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MAJOR ARTICLE

Effectiveness of MVA-BN vaccination in a population at high-risk of mpox: a Spanish cohort study

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Background

With over 7,500 cases notified since April 2022, Spain has experienced the highest incidence of mpox in Europe. From July 12th onwards, the Modified Vaccinia Ankara-Bavaria Nordic (MVA-BN) smallpox vaccine was offered as pre-exposure prophylaxis for individuals at high-risk of mpox, including those receiving pre-exposure prophylaxis for HIV (HIV-PrEP). Our aim was to assess the effectiveness of one dose of MVA-BN vaccine as pre-exposure against mpox virus (MPXV) infection in persons on HIV-PrEP.

Methods

We conducted a national retrospective cohort study between July 12 and December 12, 2022. Individuals ≥18 years, receiving HIV-PrEP as of July 12 and with no previous MPXV infection or vaccination were eligible. Each day, we matched individuals receiving a first dose of MVA-BN vaccine and unvaccinated controls of the same age group and region. We used a Kaplan-Meier estimator and calculate risk ratios (RR) and vaccine effectiveness (VE=1-RR).

Results

We included 5,660 matched pairs, with a median follow-up of 62 days (interquartile range 24-97). Mpox cumulative incidence was 5.6 per 1,000 (25 cases) in unvaccinated and 3.5 per 1,000 (18 cases) in vaccinated. No effect was found during days 0-6 post-vaccination (VE -38.3; 95% confidence interval (95%CI): -332.7; 46.4), but VE was 65% in ≥7 days (95%CI 22.9; 88.0) and 79% in ≥14 days (95%CI 33.3; 100.0) post-vaccination.

Conclusions

One dose of MVA-BN vaccine offered protection against mpox in a most-at-risk population shortly after the vaccination. Further studies need to assess the VE of a second dose and the duration of protection over time.

Keywords: mpox, monkeypox, vaccine effectiveness, MVA-BN vaccine

INTRODUCTION

In early May 2022, an outbreak of mpox (formerly named monkeypox) emerged and rapidly spread worldwide, with over 87,000 cases and 140 deaths notified by 111 countries one year later [1]. The majority are men who have sex with men (MSM) [2–5] . Spain is the country with the highest cumulative incidence in Europe and the third globally with over 7,500 notified cases [6]. In the current outbreak, person-to-person transmission has occurred predominantly through direct contact with skin lesions or with body fluids during sexual intercourse or prolonged close physical contact [2,3,7,8].

Prevention and control measures for the current outbreak included information and awareness campaigns involving civil society organizations, the closure of specific venues (e.g., saunas) linked to mpox outbreaks, and vaccination with Modified Vaccinia virus Ankara (MVA). MVA-BN (from Bavarian Nordic, BN, branded as JYNNEOS or IMVANEX in America and Europe, respectively) is a third-generation vaccine against smallpox containing a non-replicative live virus[9]. At the beginning of the outbreak, MVA-BN vaccines were scarce and prioritized as post-exposure prophylaxis [10]. With increasing availability of vaccines, pre-exposure vaccination was recommended for persons at high risk of mpox, specifically, if they had high number of sexual partners (≥10 in the last year or ≥3 in the last 3 months), had been involved group-sex activities, or had a sexually transmitted infection (STI) diagnosed in the last month [11], regardless of previous vaccination against smallpox during childhood. The recommended schedule is two doses administered ≥28 days apart, either subcutaneous (0.5 ml) or intradermal (0.1 ml). In Spain, the first dose of MVA-BN as pre-exposure prophylaxis was started on 12 July 2022 and the second dose on 6 September 2022 [12].

Before the current outbreak, no estimates of clinical efficacy were available outside of animal models [13,14]. Estimates of vaccine effectiveness (VE), when administered pre-exposure, have been produced by the United Kingdom [15], the United States [16–19] and Israel [20], though only the latter was a cohort study, and had some methodological limitations [21]. The greatest difficulty for VE studies has been the lack of a sampling frame of the population targeted for vaccination, needed to identify groups with similar risk of mpox virus (MPXV) infection independently of the probability of receiving MVA-BN vaccination.

