

Effectiveness of a single-dose Modified Vaccinia Ankara in Human Monkeypox: an observational study

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Abstract

Background

The recent global outbreak of the human monkeypox virus (MPXV) was declared a public health emergency by the World Health Organization. Modified Vaccinia Ankara (MVA) is currently the only FDA-approved vaccine against MPXV that was approved for this indication based on a study in non-human primates. Since there is currently scarce evidence of the efficacy in humans, our objective was to evaluate real-life vaccine effectiveness (VE) after providing one vaccine dose to individuals at risk of MPVX infection.

Methods

The study cohort included all Clalit Health Services (CHS) members eligible for the MVA vaccine as defined by the Israeli Ministry of Health. The study commenced on July 31, 2022, when the MVA vaccination campaign was initiated in CHS, and participants were followed until September 12, 2022. A Cox proportional-hazards regression model with time-dependent covariates was used to estimate the association between vaccination and MPXV infections with adjustment for sociodemographic and clinical risk factors.

Findings

A total of 1,970 subjects met the study eligibility criteria (0.04% of CHS members). Of them, 873 (44%) were vaccinated with MVA and completed at least 25 days of follow-up. 18 infections were confirmed in CHS during the study period, 3 in vaccinated and 15 in unvaccinated status (40.0 versus 6.4 per 100,000 person days). VE was estimated at 79% (95% CI: 24%-94%).

Interpretation

Our results suggest that a single dose of MVA is associated with a significantly lower risk for MPVX infection in high-risk individuals. These findings highlight that urgent MVA vaccination of high-risk individuals may contribute to the containment of the current MPXV outbreak.

Research In Context

Evidence before this study

The recent global outbreak of the human monkeypox virus (MPXV) was declared a public health emergency by the World Health Organization. Modified Vaccinia Ankara (MVA) is currently the only FDA-approved vaccine against MPXV that was approved for this indication based on a study in non-human primates. The effectiveness of MVA in humans is unknown.

Added value of this study

This study is one of the first to evaluate the real-world effectiveness of the MVA vaccine for preventing human monkeypox infections. We found that one dose of the MVA vaccine is associated with a 79% reduction in the risk of human monkeypox infections in high-risk individuals.

Implications of all the available evidence

Vaccination of individuals at high-risk of human monkeypox infection is an effective and essential tool for the containment of the human monkeypox breakout.

Introduction

The human monkeypox virus (MPXV) is an Orthopox virus related to smallpox (1, 2). The recent global outbreak of MPXV was first recognized in May 2022, and by September 17, 2022, nearly 65,000 laboratory-confirmed cases were reported worldwide (3). MPXV was declared a public health emergency by the WHO (4) and the US CDC (5).

Modified Vaccinia Ankara (MVA), a live attenuated non-replicating Orthopoxvirus, is currently the preferred vaccine approved for MPXV, provided as a series of two doses administered 28 days apart (2). The MVA vaccine was developed and approved for use in case of a smallpox bioterrorist attack. The FDA expanded the indication to MPXV prophylaxis based on data from an MPXV challenge study conducted in non-human primates (2), and the level of certainty for preventing MPXV in humans was considered low (5). To contain the epidemic, the Israeli Ministry of Health (MOH) initiated an MVA vaccination campaign on July 31, 2022. Due to the current shortage of MVA supply, the present policy in Israel is to administer only a single dose of the vaccine, administered subcutaneously and only to individuals at high risk for infection according to objective eligibility criteria (6).

Due to scarce evidence of the efficacy of the MVA vaccine against MPXV in humans, our objective was to evaluate the real-life vaccine effectiveness (VE) of MVA.

Methods

Study design and participants

This observational, retrospective population-based cohort study was based on data obtained from the electronic medical records of Clalit Health Services (CHS), a large healthcare organization that covers approximately 52% of the entire Israeli population. The study commenced on July 31, 2022, when the MVA vaccination campaign was initiated in CHS. Participants were followed until September 12, 2022, and for at least 25 days after vaccination. Participants vaccinated after August 18, 2022, were excluded to allow sufficient follow-up time.

The primary endpoint was MPXV infection diagnosis, determined by a laboratory-confirmed real-time polymerase chain reaction (RT-PCR) test. The estimated date of infection was defined as the earlier of the

following dates: five days before the PCR test or five days before a suspected diagnosis of MPXV was documented.

The cohort included all CHS members eligible for the MVA vaccine per the Israeli MOH guidelines when the study commenced. The MVA eligibility criteria were: (a) Males aged 18 – 42 who were dispensed HIV-PrEP at least for one month since January 1, 2022, or (b) Males aged 18 – 42 who were diagnosed with HIV and also were diagnosed with one or more of the following STIs since January 1, 2022: active Syphilis, Chlamydia, or Gonorrhea. Subjects who were infected with MPXV prior to the study period were excluded.

