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The role of vaccination and public awareness in forecasts of monkeypox incidence in the United Kingdom

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Abstract

Since May 2022, monkeypox virus (MPXV) has spread rapidly in high-income countries through close human-to-human contact primarily amongst communities of gay, bisexual and men who have sex with men (GBMSM). Behavioural change arising from increased knowledge and health warnings may have reduced the rate of transmission and Vaccinia-based vaccination is likely to be an effective longer-term intervention. We investigate the UK epidemic presenting 26-week projections using a stochastic discrete-population transmission model which includes GBMSM status, rate of formation of new sexual partnerships, and clique partitioning of the population. We find that MPXV cases peaked in mid-July, declining due to decreased

transmission rate per infected individual and infection-induced immunity among GBMSM, especially those with the highest rate of new partners. We predict cases will remain low from October 2022 to March 2023 (20-65 cases a week), and a rebound in cases due to behaviour reversion prevented by high-risk group-targeted vaccination.

Keywords: Monkeypox, Transmission modelling, Vaccinia-based vaccine

1 Introduction

The current global outbreak of monkeypox virus (MPXV) has its origins in sporadic cases reported in Nigeria from 2017 [1]. Since May 2022 there has been sustained incidence of monkeypox virus (MPXV) in European and North American countries, leading to a WHO declaration of a public health emergency of international concern on 23rd July 2022 [2]. Cases in Europe and North America have been predominantly in gay and bisexual men who have sex with men (GBMSM), with those who have greater numbers of sexual partners being more likely to be infected [3]. Vaccines developed to target smallpox have been shown to have reasonable (short-term) efficacy against MPXV-induced disease [4–6], and many countries have offered pre-exposure prophylactic vaccination targeted at higher-risk GBMSM individuals to control infection [7]. Towards this goal the UK Health Security Agency (UKHSA) and the Joint Committee on Vaccination and Immunisation (JCVI) have recommended the use of the Modified Vaccinia Ankara (MVA) smallpox vaccine Imvanex (called Jynneos in the USA) for monkeypox at-risk groups in the UK [8].

Monkeypox predominantly spreads from person-to-person through prolonged physical contact with the infectious rash, scabs and/or fluids of infected individuals [9]. Traditionally, MPXV incidence has been sporadically observed in sub-Saharan Africa following zoonotic spread from wildlife reservoirs, with uncommon person-to-person transmission being associated with household cohabitation [5]. However, as mass smallpox immunisation campaigns have declined, and the resultant background immunity to MPXV has waned, there has been a substantial increase in monkeypox incidence in some sub-Saharan African countries [10, 11].

In the recent outbreaks in Europe and North America, the epidemiology of MPXV has been skewed towards a higher case frequency among GBMSM compared to non-GBMSM groups. This is in contrast to the traditional epidemiology of MPXV described in sub-Saharan Africa, and it is likely that MPXV has found a niche in high income countries (HICs) among individuals with high frequencies of close physical contact. It also suggests that public awareness of monkeypox symptoms could be effective in limiting the overall impact of MPXV by reducing onward transmission during the symptomatic phase of infection [12]. Early epidemiological modelling of the transmission potential of MPXV in HICs has identified the potential for MPXV to spread

among sexual contact networks due to the comparatively small number of individuals with highly frequent sexual encounters, with the distribution of the number of encounters best described by a heavy-tailed distribution [3, 13]. This early concern has been confirmed, while initial modelling of MPXV without a focus on sexual contact networks has been proven over-optimistic in terms of total case load [14].

In this simulation study, we use a bespoke MPXV transmission model calibrated to the social structure and demography of the United Kingdom, as well as the epidemiology of monkeypox infections, to make projections of future incidence over a medium-term time horizon (26 weeks ahead). We use a Bayesian method to make model parameter inference from the UKHSA linelist of identified monkeypox cases in the UK (see *Methods* and *Supporting information*) as well as validating the model's sequential accuracy against redacted case data (see *Supporting information*). The proportion of reported MPXV cases among GBMSM is important in this modelling approach; where this data was missing from the linelist we used a gradient boosted decision tree (GBDT) trained using the metadata of MPXV cases with known GBMSM status to assign a GBMSM status probability (see *Supporting information*).

The MPXV transmission model is capable of exploring a range of scenarios, although here we focus on the potential impacts of vaccinating the most at-risk GBMSM and the reduction in transmission due to self-imposed reductions in physical contacts whilst having symptoms. This approach allows us to address a number of scientifically interesting challenges with clear public health outcomes. First, to quantify the likely transmission potential of MPXV among GBMSM and non-GBMSM groups in the United Kingdom. Second, to estimate the changes in effective transmissibility over time and the associated impact on the infection dynamics. Third, to assess the benefit of the vaccination campaign in reducing cases of MPXV. Finally, to make medium-term projections of MPXV case rates given that behaviour will likely return to a pre-outbreak baseline over the coming months.

2 Results

We ran Bayesian inference for the parameters in our MPXV transmission model (see *Methods*) and used the posterior parameter draws to generate model-based trajectories of cases for comparison to actual case data, to make counterfactual projections and to forecast likely future case trends over a medium-term period (26 weeks ahead).

Comparing model trajectories of case incidence generated from our posterior distribution with the inferred GBMSM and non-GBMSM case data until the end of September 2022 reveals a good agreement with case data from both populations (Fig. 1). However, the model predictions tend to be over-dispersed since nearly all data points fall within the 80% prediction interval (PI); this interval contains 80% of all simulations at each time point and captures both stochastic transmission dynamics and parameter uncertainty. This suggests

that the tails of the prediction envelope are too large, and therefore, in the following, for quantities involving multiple inferred parameters or simulations tighter 80% credible intervals (CI) or prediction intervals (PI) are presented as the scale of uncertainty in our forecasts.

