Generating epidemiological evidence for controlling emerging infectious disease outbreaks

Ewijk, C.E. van

Chapter 8

Acceptance and timeliness of post-exposure vaccination against mpox in high-risk contacts, Amsterdam, the Netherlands, May-July 2022.

Catharina E. van Ewijk , Carine Smit, Roisin Bavalia, Kylie Ainslie, Albert Vollaard, Gini van Rijckevorsel, Susan J. M. Hahné

This work has been published:
Vaccine. 2023 Nov 13;41(47): 6952-6959.
doi: 10.1016/j.vaccine.2023.10.013.

ABSTRACT

Background

May 2022, several countries reported mpox outbreaks among men-who-have-sex-with-men. In the Netherlands, high-risk contacts were offered the third-generation smallpox vaccine as post-exposure-prophylaxis (PEP) within 4 but maximum 14 days after exposure. We investigated their PEP acceptance, timeliness of uptake and development of mpox for the region of the Public Health Service (PHS) Amsterdam.

Methods

High-risk contacts identified during 20 May–22 July 2022 were included. Contacts were followed-up 21 days after exposure and classified as: no patient (no mpox symptoms or orthopoxvirus PCR-negative) or mpox patient (clinically suspected mpox or orthopoxvirus PCR-positive). We calculated time intervals between date of last exposure and first PHS consultation, PEP administration, and symptom onset.

Results

Two-hundred-ninety contacts were at high-risk of mpox predominantly due to sexual and/or direct skin-skin contact (212/290, 73%). First PHS consultation was a median of 5 (IQR 3, 7) days after exposure, at which point 26/290 (9%) contacts were ineligible for PEP. 84% (223/264) of contacts eligible for PEP, received PEP within a median of 6 (IQR 3, 8) days after exposure. Of 282 contacts (missing outcome n = 8) 38 (14%) developed mpox a median of 7 (IQR 5, 12) days after exposure, of whom 50% (19/38) developed mpox before their first PHS consultation. Among contacts eligible for PEP, 2/38 (5%) unvaccinated and 16/218 (7%) vaccinated contact developed mpox.

Conclusions

PEP acceptance among contacts of mpox patients was high. However, PEP timeliness was inadequate. Half of contacts received PEP 6 or more days after exposure, and half of contacts who developed mpox had an onset prior to their first PHS consultation. Estimating PEP vaccine effectiveness is problematic due to the timeliness of PEP and the time it takes to generate vaccine-induced immunity. It is important to assess how PEP timeliness may improve and to promote pre-exposure vaccination to control mpox outbreaks.

BACKGROUND

In May 2022 several European countries reported cases of mpox among men who identified as men-who-have-sex-with-men (MSM) [1, 2]. The World Health Organization declared the mpox outbreak a Public Health Emergency of International Concern on 23 July 2022 and cases were eventually reported in 111 countries [3, 4].

Individuals infected with monkeypoxvirus (MPXV) may develop (vesicular/pustular) rash and/or systemic symptoms such as fever and lymphadenopathy in their incubation period within 3–21 (median 7–9) days after exposure [5, 6, 7, 8]. Patients are considered infectious from symptom onset until re-epithelisation of the skin lesions, but pre- and asymptomatic transmission occur [9, 10].

The first mpox patient in the Netherlands was reported on 20 May 2022. Mpox became notifiable by law on 21 May, meaning physicians were to notify suspected mpox cases to regional Public Health Services (PHS) as soon as possible to allow preventive measures [11]. Besides (suspected) case isolation, source and contact-tracing was used to curb transmission whereby PHS identified contacts who were at high- or medium-risk of MPXV infection. High- and medium risk contacts were asked to quarantine and were offered one dose of modified vaccinia Ankara vaccine (MVA-BN; Bavarian-Nordic, Imvanex®) as post-exposure prevention (PEP) preferably within 4 but maximum 14 days after exposure [11]. Additionally, a pre-exposure vaccination (PrEP) campaign started on 25 July 2022 aiming at those at highest risk of MPXV exposure through sexual contact. Eligible individuals received two MVA-BN vaccines with an interval of 4–6 weeks for optimal protection, except for those who had received smallpox vaccination in the past, for whom one dose of MVA-BN was recommended. Also, individuals who received the vaccine as PEP and who did not develop mpox but were considered continuously at-risk of MPXV exposure, were offered a second vaccine to complete their PrEP series.

MVA-BN is a third-generation, live-attenuated, but non-replicating smallpox vaccine. Evidence on the efficacy, immunogenicity and vaccine effectiveness (VE) of the MVA-BN vaccine against mpox is limited. Recent studies on MVA-BN as PrEP suggested a VE ranging from 36 to 86% against mpox disease after one, and 66% after two doses [12, 13, 14]. Other research, however, showed that the third-generation smallpox vaccine likely induces less virus-neutralising antibodies compared to the first-generation vaccine and that they may take more than two weeks to develop [15, 16].

Contrary to PrEP where an individual is given a complete course of vaccination (two doses) to prevent mpox in case of future exposure, PEP is given after MPXV exposure and

consists of one dose. Not much is known about the effectiveness of PEP, but breakthrough infections have been reported, although this may be mainly due to late administration of PEP [17, 18]. The expected VE of vaccines used as PrEP may not apply when they are used as PEP [19].

