallpox vaccination, in some cases estimated to be about 85% effective.[16,17] In line with these results, our analysis in participants younger than 50 years, who were less likely to have been vaccinated before this outbreak, also showed slightly lower vaccine effectiveness than in those aged 50 years and older.

It is important to note that vaccine effectiveness might vary across the population. We have limited information on possible risk factors and clinical comorbidities; however four of eight of the breakthrough cases were living with HIV. There are some limitations to these analyses. Firstly, we assumed all cases are vaccine eligible GBMSM unless they reported as female or heterosexual. A small number of cases might not have been eligible for vaccination. However, given the high percentage of all

	Cases	Matched coverage*	Vaccine effectiveness (95% CI)
All ages, primary coverage			
Dose 1 interval, 0 to 13 days	32/362 (8·8%)	7·9%	–4% (–50 to 29)
Dose 1 interval, ≥14 days	8/362 (2·2%)	8·0%	78% (54 to 89)
Unvaccinated	322/362 (89·0%)	84·1%	..
All ages, high coverage			
Dose 1 interval, 0 to 13 days	32/362 (8·8%)	9·9%	23% (–11 to 47)
Dose 1 interval, ≥14 days	8/362 (2·2%)	10·0%	85% (69 to 93)
Unvaccinated	322/362 (89·0%)	80·1%	..
All ages, low coverage			
Dose 1 interval, 0 to 13 days	32/362 (8·8%)	6·6%	–30% (–89 to 10)
Dose 1 interval, ≥14 days	8/362 (2·2%)	6·7%	71% (40 to 86)
Unvaccinated	322/362 (89·0%)	86·7%	..
Younger than 50 years, primary coverage			
Dose 1 interval, 0 to 13 days	29/280 (10·4%)	8·1%	–21% (–80 to 18)
Dose 1 interval, ≥14 days	7/280 (2·5%)	7·8%	74% (43 to 88)
Unvaccinated	244/280 (87·1%)	84·1%	..
Younger than 50 years, high coverage			
Dose 1 interval, 0 to 13 days	29/280 (10·4%)	10·1%	10% (–33 to 33)
Dose 1 interval, ≥14 days	7/280 (2·5%)	9·8%	82% (61 to 92)
Unvaccinated	244/280 (87·1%)	80·1%	..
Younger than 50 years, low coverage			
Dose 1 interval, 0 to 13 days	29/280 (10·4%)	6·7%	–52% (–126 to –3)
Dose 1 interval, ≥14 days	7/280 (2·5%)	6·5%	66% (25 to 84)
Unvaccinated	244/280 (87·1%)	86·8%	..

Coverage applied for each scenario was 50% for the primary coverage, 63% for high coverage, and 42% for low coverage. One case with missing vaccination date was excluded for these analyses. Vaccine effectiveness including this case (n=363) was calculated in a sensitivity analysis: 75% (95% CI 50 to 87). *Coverage matched by index date week is substantially below the final coverage because many cases occurred in the early weeks of roll-out.

Table 3: **Estimates of vaccine effectiveness using the screening method for all ages and for cases younger than 50 years, including results from sensitivity analyses using different coverage scenarios, in England**