Data extraction

The following data were extracted for each participant: age, geographical district of primary healthcare clinic, population sector, the score for socioeconomic status, utilization of primary healthcare services, vaccines utilization, 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 Covid-19 studies (7). The data extraction date was September 19, 2022.

Statistical analysis

Descriptive statistics were used to characterize the study participants. The geographical district was classified as Tel Aviv versus other districts, as Tel Aviv is the Israeli epicenter of the LGBTQ+ community. The population sector was classified as the general Jewish sector versus two minority sectors: Arabs and Jewish-Ultraorthodox, and the sociodemographic status score was categorized as below the median versus median score or higher.

In order to avoid immortal time bias (8), 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' risk set to the 'vaccinated' risk set 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 vaccination and MPXV infection 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 $p < 0.2$. 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 multivariate Cox proportional-hazards analysis. Vaccine effectiveness was defined as 1 minus the hazard ratio.

Analyses were conducted in R statistical software version 3.5.0 (R Project for Statistical Computing). All reported p-values are two-tailed.

Results

Study participants

1,970 CHS members met the study eligibility criteria. Of them, 873 (44%) were vaccinated and had a sufficient follow-up time. The characteristics of vaccinated and unvaccinated participants are detailed in Table 1. Compared to the non-vaccinated participants, the vaccinated participants mostly attended primary healthcare clinics in the Tel-Aviv district, had higher HIV-PrEP and PDE5 inhibitors, and had higher rates of STIs yet lower rates of HIV.

Table 1: Characteristics of the vaccinated versus unvaccinated study participants

Table 1			
	Unvaccinated	Vaccinated	All
Total N	1,097	873	1,970
	N (%)	N (%)	N (%)
<i>Sociodemographic variables</i>			
Age, mean (SD)	33 (5.7)	34 (4.8)	34 (5.3)
Sex - Male	1,097 (100)	873 (100)	1,970 (100)
Tel-Aviv district	455 (41.5)	689 (78.9)	1144 (58.1)
Sociodemographic status score below median	534 (48.7)	265 (30.4)	799 (40.6)
Population sector- minority	84 (7.7)	14 (1.6)	98 (5.0)
<i>Clinical risk factors</i>			
History of HIV/AIDS	531 (48.4)	106 (12.1)	637 (32.3)
History of Syphilis infection	218 (19.9)	198 (22.7)	416 (21.1)
Recent* Syphilis infection	36 (3.3)	51 (5.8)	87 (4.4)
Recent* STI** in urinary test	35 (3.2)	57 (6.5)	92 (4.7)
Recent* STI** in pharyngeal test	51 (4.6)	145 (16.6)	196 (9.9)
Recent* STI** in rectal test	58 (5.3)	139 (15.9)	197 (10.0)
Recent Chlamydia or NE Gonorrhoea***	116 (10.6)	264 (30.2)	380 (19.3)
Purchase of PDE5 - inhibitors*	107 (9.8)	178 (20.4)	285 (14.5)
Purchase of HIV-PrEP*	560 (51.0)	748 (85.7)	1308 (66.4)

* from 01/2022 to 06/2022

** Chlamydia or NE Gonorrhoea; *** In either urinary, pharyngeal, or rectal test

Assessment of vaccine effectiveness

MPX infections occurred in 15 unvaccinated participants (40.0 per 100,000 person-days) and in 3 vaccinated participants (6.4 per 100,000 person-days). The adjusted HR of the MVA vaccine was 0.21 (95% CI: 0.06 – 0.76). Table 2 details the univariate and multivariate Cox proportional hazard analyses for MPXV infections. Figure 1 depicts the cumulative risk of infection according to vaccination status. None of the independent covariates were found to be associated with the risk of infection

Table 2- Association of MVA vaccine and MPXV infection

	Results from Univariate models	Results from a Multivariate model
Variables	HR (95% CI)	HR (95% CI)
MPX vaccination	0.28 (0.08-0.98)	0.21 (0.06-0.76)
el-Aviv district	2.55 (0.84-7.73)	3.09 (0.97-9.79)
IV PrEP use	0.97 (0.36-2.58)	
Purchase of PDE5 - inhibitors*	1.69 (0.56-5.15)	
Recent Syphilis infection*	1.88 (0.71-5.01)	
Chlamydia or NE Gonorrhoea in Rectal PCR*	1.28 (0.37-4.45)	
Chlamydia or NE Gonorrhoea in Urine PCR*	4.05 (1.17-14.01)	2.85 (0.57-14.16)
Chlamydia or NE Gonorrhoea in pharyngeal PCR*	1.14 (0.26-4.96)	
Chlamydia or NE Gonorrhoea in any recent STI PCR	2.09 (0.78-5.56)	1.46 (0.40-5.34)
Recent Syphilis infection	2.64 (0.61-11.45)	2.21 (0.50-9.75)

Discussion

Our results demonstrate that vaccination with one dose of MVA, when provided primarily before exposure to an infected person, was associated with a 79% reduction in infection risk among individuals at high risk for MPX infection.