Individuals receiving HIV pre-exposure prophylaxis (HIV-PrEP) are a well-identified population in Spain, due to its prescription at hospital pharmacy services, are at high risk of MPXV infection and who have been proactively targeted for pre-exposure MVA-BN vaccination [22]. Our aim was to estimate the reduction in the risk of MPXV infection associated to the administration of at least one dose of MVA-BN vaccine pre-exposure in persons receiving HIV-PrEP.

METHODS

Study design and setting

We constructed a retrospective cohort study by deterministic linkage of databases using any of three personal identifiers (national health system number, national identification number, and regional health system number). We collected data from 15 out of 19 Autonomous Regions in Spain, encompassing >95% of the population: Andalusia, Asturias, Balearic Islands, Canary Islands, Castile and León, Castilla-La Mancha, Catalonia, Valencian Community, Extremadura, Galicia, Community of Madrid, Region of Murcia, Navarre, Basque Country, and La Rioja. The regions reported individual-level data from three data sources: (i) all diagnoses of MPXV infection; (ii) all MVA-BN vaccine-doses; and (iii) the list of individuals receiving HIV-PrEP as of 12 July 2022. Individual identifiers were pseudo-anonymized using a HASH algorithm, a deterministic unidirectional coding system that preserves anonymity while allowing linkage. Data were linked at national level to allow the curation of duplicates and identification of all vaccines and infections, except for the Balearic Islands, Community of Madrid and Navarre, who sent the data cross-matched and completely anonymized.

Specification of the target trial

Our observational study emulated a hypothetical target trial to estimate the effect of the administration of at least one dose of MVA-BN vaccine for the prevention of MPXV infection. The target trial would start on 12 July 2022, and the eligible population would be men ≥18 years receiving HIV-PrEP, with no prior MPXV infection or MVA-BN vaccination since the beginning of the mpox outbreak, and regardless of having vaccination against smallpox during childhoood.

In the target trial, eligible individuals would be randomly assigned to either the administration of a first dose of MVA-BN vaccine (regardless of the vaccine brand or the administration route) or

to no administration of vaccine within strata defined by age and region. The outcome of interest would be laboratory-confirmed MPXV infection.

Emulation of the target trial

We emulated the target trial with the linked observational data, starting on 12 July 2022 and ending on 12 December 2022, when the first region extracted the data for the study. We excluded individuals that started HIV-PrEP before it was included in the National Health System (November 2019), with missing date of infection, or with ≥3 doses of MVA-BN vaccine during the study period. Some regions did not have the information on sex within the HIV-PreP registry and it was assumed that all were males, since nearly all HIV-PrEP users (99.7%) are men [23].

On each day between 12 July and 12 December 2022, we identified individuals who met the eligibility criteria and classified them as either having or not having received a first dose of MVA-BN vaccine that day. Each vaccinated person was matched to a randomly selected control among eligible individuals who had not received any dose of vaccine up to that date. Exact matching was performed, with replacement, on age (± 5-years) and region. Vaccinated individuals could be matched as unvaccinated controls in the period up to one day before the first dose administration.

The outcome of the study was laboratory-confirmed MPXV infection, with the date of the event defined as the earliest between the date of symptoms onset or laboratory-confirmation. For each matched pair, follow-up started on the day of administration of the first dose of MVA-BN vaccine and finished at the earliest of the date of event, death, or 12 December 2022. We followed a per-protocol approach to estimate VE, hence we censored both members of a matched pair when the control was vaccinated.

We performed a secondary analysis restricting to pairs in which both members were younger than 50 years, as a *proxy* of VE with no vaccination against smallpox during childhood since those individuals should not have had the opportunity to get smallpox vaccines. We were unable to assess the VE of two MVA-BN doses because no infection was registered after the administration of a second dose. Likewise, VE of only one dose was equivalent to VE of at least one dose (the main analysis).

