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Title

Real-world effectiveness of a single dose of mpox vaccine in males

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Abstract

The recent global outbreak of the monkeypox virus (MPXV) in humans was declared a public health emergency by the World Health Organization (WHO) in July 2022. The Smallpox and Monkeypox Vaccine (JYNNEOS; Modified Vaccinia Ankara-Bavarian Nordic) (MVA-BN), provided as a two-dose regimen, is currently the primary vaccine utilized against monkeypox (mpox). However, the efficacy of MVA-BN against mpox has never been demonstrated in clinical trials to date. Due to the limited supply of vaccines, the WHO has recommended prioritizing the vaccination of high-risk groups.

We evaluated the real-world effectiveness of a single, subcutaneous dose of MVA-BN in this observational, retrospective cohort study, which included the analysis of electronic health records of all members of Clalit Health Services (CHS) eligible for the vaccine on July 31, 2022. We used a Cox proportional-hazards regression model with time-dependent covariates to estimate the association between vaccination and mpox while adjusting for sociodemographic and clinical risk factors. In an analysis of 2,054 male individuals that met vaccine eligibility criteria, 1,037 (50%) were vaccinated during the study recruitment period and completed at least 90 days of follow-up. During the study period, 5 and 16 infections were confirmed in vaccinated and unvaccinated individuals, respectively. The adjusted vaccine effectiveness was estimated at 86% (95% CI: 59%-95%). Our results suggest that a single dose of subcutaneous MVA-BN in this high-risk cohort is associated with a significantly lower risk of MPXV infection.

Introduction

The human monkeypox virus (MPXV) is a member of the Orthopoxvirus genus and is closely related to the virus that causes smallpox. The recent global outbreak of MPXV was first recognized in May 2022, when infections were reported in several countries where MPXV cases had not been previously identified[1-3]. On July 23, 2022, the Director-General of the WHO declared mpox a public health emergency of international concern[4]. By December 22, 2022, over 83,000 laboratory-confirmed cases were reported worldwide[5]. The Smallpox and Monkeypox Vaccine (JYNNEOS Modified Vaccinia Ankara Bavarian Nordic) (MVA-BN), a live attenuated Orthopoxvirus, is currently the preferred vaccine for mpox[2,6]. Official U.S. Food and Drug Administration (FDA) prescribing information recommends providing the vaccine as a series of two subcutaneous doses administered 4 weeks apart[7]. Nevertheless, because of a limited vaccine supply, many countries have implemented a single-dose strategy and later an intradermal 1/6th dose to maximize vaccine availability [8-10].

MVA-BN was developed initially as a third-generation smallpox vaccine [11]. The FDA expanded the indication to mpox prophylaxis based on data from an MPXV challenge study conducted in non-human primates. However, efficacy data of the vaccine against mpox in humans are lacking. Therefore, evidence for the real-life effectiveness of the vaccine in preventing mpox in humans is still warranted [6,12]. Our objective was to promptly follow vaccinated individuals to assess the effectiveness of providing one dose of the vaccine in a real-world, at-risk population.

Results

Study population

2,054 CHS members met the study eligibility criteria (described in Methods). All eligible individuals were male. Of these, 1,037 (50%) were vaccinated with MVA-BN and had at least 90 days of follow-up. The majority of participants belonged to the general Jewish population sector (95.0%), followed by Arabs (2.1%) and Ultra-orthodox Jews (1.9%). The population sector was unknown for 0.9% of the study cohort. All vaccine doses were provided subcutaneously. Follow-up time was 90 to 147 days (average: 141 days).

Vaccine uptake

The characteristics of vaccinated and unvaccinated individuals and the association between these characteristics and vaccine uptake are detailed in Table 1. Vaccine uptake in individuals who attended primary healthcare clinics in the Israeli Tel-Aviv district was 2.2-fold higher than in individuals from other regions. Uptake was lower in individuals from the minority population sectors and those with a socioeconomic status score below the median by 55% and 22%, respectively. HIV-PrEP utilization, PDE5 inhibitors utilization, and recent Chlamydia or NE Gonorrhea infections were associated with a 70%, 43%, and 34% higher vaccine uptake, respectively.

