The fading of the mpox outbreak among men who have sex with men: a mathematical modelling study

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SUPPLEMENT

The transcription model

We developed a deterministic compartmental model that describes monkeypox virus (MPXV) transmission among men who have sex with men (MSM). A schematic diagram of the model is shown in Figure 1 in the main text. We accounted only for transmission via sexual or intimate contacts among main (steady) and casual sex partners (for brevity, referred to as "sexual contacts").

Sexual partners

MSM were divided into $G = 4$ sexual activity groups, based on the total number of partners with whom they had sexual/intimate contacts. The number of these partners was obtained from data from the first round of the "COVID-19, Sex, and Intimacy Survey", carried out in the summer of 2020 [1]. The survey was focussed on the impact of the first wave of the pandemic. However, as reference, participants were asked also about their sexual behaviour in the second half of 2019. We used the data of 2019, as representative of sexual activity without the temporal fluctuations caused by the COVID-19 pandemic, but also because participants were asked to report the number of male partners with whom they "had sex/intimacy in the second half of 2019". Based on this number, we divided the population into four sexual activity groups: very low, fairly low, fairly high, and very high activity. The parameters relating to sexual behaviour of each activity group are shown in Table 2.

The course of MPXV infection

Individuals enter the population as susceptible (S_i) when they become sexually active. After infection, individuals are exposed but not infectious (E_i) and later become infectious (I_i). When individuals have symptoms and/or they are tested positive for MPXV infection, they may refrain from physical/sexual contacts or may be in isolation/confinement. We refer to these individuals as "refraining from sexual contacts" (Y_i). We assumed that individuals start refraining from sexual contacts $1/$[illegible] days after becoming infectious; infectious cases refraining from sexual contacts can still infect others, with a lower probability of transmission, for instance, because they do not completely refrain from sex contacts. Most of the infectious mpox cases recover after a few weeks and become immune (R_i), but a small fraction of the infectious cases may develop complications and need hospitalization (H_i) or die due to mpox.

Individuals born before 1974 were vaccinated in their first year of age against smallpox and that protects against MPXV infection and/or disease. Smallpox vaccination ended in 1974 in the Netherlands. Therefore, we assumed that in 2022 approximately 25% of sexually active MSM is vaccinated ($5_{\square\square}$) via the old smallpox vaccination programmes, based on the age distribution of adult men in the Netherlands [2, 3]. We assumed that vaccinated men can still get infected with MPXV (and become exposed, $\square_{\square\square}$), but at a lower rate than that for unvaccinated individuals. Vaccinated exposed individuals have a lower rate of becoming infectious ($+_{\square\square}$), than unvaccinated exposed individuals. Vaccinated infectious cases may refrain from sexual contacts ($;_{\square\square}$). We assumed that vaccination reduces the level of infectivity of vaccinated infectious cases, but the recovery rate, the hospitalization rate, and the MPXV-related death rate are similar for vaccinated and unvaccinated individuals.

To account for different levels of protection by the old and the new vaccines, in the model we included individuals vaccinated in 2022 separately from those who had been vaccinated in the past (before 1974). The respective compartments in the model are denoted with $5_{„\square}$, $\square_{„\square}$, $+_{„\square}$, $;_{„\square}$ (uninfected, exposed, infectious not refraining from sexual contacts, infectious refraining from sexual contacts, respectively) with the subscript L denoting those vaccinated in 2022 by means of pre-exposure or post-exposure prophylaxis. Susceptible individuals (unvaccinated or vaccinated in the past) may be vaccinated in 2022 at a rate $\square_{5\square}$. Exposed individuals (unvaccinated or vaccinated in the past) may be vaccinated in 2022 at a rate $\square_{6\square}$. The vaccination rates $\square_{5\square}$ and $\square_{6\square}$ depend on the activity group E. We assumed that the protection of the new vaccine (against infection and disease) is higher than that from the old vaccine (Table 1). Both vaccine protections were modelled as a proportional reduction in the transmission rate.

Hospitalized cases may die due to mpox or recover and become immune ($4_{\square}$). All MSM entering the sexually active population in 2022 are unvaccinated and susceptible to MPXV.

Model equations

The model is described by the system of ordinary differential equations shown below. The subscript $\square$ denotes unvaccinated individuals, R denotes individuals vaccinated in the past (with the old vaccine), L denotes individuals vaccinated in 2022 (with the new vaccine), and $E = 1,2,\dots,\square$ denotes the Eth sexual activity group.

