Vaccine Effectiveness of Modified Vaccinia Ankara in Human Monkeypox

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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 MPXV infection.

Methods

The study cohort included all Clalit Health Services (CHS) members estimated to be at moderate to high risk for MPXV infection. The study commenced on July 31, 2022, when the MVA vaccination campaign was initiated in CHS, and participants were followed until August 10, 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.

Results

8,168 subjects met the study eligibility criteria (0.17% of CHS members). Of them, 626 (7.7%) were vaccinated with MVA and completed at least 7 days of follow-up. 14 infections were confirmed in CHS during the study period, all within the study cohort and all in unvaccinated participants. VE was estimated at 100% (95% CI: 100%-100%).

Conclusions

These short-term preliminary results suggest a very high VE of a single dose of MVA for MPVX infection in moderate to high-risk individuals. These findings suggest that urgent MVA vaccination of high-risk subjects may contribute to outbreak containment.

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 August 17, 2022, nearly 40,000 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 the benefit of avoiding 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, prioritizing individuals at high-risk for infection according to objective eligibility criteria (6). Due to the current shortage of MVA supply, the present policy in Israel is to administer only a single dose of the vaccine.

Since there is currently scarce evidence of the efficacy of the MVA vaccine against MPXV in humans, our objective was to evaluate real-life vaccine effectiveness (VE) of MVA after administering one dose to individuals at risk of MPXV infection.

**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) members, 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 August 10, 2022, the last date with confirmed infections on the data extraction date, August 15, 2022.

The primary endpoint was MPXV infection diagnosis, determined by a laboratory-confirmed real-time polymerase chain reaction (RT-PCR) test.

The cohort included all CHS members estimated to be at moderate to high risk for MPXV infection. The a-priori definition of inclusion criteria in the moderate to high-risk cohort was based on a previously reported study in CHS (6).

The moderate to high-risk cohort included all CHS male members who answered one or more of the following criteria: (a) dispense of HIV-Pre Exposure Prophylaxis medication (HIV-PrEP) since January 1, 2021; (b) at least one rectal or pharyngeal PCR-Sexually Transmitted Infection (STI) test from January 1, 2021; (c) aged 25-46 who received the Human Papilloma Virus (HPV) vaccine; and (d) HIV-positive. Participants with a follow-up shorter than a week from vaccination or infected on the vaccination day were excluded.

**Data extraction**
The following data were extracted for each participant: age, geographical district of the primary healthcare clinic, population sector, 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 and PDE5-inhibitors (Sildenafil, Tadalafil, or Vardenafil).

**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 LGTBQ+ community. The population sector was classified as the general Jewish sector versus two minority sectors: Israeli-Arabs and Jewish-Ultraorthodox, and the sociodemographic status score was categorized as below the median versus median score or higher.

The study cohort was assembled at time zero, defined as the day of the first MVA vaccinations in CHS. To avoid immortal time bias (7), we performed a time-dependent analysis in which a time-varying covariate was used to indicate the vaccination date for each vaccinated subject. In this analysis, vaccinated 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 using univariable and multivariable Cox proportional-hazards regression models with time-dependent covariates, adjusted for sociodemographic and clinical factors.

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

**Sensitivity Analyses**

Two sensitivity analyses were performed. The first sensitivity analysis included only individuals who were defined as eligible for the MVA vaccine per the Israeli MOH guidelines at the time of the study: (a) Males aged 18 – 42 who were dispensed HIV-PrEP, or (b) Males aged 18 – 42 who were diagnosed with HIV and also were diagnosed with recorded one or more of the following STIs since January 1, 2022: active Syphilis, Chlamydia, or Gonorrhea. The maximum age of 42 was determined based on the last year (1980) when smallpox vaccines were administered in Israel to all newborns.

The second sensitivity analysis evaluated VE only in the highest risk group. As detailed by a study in CHS (6), the highest risk group was identified based on the characteristics of N=58 individuals infected with MPXV before the vaccination campaign commenced. The high-risk group included participants of the study cohort who answered one or more of the following criteria in the period from January 1, 2022, and until July 18, 2022 : (a) dispense of HIV-PrEP (b) at least one recent positive rectal or pharyngeal test
result for NE Gonorrhea or Chlamydia, (c) recent dispense of PDE5-inhibitors, and (d) history of Syphilis infection. This group was shown to have a 23-fold higher risk for MPXV infection than the rest of the cohort, with a sensitivity of 93.1% for capturing MPXV cases diagnosed before the vaccination campaign commenced (6).