Here, we present the characteristics of high-risk contacts exposed to a confirmed mpox index, and investigate their PEP uptake, timeliness of PEP and development of mpox symptoms for the region of PHS Amsterdam.

METHODS

Study design and population

We performed a retrospective observational study of individuals identified as at high-risk of MPXV exposure through contact-tracing of notified confirmed mpox patients by the PHS Amsterdam between 20 May up and to 22 July 2022. Low and medium risk contacts were excluded (Box 1).

Box 1. Categorisation of high, medium and low risk contact with an mpox index during the outbreak in the Netherlands, as of July 2022

High-risk contact: a person with (one of) the following types of contact with an mpox case during their infectious period

a. Any type of sexual contact
b. Intensive skin-skin contact (such as hugging, kissing)
c. Household contact, excluding intensive skin-skin contact and sexual contact
d. Unprotected direct contact with a mpox patient and/or contaminated patient material
e. Laboratory employees with unprotected exposure accident to contaminated material

Medium-risk contact: a person with (one of) the following types of contact with an mpox case during their infectious period

a. Unprotected prolonged (cumulative more than 2 hour) face-to-face contact within 1.5 meter distance (such as caregivers without a mouth and nose mask, in social situations including public transport)

Low-risk contact : a person with (one of) the following types of contact with an mpox case during their infectious period

a. Unprotected short (cumulative less than 2 hour) face-to-face contact within 1.5 meter distance (such as caregivers without PPE)
b. Fellow airline travelers (with a journey time more than 8 hours) within 1.5 meter distance (1-2 seats around the index) and without social interaction
c. Social short (cumulative less than 2 hour) face-to-face contact within 1.5 meter distance

Contact-tracing

After notification of a suspected index to the PHS by a treating physician, a PHS professional collected, using a standardised form, information from the index on their demographics, source of infection, type of exposure, and the number and type (low, medium or high) of contacts during their infectious period. After the infection of the suspected index was confirmed, and if contact details were available and provided by the index, the PHS informed the high-risk contacts for counselling and preventive measures which included the offer of PEP, the advice to quarantine for 21 days after last MPXV exposure, and to abstain from close contact with household members and/or sexual activities. The PHS professional assessed eligibility for PEP (see Definitions) during this telephonic counselling session. Individuals eligible for PEP were informed in advance about the procedure before and after vaccination. Eligible high-risk contacts who wished to receive PEP were offered an appointment as soon as possible at the PHS where a PHS nurse administered the vaccine. They were asked about any signs and symptoms before being vaccinated, and instructed how to contact the PHS in case of any side effects or symptoms occurring after vaccination. A PHS professional actively monitored high-risk contacts daily by telephone or mail for mpox symptoms conform national guidelines. This daily monitoring protocol changed to twice weekly end of June, and to a passive follow-up protocol mid July 2022 conform national guidelines. Contacts were then, after receiving counselling, requested to self-report to the PHS in case any symptoms consistent with mpox developed during their quarantine period.

Definitions

Contacts were defined as high-risk conform national guidelines (Box 1) [11]. Unspecified high-risk contact was defined as contacts who were classified by the PHS as high-risk contacts conform national guidelines but for whom the specific nature of the high-risk exposure (e.g. sexual contact or household) was not specified in the electronic database.

If a contact developed mpox symptoms during their 21-days follow-up period they could become a confirmed or a probable mpox patient. Confirmed mpox patients were defined as contacts who tested PCR-positive for orthopoxvirus (with or without additional MPXV confirmation by sequencing or MPXV-specific PCR). Probable patients were defined as contacts who reported mpox symptoms (skin lesions consistent with mpox and/or complaints consistent with proctitis and/or one or more systemic symptoms) and were clinically judged by a PHS professional or physician as suspected mpox, but who were not PCR-tested for MPXV. During the passive follow-up period (see Contact-tracing), we assumed that contacts who did not report to the PHS during their quarantine period did not develop mpox symptoms. Contacts were considered lost to follow-up if they moved abroad or if they never responded to any of the PHS phone calls or e-mails. To assess the

acceptance of PEP among high-risk contacts, we assumed that those who never responded to any form of contact from the PHS did not accept the vaccination. PEP eligible contacts were defined as high-risk contacts who did not have mpox at time of first PHS consultation and who received their first PHS consultation within 14 days after exposure.

Data collection

Data on contacts were collected as part of epidemiological routine surveillance through contact-tracing and put into an electronic database (HPzone). For analyses, the following data on high-risk contacts were retrospectively extracted from HPzone: age, sex, type of exposure, date of most recent exposure (date of first exposure was unavailable), date of contact with the PHS, historic smallpox vaccination status, MVA-BN vaccination status and date of first and, if applicable, second vaccination, whether the contact developed mpox symptoms and was tested for mpox during their 21-day quarantine period.

Statistical analyses

We used descriptive statistics to characterise the high-risk contacts, and calculated the following median time intervals (days) with interquartile range (IQR) between: 1) date of most recent exposure and a) first PHS consultation b) PEP administration c) symptom onset; 2) date of first contact with the PHS and date of a) PEP administration, b) symptom onset, and; 3) PEP administration and date of symptom onset. Statistical analyses were performed in R 4.0.2.

