Risk Assessment of Human Monkeypox Infections for Vaccine Prioritization

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Abstract

Background

As the current global resurgence of monkeypox virus infection (MPXVi) continues, the immediate supply of vaccines is lower than the demand. Therefore, prioritization of vaccinations for the highest risk subjects using routine medical records is warranted.

Methods

This population-based cohort study included all Clalit Health Services (CHS) subjects deemed at moderate-to-high risk for MPXVi: males who purchased HIV-PrEP or tested for sexually transmitted infections since January 2021, aged 25–46 who received Human Papilloma Virus vaccine, or HIV-positive. We defined a high-risk group within the cohort and compared the risk for MPXVi to the moderate-risk group from June 6 (the first known CHS case) until Jul 25, 2022.

Results

Out of 4.8 million CHS members, 8,089 met the study eligibility criteria (0.18%). During the study period, 54 CHS members tested positive for MPXVi, 51 (94%) of whom were included in the study cohort. The highest risk group included 2,274 (28%) subjects who met the following criteria in 2022: Used HIV-PrEP or erectile dysfunction therapy or were diagnosed with STIs by rectal PCR. The hazard ratio for MPXV infection in the high-risk group compared to the moderate-risk group is 19.35 (95% CI: 8.26–45.36). The sensitivity, specificity, NPV, and PPV for MPXV infection are 88.2%, 72.3%, 99.9%, and 2.0%, respectively.

Conclusions

Subjects in the highest risk group have a nearly 20-fold risk for MPXV infection compared to the moderate risk group. Our findings may assist in prioritizing new vaccines by promptly identifying high-risk populations without the need for intrusive sexual behavior questioning.

Introduction

Human monkeypox virus (MPXV) is a double-stranded DNA virus of the Orthopoxvirus genus of the family Poxvirus. MPXV is a zoonotic disease caused by the virus with endemic circulation reported in African regions, predominantly west and central Africa (1). A global resurgence was first recognized on May 6, 2022; by Jul 26, 2022, more than 18,000 laboratory-confirmed MPXV cases were reported worldwide (2). The disease seems to spread quickly in a highly sexually active network of young men (3). Modified vaccinia virus Ankara (MVA) Vaccine, a live attenuated non-replicating Orthopoxvirus, is the only vaccine approved for MPXV (4). The US, EU (5), and the UK have ordered the vaccine, but the immediate

supply is much lower than the demand. Therefore, prioritization of vaccinations for the highest risk subjects is warranted. The UK, for example, announced that the vaccine would be made available to gay and bisexual men at high risk of exposure to MPXV (6), but the definition of high-risk is unclear and requires intrusive questioning of sexual behavior. Therefore, our objective was to identify the highest risk group using routine medical records.

Methods

Study design and participants

This population-based cohort study was conducted in Clalit Health Services (CHS) to identify the risk factors for MPXV infection and define subjects at the highest risk for MPXV infection.

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

The study was conducted in 4 stages. First, we included all CHS subjects deemed at moderate to high risk for the 2022 MPXV outbreak based on the characteristics of infected subjects worldwide (7) and the insights of LGBTQ + specialized clinicians. Second, we analyzed the risk factors for MPXV in the study cohort. The results of the analyses served to define the highest risk group as a third step. Fourth, we compared the risk for MPXV infection of the highest risk to the rest of the cohort, considered the moderate-risk group.

The study commenced on Jun 6, 2022, the first known MPXV infection in CHS members, and ended on Jul 24, 2022. The cohort included all CHS subjects deemed moderate to high risk for the 2022 MPXV outbreak. The cohort was defined as males answering one or more of the following four criteria: (a) had at least one rectal or pharyngeal PCR-STI test since Jan 1, 2021; (b) Dispense of Tenofovir Disoproxil and Emtricitabine "EMTRIVIR", the only HIV-Pre Exposure Prophylaxis medication available in Israel (HIV-PrEP), but did not purchase HIV/AIDS medications since Jan 1, 2021; (c) those aged 25–46 who received the Human Papilloma Virus (HPV) vaccine, designated primarily for MSM in this age group; and (d) HIV-positive. None of the cohort subjects had left CHS or died during the study, so none were censored.