Statistical analysis

We computed the cumulative incidence (risk) curves of MPXV infection using the Kaplan-Meier estimator [24]. We computed the Risk Ratio (RR) overall and at different points in time: for days 0-6 or ≥7 after the first dose administration or, alternatively, for days 0-13 or ≥14. To compute risk and risk ratios ≥7 and ≥14 days after vaccination, we used only matched pairs in which both individuals were still at risk at 7 (and 14) days after time zero. We computed percentile-based 95% confidence intervals (95%CI) using non-parametric bootstrapping with 500 samples [25]. We estimated vaccine effectiveness as VE = (1-RR)*100. Analyses were performed with R software version 4.1.2 (R Foundation for Statistical Computing).

To test the impact of the analytical approach [26], we conducted a sensitivity analysis using the full eligible population with time-varying vaccination status. We computed the number of events and time at risk by vaccination status, week, age group and region, and estimated adjusted Incidence Rate Ratio (IRR) with Poisson regression. The detailed methodology and results of this analysis are found in the Supplementary Material.

This study was approved by the Research Ethics Committee at the Institute of Health Carlos III (approval no. CEI PI 92_2022) and by the Research with Drugs Ethics Committee at the Community of Madrid (approval no. EV_MPOX-001).

RESULTS

Description of study participants

We identified 10,449 eligible individuals, of which 5,920 (56,7%) received a first dose of MVA-BN vaccine and 2,014 (19.3%) two doses. Both the initial and the eligible population had similar characteristics (Supplement Table S1). We matched 5,660 (95.6%) individuals who received at least one dose of MVA-BN vaccine to the same number of controls who had not received vaccination against mpox up to that day (Figure 1). The unvaccinated group included 3,899 unique individuals, with a maximum number of repetitions of a matched control of 7. Censoring because the control received the first dose of MVA-BN vaccine occurred in 42.6% (n=2,412) of matched pairs.

Compared to the eligible population (Supplement Table S1), individuals in the matched sample had similar age (median 36 years, interquartile range [IQR]: 31-43). Virtually no individuals received a dose of smallpox vaccine during childhood in the matched sample (n=2 [0.0%]) compared to the eligible population (n=135 [1.3%]). No hospitalization, ICU admission or death was recorded in the matched sample, while 19 and 11 mpox cases were hospitalized in the initial and the eligible populations, respectively.

Table 1 shows the characteristics of the matched sample by vaccination status. The number of MPXV infections recorded was 43, with a higher number of cases among unvaccinated (25 vs 18 in the vaccinated).

Figure 2a depicts the cumulative incidence in the vaccinated and unvaccinated groups. Median follow-up was 62 days (IQR: 24-97), with a maximum of 147 days. Cumulative incidence was 5.58 cases per 1,000 individuals in the unvaccinated compared to 3.46 per 1,000 in the vaccinated. Out of 25 mpox cases among unvaccinated, 8 (32%) and 13 (52%) cases were registered during the first 6 and 13 days respectively. Out of 18 mpox cases among vaccinated, 11 (61%) and 15 (83%) were reported in the same period. The last mpox case was registered after 63 days of follow-up in the unvaccinated and after 17 days in the vaccinated.

Effectiveness of one dose of MVA-BN

During the study period, the overall estimated effectiveness of one dose of MVA-BN vaccine was 37.9% (95%CI -24.4; 69.1). During the first 6 and 13 days, the estimated VE was -38.3% (95%CI -332.7; 46.4) and -14.1% (95%CI -199.7; 47.9), respectively, showing a non-statistically-significant higher risk of MPXV infection in the vaccinated group. At ≥7 days post-vaccination, the estimated VE was 65.0% (95%CI 22.9; 88.0), and it increased up to 79.3% (95%CI 33.3; 100.0) at ≥14 days.

