Title: Heavy-tailed sexual contact networks and monkeypox epidemiology in the global outbreak, 2022

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Abstract: The outbreak of monkeypox across non-endemic regions confirmed in May 2022 shows epidemiological features that are distinct from previous imported outbreaks, most notably its observed growth and predominance amongst men who have sex with men (MSM). We use a

transmission model fitted to empirical sexual partnership data to show that the heavy-tailed sexual partnership distribution, where a handful of individuals have disproportionately many partners, can explain the sustained growth of monkeypox among MSM despite the absence of such patterns previously. We suggest the basic reproduction number (R_0) for monkeypox over the MSM sexual network may be substantially above 1, which poses challenges to outbreak containment. Ensuring support and tailored messaging to facilitate prevention and early detection among MSM with highest numbers of partners is warranted.

One-Sentence Summary: Sexual partnership distributions explain sustained spread of monkeypox predominantly among men who have sex with men.

Main Text:

In May 2022 multiple countries in Europe, North America and elsewhere, reported clusters of monkeypox cases (*1–4*). As of 31 May 2022, time of analysis, a total of 728 confirmed and suspected cases have been reported in over 25 countries from previously non-endemic regions (*5*). The global case count has substantially grown since and exceeded 30,000 from over 80 countries as of 10 August 2022 (*6*). To date, the reported cases are predominantly, but not exclusively, among young males without a travel history to endemic regions in Central and West Africa (*2*, *3*). The initial epidemiological investigations suggest a link with sexual contact among men who have sex with men (MSM) (*1–3*, *7*). Prior to the current outbreak, monkeypox infections had been assumed to be primarily caused by exposure to animal reservoirs but human-to-human transmissions via direct routes including skin-to-skin contact, bodily fluids and respiratory droplets have also been documented (*8*, *9*). Sexually-associated exposure to skin lesions, droplets and fomites could plausibly be a risk for transmission, whether monkeypox is truly sexually transmissible (e.g., via semen) or not. Previous studies of monkeypox outbreaks indicate about 10% secondary attack risk (SAR) among household members without smallpox vaccination (*8–10*); the smallpox vaccine has been shown to be protective against monkeypox with estimated effectiveness of 85% (*10*). Investigation of previous outbreaks in Central and West Africa identified a relatively limited proportion of cases of human-to-human transmission, with at most seven generations observed (*8*, *9*, *11*, *12*), and previous estimates of the basic reproduction number (R_0) for monkeypox have been below 1 even in unvaccinated populations (*9*, *10*). Sporadic monkeypox outbreaks associated with imported animals or imported cases have been observed in non-endemic regions (*13–17*) but subsequent human-to-human spread was rarely observed. Prior to the current outbreak, only one healthcare worker and two household

contacts of an imported case had been identified as likely secondary cases in non-endemic settings (*15*, *17*).

The current spread of monkeypox in non-endemic regions appears in stark contrast to these previous events. Most cases have no documented exposure to animals or travel history to endemic settings. The rapid growth in notified cases and geographical dispersal suggest substantial human-to-human transmission, rather than incidence driven by spillover from an animal reservoir. This is also the first widespread outbreak of monkeypox predominantly in MSM with suggested sexually-associated transmission (*1*, *18*), although higher prevalence in young males and frequent observation of genital lesions have also been documented in a recent outbreak in Nigeria (*12*, *19*, *20*). Proposed explanations for the novel character of the current outbreak include increased importation, undetected community-wide transmission, viral evolution, and increased susceptibility due to the end of smallpox vaccination (*7*, *17*, *18*, *21*). While these theories are consistent with some aspects of the current observation, most of them are not strongly supported by external (if indirect) evidence nor do they provide a coherent explanation on why a similar monkeypox outbreak involving substantial human-to-human transmission in a focal, rather than generalised, population had not arisen from the series of importation events documented in non-endemic settings starting in 2003 (*13–17*).