Data Extraction

This observational cohort study is based on routine data from electronic medical records from CHS and includes sociodemographic and clinical information. CHS covers 4.8 Million patients, more than half of the Israeli population. The study was approved by the CHS Institutional Ethics and Data Utilization Committees.

The following data were extracted for each subject: sociodemographic variables: year of birth, location of the primary healthcare clinic (classified as Tel Aviv district versus other districts in Israel); personal history of HIV/AIDS; STIs detected in rectal or pharyngeal PCR tests, syphilis (current infection, defined as a prescription of benzathine penicillin or seroconversion from negative to positive Treponema pallidum

hemagglutination (TPHA) test since January 2022, or any infection, defined as a positive TPHA test result since January 2021), purchase of HIV-PrEP, and purchase of erectile dysfunction (ED) medications (Sildenafil, Tadafil, and Vardenafil) in 2022. The risk analysis was based on 2022 data to reflect recent diagnoses and medication use.

Urinary STIs data was not collected, as we believe it is not a specific risk factor for MPX infection.

The data was extracted from CHS data repositories. The methodology of data collection, definitions, and linkage of the CHS data files has previously been reported in detail (8).

Statistical analysis

Descriptive statistics were used to characterize the study participants, in participants with and without MPXV infection. The age group was determined by the last year when smallpox vaccines were administered (Subjects born < 1980 or > = 1980).

In the univariable analysis step, we used Cox proportional hazards models with MPXV infection event as the outcome and the date of the event as the time variable to estimate HRs for MPXV. All variables significantly associated with the outcome at a level of $p < 0.1$ were entered into the multivariate Cox proportional hazard model.

Based on the multivariate model's results, we defined high-risk groups. The risk for MPXV infection in the high-risk groups was compared to that of the moderate-risk groups using univariate Cox proportional hazard models. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for each definition of a high-risk group.

The proportional hazards assumption was tested for all Cox models based on the Schoenfeld residuals global test.

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

Role of the funding source

There was no funding source for this study.

Results

Study participants

Out of 4.8 million CHS subjects, 8,089 subjects met the study eligibility criteria (0.17%). During the study period, 54 CHS members were infected with MPXV, 51 (94%) of whom were included in our moderate to high-risk cohort. The characteristics of infected and non-infected participants are detailed in Table 1. Compared to the non-infected subjects, the infected subjects were younger, mostly attended primary

healthcare clinics in the Tel-Aviv district, had higher usage of HIV-PrEP and erectile dysfunction drugs, and had higher rates of STIs yet lower rates of HIV.

Table 1
–Characteristics of the infected versus uninfected study participants

	MPX infected, n (%)	MPX non-infected, n (%)	All, n (%)
	(N = 51)	(N = 8,038)	(N = 8,089)
Year of birth 1980 or later	45 (88%)	5693 (71%)	5738 (71%)
Tel-Aviv district	43 (84%)	3,618 (45%)	3661 (45%)
HIV-positive	8 (16%)	2,150 (27%)	2158 (27%)
HIV PrEP use	35 (69%)	1,639 (20%)	1674 (21%)
Positive rectal STI- PCR	14 (27%)	294 (4%)	308 (4%)
Positive pharyngeal STI- PCR	6 (12%)	278 (3%)	284 (4%)
Current Syphilis infection	1 (2%)	93 (1%)	94 (1%)
Any Syphilis infection	2 (4%)	160 (2%)	162 (2%)
Erectile dysfunction Tx	18 (35%)	837 (10%)	855 (11%)
Age mean (STD)	35.7 (5.8)	38.8 (11.3)	38.7 (11.3)

Assessment of risk factors for MPXV infections

Table 2 details the univariate and multivariate analysis results for each independent variable's risk for MPXV infections. The most prominent risk factors were the use of HIV-PrEP, positive rectal STI- PCR, subjects born in 1980 or later, registered to primary healthcare clinics in Tel-Aviv district, and use of erectile dysfunction medications. Positive HIV status had a borderline statistically significant association with MPXV infection. Positive pharyngeal STI-PCR was associated with MPXV infection in the univariate analysis but not in the multivariate model. Current and previous Syphilis infections were rare and not associated with MPXV infection and therefore were not included in the multivariate model.