Assessment of vaccine effectiveness

During the study period, MPXV infections occurred in 16 unvaccinated individuals (9.3 per 100,000 person-days) and 5 vaccinated individuals (4.3 per 100,000 person-days). The adjusted HR for infection in the vaccinated compared to the unvaccinated population was 0.14 (95% Confidence Interval (CI) 0.05 – 0.41). The cumulative HR curves for infection are shown in Figure 1. Univariable and multivariable Cox proportional hazard analyses assessing the association between participant characteristics and mpox are detailed in

105 Table 2. The Tel-Aviv district of the primary healthcare clinic was associated with a 4-fold

106 higher risk of mpox.

107

Discussion

Six months after the initial worldwide spread of mpox, the outbreak seems to be contained [4], mainly attributed to vaccination efforts and behavioral changes [13]. While the vaccines against smallpox were assumed to also protect against mpox, efficacy data are still limited to studies in mice and monkey models [14]. How well MVA-BN protects against mpox in humans and how much protection against mpox is elicited by providing only a single dose rather than the recommended two doses is still unclear [12]. Our results demonstrate that vaccination with one subcutaneous dose of MVA-BN was associated with an 86% reduction in the risk for mpox among vaccinated individuals considered at high risk of MPXV infection. Nevertheless, completing the second vaccine dose, per the approved label, may improve this effectiveness and provide longer-lasting protection.

In a recent observational study of 276 individuals at a single hospital setting, vaccinated post-exposure, 12 participants (4%) had a confirmed MPXV breakthrough infection; of those, 10 patients developed an infection up to five days following vaccination [15]. However, we are unaware of published studies evaluating vaccine effectiveness when provided as pre-exposure prophylaxis.

The United States CDC has reported in its December 8, 2022 update, that among 43 U.S jurisdictions, the mpox rate among individuals who were recommended to receive a vaccine was 7 times higher among unvaccinated individuals compared with those vaccinated with one dose, suggesting similar results of vaccine effectiveness as demonstrated in our study. However, these results did not control for possible differences in baseline characteristics such as age, underlying conditions, or other differences between the two groups [8].

Randomized controlled trials are yet required to provide direct evidence of the efficacy and safety of vaccines against mpox in humans. While such data would have been the gold standard for supporting mpox vaccination guidelines, the time required for such trials to be planned, executed, and published would not be sufficient for immediate policy decisions urgently needed to contain the epidemic. Therefore, controlled studies and vaccine effectiveness surveillance are critical to understanding the utility of vaccines against MPXV acquisition[16].

Our study has some noteworthy limitations. The primary limitation is the small number of participants, the younger age (18-42 years), and the low number of infections observed during the study period, even in the unvaccinated individuals. Our results should, therefore, be regarded as preliminary, and additional larger studies are still required. However, these promising results may further drive the engagement of individuals and their healthcare providers for vaccination.

Another major limitation is that the characteristics of vaccinated and not vaccinated individuals in our study cohort were significantly different despite all being identified as high-risk, according to the Israeli MOH guidelines. The vaccinated and unvaccinated groups differed in most sociodemographic and clinical variables (Table 1). The unvaccinated group had a lower socioeconomic status and included more minority sectors living outside the Tel Aviv district and a higher prevalence of HIV. Although we adjusted for known and measurable confounders, some sources of residual confounding may not have been measured or corrected adequately.