Here, we show that transmission over a sexual contact network empirically characterised by a heavy-tailed partnership distribution can reasonably explain the rapid growth of human-to-human transmissions in the current monkeypox outbreak despite the absence of such patterns of spread in the past. Specifically, it is plausible that monkeypox has had a substantial transmission

potential in the MSM sexual contact network but that due to the small cumulative number of imported cases in non-endemic settings, it had not reached members of this network with high numbers of contacts from whom onwards transmission was most probable. The main analysis of this study was conducted using only information available as of 31 May 2022, a few weeks after the outbreak had been first recognised, and the original version was submitted on 12 June 2022 (available from: (*22*)) to provide key insights from the earliest data available. We retain this original context of the analysis in this paper to highlight that the findings were obtainable in the earliest phase of the outbreak, and discuss them in retrospect given the updated situation since the time of analysis.

Previous work on sexual partnership distributions (i.e., degree distribution of sexual contact networks) often fitted Pareto distributions to the reported number of partners over a specific time window (e.g., over a year) (*23*, *24*) However, Pareto distributions can be scale-free, which causes the modelled networks to have some individuals with impossibly high numbers of partners and as a result R_0 defined in the networks tends to infinity (*25*). We found that Pareto distributions do not describe existing datasets of MSM partnerships well (see *Supplementary materials*). The Weibull distribution is an alternative distribution that also has a heavy-tailed shape (*20*) and does not exhibit the unphysical features of the Pareto distribution. Using Weibull distributions fitted to the empirical data on same-sex and opposite-sex sexual partnerships of the UK population aged 18–44 (from the National Surveys of Sexual Attitudes and Lifestyles; Natsal (*26–28*)), we constructed a branching process model of transmission over sexual contact networks. Following (*25*), we assumed that individuals can become infected at a probability proportional to their network degree (i.e., those with a large number of partners are more likely to be chosen). This assumption neglects the possible existence of densely-clustered "core group"

(*29*); see *Supplementary materials* for sensitivity analysis. We assumed an infectious period of 21 days for monkeypox based on the documented duration of illness (*30–32*), which we also varied in our sensitivity analysis to account for variation and possible behaviour changes in symptomatic individuals.

Using this model, we simulated sexually-associated outbreaks of monkeypox in MSM and non-MSM populations, under varying assumptions for the risk of transmission between sexual partners (SAR per sexually-associated contact during the infectious period) between 0–100% in the absence of empirical data on this parameter. Starting from a specified number of initial cases, we simulated the number of cases in each generation of transmission over MSM and non-MSM sexual contact networks. For the non-MSM sexual network, we assumed that the initial cases have equal chances of being male or female and that subsequent generations of infection alternate between heterosexual (HS) men and women. Women who have sex with women were not considered in our analysis as their partnership distribution suggested a substantially lower transmission potential than the HS network (see *Supplementary materials*). In the model, we considered only sexually-associated transmission over separate sexual contact networks of MSM and non-MSM and did not explicitly model other transmission routes (non-sexually-associated skin-to-skin contact, respiratory droplets, fomites, etc.) or links between MSM and non-MSM sexual contact networks, except for the initial cases. We discuss transmission dynamics of monkeypox as a mixture of these transmission routes in a separate analysis using the next generation matrix (*33*). The methodology used is described in more detail in the *Supplementary materials*.