RESULTS

Characteristics of high-risk contacts

From 20 May up and to 22 July 2022 a total of 290 individuals were identified by the PHS Amsterdam as high-risk contacts of an mpox index (Table 1). Of these high-risk contacts, 271/287 (94%) (denominators deviate due to missing data) were male by birth. The contacts had a median age of 36 (min 8 – max 72) years and included six children between 8 and 13 years old. MPXV exposure occurred predominantly through sexual and/or direct skin-skin contact (212/290, 73%). In 10% (28/290) the exposure occurred through household contact. Seven contacts reported exposure through healthcare work, four through intensive face-to-face contact and three through contact with contaminated material. In 12% (36/290) the type of high-risk contact was unspecified. Among the six children, five were exposed through direct skin-skin and one through household contact. Almost all contacts (282/290, 97%), completed the 3 week period of follow-up the majority of whom (partially) passively (174/282, 60%).

Table 1. Characteristics of high-risk contacts of mpox indexes identified through contact-tracing at PHS Amsterdam, 20 May up and to 22 July 2022 (N=290).

	Contacts of mpox indexes	
Characteristics	**N**	**%**
Total	290	100
Age in years median, (min; max)	36	(8; 72)
Born before 1978	82	29
Unknown	7	
Sex at birth		
Female	16	6
Male	271	94
Unknown	3	
Smallpox vaccinated before 1978		
Unvaccinated	22	44
Vaccinated	28	56
Unknown	240	
Type of exposure		
Sexual contact	119	41
Skin-skin contact	93	32
Household contact	28	10
Unprotected contact with contaminated material	3	1
Intensive face-face contact[a]	4	1
Healthcare worker	7	2
Unspecified high-risk contact[b]	36	12
Mpox symptoms prior to first PHS consultation		
No	268	93
Yes	19	7
Unknown	3	
Vaccinated with MVA-BN as PEP		
No	63	22
Yes	227[c]	78
Number of MVA-BN doses received		
One	80	35
Two	147	65

	Contacts of mpox indexes	
Characteristics	**N**	**%**
Reasons no MVA-BN as PEP		
Not reached	2	4
No show	2	4
Rejected	22	45
Symptoms	20	41
More than 14 days after exposure	3	6
Unknown personal reason	14	
Tested for mpox		
No	208	76
Yes, once	57	21
Yes, twice	8	3
Unknown	17	
Completed 21-day active follow-up		
No, received (partially) passive follow-up	174	60
Yes, received active follow-up	108	37
Lost to follow-up	8	3
Developed mpox[d] during three week quarantine period		
No	244	87
Probable	7	3
Confirmed	31	11
Unknown due to loss to follow-up	8	

PHS = public health service [a] classified by the PHS as high-risk due to prolonged unprotected face-to-face contact for more than two days without being officially household contacts [b] person who reported (one of) the following types of contact with a confirmed mpox patient during their infectious period in their PHS counselling session but for whom the high-risk contact was not further specified in the electronic database: i) any type of sexual contact; ii) intensive skin-skin contact, such as hugging or kissing; ii) household contact, excluding intensive skin-skin and sexual contact; iv) unprotected direct contact with a mpox patient and/or contaminated patient material v) laboratory employees with unprotected exposure accident to contaminated material. [c] Including 4 contacts who were ineligible for vaccination according to national guidelines as they received their first PHS consultation >14 days after exposure [d] Confirmed patients =contacts who tested PCR-positive for orthopoxvirus (with or without additional MPXV confirmation by sequencing or MPXV-specific PCR); Probable patient= contacts who reported mpox symptoms (i.e. skin lesions consistent with mpox and/or complaints consistent with proctitis and optionally one or more systemic symptoms) and were clinically suspected by the PHS professional and/or physician as having mpox, but who were not PCR-tested for MPXV.

Vaccine uptake

Of all 290 high-risk contacts, 264 (91%) were eligible and 26 (9%) ineligible for PEP vaccination conform national guidelines at first PHS consultation. Of the 26 ineligible contacts, 19 were ineligible as they experienced mpox symptoms prior to their first PHS

consultation and seven were ineligible as they received their first PHS consultation or were offered PEP vaccination more than 14 days after MPXV exposure. Of the seven who were ineligible due to the interval of 14 days, four did receive PEP vaccination despite being ineligible for PEP (Figure 1).

Of the 264 contacts eligible for PEP vaccination, 223 (84%) received one dose of MVA-BN as PEP, of whom more than half (66%, 147/223) received their second dose 4-6 weeks after their first dose to complete their scheme according to a PrEP series. Reasons for not receiving PEP among the eligible contacts were: unwillingness to vaccinate (22/41), development of mpox symptoms soon after first PHS consultation (1/41), no show (2/41), and not reached (2/41). For 14 contacts the personal reason for not receiving PEP was unspecified.