Table 2
Univariate and multivariate Cox proportional hazards models for MPXV infections

	Results from Univariate models		Results from a Multivariate model	
Variables	HR (95% CI)	P-value	HR (95% CI)	P-value
Year of birth 1980 or later	3.08 (1.31–7.22)	0.010	3.49 (1.43–8.54)	0.006
Tel-Aviv district	6.53 (3.07–13.89)	0.000	3.44 (1.56–7.59)	0.002
HIV-positive	0.51 (0.24–1.09)	0.081	2.32 (0.97–5.55)	0.059
HIV- PrEP	8.46 (4.68–15.28)	0.000	4.99 (2.51–9.93)	0.000
Positive rectal STI-PCR	9.84 (5.32–18.2)	0.000	3.79 (1.93–7.43)	0.000
Positive pharyngeal STI-PCR	3.70 (1.58–8.67)	0.003	0.77 (0.31–1.91)	0.579
Current Syphilis infection	1.71 (0.24–12.4)	0.594	–	–
Previous Syphilis infection	2.00 (0.49–8.23)	0.336	–	–
Erectile dysfunction Tx	4.64 (2.61–8.24)	0.000	2.94 (1.62–5.32)	0.000

Identification of the highest risk group

Based on the differences in association magnitudes of the multivariate analysis, we defined five alternative high-risk definitions within our study cohort:

(1) Year of birth 1980 or later and either HIV-PrEP use or positive rectal STI-PCR in the past 6 months; (2) Registered to clinics in Tel-Aviv district, and either HIV-PrEP use or positive rectal STI-PCR in the past 6 months; (3) HIV-PrEP use or positive rectal STI-PCR in the past 6 months, regardless of age; (4) Year of birth 1980 or later, and either HIV-PrEP use, positive rectal STI-PCR, or erectile dysfunction medication use in the past 6 months; (5) HIV-PrEP use or positive rectal STI-PCR or erectile dysfunction medication use in the past 6 months, regardless of age.

Table 3
Results for five high-risk definitions

Group	N (% of Cohort)	HR of high-risk groups (1–5) versus moderate risk (95% CI)	N of MPVX infected (out of N = 54)	Sensitivity	Specificity	PPV	NPV
1	1,361 (17%)	8.42 (4.77–14.85)	32	62.7%	83.5%	2.4%	99.7%
2	1,191 (15%)	9.87 (5.60-17.42)	32	63.0%	86.0%	2.7%	99.7%
3	1,779 (22%)	8.59 (4.70-15.69)	36	71.0%	78.0%	2.0%	99.8%
4	1,600 (20%)	14.93 (7.66–29.09)	40	78.4%	80.6%	2.5%	99.8%
5	2,274 (28%)	19.35 (8.26–45.36)	45	88.2%	72.3%	2.0%	99.9%

The best definition was (5), demonstrating the highest sensitivity (88%) and the highest NPV (99.9%), as calculated within the cohort. This definition of the highest risk group shows an HR of nearly 20-fold compared to moderate risk. Figure 1 depicts the cumulative hazard for MPXV infection during the study period in the highest risk versus moderate risk group.

Discussion

Summary of Results

The primary risk factors are using HIV-PrEP and positive rectal STI-PCR since January 2022. The birth year of 1980 or later, registration to primary clinics in the Tel Aviv district and usage of erectile dysfunction medications (in members of the study cohort) are also risk factors for MPXV infection. HIV, Syphilis, and positive pharyngeal PCR for STIs were not associated with MPXV infection.

The highest risk group criteria are HIV-PrEP use or positive rectal STI-PCR or erectile dysfunction medication use (in members of the study cohort) since January 2022. This group represents approximately 1 in 2,100 members in CHS. Their risk is twenty-fold higher than the moderate risk group, with a sensitivity of 88% and NPV of 99.9%. Therefore, the chance of missing a case of infection in the entire moderate to high-risk cohort was 1 in 1,000.