Bias in estimating vaccine effectiveness might be caused by unmeasured differences in lifestyle behaviors, including sexual behaviors, between vaccinated and unvaccinated

individuals. Vaccination might also lead to changes in behaviors that could affect the risk of mpox acquisition. Our study was based on a clinical database and, therefore, could not directly capture the sexual behavior patterns of the study participants. Sexual behavior patterns would have been extraordinarily challenging to capture and control, especially since we included all the vaccine-eligible individuals in our study cohort, not only those infected with MPXV. We attempted to overcome behavior bias by controlling for measurable factors identified by clinicians that may serve as markers for sexual behavior patterns and which include previous STIs detected in rectal, pharyngeal, or urine PCR tests, blood tests for Syphilis screening (TPHA), and dispense of HIV-PrEP therapy and PDE5-inhibitors (sildenafil, tadalafil, or vardenafil)[17].

It should be noted that no screening for mpox was carried out in Israel and that the detection of mpox was limited only to individuals who reported symptoms to their physicians. Under-reporting could occur if individuals were asymptomatic or because patients' symptoms were not attributed to mpox[18]. However, we assume that rates of undiagnosed mpox infections are not likely to differ in vaccinated and unvaccinated individuals.

Another possible source of bias is the variation of exposure to mpox during the study period. In our analysis, Schonfeld's global test confirmed that the proportional hazards assumption was met in the Cox proportional hazards model, suggesting that this variation in the risk for exposure to mpox remained similar in vaccinated and unvaccinated participants throughout the study period.

The initial mpox vaccination policy in Israel focused on pre-exposure prophylaxis in high-risk individuals, with special per-case approval for post-exposure cases. However, no

testing for the existence of mpox was done prior to vaccine administration. Therefore, some vaccinated individuals may have been infected (but undiagnosed) before vaccine administration, potentially lowering the observed effectiveness. All five cases of infection in the vaccinated individuals were diagnosed at least 21 days after vaccine uptake (21-47 days) and, therefore, probably represent vaccine breakthroughs rather than cases of post-exposure vaccinations.

We could not assess the effectiveness of the recommended two-dose regimen since only 20% of the vaccinated participants in Israel have completed the second dose to date, and due to insufficient follow-up time after the second dose.

In Israel, the vaccine was administered only by a subcutaneous route during the study period, per FDA prescribing information[8]. Transition to the intradermal route was implemented in Israel on October 26, 2022, only after the enrollment of participants in our dataset had ended. The change in route of administration was decided, like in many other countries, to advance access, equity, and chances of controlling the monkeypox outbreak, as the subcutaneous dose can be split into up to six intradermal doses[10,19,20]. Therefore, our results might not be relevant in other healthcare settings where the intradermal, lower-volume dose administration of MVA-BN was adopted earlier.

In conclusion, our results suggest that a single dose of the MVA-BN vaccine administered subcutaneously is associated with a lower risk of mpox in high-risk male individuals in Israel. These findings suggest that providing at least one dose of the vaccine might have contributed to the containment of the current mpox outbreak. Larger randomized and real-world studies are still required to validate the vaccine's effectiveness over time.

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Author Contributions

All authors contributed to the study design and execution. E.B. extracted the data under the supervision of Y.W. W.A. and N.R. cleaned and analyzed the data with the guidance of Y.W. and R.A. Y.W., R.Z. A.H. and R.A. drafted the initial manuscript and made the primary revisions. R.Z. H.M., N.G.A., G.C, A.M., G.W. H.D. and A.P. planned, revised, and approved all the clinical aspects of the study. S.Y. performed internal quality control checks. G.L. and D.N. contributed to the policy aspects of the study. R.A., G.L., and D.N. oversaw the study design and conduct. All authors revised the manuscript for critical content and clarity and approved it.

*Y.W., R.Z., and A.H authors contributed equally.

** R.A, G.L, and D.N jointly supervised this work

Competing interests

The authors declare no competing interests.