Results from secondary and sensitivity analyses

We restricted the analysis to 5,047 matched pairs in which both individuals were under 50 years of age. Among vaccinated individuals, 14 mpox cases were registered compared to 22 cases among the unvaccinated. The last case of mpox was registered 63 days after the enrollment in the unvaccinated and after 17 days in the vaccinated. The risk of MPXV infection was higher in unvaccinated individuals (5.6 per 1,000) than in the vaccinated (3.0 per 1,000) (Figure 2b and Table 3). VE from 7 days post-vaccination onwards was 72.4% (95%CI 20.9; 94.4) and from 14 days onwards 85.2% (95%CI 41.1; 100.0).

The sensitivity analysis using the full eligible population and Poisson regression obtained similar results (Supplement Table S2). Supplement Figure S1 depicts the person-days of follow-up and the distribution of cases and incidence rates by vaccination status throughout the study period. Overall VE during the study period was 43% (95%CI 7; 65). No vaccine effect was observed during the first 6 and 13 days post-vaccination, respectively. From 7 days onwards, VE was 68% (95%CI 35; 84), and from 14 days onwards the VE increased up to 76% (95%CI 39; 90).

DISCUSSION

Using a matched cohort study of population receiving HIV-PrEP, we have estimated that one dose of MVA-BN vaccine reduces the risk of MPXV infection by 65% from 7 days post-vaccination and by 79% from 14 days post-vaccination. Results were similar in a sensitivity analysis restricted to population under 50 years of age. These results confirm that MVA-BN vaccination is an effective prevention tool in a population at high-risk of MPXV infection, at least shortly after vaccine administration, with the last detected MPXV infection at around 2 months of follow-up. Since the pre-exposure vaccination campaign began when the incidence of mpox started to decrease in Spain, and has remained very low since, the effectiveness at longer times since vaccination could not be assessed. The reduction in mpox incidence was most likely driven by an increase in the risk perception , the reduction in risk sexual practices during the outbreak, and the transmission dynamic of MPXV [27], but the high acceptability of MVA-BN vaccination and the effectiveness estimated in this study may have contributed to the suppression of transmission.

In our study, the risk of MPXV infection in the immediate days after vaccination was higher (though not statistically significant) in the vaccinated group. This could be explained by some misclassification of post-exposure vaccines as pre-exposure, if people with a risk contact would seek vaccination even if they chose not to disclose such contact. Since most MPXV infections initiate symptoms within 5-7 days of exposure [28,29], it is expected that estimates of VE after 7 days of vaccination are no longer affected by the inadvertent inclusion of post-exposure vaccinations. On the other hand, it could be that vaccination was seek preferentially by those most at risk of infection (since we could not obtain information on sexual behaviour) or vaccination was erroneously perceived as granting protection, which could also result in an overall underestimation of the VE, as discussed later.

The majority of previous studies have reached similar or higher VE estimates. Two studies based on aggregated data conducted in the United States [16,17] in males 18-49 years found a risk of MPXV infection more than 7 times higher (equivalent to an 86% protection) in the unvaccinated compared to the vaccinated. One study in the United Kingdom [15] using the screening method [30] found a single dose vaccine effectiveness of 78%. Two studies in the United States, using case-control designs, have provided discordant estimates of VE with one dose of 72% [19] or 41% [18] among immunocompetent individuals, likely due to differences in the selection criteria for both cases and controls Both studies also estimated VE of full vaccination with two doses of MVA-BN vaccine at 86% and 66%, respectively [18,19].

Sagy et al. have conducted the only cohort study currently available in the literature to estimate the effectiveness of MVA-BN vaccination [20]. The study population were males who were HIV-PrEP users or were living with HIV and recently diagnosed with one or more STI. The study estimated a VE (pre- and post-exposure) of 86%, which however is probably over-estimated due to methodological limitations such as failure to identify equivalent time zero for both study groups, leading to important confounding by calendar time [21], and the exclusion of individuals vaccinated after 26 September 2022 (presumably also of their unvaccinated follow-up time), ignoring immortal time bias in observational studies [31]. To avoid mis-specification of time zero, we emulated a target trial, as described in the literature [31,32] and as widely used in the highest quality studies on effectiveness of COVID-19 vaccines [15,33,34].