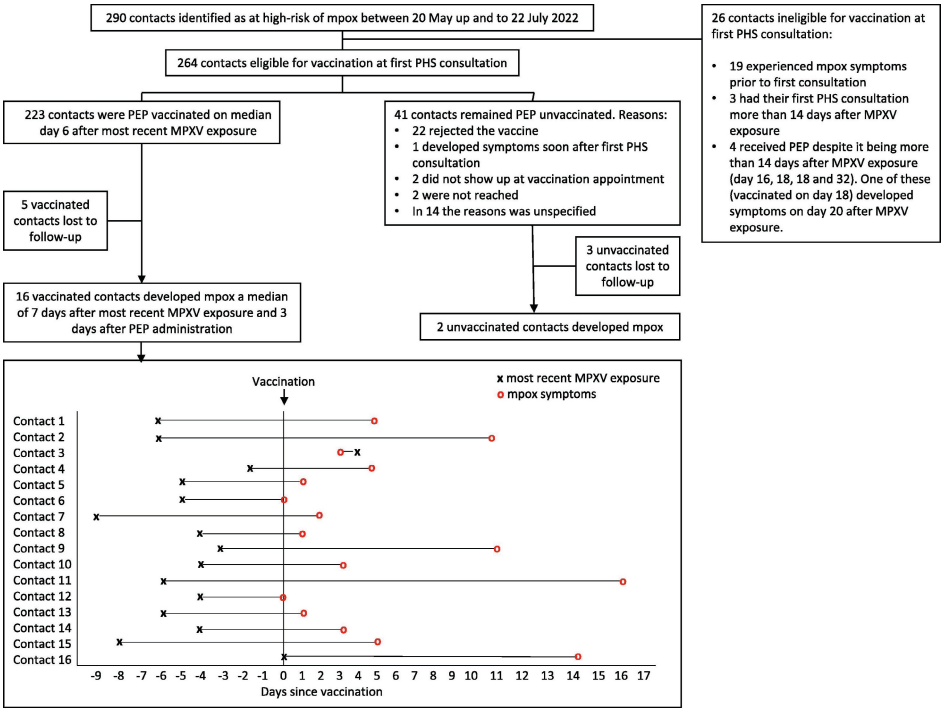

Figure 1. Flowchart of PEP vaccination and development of mpox symptoms in high-risk contacts of mpox index identified through contact-tracing at PHS Amsterdam, 20 May up and to 22 July 2022 (N=290)

PHS = public health service; PEP = post-exposure prophylaxis with MVA-BN, MPXV = monkeypoxvirus

Of the 264 contacts eligible for PEP vaccination, 223 (84%) received one dose of MVA-BN as PEP, of whom more than half (66%, 147/223) received their second dose 4–6 weeks after their first dose to complete their scheme according to a PrEP series. Reasons for not receiving PEP among the eligible contacts were: unwillingness to vaccinate (22/41), development of mpox symptoms soon after first PHS consultation (1/41), no show (2/41), and not reached (2/41). For 14 contacts the personal reason for not receiving PEP was unspecified.

Timeliness of PEP

As Fig. 2 shows, all contacts were informed and assessed by the PHS within a median of 5 (IQR 3, 7) days after most recent exposure with a range of −4 to 31 days showing that some contacts had ongoing exposure after PHS consultation, resulting in a negative time interval (denominators deviate due to missing data on dates). The 223 contacts eligible for and receiving PEP received the first vaccination within a median of 1 (IQR 0, 1; range 0, 9) day after their first PHS assessment and a median of 6 (IQR 3, 8) days after most recent exposure with a range of −4 to 14 days showing some contacts had ongoing exposure after vaccination, resulting in a negative time interval.

The 4 contacts who received vaccination despite being ineligible for PEP did so 16 to 32 days after most recent exposure (Fig. 1).

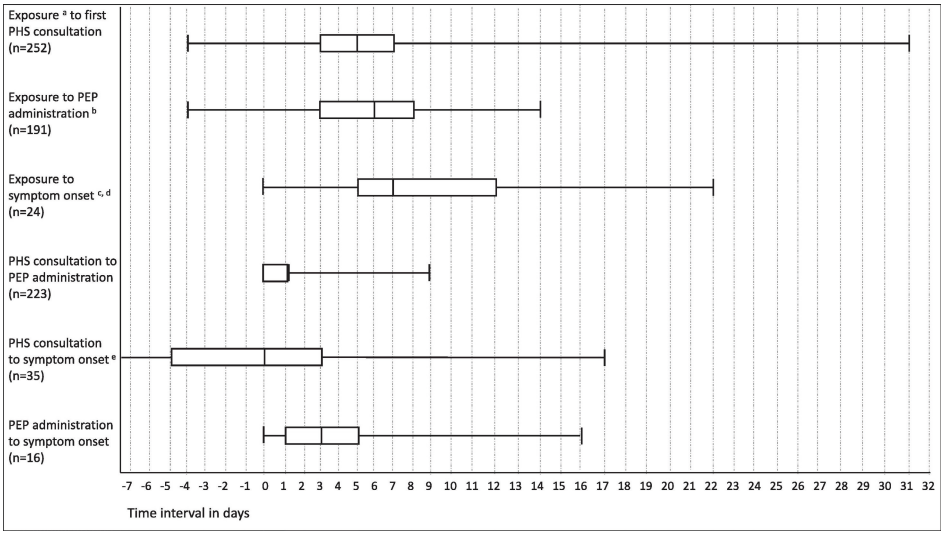

Figure 2. Time intervals in high-risk contacts op mpox indexes, Amsterdam, the Netherlands, 20 May – 22 July 2022