We first simulated the probability of observing a chain of transmission of a size equal to or greater than the current global monkeypox outbreak (728 cases as of 31 May 2022) in the MSM population generated from a given number of initial cases. We considered three scenarios for the profile of introduction events: (1) The initial cases in the MSM population acquired infection via a sexually-associated route, i.e., the numbers of their sexual partners are preferentially drawn from the tail of the sexual partnership distribution; (2) The initial cases in the MSM population were non-sexually-associated and therefore their partnership degrees were drawn from across the full distribution; (3) Initial cases were from the general population (of which 2% were assumed to be sexually-active MSM based on the Natsal datasets) who acquired infection via non-sexually-associated routes. We then simulated the probability of the current outbreak leading to a major outbreak over the MSM sexual contact network. For comparison, outbreaks over the non-MSM sexual contact network, given specified numbers of initial cases (either sexually-associated or non-sexually-associated), were also simulated. Our estimates suggest that with a range of sexually-associated SAR values comparable to or greater than the previous estimates of household SAR (*8–10*), even one event of sexually-associated transmission to the MSM population (scenario 1) is consistent with a high likelihood (20–50%) of observing an outbreak of the current size or greater (Fig. 1A). The likelihood becomes smaller (although not negligible) if non-sexually-associated exposure (e.g., exposure to animals or non-sexual direct contact with cases; scenario 2) is involved in the introduction to the MSM population (Fig. 1B). By contrast, 50–100 or more non-sexually-associated initial cases from the general population (scenario 3) would have been necessary for the likelihood of an outbreak of the current size in the MSM population to be around the order of 1–20% (Fig. 1C).

These results suggest that a small number of sexually-associated transmissions among the MSM population were sufficient to cause a large outbreak over the MSM sexual network, as we now appear to observe, but that the number of non-sexually-associated imported cases required for the virus to achieve the first few instances of sexually-associated transmission among MSM is relatively large. The cumulative number of documented imported cases in non-endemic settings had been up to around 100 prior to May 2022 (*13–17*); it is therefore unsurprising that introduction to the MSM population in non-endemic settings has never been observed previously, assuming that the importations had been mostly non-sexually-associated cases from the general population. The current outbreak in the MSM population may have been introduced by an eventual introduction following non-sexually-associated importations or, alternatively, by one or more sexually-associated importations acquired in the endemic setting. In the latter case, a sexually-associated outbreak among MSM might also be ongoing in the endemic settings, which warrants further surveillance. All scenarios projected that, without interventions or changes to sexual behaviour, a major outbreak in the MSM population (defined as ≥ 10,000 cases excluding initial cases) was highly likely given the current outbreak size (Table 1); this projection, based on the data as of 31 May 2022, turned out correct in retrospect (*6*). In contrast, sustained transmission over the non-MSM sexual contact network was unlikely in all scenarios considered (Table 1), owing to the less heavy tail of the corresponding partnership distribution, although from 10 to 3,000 additional cases may be observed if a substantial number of infections are introduced into the non-MSM sexual contact network (Fig. 1D). A caveat must be noted, however, that sustained transmission in a local subnetwork among non-MSM that is more densely clustered than modelled may still be possible (Fig. S4).

The projected values of R_0 were almost always above 1 in the MSM sexual network for a range of sexually-associated SAR, while R_0 for the non-MSM sexual network was found to be below 1 unless SAR was nearly 100% (Fig. 2A). The potentially high R_0 for the MSM sexual network is particularly concerning because it can pose challenges to the control efforts (Fig. 2B). Contact tracing and ring vaccination approaches, now being conducted extensively in many places with cases, may need to identify almost all contacts of a case to bring the epidemic under control (which would not be easily achievable in practice (*2*)) because untraced transmission may well lead to other sustained transmission chains. Another possible approach would be to focus resources on identifying acceptable and effective means of preventing transmission among those men with the highest number of sexual partners, which could have a disproportionate effect on transmission overall. We modelled the possible effect of such interventions by varying the Weibull parameters for the MSM partnerships such that the (effective) numbers of partners at the distribution tail are selectively controlled, e.g. via reduced contacts or reduced chance of transmission per contact (see *Supplementary materials* for technical details). The level of control at the tail is represented by the upper 1st percentile among those with at least one partner over 21 days. The R_0 may sharply decrease if control efforts are effective in reducing transmissions at the tail part of the partnership distribution (Fig. 2C). This would also lower the required intensity of other (non-focused) measures to achieve outbreak control (Fig. 2D). Fig. 2E shows the tail part of the modelled Weibull distributions under focused interventions. These distributions are most different in the region $x \geq 10$, suggesting that focusing on those with more than 10 partners over 21 days would be of particular importance.