2.1 Transmission potential of monkeypox in the United Kingdom

We infer that the on-going high ratio of GBMSM cases compared to non-GBMSM cases observed in the UK is due to MPXV having a low transmission potential outside high-frequency sexual contact groups. On 1st May, before any behaviour change, the basic reproduction number (R_0) for other (non-sexual) transmission pathways was estimated to be 0.155, (0.045-0.294; 95%CI) hence we expect infection to decline in the absence of spill-over from the high sexual activity GBMSM group. In contrast, the basic reproduction number due to sexual contacts in the GBMSM population was estimated at 6.91 (3.86-10.47; 80%CI, see *supporting information A.1* for reproductive ratio and predicted case distribution details), which is composed of a 36.6% (14.1-61.9%; 95%CI) transmission risk per sexual contact, a power-law distribution for the number of partners over time (see *Methods*), and an effective average infectious period of 10.4 days (3.74-19.0; 95%CI) (Table A1 and Fig. A2 detail inferred values for all parameters). These parameters suggest that the average number of secondary cases will be greater than one for any individuals who typically have two or more sexual contacts per week. We note that our inferred effective infectious period is shorter than typically reported from clinical observation (2-4 weeks [9, 15]), which we interpret as a shortening of the generation time of MPXV due to transmission being less likely to occur once severe symptoms manifest. The overall reproduction number for all MPXV transmission pathways on 1st May was estimated as 6.91 (3.86-9.96; 80%CI); extremely close to the reproductive number due to only sexual contacts in the GBMSM population.

In our inference of underlying clique sizes that form the metapopulation structure for GBMSM sexual partnerships (see *Methods*), we find that several large subpopulations are preferred, with the largest accounting for more than 10% of the population and the largest ten subpopulations containing the majority of individuals; as such there is limited inferred population structure with the majority of the GBMSM population being well connected (see *supporting information 4.2* and Fig. A3).

2.2 Behaviour change and reduced transmission risk of monkeypox in the United Kingdom

We find significant evidence that the risk associated with both sexual and non-sexual transmission pathways decreased over June and July 2022. Immediately before the WHO declaration of a public health emergency of international concern on 23rd July 2022, we estimate that the reproductive number for both sexual transmission within the GBMSM community and all other transmission

pathways had decreased by approximately 50-60% (Fig. 1): GBMSM $R_0 = 3.20$ (1.72-4.68; 80%CI) and other transmission pathways $R_0 = 0.063$ (0.020-0.106; 80%CI). Immediately after the WHO declaration our posterior mean prediction was for a further decrease in these reproductive numbers: GBMSM $R_0 = 2.30$ (1.13-3.47; 80%CI) and other transmission pathways $R_0 = 0.048$ (0.011-0.086; 80%CI; Fig. 1).

We interpret the decreased transmission potential of MPXV over this period as being due to greater public awareness of monkeypox disease, such that higher-risk physical contacts that would normally have occurred were avoided in May-July 2022 by individuals with MPXV symptoms (from a modelling perspective, this can be captured by maintaining the network structure of sexual contacts but reducing the transmission risk to account for some of these contacts no-longer occurring). The level of transmission within the high-risk GBMSM groups has been further limited by immunisation, providing 70-85% protection against infection [16]. In the UK, the first person believed to be at high risk of MPXV exposure volunteered for a dose of the Imvanex/Jynneos vaccine on 16th/17th July, with current estimates suggesting 5,000 doses per week were offered in London throughout August [16]. This is slightly later than the observed peak in MPXV cases in the United Kingdom (11th July 2022); therefore, the evidence points towards diminishing risk of transmission due to behavioural change as the cause of declining MPXV cases rather than the vaccination programme.

2.3 Nowcasting monkeypox exposure and medium-term projections under behaviour reversion and continued monkeypox vaccination

Sequential projections made during the UK outbreak (Fig A4), show that very early projections (formulated in late May) accurately captured the mean peak height but were extremely uncertain, while later projections (late June and July) overestimated the peak. It is not until August and September that projections could be confident that we were past the immediate peak. All projections before or at the peak predicted peak timing to within 4 weeks accuracy (see *supporting information A4*).

We predict that MPXV case incidence among GBMSM peaked during the week starting 11th July 2022 with an expected 340 cases that week (134-524; 80%PI); this compares reasonably with the observed peak in inferred GBMSM cases of 407 in that week. In non-GBMSM we predict a peak of 27.3 cases (6.0-53.1; 80%PI), again in the week starting 11th July 2022; the observed number of cases in that week was inferred to be 24, although the true peak occurred some weeks later (Fig. 1).

Cases and our model projections of incidence have continued to decline throughout August and September 2022, albeit with higher relative volatility in inferred non-GBMSM cases. By October 2022, our model assigns a high probability (> 90%) to at least 10% of those GBMSM individuals with a high number of new monthly partners (> 20 per month) having been infected with

monkeypox. The proportion of GBMSM who have been infected with MPXV increases with their rate of new partnerships, such that we project that the majority of GBMSM with a very high numbers of monthly partners (> 39 per month) will already have been infected (Fig. 2). However, such high-risk individuals only constitute a small proportion of the population, such that by 1st October we expect only 1.95% of GBMSM (0.395-4.1%; 80%PI) and just 0.0028% of non-GBMSM (0.000349-0.00472%; 80%PI) to have been infected - further illustrating the highly skewed nature of MPX transmission in the UK.

Projecting the dynamics forward 26 weeks, from October 2022 to late-March 2023 requires making assumptions about the long-term behaviour of the population. We expect an eventual return to pre-outbreak mixing and behaviour, as awareness and attention declines; and we consider this reversion over two different time scales (black and orange lines in Fig. 1). A more prompt reversion (orange) is predicted to lead to a slight rise in cases in the GBMSM population, but a relatively larger rise in the non-GBMSM population where immunity (through infection or vaccination) is far less. A slower reversion (black) generates a far smaller secondary peak, but cases are still expected to persist (at > 25 per week) across the entire simulated time-scale. By late-March 2023, if reversion to normal behaviour occurs over 12 weeks (black curves), we project a cumulative number of 4,700 MPXV cases among GBMSM (3,951-5,991 %80PI) and 448 MPXV cases among non-GBMSM (310-666 80%PI). If reversion to normal behaviour happens faster (over 4 weeks, orange curves) then our projection of cumulative MPXV cases is slightly higher: 5,348 MPXV cases among GBMSM (3,977-7,668 %80PI) and 600 MPXV cases among non-GBMSM (323-1,043 80%PI; Fig.2).