Tables

Table 1: Association between participant characteristics and vaccine uptake

	Unvaccinated	Vaccinated	All	HR[4] (95% CI)
	N (%)	N (%)	N (%)	
Total N	1,017 (50%)	1,037 (50%)	2,054 (100%)	
Sociodemographic variables				
Age, mean (SD)	33.5 (5.8)	34.1 (4.9)	33.8 (5.4)	1.02 (1.01, 1.03)
Sex – Male	1,017 (100)	1,037 (100)	2,054 (100)	All male
Tel-Aviv district	406 (39.9)	783 (75.5)	1,189 (57.9)	2.23 (1.92, 2.59)
Sociodemographic status score below median	501 (49.3)	326 (31.4)	827 (40.3)	0.78 (0.69, 0.89)
Population sector - General Jewish	935 (91.9)	1017 (52)	1952	reference
Population sector- others	82 (8.1)	20 (1.9)	102 (5.0)	0.45 (0.29, 0.71)
Arab	40 (3.9)	4 (0.4)	44 (2.1)	
Ultraorthodox Jewish	30 (2.9)	9 (0.9)	39 (1.9)	
Unknown	12 (1.2)	7 (0.7)	19 (0.9)	
Clinical risk factors				
History of HIV/AIDS	511 (50.2)	136 (13.1)	647 (31.5)	0.46 (0.34, 0.63)
History of Syphilis infection	199 (19.6)	233 (22.5)	432 (21.0)	1.05 (0.89, 1.24)
Recent[1] Syphilis infection	31 (3.0)	61 (5.9)	92 (4.5)	1.05 (0.79, 1.40)
Recent[1] STI[2] in urinary test	31 (3.0)	67 (6.5)	98 (4.8)	0.88 (0.65, 1.20)
Recent[1] STI[2] in pharyngeal test	46 (4.5)	159 (15.3)	205 (10.0)	1.25 (0.96, 1.64)
Recent[1] STI[2] in rectal test	46 (4.5)	157 (15.1)	203 (9.9)	1.02 (0.78, 1.32)
Recent Chlamydia or NE Gonorrhea[3]	100 (9.8)	298 (28.7)	398 (19.4)	1.34 (0.99, 1.82)
Purchase of PDE5 – inhibitors[1]	98 (9.6)	202 (19.5)	300 (14.6)	1.43 (1.22, 1.67)
Purchase of HIV-PrEP[1]	506 (49.8)	876 (84.5)	1,382 (67.3)	1.70 (1.29, 2.24)

Table 1 footnotes: **1**- Recent: from 01/2022 to 06/2022; **2**- STI: Chlamydia or NE Gonorrhea;

222 **3**- Recent Chlamydia or NE Gonorrhea: in an either urinary, pharyngeal, or rectal test. **4**- The
223 association between all covariates and MVA-BN vaccine uptake was estimated using a
224 multivariate Cox proportional-hazards regression model. The higher the hazard ratio, the
225 greater the association between the listed characteristic and vaccine uptake**.**
226

Table 2- Association of participant characteristics and MPXV infection

Variables	Results of the Univariable[2] models	Results of the Multivariable[3] model
	HR (95% CI)	HR (95% CI)
Vaccination	0.30 (0.11, 0.83)	0.14 (0.05, 0.41)
Tel-Aviv district	3.11 (1.05, 9.23)	3.98 (1.29, 12.33)
HIV PrEP use[1]	0.97 (0.39, 2.41)	
Purchase of PDE5 – inhibitors[1]	1.84 (0.67, 5.02)	2.14 (0.76, 5.99)
History of HIV/Aids	0.87 (0.34, 2.24)	
Any Syphilis infection	1.89 (0.76, 4.67)	1.11 (0.39, 3.18)
Chlamydia or NE Gonorrhea in recent[1] Rectal PCR	2.15 (0.72, 6.39)	
Chlamydia or NE Gonorrhea in recent[1] Urine PCR	3.38 (1.00, 11.48)	
Chlamydia or NE Gonorrhea in recent[1] pharyngeal PCR	0.95 (0.22, 4.09)	
Chlamydia or NE Gonorrhea in any recent[1] STI PCR	2.09 (0.84, 5.19)	2.53 (0.98, 6.52)
Recent[1] Syphilis infection	3.58 (1.05, 12.15)	3.20 (0.78, 13.17)

Table 2 footnotes:

1- Recent: from 01/2022 to 06/2022; **2**- STI: Chlamydia or NE Gonorrhea; 2- The associations between each of the covariates and mpox were estimated using a series of univariate Cox proportional-hazards regression models. **3**- A multivariate Cox proportional-hazards regression model was used to estimate the association between vaccine and mpox while controlling for the covariates found to be associated with mpox in the univariate analyses. The higher the hazard ratio, the greater the association between the listed characteristic and vaccine uptake**.**

Figure legend

Figure 1: Cumulative Hazard for mpox infection (95% confidence intervals)

Figure footnotes: For unvaccinated participants, time zero corresponds to July 31, 2022, when the vaccination campaign was initiated.

For vaccinated participants, time zero corresponds to the date of vaccine uptake. The shaded areas indicate the 95% confidence intervals.

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Methods

The study was approved by CHS's Community Institutional Review Board Committee and the Clalit Health Services Data Utilization Committee. The study was exempt from the requirement to obtain informed consent owing to the retrospective design.

Study participants

This observational, retrospective population-based cohort study was based on data obtained from the electronic medical records of Clalit Health Services (CHS), the largest of four integrated healthcare organizations in Israel, which insures 4.78 million patients (52% of the population).

In response to the current mpox outbreak, the Israeli Ministry of Health (MOH) initiated a vaccination campaign on July 31, 2022, for individuals considered at high risk for infection. The eligibility criteria were: (a) males aged 18 – 42 years who were dispensed HIV-PrEP at least for one month since January 1, 2022, or (b) males aged 18 – 42 years who were diagnosed with HIV and also were diagnosed with one or more sexually transmitted infections (STIs) since January 1, 2022. However, due to the limited vaccine supply, the policy in Israel when the vaccination campaign was initiated was to administer only a single subcutaneous dose of the vaccine. The cohort included all CHS members eligible for the vaccine per the Israeli MOH guidelines when the study commenced who had completed at least 90 days of follow-up after vaccination. Individuals who were infected with mpox prior to the study period were excluded.

Study design and timeline

The follow-up of participants' data started on July 31, 2022, when the vaccination campaign was initiated in CHS. The data was collected until December 25, 2022, and

participants vaccinated after September 26, 2022, were excluded to allow sufficient follow-up time. Vaccination with a second dose of MVA-BN was introduced in Israel on September 13, 2022. Therefore, follow-up of individuals who received a second vaccine dose was censored at the date of the second vaccine.

Participants were evaluated as part of the unvaccinated group until the vaccination date. For unvaccinated participants, time zero corresponds to July 31, 2022, when the vaccination campaign was initiated. For vaccinated participants, time zero corresponds to the date of vaccine uptake. Participants moved from the unvaccinated group to the vaccinated on the day they were vaccinated. In the vaccinated participants, the first time period accounts for the days from the follow-up start date (July 31, 2022, when the vaccination campaign was initiated) until the vaccination date. During this period, the follow-up days of the participants are a part of the "unvaccinated status." The second follow-up period of the vaccinated participants accounts for the days from the vaccination day until the end of follow-up (December 25, 2022) and is counted as part of the "vaccinated status." The study timeline and the transition between the unvaccinated and vaccinated status are depicted in the extended data figure 1.

The study's primary endpoint was mpox diagnosis, determined by a laboratory-confirmed real-time polymerase chain reaction (RT-PCR) test. Since the minimum time between infection and symptoms onset was initially reported to be 5 days [21], the estimated date of infection was defined as the earlier of five days before the positive PCR test result or of a physician-documented suspected diagnosis of mpox. Any infection according to the above definition occurring later than the date of vaccination was considered as a breakthrough infection.

Data extraction

The following data were extracted for each participant: MVA-BN vaccination, mpox diagnosis, and RT-PCR lab results, age, geographical district of primary healthcare clinic, population sector, the score for socioeconomic status, history of HIV/AIDS, STIs detected in rectal, pharyngeal, or urine PCR tests, blood test for Syphilis screening (TPHA), and dispense of HIV-PrEP therapy and PDE5-inhibitors (sildenafil, tadalafil, or vardenafil).