Equations for unvaccinated individuals:

$$\frac{\square 5_{\square}}{P\square} = \square(\square_{\square} + \square_{\square\square} + \square)\square_{\square} + \square\square_{\square}$$

[illegible]

[illegible]

[illegible]

Equations for individuals vaccinated in the past:

[illegible]

[illegible]

[illegible]

[illegible]

Equations for individuals vaccinated in 2022:

[illegible]

[illegible]

[illegible]

[illegible]

Equations for recovered/immune and hospitalized individuals:

[illegible]

[illegible]

The parameters and variables in these equations are explained in the following sections and in Tables 1-3.

Transmission rate

The rate at which MSM in activity group [illegible] get infected with MPXV is [illegible], where [illegible] and [illegible] denote the rates of getting infected by main and casual partners, respectively:

- The rate of getting infected by main regular partners:

$$[\text{illegible}] [1 - (1 - [\text{illegible}])^{[\text{illegible}]}] \frac{[\text{illegible}] + [\text{illegible}]}{[\text{illegible}]}$$

- The rate of getting infected by casual partners:

$$[\text{illegible}] \frac{[\text{illegible}] + [\text{illegible}]}{[\text{illegible}]}$$

In these equations, the following notation is used:

- [illegible] is the fraction of MSM of activity group [illegible] with a main regular partner.
- [illegible] is the frequency of sex contacts between main sexual partners of activity groups [illegible], calculated as [illegible] = ([illegible] + [illegible])/2, from the contact frequency [illegible] and [illegible] of sexual activity groups [illegible] and [illegible], respectively.
- [illegible] is the probability of transmission of MPXV per sexual/intimate contact from an infectious individual who is unvaccinated ([illegible]), vaccinated in the past ([illegible]), or vaccinated in 2022 ([illegible]), with [illegible], [illegible], [illegible]. The probability [illegible] of transmission per sexual contact with an unvaccinated individual is reduced by [illegible] for those who were vaccinated in the past and by [illegible] for those vaccinated in 2022.
- [illegible] is a factor reducing the transmission potential of an infectious individual practicing sexual abstinence compared to infectious individuals not in abstinence.
- [illegible] is the number of casual sex contacts per day for men in activity group [illegible].
- [illegible] is the total size of activity group [illegible] and [illegible] is the total size of the MSM population.
- [illegible] and [illegible] are parameters that define the level of mixing between sexual activity groups [illegible] when forming main and casual partnerships, respectively. These are defined by the equations:

[illegible] and [illegible],

where [illegible] is the Kronecker delta (being equal to 1, if [illegible] = [illegible] and equal to 0, otherwise) and the parameters [illegible], [illegible] determine the level of assortativeness in mixing of activity groups when forming main and casual partnerships, respectively (if [illegible] = 1, then mixing is assortative; if [illegible] = 0, then mixing is proportionate).

The size of the MSM population

Estimates of the size of the MSM population vary from 111,072 [4] to 392,000 [5]. The variation depends mostly on the ages included in the estimate (for instance, from 15 or 17 years old; up to 65 or 69 years old) and the definition of MSM (men who had sex with men in the previous six/twelve months; or ever having sex with men; or identifying themselves as homosexual/bisexual). Based on the size of the male population [2] and prevalence estimates of same-sex behaviour [5], we assumed that the number of MSM in 2022 was around 250,000. Due to uncertainty about this estimate, we repeated the analyses with 200,000 MSM and 300,000 MSM.

Adaptations that may have occurred in the first three months of the outbreak

By ordering diagnosed mpox cases according to date of symptom onset, the peak was between 6 and 10 July 2022. The first diagnosis of mpox was on 20 May 2022. By the beginning of June, the number of diagnoses was increasing and there were messages about mpox in the news, social media, and MSM websites [6-9]. This has probably enhanced awareness among MSM and health care practitioners, enabling earlier recognition of mpox symptoms, even during the prodromal phase with systemic symptoms like fever, fatigue, and ache. In an online survey carried out in August 2022, most MSM responded correctly to questions about symptomatology and routes of transmission of mpox and reported to be willing to refrain from close physical and sexual contacts if they were infected with MPXV [10]. As the severity of the outbreak was increasing, MSM were possibly more willing to refrain from sexual/intimate contacts when they suspected or were diagnosed with MPXV infection, thus reducing the time they were infectious and not yet refraining from sexual contacts. The spread of information about mpox and the severity of the outbreak may have also influenced the sexual behaviour of MSM. In the same survey, more than half of the participants reported a reduction in their sexual activity due to the mpox outbreak [10]. Furthermore, sex venues and parties reported low numbers of visitors in July 2022 [11], with the reduction reaching its maximum at the end of July, when some club owners observed up to 30% less visitors than what was expected (P. Zantkuijl, personal communication). This points to a decline in sexual activity of men visiting these accommodations.