As a counterfactual, we also investigated the dynamics if vaccination had not been deployed (dashed lines in Fig 1). This highlights how the decline in cases is primarily attributable to the change in behaviour, with the no-vaccination projections only significantly departing from the observations in September 2022. However, without the protection offered by vaccination the reversion in behaviour leads to substantial second waves of infection and cases, especially compared to the first wave in the non-GBMSM (Fig. 1, dashed lines). By the end of March 2023 this no-vaccine counterfactual generates far more cases: reaching 8,859 (4,053-17,164 80%PI) for 12 week reversion and 10,222 (4,133-19,470; 80%PI) for 4 week reversion in the GBMSM groups, and 1,156 (333-2,600; 80%PI) for 12 week reversion and 1,531 (370-3,345; 80%PI) among non-GBMSM (Fig. 2). Given we have optimistically assumed that the vaccine has been offered to those GBMSM most at risk, which we define as those having typically more than 1 new sexual partner per month, the solid lines represent a lower bound on future waves while the dashed lines represent upper bounds when the vaccine is taken up by lower risk groups and therefore is less effective. As a final counterfactual, we considered an uncontrolled outbreak without vaccination or behaviour change; this is predicted to generate around 16,400 cases by end of March 2023 (of which 83% are in the GBMSM population),

with around 11,000 cases already observed by the beginning of October 2023, nearly three times higher than has been observed to date (Fig. 2).

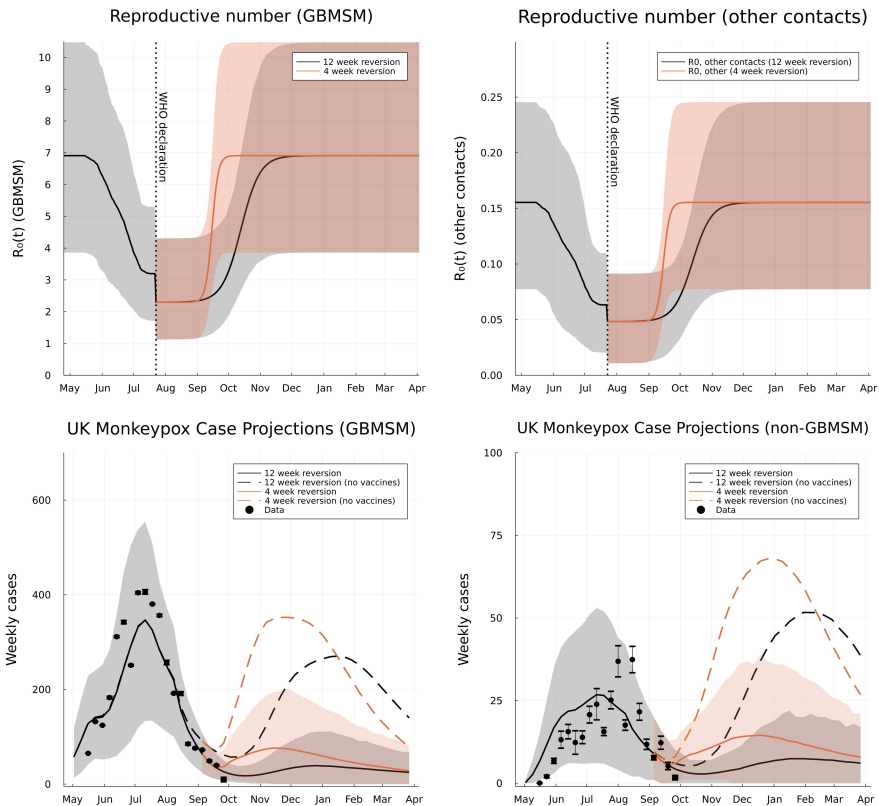


Fig. 1 Reproductive numbers and model-based case projections. *Top row:* Inferred basic reproductive numbers for transmission via sexual partnership among GBMSM people (*Top left*) and all other transmission pathways (*Top Right*) over time. Reversion towards baseline behaviour begins on 1st September and reaches 99% of pre-outbreak behaviour either 4 weeks (*orange curve*) or 12 weeks (*black curve*). The reproductive numbers shown are basic rather than instantaneous; they do not account for population immunity. *Bottom row:* Weekly monkeypox confirmed case data from UKHSA listint with inferred GBMSM status (black markers; GBMSM left, non-GBMSM right). The last week of available data (black squares) was not used in inference. Error bars on data points indicate 95% confidence intervals for GBMSM status inference. The posterior mean over model projections are shown for 4 weeks reversion and 12 weeks reversion to baseline behaviour (solid lines). The posterior mean model projections for the counterfactual scenario where vaccines are either absent or ineffective generate substantial secondary peaks (dashed curves). Background shading indicates 80% credible or prediction intervals; intervals for the counterfactual results are omitted for clarity.

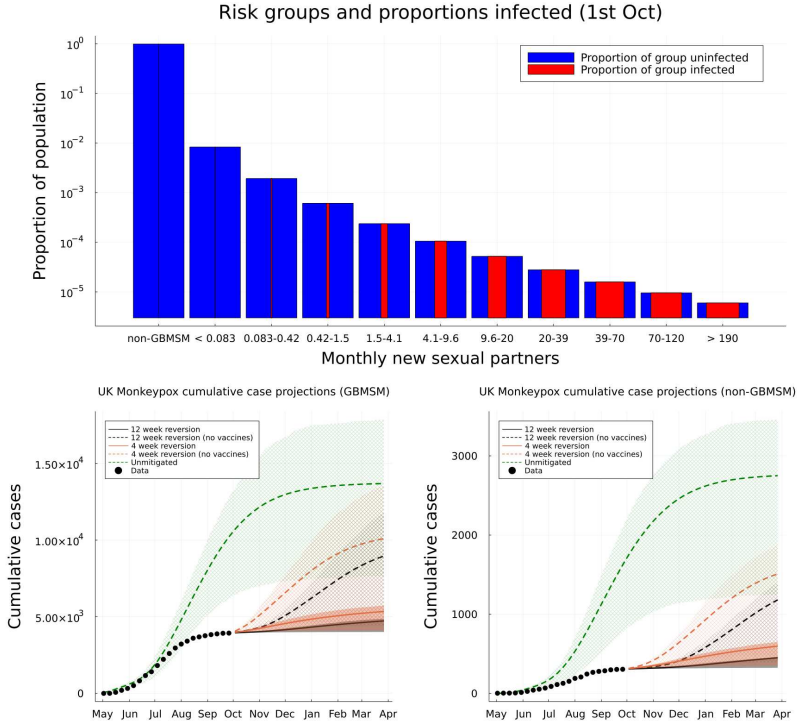


Fig. 2 Population exposure and medium-term cumulative case projections. *Top:* The proportion of the whole UK population in each risk group: non-GBMSM and 10 GBMSM sexual activity groups (bars). The posterior mean of proportion in each risk group uninfected (blue) and infected (red) by 1st October 2022 is shown as proportion shaded in each bar. *Bottom row:* Posterior mean model projections of cumulative cases among GBMSM (*left*) and non-GBMSM (*right*) for 4-week (orange) or 12-week (black) reversion to baseline behaviour. Also shown are counterfactual results without vaccination but with behaviour change (dashed orange and black), and without either vaccination or behavioural change (dashed green). Shaded and cross-hatched regions show the 80% prediction intervals associated with each curve.