The analysis presented here only considered a single outbreak over either the MSM or non-MSM sexual contact network with a given number of introductions. However, understanding the

disease dynamics as a mixture of interacting populations via multiple modes of transmission is crucial in projecting possible future scenarios, especially given the known or suggested non-sexually-associated routes of transmission including via droplets, fomites or aerosols (*9*, *34*). One of the key questions is whether the current monkeypox outbreak can be sustained in the general community via non-sexually-associated routes, i.e., whether the R_0 corresponding to non-sexually-associated transmission is above or below 1. Although we are unable to directly answer this question because the presence of non-sexually-associated epidemiological links in the current outbreak is so far largely uncertain/unknown, we propose a possible approach to inferring the role of such transmission. We show in Fig. 2F that, in an exponential growth phase, the proportion of cases without a sexually-associated epidemiological link among total cases will approximately approach the ratio between R_0's over the MSM sexual network and general non-sexually-associated transmission routes as the outbreak progresses. One should be able to conclude that the non-sexually-associated R_0 for monkeypox is substantially lower than R_0 over the MSM sexual network if the proportion of non-sexually-associated cases remained low in the future (*35*); however, caution is warranted as even in that case the general transmission R_0 may still be above 1 if R_0 over the MSM sexual network is as high as suggested in some scenarios presented in our analysis. As of 10 August 2022, there have been sporadic reports of probable non-sexually-associated cases including 26 known pediatric cases aged 0–4 (*35*). However, there has been no clear evidence supporting sustained transmission via non-sexually-associated routes. Available data among cases from WHO (98.7% male, 97.2% self-identified MSM and 91.5% with reported sexual encounters, among those who provided information) suggests that the central mode of transmission likely remains to be over the MSM sexual contact network, although uncertainty and the possibility of bias remain due to excessive missing values (*35*).

Without needing a novel hypothesis, our results, using empirical sexual partnership data, propose a simple but coherent explanation for a rapidly growing sexually-associated monkeypox outbreak in non-endemic regions linked to the MSM population. We also suggest that R_0 over the MSM sexual network can be substantially higher than previous estimates in non-sexually-associated contexts, if the sexually-associated SAR is comparable to or greater than the household SAR.

These findings need to be translated into control efforts to inform and protect the MSM community. Self-sustained transmission over the entire non-MSM sexual network or via non-sexually-associated routes appears less likely, although many cases may still be observed if the outbreak continues to grow in the subsets of sexual contact networks at a higher risk of transmission. Control efforts, such as contact tracing and ring vaccination, need to achieve high effectiveness given the large R_0 values we have estimated; focused public health messaging and support for individuals with multiple sexual partners would complement these approaches to bring the outbreak under control.

Our conclusions hinge on the assumed parameters from previous outbreaks with different transmission routes, including the SAR and infectious period of monkeypox, as well as the observed characteristics of the sexual partnership distribution in the UK and accompanying assumptions. We modelled the global transmission of monkeypox over a single connected sexual contact network fitted to the datasets of the UK population aged 18–44. Populations not represented by those datasets may be more or less vulnerable to the sexually-associated monkeypox outbreak as a result of different partnership patterns and R_0 values. This may also

explain the limited observation of possible sexually-associated outbreaks in endemic countries previously, although this may in part result from insufficient case ascertainment. Our sensitivity analysis using only case counts within the UK yielded almost identical results (Table S3) and the same approach could also be applied to other population settings where sexual partnership data is available. Meanwhile, depletion of susceptibles, especially those with many partners, may have visible effects in finite MSM populations at country-level, which can lead to smaller final outbreak sizes than projected by the branching process model (Fig. S5). Some of the countries with early introductions of cases including the UK have seen a slowdown in growth of cases as of 10 August 2022 (*6*); depletion of susceptibles and other factors such as vaccination and increased awareness (*36*) may have contributed to these trend changes. We did not consider the possibility of degree assortativity or clustering, which would lead to more densely-clustered local subnetworks than we modelled (*37*). It is plausible that there could be core parts or clusters of the non-MSM sexual contact networks over which transmission could be sustained, which is not captured by modelling transmission over the non-MSM partnership distribution as a whole. Finally, because of the limited sample size of MSM partnerships in the Natsal datasets ($N = 409$), uncertainty remains around their R_0 values (Table S1, Fig. S2). Our estimates should be viewed as a qualitative projection rather than precise estimates of R_0. Future empirical evidence from the current outbreak and estimates of key epidemiological parameters, as well as the effectiveness of interventions will inform our projections on the current and future epidemiology of the monkeypox outbreak.