Figure 2 *Continued*

The figure shows the time intervals (days) between most recent exposure and PHS consultation, PEP administration and symptoms onset; PHS consultation and PEP administration and symptom onset; PEP administration and symptom onset. For example: the median time between most recent exposure and first PHS consultation was 5 days with an interquartile range of 3 and 7 days and a range of -4 and 31 days, showing that some contacts had ongoing exposure after PHS consultation resulting in a negative time interval. Numbers deviate due to missing data on date of PHS consultation and/or PEP administration and/or symptom onset. PHS = public health service; PEP = post-exposure prophylaxis vaccination. [a] most recent exposure, as date of first exposure was unavailable, [b] among contacts eligible for vaccination [c] from both probable and confirmed mpox. Confirmed patients = contacts who tested PCR-positive for orthopoxvirus (with or without additional MPXV confirmation by sequencing or MPXV-specific PCR); Probable patient= contacts who reported mpox symptoms (i.e. skin lesions consistent with mpox and/or complaints consistent with proctitis and optionally one or more systemic symptoms) and were clinically suspected by the PHS professional and/or physician as having mpox, but who were not PCR-tested for MPXV, [d] excluding eight contacts with continuous exposure, [e] minimum interval -15 days.

Development of mpox symptoms

Eight contacts (3%) were lost to follow-up during their three week quarantine period, of whom five had received and three had not received PEP. Of the 282 contacts with a complete follow up, 38 (14%) contacts developed mpox symptoms, among whom 31 were laboratory confirmed and 7 were probable infections. Half of the contacts with mpox (19/38; 50%) had developed mpox before they were reached by the PHS and were therefore ineligible for PEP. Two of the 38 contacts with mpox were eligible for PEP but were not vaccinated: one refused and one developed mpox before the vaccine could be administered. Seventeen contacts developed symptoms despite PEP vaccination, of whom one received PEP more than 14 days after exposure and had been therefore ineligible for PEP according to national guidelines (Fig. 1).

As Fig. 2 shows (denominators deviate due to missing data on dates), the contacts with mpox had an onset of symptoms within a median of 7 (IQR 5, 12; range 0, 22) days after most recent exposure, excluding eight contacts who reported continuous exposure to the index making it difficult to determine time between exposure to symptom onset. Development of mpox symptoms was highest among contacts who had MPXV exposure through sexual contact (23%, 27/118), followed by direct skin-skin contact (9%, 8/90) (Table 2). None of the children or healthcare workers developed mpox symptoms.

Table 2. Proportion of contacts developing mpox among high-risk contacts of mpox indexes during their three week quarantine period by type of exposure, PEP eligibility, and post-exposure prophylaxis vaccination status, Amsterdam, the Netherlands (N = 282)[a], 20 May – 22 July 2022

Type of exposure	PEP eligibility[b]	PEP vaccination status	Number of mpox patients	Total number of contacts	Percentage of contacts with mpox
All high-risk	Overall		38[c]	282[a]	14%
	PEP ineligible[d]		20	26	77%
	PEP eligible	PEP unvaccinated	2	38	5%
		PEP vaccinated	16	218	7%
Sexual	Overall		27	118	23%
	PEP ineligible		14	17	82%
	PEP eligible	PEP unvaccinated	1	13	8%
		PEP vaccinated	12	88	14%
Direct skin-skin	Overall		8	90	9%
	PEP ineligible		3	4	75%
	PEP eligible	PEP unvaccinated	1	7	14%
		PEP vaccinated	4	79	5%
Household	Overall		2	28	7%
	PEP ineligible		2	3	67%
	PEP eligible	PEP unvaccinated	0	8	0%
		PEP vaccinated	0	17	0%
Intensive face-face	Overall		0	4	0%
	PEP ineligible		NA	NA	NA
	PEP eligible	PEP unvaccinated	0	2	0%
		PEP vaccinated	0	2	0%
Healthcare worker	Overall		0	7	0%
	PEP ineligible		NA	NA	NA
	PEP eligible	PEP unvaccinated	0	2	0%
		PEP vaccinated	0	5	0%
Contaminated material	Overall		0	3	0%

Table 2 *Cotinued*

Type of exposure	PEP eligibility[b]	PEP vaccination status	Number of mpox patients	Total number of contacts	Percentage of contacts with mpox
	PEP ineligible		NA	NA	NA
	PEP eligible	PEP unvaccinated	0	3	0%
		PEP vaccinated	NA	NA	NA
Unspecified high-risk	Overall		1	32	3%
	PEP ineligible		1	2	50%
	PEP eligible	PEP unvaccinated	0	3	0%
		PEP vaccinated	0	27	0%

PEP = post-exposure prophylaxis with MVA-BN. [a] 8 missing on disease outcome due to lost to follow-up (3 unvaccinated and 5 vaccinated contacts) [b] PEP eligible contacts were defined as high-risk contacts who did not have mpox at time of first PHS consultation and who received their first PHS consultation within 14 days after exposure. [c] both probable (n=7) and confirmed (n=31) mpox. Confirmed patient = contacts who tested PCR-positive for orthopoxvirus (with or without MPXV confirmation by sequencing or MPXV-specific PCR); Probable patient = contacts who reported mpox symptoms (i.e. skin lesions consistent with mpox and/or complaints consistent with proctitis and optionally one or more systemic symptoms) and who were clinically suspected by the PHS professional and/or physician as having mpox, but who were not PCR-tested for MPXV. [d] including 19 contacts who experienced mpox before their first PHS consultation and were therefore ineligible for PEP, and 7 contacts who received their first PHS consultation >14 days of whom 4 received PEP despite being ineligible for PEP.