Randomized controlled trial data evaluating the efficacy of MVA for the prevention of MPXV are limited to studies in murine and primate models (8, 9). These studies demonstrated rapid immune response and protection from monkeypox inoculation 6 to 10 days after the first vaccine dose.

In a recent observational study of 276 human individuals who were vaccinated post-exposure, 12 (4%) had a confirmed MPX breakthrough infection, and of those, 10 patients developed an infection up to five

days following vaccination (10). We are unaware of any published evidence regarding VE when MVA is provided as PrEP.

Our study has some noteworthy limitations. The primary limitation is that a low number of infections were observed during the study period. However, our study provides critical primary evidence that may further drive the engagement of patients and their healthcare providers for vaccination

The MPXV vaccination policy in Israel focuses on pre-exposure prophylaxis in high-risk individuals, with special per-case approval for post-exposure cases. However, no testing for the existence of MPXV was done prior to vaccine administration. Therefore, some high-risk vaccinated individuals may have been infected (but undiagnosed) before vaccine administration and lowered the observed VE. It should be noted that the three observed cases of infection in vaccinated individuals were diagnosed more than two weeks after vaccine uptake (16-18 days) and, therefore, probably represent vaccine breakthroughs rather than cases of post-exposure vaccinations.

A potential source of overestimating VE is a difference in behavior between the vaccinated and the unvaccinated; vaccinated participants are more oriented toward a healthier lifestyle and may be more careful in their sexual behavior. We attempted to overcome behavior bias by controlling the measurable risk factors, but measuring actual behavior is not feasible. Moreover, in this cohort of individuals at high risk for MPXV infection (as defined by the eligibility criteria for vaccination set by the Israeli MOH), none of the measured characteristics were found in our study associated with the risk for infection.

It should be noted that the evaluation of adverse events and safety data reports was beyond the scope of this study. Future studies will be needed to assess the short- and long-term safety of MVA administration in real-world settings.

Conclusions And Implications For Policy

In conclusion, our results suggest that in case of limited vaccine availability, a single dose of MVA is associated with a lower risk of MPVX infection in high-risk individuals. These findings highlight that even one dose of the MVA vaccine could contribute to the containment of the current MPXV outbreak. However, completing the second vaccine dose per the manufacturer's label may improve this effectiveness.

Declarations

1. The study was conducted using CHS internal resources without external funding.
2. The CHS Institutional Helsinki and Data Utilization Committees approved the study.
3. All authors report no conflict of interest.

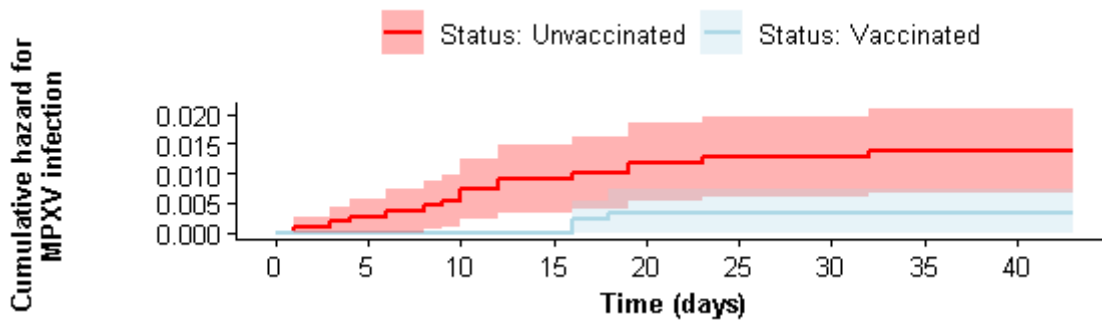
Data Sharing Statement

According to this study's CHS Helsinki and data utilization committees guidelines, no patient-level data is to be shared outside the permitted researchers.

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Figures



Number at risk

Unvaccinated	1100	1096	1093	1089	1086	1085	1085	1084	1084
Vaccinated	871	872	872	872	869	869	773	708	548

Cumulative number of events

Unvaccinated	0	3	8	10	13	14	14	15	15
Vaccinated	0	0	0	0	3	3	3	3	3

Figure 1

Cumulative Risk for Infection