The main strengths of our study are, first, the careful specification of the start and end of the individual follow-up time and the dynamic matching to account for the time-changing baseline risk in the context of the mpox outbreak. Secondly, the availability of the vaccine indication allowed to specifically estimate its effectiveness administered pre-exposure, although we cannot rule out certain misclassification, as discussed before, or data collection errors. Finally, the choice of individuals on HIV-PrEP as study population has higher chances to result in a group with homogenous sexual practices and behavior, compared to studies including diverse population groups. Moreover, because MVA-MB vaccine was actively recommended in this group (in some regions even via SMS advices), we ensure that all participants had the opportunity to be vaccinated, especially since it is a group with good demonstrated access to the health-care system. This may

have decreased the chance of confounding by preferential vaccine uptake in groups with different risk of exposure and the possible differential ascertainment of mpox infection.

Our study has some limitations. First, even we identified over 10,000 eligible individuals, with more than 700 MPXV diagnosed infections, a limited number of events were detected in the vaccinated group, which results in wide confidence intervals. Moreover, we were not able to estimate the effectiveness of two doses of MVA-BN vaccine since all MPXV infections were registered in the first two months of follow-up, when no second doses had been administered. The lack of hospitalization or death events prevented any estimate of effectiveness against these outcomes.

Second, we lacked any information on risk practices and behaviours. It is possible that individuals seeking MVA-BN vaccination were those at higher risk of mpox, for example, if individuals receiving HIV-PrEP due to living in a serodiscordant monogamous relationship or with lower number of sexual partners decided not to vaccinate due to their lower risk. Also, it is possible that sexual behaviours could change following vaccination, due to the perceived sense of protection. Both situations would result in an underestimation of the VE. Contrarily, those more preoccupied with preventive measures in general could have higher acceptance of vaccination, which would overestimate VE.

Third, we also did not have good quality information about smallpox vaccine doses administered during childhood. However, the VE for those under 50 years, for whom childhood smallpox vaccination was rare [35], yielded similar results than the main analysis, suggesting that the overall VE estimates are not significantly biased.

Finally, regarding the generalizability, our study was restricted to men receiving HIV-PrEP and our estimates may not be valid for the general population or for immunocompromised individuals.

CONCLUSION

The administration of one dose of MVA-BN vaccine pre-exposure reduces the risk of MPXV infection in individuals on HIV-PrEP, at least shortly after vaccination. The results indicate that vaccination is an important tool for prevention and control of mpox during an outbreak. However, more studies are needed to evaluate the protection conferred by two doses of MVA-BN vaccines and the duration of the protection.

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Author's contributions: SM, AD, AL, VH and CO conceived the idea and elaborated the study protocol. AD, VH, CO, TV and SM coordinated the data collection. Authors from public health administrations in the Autonomous Regions were in charge of implementation of the protocol for data extraction and sharing. MF, TV and SM were in charge of data curation. MF carried out the statistical analysis and wrote the first draft of the manuscript, under the supervision of SM and with the support from AD and VH. MF is the guarantor. All authors were involved in the interpretation of study results and critically reviewed the manuscript content.

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Table 1. Characteristics of the individuals of the matched sample (N=11,320) by vaccination status