Of all 256 contacts who were eligible for PEP and with complete follow-up (denominators deviate due to missing data on outcome in 5 vaccinated and 3 unvaccinated contacts), 18 (7%) developed symptoms: 16/218 (7%) PEP vaccinated and 2/38 (5%) unvaccinated contacts developed symptoms (Fig. 1; Table 2). Most contacts eligible for PEP did not develop symptoms (93%, 238/256), despite 36 not having received the vaccination.

The vaccinated eligible contacts who developed mpox (n = 16) had a symptom onset within a median of 7 (IQR 6, 13; range −1, 22) days after most recent exposure and 3 (IQR 1, 7; range 0, 16) days after vaccination (Fig. 1).

Among the vaccinated eligible contacts, those who developed mpox had received PEP a median of 5 (IQR 4, 6; range −4; 9) days after most recent exposure, compared to a median of 6 (IQR 4, 8; range −2, 14) days for those who did not develop mpox.

Among eligible contacts who received PEP within the 4 days after most recent exposure 9% (4/47) developed mpox regardless of vaccination, which was similar for contacts who received PEP 4–14 days after most recent exposure (9%, 12/141) (denominators deviate due to missing data on time between PEP and exposure n = 32, and outcome n = 3).

DISCUSSION

We described the high-risk contacts of mpox cases and the acceptance and timeliness of PEP during the first nine weeks of the mpox outbreak for the region of PHS Amsterdam, 20 May up and to 22 July 2022. The majority of contacts were identified as high-risk of mpox through sexual and/or direct skin-skin contact. Overall, 84% of the contacts eligible for PEP were vaccinated with MVA-BN within one day after first PHS assessment, showing a high vaccine uptake. The main reason for not receiving PEP despite being eligible was non-acceptance to be vaccinated. The other prime reason for not receiving PEP was the presence of mpox symptoms at the time of the first assessment, making these contacts ineligible for PEP. The development of symptoms among high-risk contacts in the three week monitoring period after last date of exposure was 14% (38 cases), half of whom had developed symptoms before they received their first PHS consultation. Seventeen contacts, among whom sixteen eligible for PEP, developed symptoms despite PEP vaccination. The majority of whom had received their PEP within 6 (range −4, 9) and developed symptoms within 13 (range −1, 22) days after most recent exposure. The negative time intervals between vaccination or symptom onset with most recent exposure indicate that some contacts reported exposure with a confirmed mpox index after vaccination or after they developed mpox themselves. There were no healthcare workers among the contacts who developed mpox.

Explanations for developing mpox despite vaccination might be vaccinating during the incubation time whilst in the absence of, or not (yet) sufficient, cross-protective antibodies to prevent mpox in an already infected individual. Despite the rapid administration of PEP to identified contacts after first assessment, half of the contacts received PEP 6 or more days after most recent exposure. A timeframe which includes the median incubation period, and which exceeds the recommended preferred window of within 4 days, although remaining within 14 days, after first exposure according to the current guidelines [11]. As our results show, half of the contacts had developed mpox symptoms upon the first PHS consultation.

Research suggests that the median mpox incubation period is 7–9 days, whilst the average time to seroconversion seems more than two weeks [15, 6, 7, 8]. MPXV neutralising antibodies were observed in 10% of the participants at two weeks, increasing to 100% at four weeks after their first MVA-BN vaccination, suggesting that vaccine-induced protection takes at least two weeks to develop [15, 20]. The window of opportunity for PEP to prevent mpox in contacts is therefore very brief and for some even non-existent. This raises questions about the usefulness of PEP to prevent mpox and whether the currently advised maximum window for vaccination of 14 days should be reduced. However, the study on the development of MPXV neutralising antibodies did not include participants who may have been infected with

MPXV prior to vaccination and more immunological studies are needed to investigate the interplay between the development of an immune response following MPXV exposure and MVA-BN, and the subsequent development of mpox disease.

Data on the timing and effectiveness of MVA-BN as PEP for mpox is scarce. A study in prairie dogs showed a beneficial effect of MVA-BN as PEP against mortality when PEP was given within 1–3 days after a low dose MPXV inoculation. This beneficial effect of MVA-BN was not seen after a higher dose MPXV inoculation [21]. The short incubation period of mpox, the timing of PEP administration and the time it takes to generate vaccine-induced immunity suggest that for the majority of contacts PEP will be too late to prevent mpox, although it remains to be determined whether PEP can be used to mitigate severity of disease. Future studies should determine whether antivirals used as PEP may be more efficient in the prevention of infection after exposure.

We were unable to calculate the vaccine effectiveness of MVA-BN PEP with the data available. Estimating VE for mpox PEP is problematic since only contacts can be included who were assessed timely enough by the PHS to be offered PEP, consequently excluding cases who had an onset prior to assessment. Additionally cases who had an onset in the period before vaccine-induced immunity is developed have to be counted as unvaccinated. This leaves very few contacts in the analyses, with only cases who are in the tail of the incubation distribution, limiting generalisability.