3 Discussion

We have developed a novel, stochastic, discrete population model to enhance understanding and make projections of MPX incidence in the UK. The epidemiology of MPX in the UK suggests an individual-based network modelling approach would also be applicable, but this more computationally intensive methodology would mean it is challenging to make rapid inference against the continually evolving data. Our relatively simple model aimed to capture much of the essential features of a transmission network, in particular differential behaviour, whilst being feasible to fit and re-fit to available data streams, hence providing a rapid projection tool generating results of immediate benefit to policy advisors. We allow our population to be sub-divided, using a metapopulation framework to capture the partitioning of network into

different cliques [17]. This metapopulation partitioning is inferred from the observed case dynamics (see *Methods*), and is sufficiently flexible to account for additional spatial or social structure; although our inference favours a well connected social structure for GBMSM partnerships.

Our investigation leads us to believe that the rate of monkeypox case incidence peaked and subsequently turned over in mid-July, due to behaviour change decreasing the transmission potential from people infected with monkeypox. This is supported by two factors: i) very few vaccine doses had been deployed by mid-July and ii) we infer insufficient population immunity from natural infection curtail the monkeypox outbreak in less than 3 months without a decrease in the fundamental reproductive number. The model-based inference on the epidemic trajectory suggests that transmission potential per infected person (either GBMSM/non-GBMSM) decreased significantly (by approximately 50%) since start of the outbreak, which we interpret as the effect of public awareness of the threat of MPX and its symptomatic identifiability.

We predict that a mixture of vaccination and an already fairly high population exposure among the small number of people in the most sexually active groups by October 2022 will limit the size of the epidemic going forwards. We expect that behaviour changes that decreased the transmission potential of monkeypox will revert towards a pre-outbreak baseline over the coming months, although predicting the speed of such behaviour change is difficult [18]. If this behavioural reversion is rapid (e.g. over 4 weeks) then it is likely that there will be a moderate resurgence in monkeypox cases in the United Kingdom, however, we expect that this resurgent wave will be much smaller than the wave that peaked in mid-July.

Our expectation that the transmission potential of people infected with monkeypox will increase over the coming months as behaviour reverts towards a pre-outbreak baseline underlines the likely importance of the Imvanex vaccination campaign aimed at GBMSM people deemed at higher risk of MPXV and health care professionals. Our model-based analysis suggests that the vaccine doses given whilst transmission potential was comparatively low in August and September will contribute significantly to the population immunity of the most at-risk GBMSM people, and therefore, avoids a substantial second wave of MPXV incidence in the United Kingdom. In the scenario used in this modelling study (that is where Imvanex doses have been taken up efficiently by those GBMSM people having typically more than 1 new sexual partner a month) we projected that the vaccination campaign will roughly halve the number of cases up until the end of March 2023 compared to the alternative of no vaccines (or highly inefficient uptake of vaccines).

The relative simplicity of the model and gaps in the epidemiological data lead to limitations of our work. The delay between symptom onset, seeking treatment, case confirmation and reporting has changed over the course of outbreak; for example, symptom onsets across all of April were included in the first week of May reporting, which could influence our parameter inference. In mitigation we use a robust Bayesian inference method and note that the

longer delay in reporting occurred early in the outbreak when case numbers were small. This potential mismatch causes the model predictions to be more over-dispersed compared to the data, since nearly all data points are within the 80% prediction envelope of the model results. Additionally, it is not possible using this model to infer a changing trend in probability of detecting infected individuals, this model could erroneously attribute the effect of changing case detection rate to behavioural change - although given the severity of some symptoms we do not expect a major change in case detection.

The key public health conclusions from our analysis are: that the current case data suggest that monkeypox infection is unlikely to be sustained outside the GBMSM population (other transmission $R_0 \sim 0.15$) although sporadic cases may still occur; that public awareness of monkeypox and subsequent behaviour change has had a substantive impact on the monkeypox trajectory in the United Kingdom, although we expect this effect to dissipate over time; finally that the vaccine rollout is important to reduce the risk of monkeypox resurgence in the United Kingdom over the medium term. The low level of transmission we infer outside of the GBMSM population is consistent with empirical estimates suggesting low risk of infection following exposures in schools[19]. The longer-term dynamics are likely to be governed by the replenishment of susceptible individuals into the highly-active GBMSM population, the deployment of vaccine to such individuals and the level of imports from countries with higher incidence.

4 Methods

We simulated MPXV transmission in the United Kingdom as a dynamical process where the underlying population at risk was represented as integer sized and subdivided by GBMSM status, frequency of sexual activity, and into multiple, randomly-sized subpopulations. The daily dynamics of the spread of MPXV were encapsulated in a series of discrete events: transmission, incubation, and recovery, which were assumed to occur stochastically. Each week a sub-sample of individuals that had their symptom onsets the previous week are reported cases, which connects the underlying transmission model to the observable data.

The design philosophy of this MPXV transmission model was to:

1. Create a sufficiently parsimonious representation of the MPXV transmission structure that Bayesian posteriors for model parameters could be inferred within reasonable time with limited computational resources.
2. Capture the important features of heavy-tailed sexual contact networks, by sub-dividing the GBMSM population into sexual activity groups by their rate of forming new sexual partnerships.
3. Capture the effect of any additional population structure using a random sized metapopulation subdivision of the GBMSM population; metapopulation models being known to be reasonable approximations to more detailed individual based models [17].

The modelling approach in this paper is a hybrid of two well-known transmission model types. If there was only one metapopulation then the transmission model used here would be a random partnership model [20], whereas if there was only one sexual activity group then the transmission model used here would be a metapopulation model [21]. MPXV spread via other pathways than newly formed GBMSM sexual partnerships is modelled as a simple homogeneous transmission process.