Therefore, in this study, we examined two possible adaptations: (a) MSM may start refraining from sexual contacts earlier during the infectious period, thus resulting in shorter infectious period while not refraining from sexual contacts and (b) a reduction in the number of casual partners. The level and the timing of the adaptations was obtained from the fitting process. We examined two scenarios with adaptations either (a) at one time point t_2 in the period 5-15 July 2022 or (b) at two time points t_1 in the period 17-27 June 2022 and t_2 in the period 5-15 July 2022. These time periods were close to messages placed on ManTotMan socials and the announcement of the Dutch government on 7 July 2022 to start with the monkeypox vaccination programme.

We included a reduction δ_{4l} in the number of casual partners of men in the very high sexual activity group, δ_{3l} for men in the fairly high sexual activity group, and a reduction δ_{2l} for men in the very low and fairly low sexual activity groups. The reduction δ_{kl} occurred on day t_l = ? or t_l = ?. The six values δ_{kl} (k = 2,3,4 and l = 1,2) were sampled from the same range (0-30% reduction), since we are uncertain about the occurrence of the decline. Similarly, we sampled three values for the duration of the infectious period before refraining from sexual contacts: one for the duration in the beginning of the outbreak, a second value for the period between t_1 and t_2, and a third value for the period after t_2. All three values were sampled from the same range (2-8 days) since we were uncertain whether an adaptation in this duration occurred and when.

Model fitting

The model was fitted to data on the number of diagnosed mpox cases using a Bayesian approach. Parameters relating to sexual behaviour were estimated from data or obtained from the literature (Table 2), except from: (a) the two parameters for assortativeness in sexual mixing and (b) the number of casual partners of the group with a very high sexual activity level. These were included as uncertain parameters, due to lack of reliable data and because the model results were very sensitive to these parameters (based on our preliminary analyses). Further, most of the parameters relating to mpox were uncertain (Table 1) and were obtained via the fitting process.

The uncertain parameters were divided into two groups:

1. Parameters relating to behavioural adaptations that occurred in June/July 2022 (Table 3): adaptation in the number of casual partners; adaptation in the number of days that an individual is infectious and not in abstinence; and two parameters for the timing of these adaptations.
2. Main parameters (Table 1): all the other parameters, except those relating to the adaptations that occurred in June/July 2022.

The fitting process was carried out in two steps:

1. In the first step, we fitted the model to the numbers of daily mpox cases registered in the national database of notifiable infectious diseases of the Netherlands until 17 June or until 5 July 2022. We defined uniform prior distributions for the uncertain parameters (Tables 1). Using Latin Hypercube Sampling [12], we sampled 10,000 combinations of values from the prior distributions and repeated the model calculations with each parameter combination. From the model, we calculated the daily numbers of mpox cases with each parameter combination. We calculated the Poisson likelihood of the above numbers, thus obtaining the posterior distributions of the uncertain parameters (except those relating to the behavioural adaptations in June/July 2022), reflecting the situation in the beginning of the outbreak.
2. In the second step, we used the posterior distributions obtained from the first step of the fitting process and fitted the model to data from 17 June or 5 July 2022 until 25 July 2022. The modelled mpox cases were compared with the respective data with date of symptom onset in this time interval. We calculated their Poisson likelihood and obtained the posterior distributions of the uncertain parameters relating to behavioural adaptations that occurred in June/July 2022.

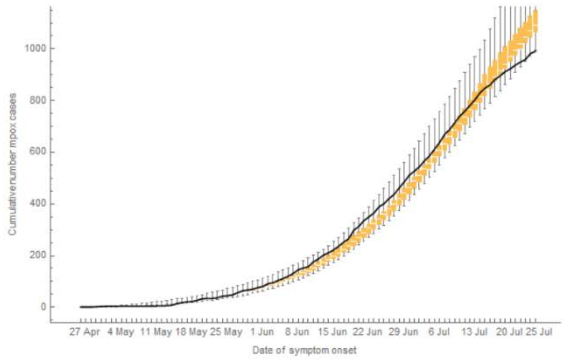
Data sources

The following data sources were used in this study.

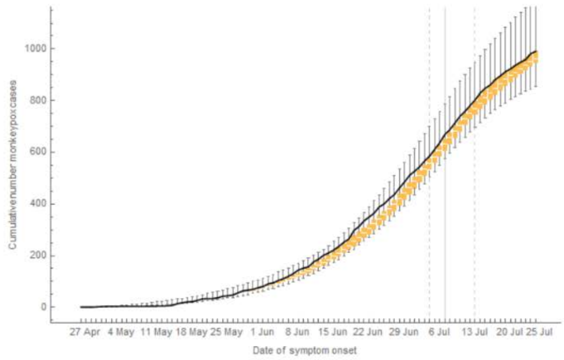
National surveillance system for notifiable diseases (OSIRIS): Individuals seeking mpox testing or presenting with symptoms suggestive of mpox to general practitioners or health centra were referred and notified to the regional public health service for mpox diagnostics [9]. Notification of confirmed mpox cases from regional public health services to the National Institute of Public Health and the Environment was accompanied by a questionnaire with demographical, clinical, and epidemiological information of cases. The numbers of confirmed mpox cases according to date of symptom onset were extracted from this database. These numbers were continuously updated during the outbreak and were available online on https://www.rivm.nl/mpox-apenpokken.