cases in England self-reporting as GBMSM (96·8%),[22] this should not have a measurable influence in the final analyses. Because there is no vaccination registry for this programme and clinical records are anonymised and follow a lag, we relied on self-reported questionnaire data to obtain case vaccination status. The questionnaire return rate was low (about 33%) and, potentially, if vaccinated cases are more likely to return completed questionnaires, vaccine effectiveness would be underestimated. There is also some uncertainty on the GBMSM denominator, resulting in a range of vaccine effectiveness from 75% to 87% in the sensitivity analyses. Given the aggregated nature of the vaccine coverage data, we were also unable to adjust for potential confounders other than time period. This could lead to vaccine effectiveness being overestimated or underestimated. For example, if cases within the GBMSM population included in the study were younger, but vaccine uptake was higher in older individuals, then vaccine effectiveness would be overestimated (and note that the age of cases included in the study compared with all cases was slightly younger, but we do not know if coverage differed by age). Behavioural changes post-vaccination might also have affected vaccine effectiveness estimates; for example, if vaccinated individuals were less likely to abstain from high-risk sexual activity because of having received the vaccine then the pharmacological effectiveness would be underestimated. We considered individuals vaccinated before 2022 as unvaccinated because we could only assess the effect of vaccination as part of the 2022 immunisation campaign since it was not possible to split vaccine coverage by previous vaccine status. If previous vaccination has some residual protection, then this means that our estimates might be lower than the true vaccine effectiveness. The fact that vaccine effectiveness was similar when restricting to cases aged 50 or younger, who were less likely to have received a vaccine before 2022, suggests the bias might be small. However, many mpox cases are in people born outside of the UK, including from regions where smallpox vaccination programmes might have ended later than 1971. Furthermore, some GBMSM cases might be health-care workers or laboratory workers who might have received vaccination. Therefore, this age cutoff still includes some cases who had been previously vaccinated. 7% of those younger than age 50 years reported vaccination between 1971 and 2021 but this figure probably reflects recall bias given the very low eligibility since 1971.[23] It is possible that some cases were given post-exposure prophylaxis. However, when we removed participants with an onset in the 0–13-day interval who were vaccinated within 14 days of a known exposure, vaccine effectiveness for 0–13 days remained low (13% [95% CI −30 to 42]). We are only able to estimate relatively short-term effectiveness of one dose of vaccine given the time that has elapsed since the start of the programme, but further follow-up will be needed to estimate the duration of protection.

It is important to note that most of these potential biases would also affect our vaccine effectiveness estimates during 0–13 days after vaccination. The fact that this estimate is close to zero provides some reassurance that these potential biases are unlikely to be having a major effect on our vaccine effectiveness estimates for 14 days or longer post-vaccination. Furthermore, while the number of cases in this study is relatively small, the confidence intervals in our study very clearly indicate a high vaccine effectiveness.

Finally, vaccination using an intradermal vaccination route instead of subcutaneous to maximise the number of doses was recommended in the UK from Aug 22, 2022, with variable roll-out dates across the country and with variable implementation between clinics.[7] By November, 2022, 65% of sites were offering intradermal vaccinations. Consequently, most doses in our analysis would have been administered subcutaneously and, therefore, our vaccine effectiveness estimates relate mainly to subcutaneous vaccinations. Any vaccine effectiveness differences between subcutaneous and intradermal administration will need to be assessed in future studies.

Our results suggest a relatively high level of protection from a single dose of MVA–BN against symptomatic mpox in a predominantly young adult GBMSM population—making it a useful tool for mpox outbreak control when rapid protection is needed. This suggests that where numbers at highest risk of infection exceed vaccine supply of two doses, there might be benefit in prioritising delivery of first doses. Further work is needed to evaluate the duration of protection as well as the effectiveness of a full two-dose course. Further work is also needed to evaluate whether vaccine effectiveness varies across population groups or with different viral clades.

Contributors

JLB, NA, MR, and GA were responsible for the conceptualisation and methodology of this study. JLB was the main supervisor. NA undertook formal analysis, and with MB verified all the data used in the analyses. PB, JH, MG, CT, MB, CD, JB, BD, and RL were involved in data curation. MB, NA, and JLB wrote the original draft. All authors were involved in writing, reviewing, and editing of the final manuscript. All authors confirm they had full access to all the data in the study and accept responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

This work is carried out under Regulation 3 of The Health Service (Control of Patient Information; Secretary of State for Health, 2002) using patient identification information without individual patient consent as part of the UKHSA legal requirement for public health surveillance and monitoring of vaccines. As such, authors cannot make the underlying dataset publicly available for ethical and legal reasons, particularly due to the sensitive information included. However, all the data used for this analysis is included in the manuscript tables and appendix so the analysis could be reproduced. Applications for relevant anonymised data should be submitted to the UKHSA Office for Data Release at https://www.gov.uk/government/publications/accessing-ukhsa-protected-data.

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