4.1 Infectious episode progression model

We model the progression of MPXV infection as a SE_nIR compartmental epidemic model [20]: susceptible individuals (S) contract MPXV and are infected without being infectious for the duration of a n -stage process (E_k , $k = 1 \dots n$, with n inferred) before becoming actively infectious (I), during which time they can infect other individuals and thus generate further cases. After the actively infectious period individuals recover (R) and remain immune to reinfection over the remaining simulation period.

Following the bulk of the MPXV literature, we assume that the latency period (duration between infection and becoming actively infectious) and the incubation period (duration between infection and developing symptomatic disease) are the same; that is that infected individuals are infectious when they show symptoms [6]. A recent study on the incubation period of MPXV estimates a mean incubation period of 8.5-9.6 days [22]; reusing this data and code to make inference on the incubation period as a Gamma distribution of shape and scale parameters k and θ , respectively, gave mean posterior estimates of $\hat{k} = 6.77$ and $\hat{\theta} = 1.30$. For a daily probability p_{inc} of progressing between successive stages of our model's n -stage incubation period, the number of days spent in the incubation class will be given by $n + d$, where the distribution f of d is negative binomial,

$$f(d \mid n, p_{inc}) = \binom{d+n-1}{d} p_{inc}^n (1-p_{inc})^d \quad (1)$$

(since d is just the number of days in the incubation period where the individual does not progress to the next stage of infection). Using the method of moments to find a negative binomial distribution with identical mean, and minimised difference in standard deviation, to the Gamma distribution inferred from data, we found that a four stage incubation process (i.e. $n = 4$ in the SE_nIR compartmental structure) with a daily probability of $p_{inc} = 0.455$ of transitioning between successive stages of infection provided an optimal match between our negative binomial model and the Gamma distribution (average incubation period is $n + \bar{k} \approx 8.8$ days vs Gamma mean $\hat{k}\hat{\theta} \approx 8.8$ days, standard deviation $\sqrt{(1-p_{inc})n/p_{inc}^2} \approx 3.25$ vs Gamma standard deviation $\sqrt{\hat{k}\hat{\theta}^2} \approx 3.38$, Fig. 3).

While it is likely that infected individuals are infectious whilst symptoms persist, which is typically 2-4 weeks [9], we assume that their effective infectious period is potentially self-limiting due to infected individuals reducing

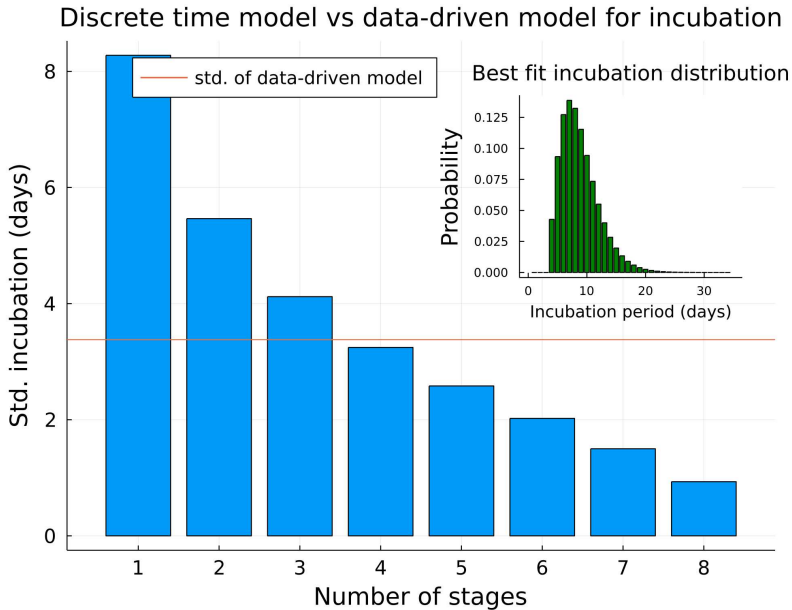


Fig. 3 Standard deviation for multi-stage discrete time incubation model when mean is fixed to be 8.8 days by number of stages. The standard deviation for incubation period fitted from data is given as a horizontal red line. The closest match ($n=4$ stages) was used in simulations.

their contacts in response to deteriorating MPXV symptoms. We model the infectious period as a one stage process with the mean period μ_{inf} being a target for inference; using the same reasoning applied for the total incubation period, the duration of an individual's infectious period is given by d where d is negative binomially distributed with parameters 1 and p_{rec} , so that the mean duration is given by $\mu_{inf} = 1 + p_{rec}/(1 - p_{rec}) = 1/p_{rec}$.

4.2 Population structure

We subdivided the population of the United Kingdom ($N = 67.2$ million) into gay, bisexual and men who have sex with men (GBMSM) and non-GBMSM. We further subdivided the GBMSM population so that each person belonged to one of 10 sexual activity groups $g = 1, \dots, 10$ and one of a random number of metapopulation sub-groups $m = 1, 2, \dots$.

The proportion of the over 18 year old male population identifying as Lesbian, gay and bisexual (LGB) in the UK has been estimated as 3.4% [23], and the proportion of MSM having at least one new sexual contact with another man in a year, has been estimated as 84.6% [13]. We combine these to make a crude estimate of the size of the sexually active GBMSM population in the UK, $N_{gbmsm} = 760, 839$.

The population distribution of new sexual contacts per year for members of the sexually active GBMSM community, k , has previously been estimated

as a power law $f(k) \sim k^{-1.82}$ [13]. We assumed that the maximum number of new sexual contacts per year was 3,650, which defined a proper distribution of yearly sexual contacts; if infinitely large k values were allowed then given the power exponent is relatively small the variance would also be infinite, the strict upper bound prevents this from occurring. We divided the GBMSM population into 10 sexual activity groups by the partitioning the yearly contact rate $1 = k_1 < k_2 < \dots < k_9 < k_{10} \leq 3650$ such that,

$$\int_{k_i}^{k_{i+1}} k \times f(k) dk = \mathbb{E}[k]/10, \quad \forall i \in 1, 2, \dots, 10. \quad (2)$$

By dividing according to equation (2) the expected rate of new sexual partnerships was equal across groups, which minimises the loss of information in sexual partnership formation implied by discretising the active GBMSM population. The size of the most active of the sexual activity groups (over the entire metapopulation) was only ~ 400 out of 760,839 people ($\sim 0.05\%$ of the GBMSM population in UK). In general, this defined both p_g , the proportion of GBMSM typically in each sexual activity group, and, μ_g , the mean daily rate of creating a new sexual contact conditional on being a member of a sexual activity group g (Fig. 4).