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References and Notes

1. European Centre for Disease Prevention and Control, “Epidemiological update: Monkeypox outbreak” (2022), (available at https://www.ecdc.europa.eu/en/news-events/epidemiological-update-monkeypox-outbreak).

2. R. Vivancos, C. Anderson, P. Blomquist, S. Balasegaram, A. Bell, L. Bishop, C. S. Brown, Y. Chow, O. Edeghere, I. Florence, S. Logan, P. Manley, W. Crowe, A. McAuley, A. G. Shankar, B. Mora-Peris, K. Paranthaman, M. Prochazka, C. Ryan, D. Simons, R. Vipond, C. Byers, N. A. Watkins, U. M. I. M. Team, W. Welfare, E. Whittaker, C. Dewsnap, A. Wilson, Y. Young, M. Chand, S. Riley, S. Hopkins, Community transmission of monkeypox in the United Kingdom, April to May 2022. *Eurosurveillance*. **27**, 2200422 (2022).

3. M. P. Duque, S. Ribeiro, J. V. Martins, P. Casaca, P. P. Leite, M. Tavares, K. Mansinho, L. M. Duque, C. Fernandes, R. Cordeiro, M. J. Borrego, A. Pelerito, I. L. de Carvalho, S. Núncio, V. Manageiro, C. Minetti, J. Machado, J. M. Haussig, R. Croci, G. Spiteri, A. S. Casal, D. Mendes, T. Souto, S. Pocinho, T. Fernandes, A. Firme, P. Vasconcelos, G. Freitas, Ongoing monkeypox virus outbreak, Portugal, 29 April to 23 May 2022. *Eurosurveillance*. **27**, 2200424 (2022).

4. World Health Organization, Multi-country monkeypox outbreak in non-endemic countries, (available at https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON385).

5. Global.health, Monkeypox data (accessed: 29 May 2022) (2022), (available at https://github.com/globaldothealth/monkeypox).

6. Global.health, Monkeypox data (accessed: 11 August 2022) (2022), (available at https://github.com/globaldothealth/monkeypox).

7. N. Haider, J. Guitian, D. Simons, D. Asogun, R. Ansumana, I. Honeyborne, T. P. Velavan, F. Ntoumi, S. R. Valdoleiros, E. Petersen, R. Kock, A. Zumla, Increased outbreaks of monkeypox highlight gaps in actual disease burden in Sub-Saharan Africa and in animal reservoirs. *International Journal of Infectious Diseases*. **0** (2022), doi:10.1016/j.ijid.2022.05.058.

8. Z. Jezek, B. Grab, K. M. Paluku, M. V. Szczeniowski, Human monkeypox: disease pattern, incidence and attack rates in a rural area of northern Zaire. *Trop Geogr Med*. **40**, 73–83 (1988).

9. E. M. Beer, V. B. Rao, A systematic review of the epidemiology of human monkeypox outbreaks and implications for outbreak strategy. *PLOS Neglected Tropical Diseases*. **13**, e0007791 (2019).

10. P. E. Fine, Z. Jezek, B. Grab, H. Dixon, The transmission potential of monkeypox virus in human populations. *Int J Epidemiol*. **17**, 643–650 (1988).

11. Z. Ježek, B. Grab, M. V. Szczeniowski, K. M. Paluku, M. Mutombo, Human monkeypox: secondary attack rates. *Bull World Health Organ*. **66**, 465–470 (1988).