Results

Study participants

8,168 CHS members met the study eligibility criteria. During the study period, 625 (7.7%) were vaccinated with the MPXV vaccine 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 were younger, mostly attended primary healthcare clinics in the Tel-Aviv district, had higher usage of 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>
<thead>
<tr>
<th></th>
<th>Unvaccinated</th>
<th>Vaccinated</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total N</td>
<td>7,543</td>
<td>625</td>
<td>8,168</td>
</tr>
<tr>
<td>N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Sociodemographic variables**

<table>
<thead>
<tr>
<th></th>
<th>Unvaccinated</th>
<th>Vaccinated</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year of birth before 1980</td>
<td>2351 (31.2%)</td>
<td>0 (0%)</td>
<td>2351 (28.8%)</td>
</tr>
<tr>
<td>Tel-Aviv district</td>
<td>3121 (41.4%)</td>
<td>525 (83.9%)</td>
<td>3646 (44.6%)</td>
</tr>
<tr>
<td>Population sector- minority</td>
<td>496 (6.6%)</td>
<td>8 (1.3%)</td>
<td>504 (6.2%)</td>
</tr>
<tr>
<td>Sociodemographic status score below the median</td>
<td>2757 (36.6%)</td>
<td>199 (31.8%)</td>
<td>2956 (36.2%)</td>
</tr>
</tbody>
</table>

**Clinical risk factors**

<table>
<thead>
<tr>
<th></th>
<th>Unvaccinated</th>
<th>Vaccinated</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of HIV/AIDS</td>
<td>2070 (27.4%)</td>
<td>68 (10.9%)</td>
<td>2138 (26.2%)</td>
</tr>
<tr>
<td>History of Syphilis infection</td>
<td>949 (12.6%)</td>
<td>149 (23.8%)</td>
<td>1098 (13.4%)</td>
</tr>
<tr>
<td>Recent Syphilis infection</td>
<td>188 (2.5%)</td>
<td>43 (6.9%)</td>
<td>231 (2.8%)</td>
</tr>
<tr>
<td>Recent STI in urinary test</td>
<td>153 (2.0%)</td>
<td>38 (6.1%)</td>
<td>191 (2.3%)</td>
</tr>
<tr>
<td>Recent STI in pharyngeal test</td>
<td>215 (2.9%)</td>
<td>110 (17.6%)</td>
<td>325 (4.0%)</td>
</tr>
<tr>
<td>Recent STI in rectal test</td>
<td>239 (3.2%)</td>
<td>96 (15.3%)</td>
<td>335 (4.1%)</td>
</tr>
<tr>
<td>Any recent STI</td>
<td>495 (6.6%)</td>
<td>192 (30.7%)</td>
<td>687 (8.4%)</td>
</tr>
</tbody>
</table>

**Healthcare services utilization**

<table>
<thead>
<tr>
<th></th>
<th>Unvaccinated</th>
<th>Vaccinated</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dispense of HIV-PrEP</td>
<td>1269 (16.8%)</td>
<td>543 (86.7%)</td>
<td>1812 (22.2%)</td>
</tr>
<tr>
<td>Dispense of PDE5-inhibitors</td>
<td>766 (10.2%)</td>
<td>134 (21.4%)</td>
<td>900 (11.0%)</td>
</tr>
</tbody>
</table>

**Assessment of vaccine effectiveness**

MPX infections occurred in 14 untreated patients (18.6 per 100,000 person-days) and 0 treated patients (0 per 100,000 person-days). All MPXV infection cases diagnosed during the study were within the predefined moderate to high-risk cohort. The adjusted HR of the MVA vaccine was 0% (95% CI: 0.00% - 0.00%). Table 2 details each independent variable's risk for MPXV infections and results from the
multivariable Cox proportional hazard models for MPXV infections. Figure 1 depicts the cumulative risk of infection according to vaccination status.

The sociodemographic risk factors were a year of birth 1980 or later and registration to primary healthcare clinics in the Tel-Aviv district. Clinical risk factors were using HIV-PrEP or PDE5-inhibitors medications, recent Chlamydia or NE Gonorrhea in Rectal PCR, and a history of syphilis infection.

### Table 2- Association of MVA vaccine and MPXV infection

<table>
<thead>
<tr>
<th>Variables</th>
<th>Results of the <strong>Univariate</strong> models</th>
<th>Results of the <strong>Multivariate</strong> model</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVA vaccination</td>
<td>0.00 (0.00-0.00)</td>
<td>0.00 (0.00-0.00)</td>
</tr>
<tr>
<td>Year of birth 1980 or later</td>
<td>2.46 (0.55-10.98)</td>
<td>4.73 (0.91-2.45)</td>
</tr>
<tr>
<td>Tel-Aviv district</td>
<td>4.62 (1.29-16.57)</td>
<td>2.83 (0.68-11.72)</td>
</tr>
<tr>
<td>Dispense of HIV-PrEP</td>
<td>3.64 (1.28-10.38)</td>
<td>2.51 (0.91-6.92)</td>
</tr>
<tr>
<td>Dispense of PDE5-inhibitors</td>
<td>4.62 (1.55-13.79)</td>
<td>4.04 (1.17-13.98)</td>
</tr>
<tr>
<td>History of Syphilis infection</td>
<td>4.95 (1.72-14.26)</td>
<td>3.28 (1.03-10.49)</td>
</tr>
<tr>
<td>Chlamydia or NE Gonorrhea in Rectal PCR</td>
<td>10.00 (3.13-31.909)</td>
<td>4.88 (1.47-16.14)</td>
</tr>
</tbody>
</table>

1. The HR of the MVA vaccination in the univariable model was $3.64 \times 10^{-8} (2.14 \times 10^{-8} - 6.18 \times 10^{-8})$

2. The HR of the MVA vaccination in the multivariable model was $3.78 \times 10^{-9} (1.59 \times 10^{-9} - 8.96 \times 10^{-9})$

### Sensitivity Analysis

The results of the sensitivity analyses are presented in table 3, and are consistent with the primary results.