The CHS data repositories and the definition of the sociodemographic variables were previously described in published COVID-19 studies [22]. The data extraction date was December 29, 2022.

Statistical analysis

Descriptive statistics were used to characterize the study participants, and the study population was divided into two groups, those who had received the vaccine and those who had not. The geographical district of the primary clinic where each participant is registered was based on the administrative classification of CHS, dividing the entire state of Israel into 9 districts. This covariate was categorized as Tel Aviv versus the other 8 geographical districts, as most of the study population (58%) resided in this area. The population sector was based on CHS's administrative classification of the primary clinic where each participant is registered: general Jewish, Arab and Jewish-ultraorthodox. This covariate was dichotomously divided into the majority sector (general Jewish, 95.0% of the study population) and minority sectors (including Arabs, Jewish-ultraorthodox, and those with unknown sector classification). The sociodemographic status score was categorized as below the median versus median score or higher. A multivariate Cox proportional-hazards regression model was used to estimate the association of all covariates and uptake of the

MVA-BN vaccine.

In order to avoid immortal time bias [23], we performed a time-dependent analysis in which a time-varying covariate was used to indicate the initiation of vaccination for each vaccinated patient. Participants were transferred from the 'unvaccinated' group to the 'vaccinated' group when vaccinated, modifying their vaccination status from unvaccinated to vaccinated. Consequently, the follow-up of vaccinated patients started at the end of the immortal period.

The association between MVA-BN vaccination and mpox was estimated as follows: first, a univariate Kaplan-Meier analysis with a log-rank test was applied to test the associations of each independent candidate variable with the primary outcome. The threshold for the first testing criteria was set at $p<0.25$ [24]. Then, the proportional hazard assumption was validated for those variables using Schoenfeld's global test. Variables that met these two testing criteria served as inputs for multivariable Cox proportional-hazards analysis. Vaccine effectiveness was defined as 1 minus the hazard ratio.. All reported p-values are two-tailed.

Data availability

Due to Clalit Health Services' data privacy regulations and as per the institutional Helsinki and data utilization committee approvals for this study, the data used for this study cannot be shared.

Code availability

R statistical software version 4.0.1 (R Project for Statistical Computing) was used for the univariate and multivariate survival analysis with time-dependent covariates. The following R packages were used: survival (3.2-13), ggplot2 (3.3.5), ggpubr (0.4.0), survminer (0.4.9), and table1 (1.4.2). All R packages are freely available.