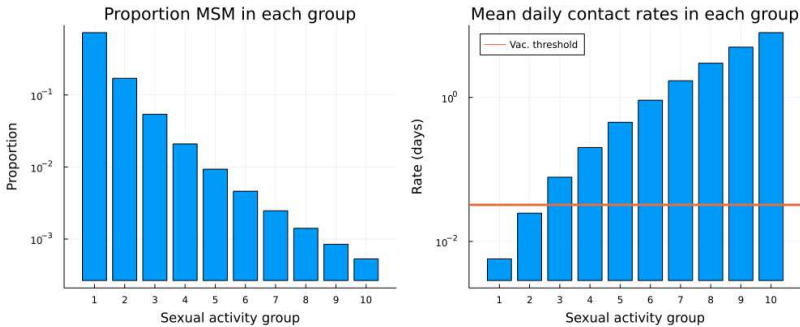


Fig. 4 Proportion of GBMSM in each sexual activity group, and daily rate of new sexual partnership formation. The proportion of the active GBMSM population in each sexual activity group (left); NB this is shown on a log-scale. The mean rate of forming new sexual partnerships by sexual activity group (right). Throughout this paper it is assumed that the GBMSM individuals being offered vaccination are those who typically have at least one new sexual partner per month (shown as red line). For this model structure this corresponds to sexual activity groups 3-10 (the 9.4% of the active GBMSM population most sexually active).

The random sized metapopulation structure was generated according to a Dirichlet multinomial distribution, that is a multinomial where the vector of choice probabilities is drawn from a Dirichlet distribution, $\mathbf{n}_{meta} \sim \text{DirichletMultinomial}(N_{gbmsm}, \alpha_m \mathbf{1})$, where α_m is a real-valued dispersion parameter, $\mathbf{1}$ is a length 50 vector of ones, and n_{meta} is the resulting vector of metapopulation sizes. Any metapopulation with size 0 was then eliminated

from the simulation. It should be noted that $\alpha_m \rightarrow 0$ implies that with probability 1 there will only be one metapopulation of size N_{gbmsm} , whereas in the limit $\alpha_m \rightarrow \infty$ the metapopulation size distribution is asymptotically multinomial distributed with on average equal sized metapopulations with mean size $N_{gbmsm}/50 = 15,216$.

After generating the randomly sized metapopulations, each metapopulation is further subdivided into sexual activity groups according to a multinomial sample on p_g . That is, the generated population size of the sexual activity group g in the metapopulation m ($N_{g,m}$) is conditionally distributed $N_{g,m} | n_{meta} \sim \text{Multinomial}(n_{meta}[m], p_g)$.

A new random metapopulation structure was generated for each simulation, with α_m a target parameter for inference (see subsection 4.7).

4.3 Vaccination rollout modelling

UKHSA has secured thousands of vaccines which are being offered to front-line healthcare workers, contacts of cases, and LGB men at highest risk [24]. Within the model we interpret LGB men at highest risk as people within the GBMSM group who typically have a new sexual contact at least once a month (sexual activity groups 3-10, representing the 9.4% of most sexually active MSM people; Fig. 4).

It has been logistically challenging to capture exact numbers of vaccines that have been taken up by LGB men. However in London (capital city of the United Kingdom) the reported number of vaccines delivered to GBMSM people was around 1000 on the weekend of the 16th/17th July, was expected to be around 2000 on weekend of 23rd/24th July, and sufficient vaccines had been ordered to offer around 5000 doses each weekend in August [16]. In our modelling we assume that the NHS meets these targets in London, and that an additional 67.5% of vaccines are accepted by GBMSM people outside London (Fig. 5), which aligns with the cumulative number of vaccine doses reported as given to GBMSM individuals by 30th August 2022 [25]. However, then the uptake rate decreases to 650 doses per week across the country which aligns with the cumulative number of doses reported by 22nd September 2022 [26] (Fig. 5). The UK government has not committing to buying more than 100k vaccine doses, therefore, we limit the number of first doses to 50k. We do not explicitly model follow-up second doses in this paper which will have a longer term effect on the population immunity. Within the model all vaccines are deployed at the end of each week, and are modelled as becoming effective after a one week delay.

The effectiveness of smallpox vaccine against monkeypox has been estimated as 85% [5, 27]. We interpret this as the efficacy of smallpox vaccine against acquisition of monkeypox rather than just an endpoint efficacy against disease, although it is not possible to distinguish between the two in the data that is publicly available. The proposed dose regime in the UK is to give as many first vaccine doses as possible to LGB men at highest risk, with second doses to be given later as supplies become available [24]. It is possible

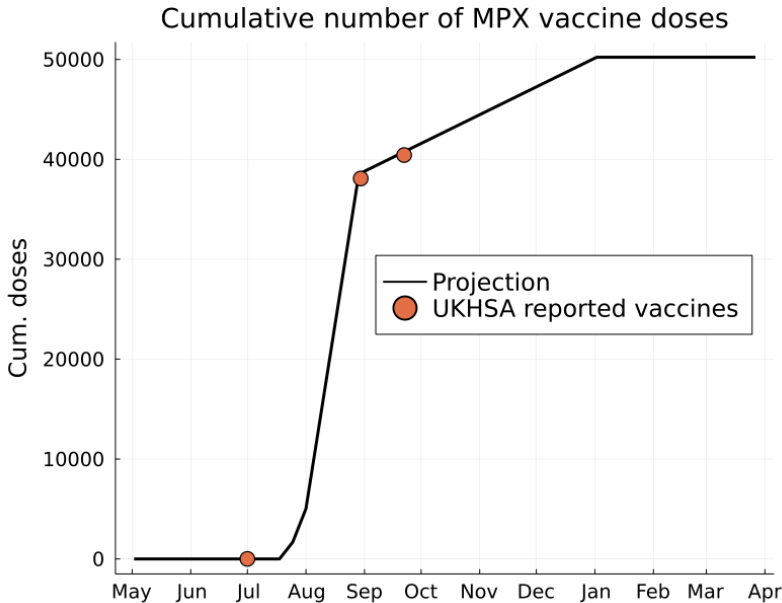


Fig. 5 Projected number of cumulative vaccine doses given in the United Kingdom.

that vaccination against monkeypox will be less efficacious than 85% against acquisition under this dose regime, therefore whenever modelling the effect of vaccines we draw a vaccine effectiveness parameter $v_{\text{eff}} \sim \mathcal{U}(0.7, 0.85)$ at the start of each simulation.