COVID-19, Sex, and Intimacy Survey: This is a repeated cross-sectional self-report survey. The first round of data collection was carried out from the end of July 2020 to the beginning of September 2020 [13, 14]. Participants were recruited via social media advertisement on Facebook and Instagram. People were eligible to participate if they: lived in the Netherlands, were 18 years or older, identified as male and ever had sex with a man. All participants provided informed consent and received no compensation. Only responses from eligible participants who fully completed the questionnaire were used for the analyses presented here. The aim of the survey was to investigate the impact of the COVID-19 pandemic on sexual behaviour. Therefore, respondents were asked to report on their sexual behaviour during the first half of 2020 and, as reference, their sexual behaviour during the last six months of 2019. In the present study, we used data only from the responses for the period July-December 2019. For these questions, 5,683 participants reported their sexual behaviour.

(a)



(b)



(c)

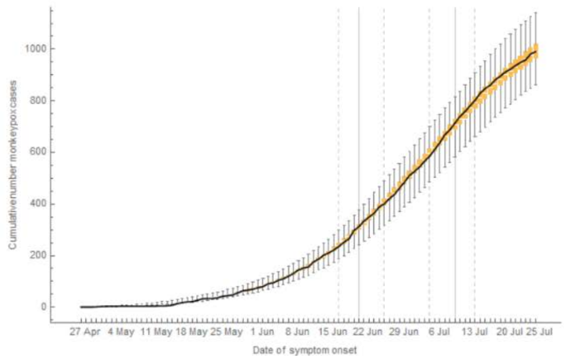


Figure S1. The cumulative number of mpox cases among MSM in the Netherlands from 27 April to 25 July 2022. Cases are shown according to date of symptom onset (on horizontal axes). Solid black line shows data from 27 April to 25 July 2022, from the national database of notifiable infectious diseases of the Netherlands. Orange box-plots show the medians and interquartile ranges obtained from the model in a population of 250,000 MSM (a) without behavioural adaptations; (b) with behavioural adaptations only in July 2022; (c) with behavioural adaptations in June and in July 2022. In (b)-(c), the vertical grey lines show the medians (solid line) and the 95% credible intervals (dashed lines) of the time point at which the adaptations occurred, as obtained from the model fitting.