Comparison to known literature

Since the beginning of the current 2022 outbreak of MPXV, almost all cases were identified in men having sex with men (MSM) (7) (9). Some of the characteristics of our study cohort and risk factors we identified are in line with previous reports on the characteristics of infected subjects: the inclusion of males who underwent STI screening; and the identification as risk factors of recent STIs and year of birth before 1980 as a proxy for personal history of smallpox vaccination (7) (9). Assessing some risk factors previously reported requires intrusive questioning of sexual behavior (7) (9). Such questioning is challenging to conduct in many aspects, including the time and cost required for active questioning, possible compromised validity due to personal and cultural reasons, and ethical aspects of the desired balance between medical information and patients' rights for privacy. Therefore, questioning sexual behavior is not a feasible screening tool at the population level for prioritizing vaccines. However, our findings are based on the utilization of medications and laboratory-confirmed diagnoses.

First-generation virus vaccines smallpox vaccine demonstrated 85% cross-protective immunity against MPXV, but this result was obtained more than three decades ago, primarily in Africa and for previous clades (10) (11). The majority of Israeli residents born before 1980 were given the smallpox vaccine. Our results show an adjusted HR of 3.49 (1.43–8.54), translating into estimated vaccine effectiveness of 71% for the 2022 MPXV outbreak.

Based on the known literature, all male CHS members living with HIV were included in our moderate-to-high risk cohort. The proportion of HIV-positive in MPXV infected individuals (16%) is much higher than their proportion in the general population but lower than reported in the UK (24%) (9) and by an international collaborative group (41%) (7). Moreover, HIV was not associated with MPXV infection within the study cohort. This may be explained by the fact that Israeli residents living with HIV are diverse, including persons who immigrated to Israel from countries with endemic HIV.

Limitations

Our study has some noteworthy limitations. The primary limitation is that data is still preliminary, with cases expected to increase significantly. The epidemic is still ongoing, with changes in disease spread within different populations. However, it is critical to make fast prioritization decisions at this epidemic stage, when there is still a high chance of containing the pandemic. Therefore, we believe that although these analyses are preliminary, they carry a high value at this time of global health emergency.

We also believe that our current data represents the underdiagnosis of MPXV in Israel (and probably worldwide) for a few reasons. First, contact tracing for MPXV cases is complicated and sometimes unfeasible. According to current reports, most cases engaged in risky sexual behaviors with multiple partners, many of them anonymous (7). This, along with the long incubation period, makes tracing and identifying subsequent cases almost impossible.

The second cause of potential underdiagnosis is low awareness among healthcare providers. MPXV is a disease with a prodrome similar to many other viral diseases. The clinical course can be nonspecific and difficult to identify, especially in patients with mild disease and few skin lesions. Healthcare providers not

working in areas with clusters of cases and large at-risk populations, especially in central, urban Israel, may be less vigilant and easily miss cases. Many cases outside of this central area have likely been missed. Moreover, there may be many symptomatic patients who were not tested for MPXV for various reasons.

Furthermore, we assume that most of the population born before 1980 in Israel has been vaccinated with the smallpox vaccine, though this is not documented in medical records, and we do not have individual data on vaccination status. Vaccination of children in Israel was gradually terminated in the late 1970s'. Therefore, we assume this population was vaccinated, though the actual immunization rate within this age group is unknown. We suggest adopting the age cutoff based on other countries' national smallpox vaccination strategies.

Documented Syphilis infections were rare, a finding we believe to indicate underdiagnosis due to various factors. This may be because many diagnostic tests and therapies for syphilis are administered outside CHS and not reported to CHS. Underdiagnosis may also be due to past infections, with unsatisfactory follow-up, not tested again after Jan 1, 2021.

Another limitation of the current study is that transgender women who may be at moderate to high risk were not included in the study cohort if their current gender was updated in CHS registries.

Implications for Policy

Our findings are significant for vaccine allocation, as mass vaccination with newer generation vaccines is not feasible in the immediate future, and prioritization of the highest risk group is crucial. Accordingly, the Israeli ministry of health (MOH) has adopted a vaccination strategy based on our preliminary findings (Risk-group 1). The vaccination campaign should be coupled with general public health interventions, such as home isolation, sexual health promotion, education, and awareness among healthcare professionals. Implementing these measures promptly may end the epidemic in a short time.