	Vaccinated (n=5,660)		Unvaccinated (n=5,660)	
	n	%	n	%
Age group, years				
18-29	964	17.0	1,003	17.7
30-39	2,622	46.4	2,607	46.1
40-49	1,557	27.5	1,534	27.1
≥ 50	517	9.1	516	9.1
Childhood smallpox vaccination				
Yes	1	0.0	1	0.0
No	44	0.8	48	0.8
Unknown	5,615	99.2	5,611	99.2
Autonomous Region				
Andalusia	926	16.4	926	16.4
Asturias	37	0.7	37	0.7
Balearic Islands	361	6.4	361	6.4
Canary Islands	212	3.7	212	3.7
Castile and León	59	1.0	59	1.0
Castilla-La Mancha	59	1.0	59	1.0
Catalonia	2,121	37.5	2,121	37.5
Valencian Community	351	6.2	351	6.2
Extremadura	27	0.5	27	0.5
Galicia	252	4.5	252	4.5
Community of Madrid	830	14.7	830	14.7
Region of Murcia	129	2.3	129	2.3
Navarre	44	0.8	44	0.8
Basque Country	293	5.2	293	5.2
La Rioja	2	0.0	2	0.0
MPXV infection				
Yes	18	0.3	25	0.4

	No	5,642	99.7	5,635	99.6
Mpox symptoms*					
	Yes	18	100.0	25	100.0
	No	0	0.0	0	0.0
Hospitalization*					
	Yes	0	0.0	0	0.0
	No	18	100.0	25	100.0
Admitted to ICU*					
	Yes	0	0.0	0	0.0
	No	18	100.0	25	100.0
Death*					
	Yes	0	0.0	0	0.0
	No	18	100.0	25	100.0
MVA-BN product					
	IMVANEX	340	6.0	-	-
	JYNNEOS	3,554	62.8	-	-
	Unknown	1,766	31.2	-	-
MVA-BN route of administration					
	Intradermal (0.1 ml)	3,502	61.9	-	-
	Subcutaneous (0.5 ml)	1,707	30.2	-	-
	Unknown	451	7.9	-	-

*Proportion is over the total number of MPXV infections

Table 2. Number of events, estimated risk, risk ratios, vaccine effectiveness (VE) and 95% confidence intervals (95% CI), overall and by time since vaccination, of one dose of MVA-BN vaccine

Time since vaccination	Unvaccinated		Vaccinated		Risk Ratio (95% CI)	VE (95% CI)
	Events	Risk per 1,000	Events	Risk per 1,000		
Overall	25	5.58	18	3.46	0.62 (0.31 ; 1.24)	37.9% (-24.4 ; 69.1)
0-6 days	8	1.46	11	2.02	1.38 (0.54 ; 4.33)	-38.3% (-332.7 ; 46.4)
0-13 days	13	2.47	15	2.82	1.14 (0.52 ; 3.00)	-14.1% (-199.7 ; 47.9)
≥ 7 days	17	4.13	7	1.44	0.35 (0.12 ; 0.77)	65.0% (22.9 ; 88.0)
≥ 14 days	12	3.12	3	0.65	0.21 (0.00 ; 0.67)	79.3% (33.3 ; 100.0)

Table 3. Number of events, estimated risk, risk ratios, vaccine effectiveness (VE) and 95% confidence intervals (95% CI), overall and by time since vaccination, of one dose of MVA-BN vaccine among individuals under 50 years of age

Time since vaccination	Unvaccinated		Vaccinated		Risk Ratio (95% CI)	VE (95% CI)
	Events	Risk per 1,000	Events	Risk per 1,000		
Overall	22	5.58	14	3.00	0.54 (0.25 ; 1.03)	46.3 (-3.4 ; 75.4)
0-6 days	7	1.44	9	1.86	1.29 (0.48 ; 3.93)	-29.2 (-292.8 ; 51.9)
0-13 days	11	2.34	12	2.52	1.08 (0.44 ; 2.52)	-7.8 (-151.7 ; 56.0)
≥ 7 days	15	4.15	5	1.15	0.28 (0.06 ; 0.79)	72.4 (20.9 ; 94.4)
≥ 14 days	11	3.26	2	0.48	0.15 (0.00 ; 0.59)	85.2 (41.1 ; 100.0)

Figure 1. Sample selection flowchart. Abbreviation: HIV-PrEP, HIV pre-exposure prophylaxis.