Nonetheless, MVA-BN as PEP may contribute to prevent future disease and transmission: most individuals who are at high-risk of MPXV exposure are likely to be exposed more than once during an outbreak. PEP has been described as an effective way of identifying and targeting at-risk individuals for vaccination compared to a more general vaccination campaign [22]. MVA-BN as PEP may still constitute an essential instrument in outbreak control regardless of the lack of established vaccine effectiveness: considering an attack rate of at most 23% after sexual contact (as seen in our cohort) it means that at least 77% of this at-high-risk population the PEP dose will serve as the first of the two recommended pre-exposure vaccinations. Consequently, it could be considered to offer any high-risk contact a first vaccine dose of two pre-exposure vaccinations regardless of a specific number of days after exposure, unless symptoms develop before the first dose or within the period before the second dose can be administered. In the Netherlands, a second vaccination is given after 6 weeks to those who were at continuous high-risk of MPXV exposure for completion of pre-exposure vaccination to curb transmission in the at-risk population. In our cohort, 66% of vaccinated PEP eligible contacts received their second vaccine, showing the importance of contact-tracing in identifying the at-risk population and therefore contributing in preventing future disease and spread.

Additionally, PEP may protect against severe disease [20]. One study showed a decrease in systemic symptoms and hospitalisations due to mpox in individuals who were vaccinated with MVA-BN more than 14 days before symptom onset compared to unvaccinated individuals [23]. We did not assess the difference in symptoms between PEP vaccinated and unvaccinated contacts who developed mpox. Future studies should determine whether PEP mitigates severity of disease.

The benefit of MVA-BN as PEP can likely be increased by decreasing time between exposure and vaccination, and if more contacts who were at-risk of MPXV are reached, e.g. through communicating the importance of the intervention with the population at-risk, scaling up the contact-tracing efforts and rapid access to vaccination free of charge.

There are several limitations to our study. We lack data on the date of first exposure. Contacts might have had several days of MPXV exposure and to assess timeliness of PEP preferably the date of first exposure is used. In our study, only the most recent MPXV exposure date was available, which likely contributed to the slightly shorter mpox incubation period we observed compared to previously reported in the literature [5, 6, 7, 8]. Consequently, PEP was potentially administered later than the observed median of 6 days after MPXV exposure.

Another limitation is that the source of the high-risk contacts was not assessed in a research setting. A high-risk contact is marked as a contact of a confirmed index, but may have been exposed to the same source as the index or may even have been the source of infection for the index.

Furthermore, selection bias might have occurred as it is possible that through contact-tracing the more reachable contacts were captured, such as household members and permanent partners, compared to casual and/or anonymous sexual partners.

Lastly, we used observational data collected through routine infection control efforts and epidemiological surveillance. As a consequence, the data might be of lesser quality compared to data collected in a research setting. Also, not all contacts were tested by the end of the incubation period, whereas research shows that asymptomatic mpox infections can occur [9, 10, 24]. Therefore, contacts who were subclinical or asymptomatic might have been misclassified as non-cases at the end of their quarantine period. Moreover, not all contacts were actively followed-up. In mid-July, the contact–tracing protocol changed from active to passive follow-up, meaning that contacts had to self-report to the PHS if they developed mpox symptoms. Therefore, contacts might have developed symptoms without reporting to the PHS or being tested.

CONCLUSION

In our analysis of 290 high-risk contacts of mpox indexes, contacts developed mpox predominantly after sexual and direct skin-skin contact. There were no contacts who developed mpox among healthcare workers. PEP acceptance among high-risk contacts eligible for vaccination was high. However, timeliness of PEP was inadequate. Half of the contacts received PEP 6 days or more after the recorded last date of exposure. Additionally, half of contacts who developed mpox during their quarantine period experienced symptoms before their first PHS consultation and were therefore ineligible for PEP. The difficulties of timely PEP administration highlight the importance of PrEP in the control of mpox outbreaks. PEP could nevertheless still be recommended since it may modify disease severity and also serves as PrEP.

FUNDING

The study is funded by the Ministry of Health, Welfare and Sports.

ETHICAL STATEMENT

This study was reviewed by the Centre for Clinical Expertise (KEC) (EPI-600) at the RIVM and considered not being subject to the Act on Research Involving Human Subjects (WMO).

ACKNOWLEDGEMENTS

We would like to thank Mirjam Knol, Susan van der Hof, Eline Op de Coul and Jacco Wallinga for valuable discussions. We would also like the thank the colleagues from the Public Health Services of Amsterdam for their hard work and dedication in the control of the mpox outbreak.