Conclusions

The group with the highest risk was males with HIV-PrEP use or positive rectal STI-PCR or erectile dysfunction medication use (within the study cohort) in the past 6 months. Our findings may assist in prioritizing new vaccines and facilitating a process for promptly reaching at-risk populations based on clear, objective risk factors in medical records without the need for intrusive sexual behavior questioning.

Declarations

Competing interests:

The authors declare no competing interests.

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Figures

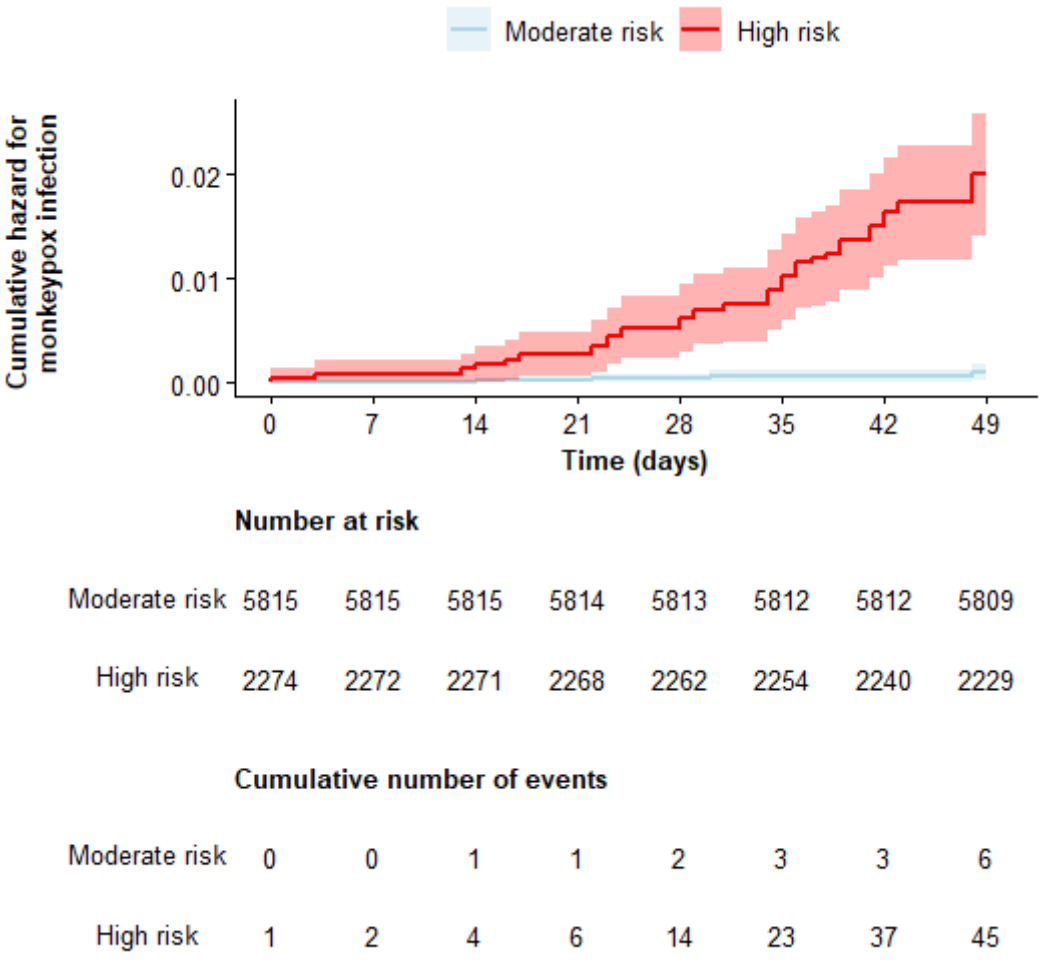

Figure 1

Cumulative hazard for MPXV infection, high versus moderate risk groups (95%CI)