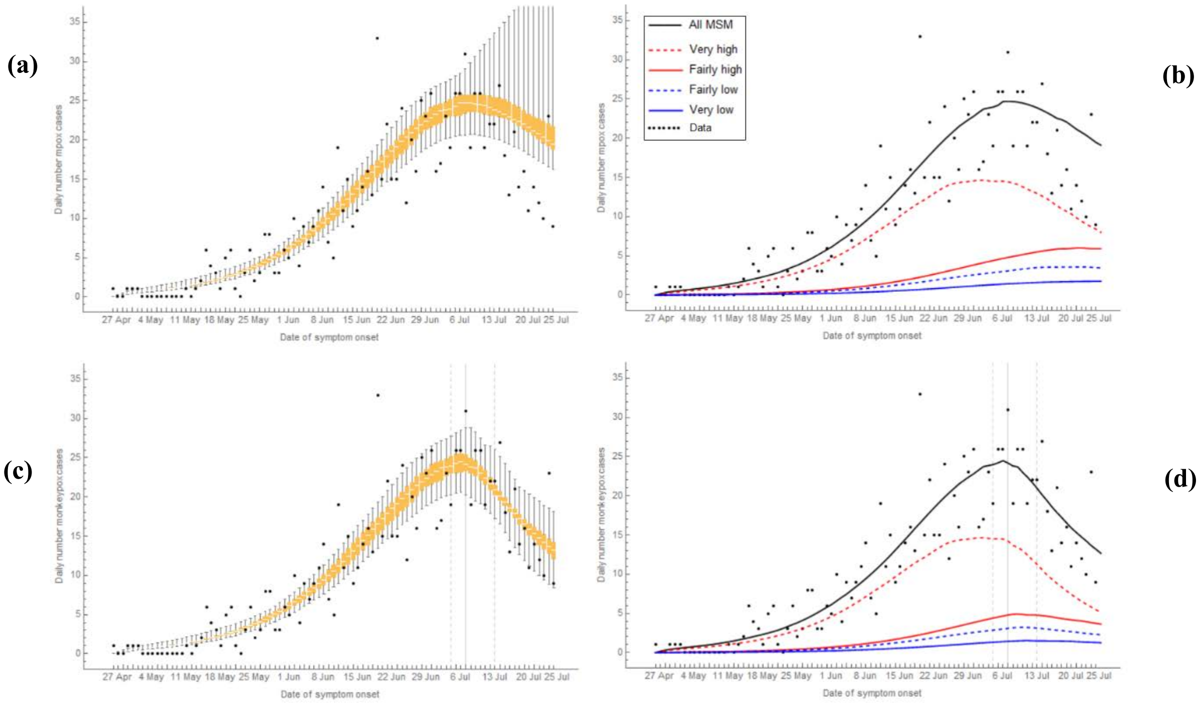


Figure S2. The daily number of mpox cases among MSM in the Netherlands from 27 April to 25 July 2022. Black bullets show data from the national database of notifiable diseases of the Netherlands; the other lines were calculated from the model. Mpox cases are shown according to date of symptom onset. Left panels: box-plots of daily number of mpox cases in the overall MSM population. Right panels: median daily number of mpox cases in the overall MSM population (black line), in the groups with high sexual activity level (red lines), and in the groups with low sexual activity level (blue lines). (a), (b): without behavioural adaptations; (c), (d): with behavioural adaptations in July 2022. Vertical grey lines show median (solid line) and 95% credible interval (dashed lines) of the day at which the behavioural adaptations occurred, as obtained from the model fitting. Model results were calculated in a population of 200,000 MSM.

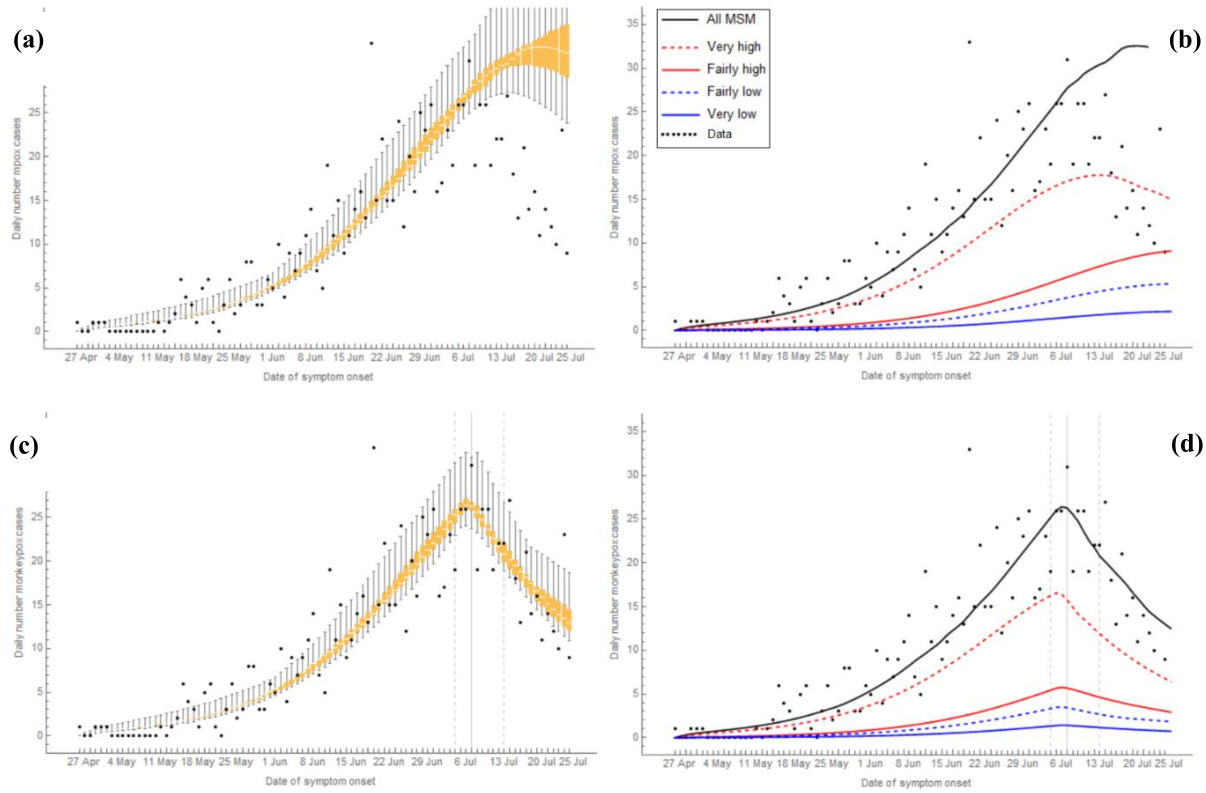


Figure S3. The daily number of mpox cases among MSM in the Netherlands from 27 April to 25 July 2022. Black bullets show data from the national database of notifiable diseases of the Netherlands; the other lines were calculated from the model. Mpox cases are shown according to date of symptom onset. Left panels: box-plots of daily number of mpox cases in the overall MSM population. Right panels: median daily number of mpox cases in the overall MSM population (black line), in the groups with high sexual activity level (red lines), and in the groups with low sexual activity level (blue lines). (a), (b): without behavioural adaptations; (c), (d): with behavioural adaptations in July 2022. Vertical grey lines show median (solid line) and 95% credible interval (dashed lines) of the day at which the behavioural adaptations occurred, as obtained from the model fitting. Model results were calculated in a population of 300,000 MSM.