### Table 3: Sensitivity analysis of the Association of MVA vaccine and MPXV infection
<table>
<thead>
<tr>
<th>Group</th>
<th>N in group</th>
<th>N vaccinated(^a) (% of group)</th>
<th>n of MPXV cases (% of all infections)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate to high-risk cohort (Primary Analysis)</td>
<td>8,168</td>
<td>625 (7.7%)</td>
<td>14 (100% reference)</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.00-0.00(^b))</td>
</tr>
<tr>
<td>High-risk group</td>
<td>3,030</td>
<td>596 (19.7%)</td>
<td>11 (79%)</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.00-0.00(^c))</td>
</tr>
<tr>
<td>Eligible for MVA vaccine</td>
<td>2,106</td>
<td>625 (29.7%)</td>
<td>7 (50%)</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.00-0.00(^d))</td>
</tr>
</tbody>
</table>

1. Vaccinated from July 31, 2022, to August 4, 2022
2. The HR of the MVA vaccination in the entire moderate to high-risk cohort was 3.78 \(10^{-9}\) (1.59 \(10^{-9}\) - 8.96\(10^{-9}\)), p<0.001
3. The HR of the MVA vaccination in the high-risk group was 3.49 \(10^{-9}\) (1.83\(10^{-9}\) - 6.65\(10^{-9}\)), p<0.001
4. The HR of the MVA vaccination in participants eligible for the vaccine was 8.31\(10^{-9}\) (3.94 \(10^{-9}\) - 1.75\(10^{-8}\)), p<0.001

**Discussion**

In this early and preliminary analysis of VE, vaccination with one dose of MVA, when provided primarily as pre-exposure prophylaxis (PrEP) measure, was associated with a 100% reduction in infection rate among individuals with moderate to high risk for infection. These results were consistent while restricting the cohort to those at the highest risk for infection or only to those eligible for vaccination by the Israeli MOH guidelines.

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

When MVA was compared to the older generation ACAM2000 vaccine, a single dose of MVA was inducing neutralizing antibody titers comparable with ACAM2000 at Day 14, indicating the potential for the use of the vaccine to protect the general population. Moreover, peak neutralizing antibodies induced by 2 doses of MVA were statistically higher than those stimulated by ACAM2000 (153.5 at week 6) compared to 79.3 at week 4 with ACAM2000 (10).

In a recent observational study of 276 human individuals who were vaccinated post-exposure (PEP), 12 (4%) had a confirmed MPX breakthrough infection, and of those 10 patients developed an infection up to
five days following vaccination (11). We are unaware of any published evidence regarding VE when MVA is provided as PrEP.

The vaccination campaign in Israel was coupled with other general public health interventions. These included sexual health campaigns collaborating with the LGBTQ+ leadership key players and organizations. Additionally, webinars and regular updates were utilized to increase awareness among healthcare professionals.

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.

Our study has some noteworthy limitations. The primary limitation is that data is still preliminary, with a short follow-up time and a low number of infections. However, we believe that although these analyses are early, they provide critical primary evidence that may further drive the engagement of both patients and healthcare providers for vaccination at the stage where there is still a high chance of containing the pandemic.

The MPXV vaccination policy in Israel focuses on PrEP in high-risk individuals, with special per-case approval for PEP 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.

A third limitation is that we tested only a single dose regimen instead of the recommended and FDA-approved double dose. This may underestimate the VE of the approved double-dose.

Another potential source of underestimating VE is the difference in the characteristics between the vaccinated and unvaccinated individuals. Several factors associated with a higher chance of receiving the vaccine were also associated with a higher risk for MPXV infection, as demonstrated in a previous study (6). Therefore, the a-priori risk for infection in the vaccinated group was higher than in the unvaccinated group.

A potential source of overestimating VE is a difference in behavior between the vaccinated and 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.

In conclusion, our preliminary results suggest a very high VE of a single dose of MVA for MPVX infection prophylaxis in moderate to high-risk individuals. These findings highlight that urgent MVA vaccination of high-risk individuals may contribute to the containment of the current MPXV outbreak.

Declarations
The study was conducted using CHS internal resources without external funding.
The CHS Institutional Helsinki and Data Utilization Committees approved the study.

All authors report no conflict of interest.

References


6. Roy Zucker, Gil Lavie, Yael Wolff Sagy et al. Risk Assessment of Human Monkeypox Infections for Vaccine Prioritization, August 2 2022, PREPRINT available at Research Square [https://doi.org/10.21203/rs.3.rs-1904714/v1]


Figures
Figure 1
Cumulative hazard for MPXV infection by vaccination status (95%CI)