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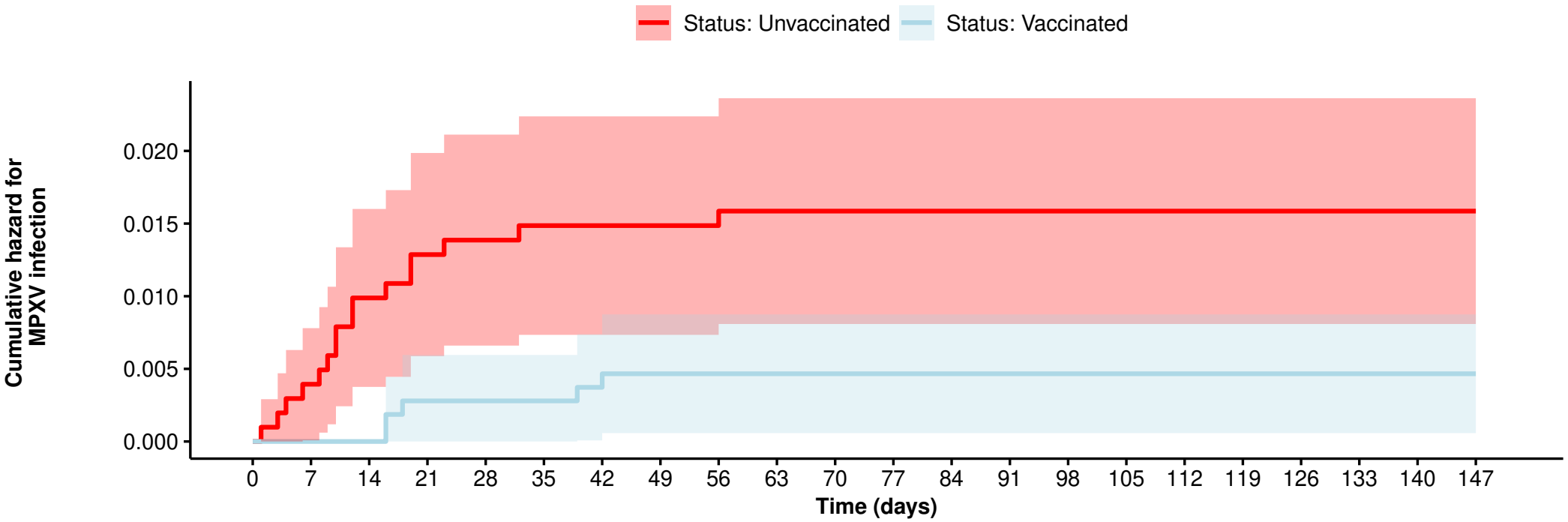
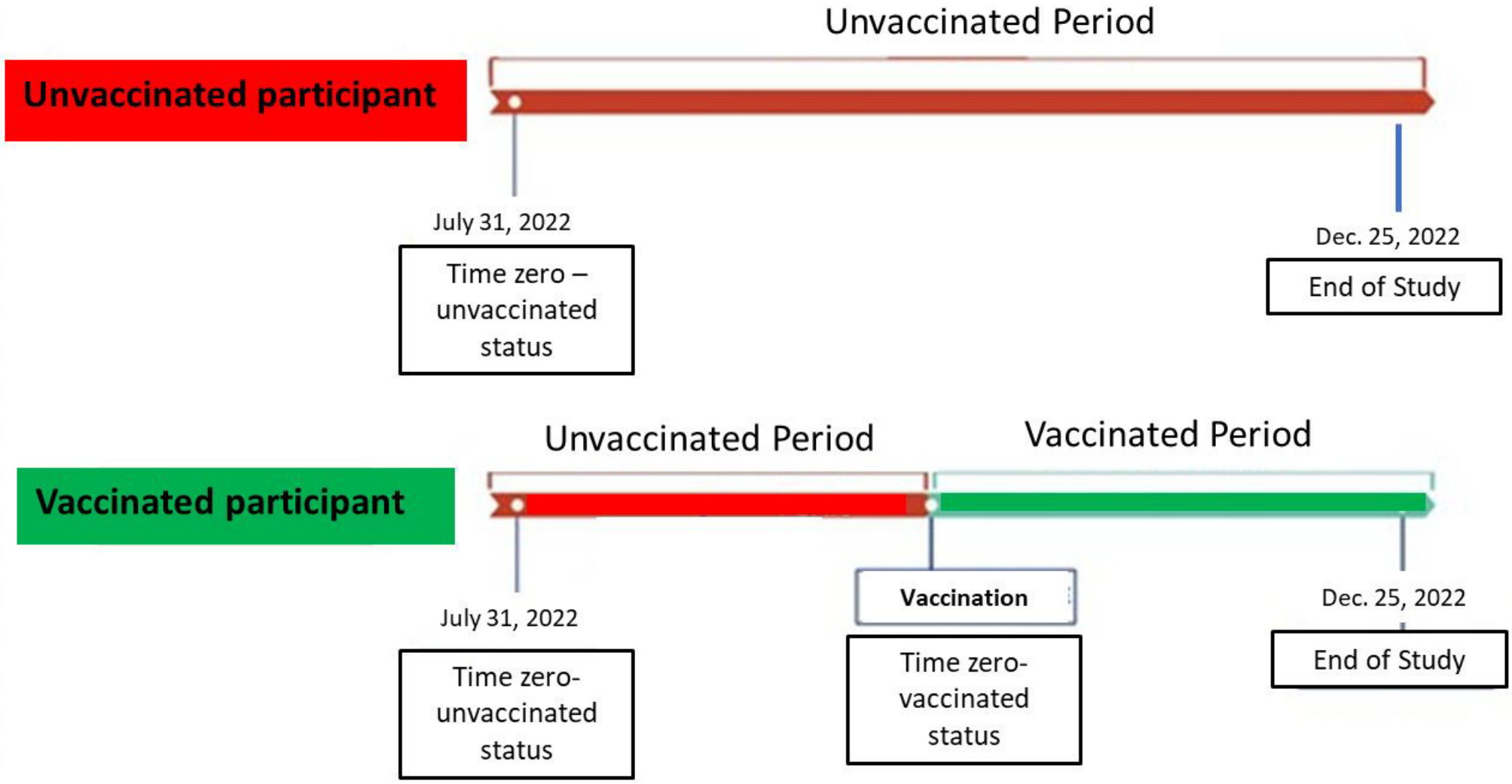