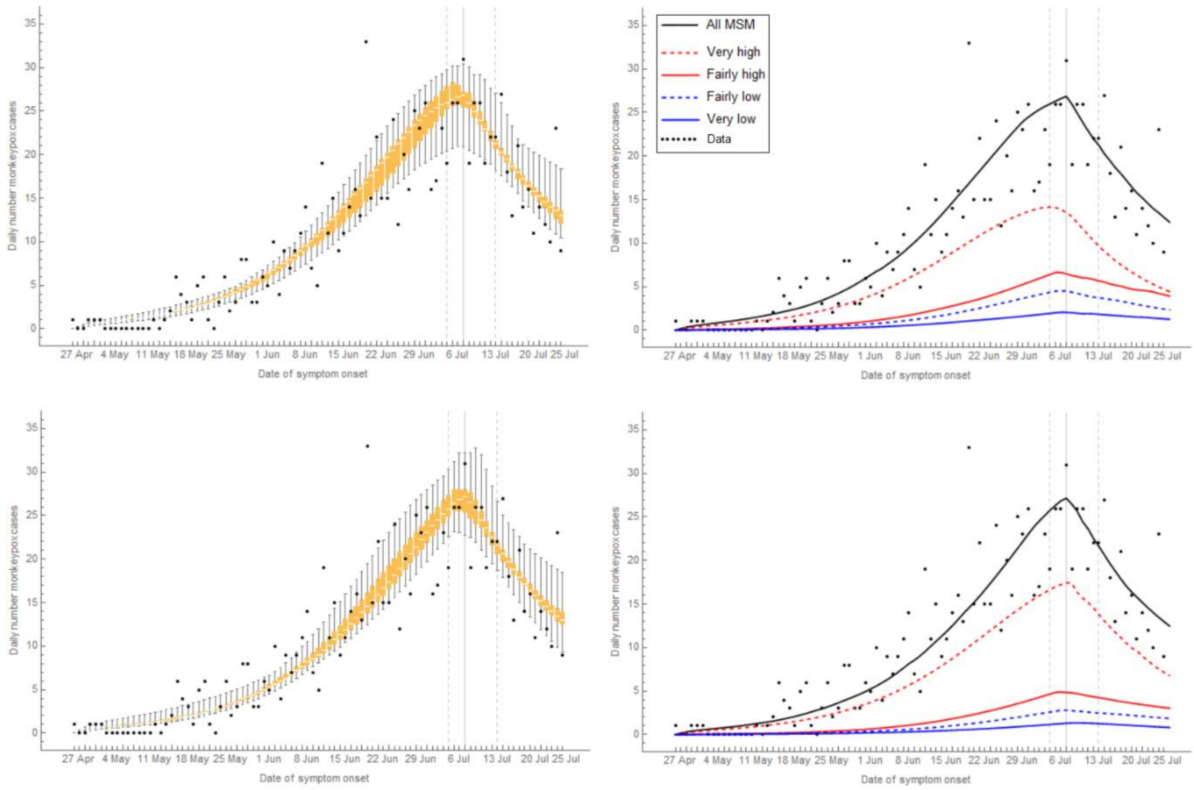


Figure S4. Sensitivity analyses for the percentage of the population being vaccinated in the past (before 1974), via the old smallpox vaccination programme. Two scenarios are shown, with behavioural adaptations in July 2022, in a population of 250,000 MSM, of whom 25% in total had been vaccinated in the past. Top panels: the percentage vaccinated in the past was the highest in the group with the highest level of sexual activity: 23%, 25%, 30%, 40% vaccinated in the group with very low, fairly low, fairly high, or very high level of sexual activity, respectively. Bottom panels: the percentage vaccinated in the past was the highest in the group with the lowest level of sexual activity: 29%, 25%, 15%, 10% vaccinated in the group with very low, fairly low, fairly high, or very high level of sexual activity, respectively. Numbers shown are the daily numbers of mpox cases among MSM in the Netherlands from 27 April to 25 July 2022, from the data (black bullets) and from the model (orange box plots and lines) – the plots are as explained in Figure S3.