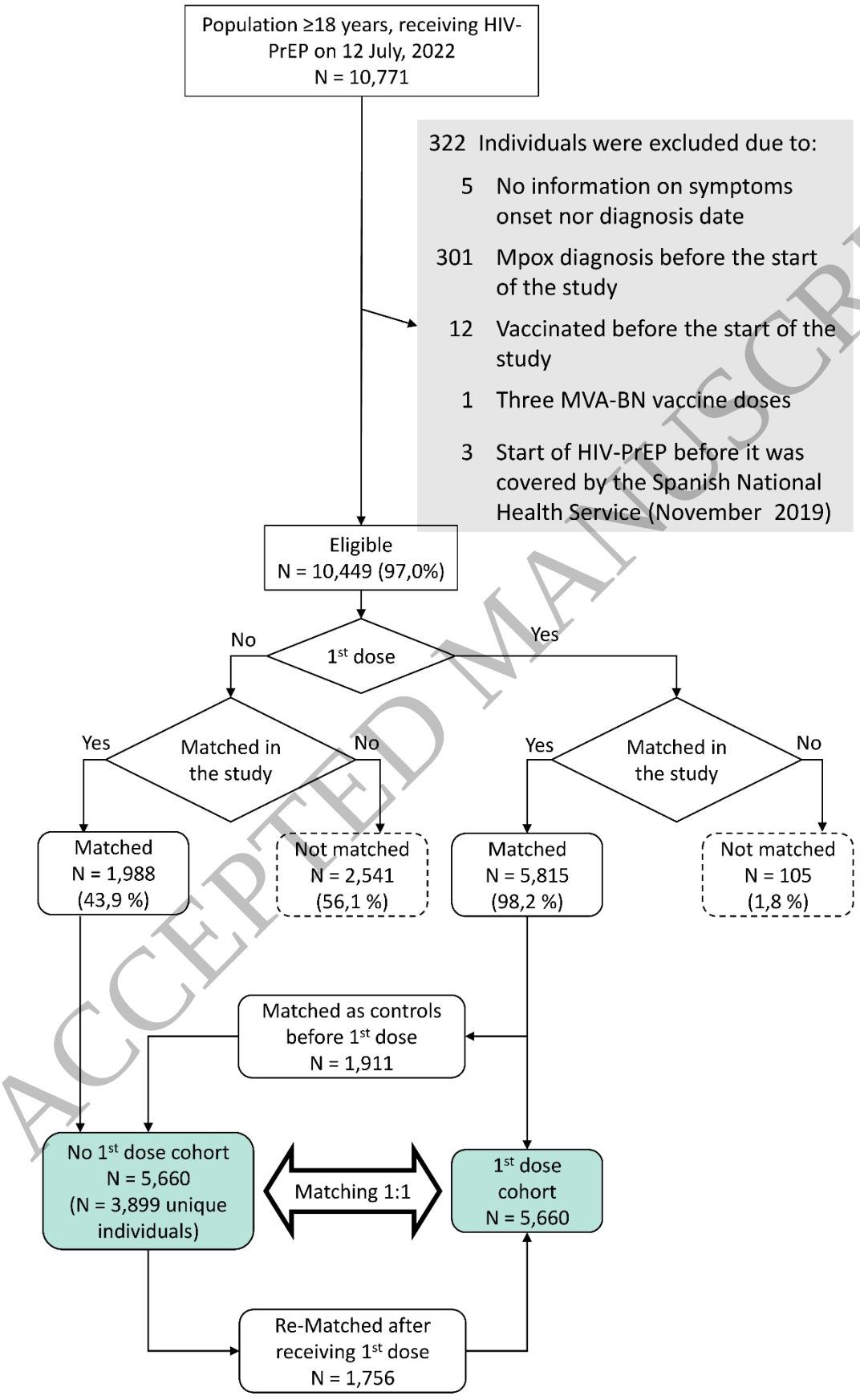

Figure 2. Estimated MPXV infection risk in the sample of individuals vaccinated with at least one dose of MBA-BN vaccines and matched unvaccinated controls, overall (a) and in individuals under 50 years of age (b)