4.4 Modelling behavioural change due to monkeypox epidemic

Behavioural response and attitude to risk can significantly affect an epidemic trajectory, as also seen in the COVID-19 pandemic [18, 28]. Here, we model behavioural change leading to lower transmission risk per infected person as occurring at two change points, but reversion to pre-outbreak baseline as happening continuously over time with a midpoint for reversion T_r that depends of whether reversion mainly occurs over 4 or 12 weeks (the two scenarios considered in the paper):

1. On some date T_1 between 1st May 2022 and 18th July 2022 (the change point date is a target for inference).
2. $T_2 = 23\text{rd}$ July 2022, the date of the announcement by the WHO that monkeypox represented a public health emergency of international concern (PHEIC) [2].
3. $T_r = 15\text{th}$ September 2022 (4 week reversion), or, 13th October 2022 (12 week reversion).

We note that the smooth change shown in Figure 1 (top panels) is the average over possible step change dates between 1st May and 18th July 2022. The effect of behavioural change is assumed to reduce transmission for infectious individuals in both the GBMSM and non-GBMSM populations through some combination of:

- Voluntary self-isolation during MPX symptoms.
- The effect of any treatments against MPX.
- The effect of contact tracing in raising awareness of their exposure, and guiding safer behaviours.
- The social avoidance of other individuals towards those with MPX symptoms.

At the behavioural change points the probability of infection per new sexual contact between GBMSM individuals ($p_{gbmsm}(t)$) and the reproductive number for other routes of transmission ($R_{other}(t)$) decrease by some proportion (see subsection 4.5); these proportions of transmission decrease were a target for inference along with the timing of the change point T_1 .

The probability of transmission per sexual contact $p_{gbmsm}(t)$ and the reproductive number for other transmission pathways $R_{other}(t)$ varied over time because of behavioural change (see subsection 4.4) as follows:

$$\begin{aligned} \frac{p_{gbmsm}(t)}{p_{gbmsm}(0)} &= \prod_{k=1,2} \left[1(t < T_k) + 1(t \geq T_k)(1 - \rho_{gbmsm,k}) \right] + \Delta\rho_{gbmsm}\sigma((t - T_r)/\kappa), \\ \frac{R_{other}(t)}{R_{other}(0)} &= \prod_{k=1,2} \left[1(t < T_k) + 1(t \geq T_k)(1 - \rho_{other,k}) \right] + \Delta\rho_{other}\sigma((t - T_r)/\kappa), \end{aligned} \quad (3)$$

where $\rho_{gbmsm,1}$ and $\rho_{gbmsm,2}$ are the proportional risk reductions in GBMSM sexual contacts at change points 1 and 2 respectively, and $\rho_{other,1}$ and $\rho_{other,2}$ are the proportional risk reductions of other transmission pathways at change points 1 and 2 respectively, with $\Delta\rho_{gbmsm} = 1 - (1 - \rho_{gbmsm,1})(1 - \rho_{gbmsm,2})$ and $\Delta\rho_{other} = 1 - (1 - \rho_{other,1})(1 - \rho_{other,2})$ being the proportionate change from 1st May to the minimum point after T_2 . $\sigma(x) = 1/(1 + e^{-x})$ is the logistic curve governing reversion to baseline risk. κ was chosen so that logistic reversion was at 1% on 1st September 2022 and at 99% 2 or 6 weeks after the reversion midpoint T_r , depending on whether most reversion was assumed to occur over 4 or 12 weeks.

4.5 Force of infection

We consider two transmission pathways for MPX: 1) transmission during close contact when GBMSM individuals form new sexual partnerships, and 2) all other routes of transmission, including non-GBMSM sexual partnerships and stable GBMSM sexual partnerships, household cohabitation and other known transmission pathways for MPXV. The force of infection for each pathway was,

respectively,

$$\begin{aligned}\lambda_{gbmsm}(g, m, t) &= \sum_{g', m'} p_{gbmsm}(t) \mu_{g'} T_{m, m'} I_{g', m'}(t) / 10 N_{g, m}, \\ \lambda_{other} &= \gamma_{\text{eff}} R_{other}(t) I(t) / N.\end{aligned}\tag{4}$$

Here $I_{g, m}(t)$ is the number of infectious GBMSM people in sexual activity group g and metapopulation m , $I(t)$ is the the total number of infectious people across the whole population (GBMSM and non-GBMSM), and N is the total UK population size. We define the between metapopulation contact structure $T_{m, m'}$ as having 99% of sexual contacts within group, with the rest distributed to other subpopulations by size,

$$T_{m, m'} = 0.99 \delta_{m, m'} + 0.01 \times (1 - \delta_{m, m'}) (N_m / \sum_{m' \neq m} N_{m'}).\tag{5}$$

This implicitly sets the meaning of the metapopulation model. The reason for the factor of 10 in the denominator of equation (4) is that, by construction, sexual partnerships are spread equally between the different sexual activity groups.

Note that in the limit $\alpha_m \rightarrow 0$, this transmission model recovers the random partnership (or configuration) model with respect to new sexual formation [20, 29]; this is slightly obscured by the construction of the sexual activity groups, that is that each group has the same rate of sexual contacts overall even though the higher activity groups have far fewer members. Therefore, parameter inference is capable of recreating the random partnership model as the most plausible explanation for spread among active GBMSM, as well as allowing for more complicated transmission structure within the GBMSM community if that is a more plausible explanation.