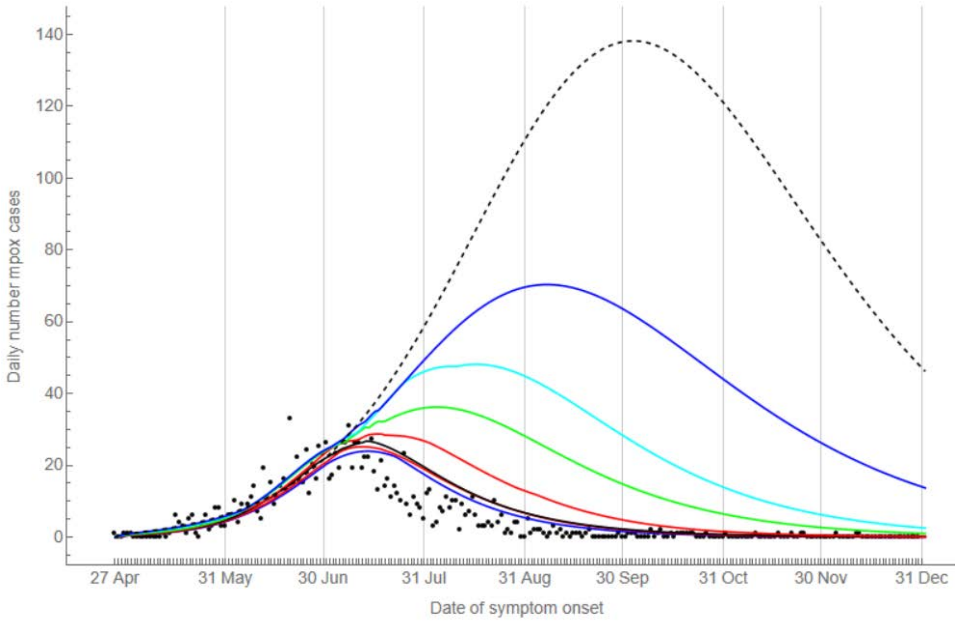


Figure S5. The daily number of mpox cases among MSM in the Netherlands from 27 April to 31 December 2022, in the scenario without behavioural adaptations. Black bullets show data from the national database of notifiable diseases of the Netherlands, as shown in Figure 4a in the main text. The lines were calculated from the model. Mpox cases are shown according to date of symptom onset. Black solid line: median; black dashed line: maximum; red lines: interquartile range; blue lines, 95% credible interval; cyan line, upper 5th percentile; green line, upper 10th percentile. Vertical grey lines show the last day of each calendar month. Model results were calculated in a population of 250,000 MSM.

Table S1. Posterior distributions of uncertain model parameters obtained from the fitting process for the two scenarios with adaptations in behaviour of MSM only in July 2022 or in June and July 2022. Results shown are the medians and 95% credible intervals, in a population of 250,000 MSM.

	Adaptations only in July 2022			**Adaptations in June & July 2022**		
	Median	**95% range**		**Median**	**95% range**	
Latent period, days (1/)	5.67	5.03	6.97	5.80	5.10	7.81
Infectious period (1/ +1/)	16.75	14.27	24.07	18.41	14.26	24.46
Transmission probability per sex act	0.48	0.39	0.81	0.48	0.39	0.67
Number casual partners per day, very-high activity group	0.89	0.73	1.00	0.90	0.73	1.00
Factor reducing transmission when in abstinence ( )	19%	15%	37%	22%	16%	46%
Assortativeness mixing with main partners ( )	0.72	0.13	0.88	0.69	0.12	0.85
Assortativeness mixing with casual partners ( )	0.87	0.20	0.90	0.84	0.48	0.90
Vaccination rate before 25 July 2022	0.04%	0.03%	0.05%	0.04%	0.03%	0.05%
Efficacy old vaccine (=)	56%	52%	65%	58%	50%	63%
Efficacy new vaccine (=)	85%	80%	90%	85%	80%	89%
Hospitalization rate,	1%	1%	2%	2%	1%	2%
Days infectious not refraining from sex, before	6.05	4.45	7.80	6.89	3.74	7.78
Days infectious not refraining from sex, between and	As before			5.60	2.94	7.83
Days infectious not refraining from sex, after	2.55	2.00	4.31	2.44	2.02	4.87
Date of adaptations in June,	Not applicable			21-6-2022	17-6-2022	26-6-2022
Date of adaptations in July,	7-7-2022	5-7-2022	11-7-2022	10-7-2022	5-7-2022	14-7-2022
% reduction casual partners, low activity groups, after	13%	1%	28%	13%	0%	28%
% reduction casual partners, fairly-high activity group, after	15%	1%	29%	18%	3%	29%
% reduction casual partners, very-high activity group, after	24%	1%	30%	22%	4%	30%
% reduction casual partners, low activity groups, between and	Not applicable			17%	2%	29%
% reduction casual partners, fairly-high activity group, between and				16%	1%	29%
% reduction casual partners, very-high activity group, between and				18%	1%	29%

Table S2. Posterior distributions of uncertain model parameters obtained from the fitting process for the scenario with adaptations in behaviour of MSM only in July 2022. Results shown are the medians and 95% credible intervals, in a population of 200,000 or 300,000 MSM.