REFERENCES

1. European Centre for Disease Prevention and Control (ECDC). Monkeypox multi-country outbreak – 23 May 2022. ECDC: Stockholm. 2022.
2. World Health Organization (WHO). Multi-country monkeypox outbreak in non-endemic countries: Update. Geneva: WHO. [Accessed: 25 July 2022]. 2022.
3. World Health Organization - WHO Director-General declares the ongoing monkeypox outbreak a Public Health Emergency of International Concern 2022 [Available from: https://www.who.int/europe/news/item/23-07-2022-who-director-general-declares-the-ongoing-monkeypox-outbreak-a-public-health-event-of-international-concern.
4. World Health Organization - 2022-23 Mpox (Monkeypox) Outbreak: Global Trends 16-05-2023 [Available from: https://worldhealthorg.shinyapps.io/mpx_global/.
5. Charniga K, Masters NB, Slayton RB, Gosdin L, Minhaj FS, Philpott D, et al. Estimating the incubation period of monkeypox virus during the 2022 multi-national outbreak. 2022.
6. Guzzetta G, Mammone A, Ferraro F, Caraglia A, Rapiti A, Marziano V, et al. Early Estimates of Monkeypox Incubation Period, Generation Time, and Reproduction Number, Italy, May-June 2022. Emerging infectious diseases. 2022;28(10).
7. Ward T, Christie R, Paton RS, Cumming F, Overton CE. Transmission dynamics of monkeypox in the United Kingdom: contact tracing study. BMJ (Clinical research ed). 2022;379:e073153.
8. Miura F, van Ewijk CE, Backer JA, Xiridou M, Franz E, de Coul EO, et al. Estimated incubation period for monkeypox cases confirmed in the Netherlands, May 2022. Eurosurveillance. 2022;27(24).
9. Miura F, Backer JA, van Rijckevorsel G, Bavalia R, Raven S, Petrignani M, et al. Time scales of human mpox transmission in the Netherlands. medRxiv. 2022:2022.12.03.22283056.
10. Brosius I, Van Dijck C, Coppens J, Vandenhove L, Bangwen E, Vanroye F, et al. Pre- and asymptomatic viral shedding in high-risk contacts of monkeypox cases: A prospective cohort study. 2022.
11. RIVM. Monkeypox 2022 [Available from: https://lci.rivm.nl/richtlijnen/monkeypox-apenpokken.
12. Bertran M, Andrews N, Davison C, Dugbazah B, Boateng J, Lunt R, et al. Effectiveness of one dose of MVA-BN smallpox vaccine against mpox in England using the case-coverage method: an observational study. Lancet Infect Dis. 2023.

13. Wolff Sagy Y, Zucker R, Hammerman A, Markovits H, Arieh NG, Abu Ahmad W, et al. Real-world effectiveness of a single dose of mpox vaccine in males. Nature Medicine. 2023;29(3):748-52.

14. Deputy NP, Deckert J, Chard AN, Sandberg N, Moulia DL, Barkley E, et al. Vaccine Effectiveness of JYNNEOS against Mpox Disease in the United States. New England Journal of Medicine. 2023;388(26):2434-43.

15. Zaeck LM, Lamers MM, Verstrepen BE, Bestebroer TM, van Royen ME, Götz H, et al. Low levels of monkeypox virus-neutralizing antibodies after MVA-BN vaccination in healthy individuals. Nature Medicine. 2022.

16. Cohn H, Bloom N, Cai GY, Clark JJ, Tarke A, Bermúdez-González MC, et al. Mpox vaccine and infection-driven human immune signatures: an immunological analysis of an observational study. Lancet Infect Dis. 2023.

17. Merad Y, Gaymard A, Cotte L, Perpoint T, Alfaiate D, Godinot M, et al. Outcomes of post-exposure vaccination by modified vaccinia Ankara to prevent mpox (formerly monkeypox): a retrospective observational study in Lyon, France, June to August 2022. Eurosurveillance. 2022;27(50):2200882.

18. Thy M, Peiffer-Smadja N, Mailhe M, Kramer L, Ferré VM, Houhou N, et al. Breakthrough Infections after Postexposure Vaccination against Mpox. New England Journal of Medicine. 2022;387(26):2477-9.

19. Payne AB, Ray LC, Cole MM, Canning M, Houck K, Shah HJ, et al. Reduced Risk for Mpox After Receipt of 1 or 2 Doses of JYNNEOS Vaccine Compared with Risk Among Unvaccinated Persons - 43 U.S. Jurisdictions, July 31-October 1, 2022. MMWR Morbidity and mortality weekly report. 2022;71(49):1560-4.

20. Smallpox and mpox (monkeypox): the green book, chapter 29 [Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1106454/Green-Book-chapter-29_Smallpox-and-monkeypox_26September2022.pdf.

21. Keckler MS, Salzer JS, Patel N, Townsend MB, Nakazawa YJ, Doty JB, et al. IMVAMUNE® and ACAM2000® Provide Different Protection against Disease When Administered Postexposure in an Intranasal Monkeypox Challenge Prairie Dog Model. Vaccines. 2020;8(3):396.

22. Xiridou M, Miura F, Adam P, Op de Coul E, de Wit J, Wallinga J. The fading of the mpox outbreak among men who have sex with men: a mathematical modelling study. medRxiv. 2023:2023.01.31.23285294.

23. Farrar JL, Lewis NM, Houck K, Canning M, Fothergill A, Payne AB, et al. Demographic and Clinical Characteristics of Mpox in Persons Who Had Previously Received 1 Dose of JYNNEOS Vaccine and in Unvaccinated Persons - 29 U.S. Jurisdictions, May 22-September 3, 2022. MMWR Morb Mortal Wkly Rep. 2022;71(5152):1610-5.

24. De Baetselier I, Van Dijck C, Kenyon C, Coppens J, Van den Bossche D, Smet H, et al. Asymptomatic monkeypox virus infections among male sexual health clinic attendees in Belgium. 2022.