Based on the underlying rates, the daily probability of becoming infected for (1) unvaccinated GBMSM in sexual activity group g and metapopulation m , (2) vaccinated GBMSM in sexual activity group g and metapopulation m and (3) non-MSM people, respectively are:

$$\begin{aligned}P_{inf}(t \mid gbmsm, g, m, unvac) &= 1 - \exp\{-[\lambda_{gbmsm}((g, m, t) + \lambda_{other}(t))]\}, \\ P_{inf}(t \mid gbmsm, g, m, vac) &= 1 - \exp\{-v_{\text{eff}}[\lambda_{gbmsm}((g, m, t) + \lambda_{other}(t))]\}, \\ P_{inf}(t \mid other) &= 1 - \exp\{-\lambda_{other}(t)\}.\end{aligned}\tag{6}$$

4.6 Case detection model

We assume that those MPX cases which are detected have a one week reporting lag after onset of symptoms (i.e. around a 7-day delay with 1-14 day delays possible), which is broadly in-line with the estimated reporting delay in July 2022 [30]. Cases are differentiated by GBMSM and non-GBMSM but not by

underlying metapopulation or sexual activity group. We modelled the number of cases as being a Beta-Binomial distributed sample over the simulated onsets in the previous week. This is probabilistically equivalent to Binomial sampling but with the probability of detection being independently Beta distributed each week. This is a robust approach to Bayesian inference which reduces the effect of outliers on inference [31], and it has been suggested that stochastic components to detection rate can improve inference in epidemiological modelling by absorbing some of the effect of model misspecification [32], which could be important in this model because in April/May 2022 the reporting delay was probably longer [30]. However, because each week's detection probability is drawn from an independent Beta distribution our model will not capture temporal directional trends in case detection, for example a trend towards lower chance of detection over time.

The number of GBMSM and non-GBMSM (other) cases observed in each week w is

$$C_{gbmsm}(w) \sim \text{BetaBinomial}\left(\sum_{g,m} O_{gbmsm}(g, m, w-1), p_d, \phi_d\right)$$

$$C_{other}(w) \sim \text{BetaBinomial}\left(O_{other}(w-1), p_d, \phi_d\right) \quad (7)$$

where $O_{gbmsm}(g, m, w-1)$ was the simulated number of symptom onsets in week $w-1$ in sexual activity group g and metapopulation m of the GBMSM population, $O_{other}(w-1)$ was the simulated number of symptom onsets in week $w-1$ in the non-GBMSM population, p_d was the mean value of the weekly Beta distributed detection rate, and ϕ_d is a dispersion parameter for the weekly Beta distributed detection rate. Given n onsets in a week the mean and variance in number of cases in the next week are, respectively, np_d and $np_d(1-p_d)(1+(n-1)d)$. The more common $Beta(\alpha, \beta)$ parameterization can be recovered via the relationships, $p_d = \alpha/(\alpha + \beta)$ and $\phi_d = 1/(\alpha + \beta + 1)$.

4.7 Data and Parameter Inference

Data on confirmed Monkeypox cases in UK is maintained by UKHSA and include patients' characteristics, such as their basic demographics (age and sex), clinical and laboratory records, contact data, and travel histories and gender (GBMSM or non-GBMSM) obtained from questionnaires - although this full spectrum of information is not available for all cases.

Weeks $w = 1, 2, 3, \dots$ were labelled by their Monday date, and all confirmed cases reported were aggregated by week. For each week w , we considered the numbers $C_{gbmsm}^*(w)$ and $C_{other}^*(w)$ of reported cases that identify as GBMSM or non-GBMSM, respectively, and the number $C_{NA}(w)$ of cases for which GBMSM information is missing. Missing values were handled with an imputation method based on gradient boosted decision trees (GBDTs). A GBDT is a machine learning model consisting of an ensemble of single decision trees, each including a series of nodes representing binary decision splits against one of the

predictor variables [33, 34]. GBDMs were trained to learn the probability that a case identifies as GBMSM, given all other available data (SI appendix A.6).

The probabilities of GBMSM for the cases to be imputed were also averaged by week, in order to estimate the weekly fraction $p(w)$ of GBMSM cases in $C_{NA}(w)$ (Figure A5) as follows:

$$\begin{aligned} C_{gbmsm}(w) &= C_{gbmsm}^*(w) + p(w) \times C_{NA}(w), \\ C_{other}(w) &= C_{other}^*(w) + (1 - p(w)) \times C_{NA}(w). \end{aligned} \quad (8)$$

While this implied that $C_{gbmsm}(w)$ and $C_{other}(w)$ were not necessarily integer valued, the error measure we used in our inference (see Equation (9)) did not require integer reference data.

We performed Bayesian inference on the model parameters (see Table A1 for full list of parameters, priors used and posterior mean and 95% CIs) using sequential Monte Carlo based approximate Bayesian computation (SMC-ABC [35]) implemented in the Julia language package ApproxBayes.jl [36]. Forward simulations were performed by solving the stochastic monkeypox transmission model using the DifferentialEquations.jl ecosystem of dynamical system solvers for the Julia programming language [37].

After drawing model parameters from the prior distributions, simulations were initialised at the beginning of the week immediately previous to the week with first reported cases (Monday 25th April 2022, $w = 0$) as follows:

1. A random metapopulation and sexual activity group distribution for GBMSM people was generated (see subsection 4.2).
2. One metapopulation was randomly selected proportionally to metapopulation size.
3. For the selected metapopulation a Poisson distributed number of individuals were assigned to each incubation stage and the infectious stage (uniformly likely) in each sexual activity group (proportional to population frequency) such that conditional on the chosen p_d and inf parameters the expected number of GBMSM cases on week $w = 1$ was ι_0 , which was a target parameter for inference.

During each simulation a predicted (integer) number of reported cases for GBMSM and non-GBMSM on each week was generated using equation (7): $C_{gbmsm}(w)$, $C_{other}(w)$ for $w = 1, 2, 3, \dots$. The error metric for the simulation used by the SMC-ABC algorithm against the true data was $d_1(\hat{C}, C)$, defined as:

$$d_1(\hat{C}, C) = \frac{\sum_w |\hat{C}_{gbmsm}(w) - C_{gbmsm}(w)|_1 + \sum_w |\hat{C}_{other}(w) - C_{other}(w)|_1}{\sum_{w'} C_{gbmsm}(w') + C_{other}(w')} \quad (9)$$

where $|\cdot|_1$ denotes L1 norm. The last week of available case data was not used in inference because of potentially confounding right-censoring.

Before running SMC-ABC we performed prior predictive model checking and simulation-based calibration for the error target value (see SI appendix A.2).

4.8 Code availability and ongoing projections

All code and data used in running the model is available at the open github repository: <https://github.com/SamuelBrand1/monkeypoxUK>. As more data becomes available we will be periodically updating this repository with the most recent projections.

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Supplementary Files

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- [UKmonkeypoxmodelingdraftSI.pdf](#)