	200,000 MSM			**300,000 MSM**		
	Median	**95% range**		**Median**	**95% range**	
Latent period, days (1/)	5.51	5.04	7.77	5.67	5.04	7.74
Infectious period (1/ +1/)	18.41	14.51	26.75	15.54	14.22	25.88
Transmission probability per sex act	0.50	0.39	0.66	0.49	0.45	0.81
Number casual partners per day, very-high activity group	0.91	0.72	1.00	0.90	0.72	0.98
Factor reducing transmission when in abstinence ( )	23%	17%	60%	20%	15%	30%
Assortativeness mixing with main partners ( )	0.72	0.31	0.87	0.75	0.14	0.88
Assortativeness mixing with casual partners ( )	0.85	0.66	0.89	0.75	0.20	0.89
Vaccination rate before 25 July 2022	0.04%	0.03%	0.05%	0.04%	0.03%	0.05%
Efficacy old vaccine (=)	57%	50%	65%	56%	51%	65%
Efficacy new vaccine (=)	85%	80%	90%	82%	80%	90%
Hospitalization rate,	2%	1%	2%	2%	1%	2%
Days infectious not refraining from sex, before	6.20	2.73	7.87	5.82	4.62	7.98
Days infectious not refraining from sex, after	2.80	2.02	6.60	2.24	2.02	2.80
Date of adaptations in July,	8-7-2022	5-7-2022	14-7-2022	6-7-2022	5-7-2022	9-7-2022
% reduction casual partners, low activity groups, after	13%	0%	29%	11%	0%	28%
% reduction casual partners, fairly-high activity group, after	17%	1%	29%	14%	1%	29%
% reduction casual partners, very-high activity group, after	22%	2%	29%	22%	2%	29%

Table S3. Sensitivity analysis for the percentage of MSM vaccinated in the past via the old smallpox vaccination programme. Posterior distributions of uncertain model parameters obtained from the fitting process for the scenario with adaptations in behaviour of MSM only in July 2022. Results shown are the medians and 95% credible intervals, in a population of 250,000 MSM.

	Higher % vaccinated in group with highest level of sexual activity*			Higher % vaccinated in group with lowest level of sexual activity**		
	Median	95% range		Median	95% range	
Latent period, days (1/)	5.67	5.11	6.76	5.53	5.02	6.92
Infectious period (1/ +1/)	16.08	14.48	26.54	17.61	14.48	26.61
Transmission probability per sex act	0.60	0.47	0.80	0.42	0.32	0.68
Number casual partners per day, very-high activity group	0.90	0.73	0.98	0.85	0.73	0.99
Factor reducing transmission when in abstinence ( )	21%	16%	41%	20%	16%	37%
Assortativeness mixing with main partners ( )	0.75	0.21	0.90	0.67	0.10	0.88
Assortativeness mixing with casual partners ( )	0.79	0.27	0.90	0.82	0.33	0.90
Vaccination rate before 25 July 2022	0.04%	0.03%	0.05%	0.04%	0.03%	0.05%
Efficacy old vaccine (=)	59%	50%	65%	55%	51%	64%
Efficacy new vaccine (=)	84%	81%	89%	82%	80%	90%
Hospitalization rate,	2%	1%	2%	2%	1%	2%
Days infectious not refraining from sex, before	6.31	4.25	7.82	6.68	3.80	7.98
Days infectious not refraining from sex, after	2.41	2.08	4.36	2.36	2.01	4.24
Date of adaptations in July,	6-7-2022	5-7-2022	11-7-2022	6-7-2022	5-7-2022	10-7-2022
% reduction casual partners, low activity groups, after	16%	2%	29%	12%	1%	29%
% reduction casual partners, fairly-high activity group, after	20%	1%	30%	16%	3%	28%
% reduction casual partners, very-high activity group, after	23%	4%	29%	26%	5%	30%

* The percentage vaccinated in the past in the group with very low, fairly low, fairly high, or very high level of sexual activity was 23%, 25%, 30%, 40%, respectively. This results in a total of 25% being vaccinated in the total MSM population.

** The percentage vaccinated in the past in the group with very low, fairly low, fairly high, or very high level of sexual activity was 29%, 25%, 15%, 10%, respectively. This results in a total of 25% being vaccinated in the total MSM population.

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