Number at risk

Unvaccinated	1017	1013	1007	1004	1003	1002	1002	1002	1002	1001	1001	1001	1001	1001	1001	1001	1001	1001	1001	1001	1001	1001
Vaccinated	1075	1075	1075	1072	1072	1072	1071	1067	1064	1062	1055	1043	1008	939	882	837	789	741	689	617	504	76

Cumulative number of events

Unvaccinated	0	4	10	13	14	15	15	15	16	16	16	16	16	16	16	16	16	16	16	16	16	16
Vaccinated	0	0	0	3	3	3	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5


Unvaccinated Period
Unvaccinated participant
July 31, 2022
Time zero – unvaccinated status
Dec. 25, 2022
End of Study
Unvaccinated Period
Vaccinated Period
Vaccinated participant
July 31, 2022
Time zero- unvaccinated status
Vaccination
Time zero- vaccinated status
Dec. 25, 2022
End of Study

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Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☒	☐ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒ A description of all covariates tested
☐	☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	Data was collected from CHS databases using SQL V18.6
Data analysis	R statistical software version 4.0.1 (R Project for Statistical Computing) was used for the univariate and multivariate survival analysis with time-dependent covariates. The following R packages were used: survival (3.2-13), ggplot2 (3.3.5), ggpubr (0.4.0), survminer (0.4.9), table1 (1.4.2). All R packages are freely available.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

Due to Clalit Health Services data privacy regulations ans as per the institutional Helsinki and data utilization committee apptovals for this study, the patient-level data used for this study cannot be shared.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	All eligible subjects in Clalit Health Services were included in the study
Data exclusions	Subjects who were infected with MPXV prior to the study period were excluded. Additionally, participants vaccinated after October 21, 2022 were excluded to allow a minimal follow-up time of 25 days after vaccination.
Replication	Replication is not feasible for this study due to the limited number of subjects eligible for the study cohort and their unique characteristics
Randomization	Randomization was not applicable in this study, as this an observational cohort study, based on electronic medical records
Blinding	Blinding was not applicable in this study, as this an observational cohort study, based on electronic medical records

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Human research participants

Policy information about studies involving human research participants

Population characteristics	All eligible subjects in Clalit Health Services were included in the study. The mean age of the study participants was 34 (SD 5.3). All participants were males.
Recruitment	Participants were not recruited: data for all eligible participants was extracted retrospectively from Clalit Health Services database. Participants' sex was also extracted from Clalit Health Services database, as registered in participants' medical records.
Ethics oversight	The study was approved by CHS's Community Institutional Review Board Committee and the Clalit Health Services Data Utilization Committee. The study was exempt from the requirement to obtain informed consent owing to the retrospective design.

Note that full information on the approval of the study protocol must also be provided in the manuscript.