12. A. Yinka-Ogunleye, O. Aruna, D. Ogoina, N. Aworabhi, W. Eteng, S. Badaru, A. Mohammed, J. Agenyi, E. N. Etebu, T.-W. Numbere, A. Ndoreraho, E. Nkunzimana, Y. Disu, M. Dalhat, P. Nguku, A. Mohammed, M. Saleh, A. McCollum, K. Wilkins, O. Faye,

A. Sall, C. Happi, N. Mba, O. Ojo, C. Ihekweazu, Reemergence of Human Monkeypox in Nigeria, 2017. *Emerg Infect Dis*. **24**, 1149–1151 (2018).

13. Centers for Disease Control and Prevention (CDC), Update: multistate outbreak of monkeypox--Illinois, Indiana, Kansas, Missouri, Ohio, and Wisconsin, 2003. *MMWR Morb Mortal Wkly Rep*. **52**, 642–646 (2003).

14. N. Erez, H. Achdout, E. Milrot, Y. Schwartz, Y. Wiener-Well, N. Paran, B. Politi, H. Tamir, T. Israely, S. Weiss, A. Beth-Din, O. Shifman, O. Israeli, S. Yitzhaki, S. C. Shapira, S. Melamed, E. Schwartz, Diagnosis of Imported Monkeypox, Israel, 2018. *Emerg Infect Dis*. **25**, 980–983 (2019).

15. A. Vaughan, E. Aarons, J. Astbury, T. Brooks, M. Chand, P. Flegg, A. Hardman, N. Harper, R. Jarvis, S. Mawdsley, M. McGivern, D. Morgan, G. Morris, G. Nixon, C. O'Connor, R. Palmer, N. Phin, D. A. Price, K. Russell, B. Said, M. L. Schmid, R. Vivancos, A. Walsh, W. Welfare, J. Wilburn, J. Dunning, Human-to-Human Transmission of Monkeypox Virus, United Kingdom, October 2018. *Emerg Infect Dis*. **26**, 782–785 (2020).

16. S. E. F. Yong, O. T. Ng, Z. J. M. Ho, T. M. Mak, K. Marimuthu, S. Vasoo, T. W. Yeo, Y. K. Ng, L. Cui, Z. Ferdous, P. Y. Chia, B. J. W. Aw, C. M. Manauis, C. K. K. Low, G. Chan, X. Peh, P. L. Lim, L. P. A. Chow, M. Chan, V. J. M. Lee, R. T. P. Lin, M. K. D. Heng, Y. S. Leo, Imported Monkeypox, Singapore. *Emerg Infect Dis*. **26**, 1826–1830 (2020).

17. H. Adler, S. Gould, P. Hine, L. B. Snell, W. Wong, C. F. Houlihan, J. C. Osborne, T. Rampling, M. B. Beadsworth, C. J. Duncan, J. Dunning, T. E. Fletcher, E. R. Hunter, M. Jacobs, S. H. Khoo, W. Newsholme, D. Porter, R. J. Porter, L. Ratcliffe, M. L. Schmid, M. G. Semple, A. J. Tunbridge, T. Wingfield, N. M. Price, M. Abouyannis, A. Al-Balushi, S. Aston, R. Ball, N. J. Beeching, T. J. Blanchard, F. Carlin, G. Davies, A. Gillespie, S. R. Hicks, M.-C. Hoyle, C. Ilozue, L. Mair, S. Marshall, A. Neary, E. Nsutebu, S. Parker, H. Ryan, L. Turtle, C. Smith, J. van Aartsen, N. F. Walker, S. Woolley, A. Chawla, I. Hart, A. Smielewska, E. Joekes, C. Benson, C. Brindley, U. Das, C. K. Eyton-Chong, C. Gnanalingham, C. Halfhide, B. Larru, S. Mayell, J. McBride, C. Oliver, P. Paul, A. Riordan, L. Sridhar, M. Storey, A. Abdul, J. Abrahamsen, B. Athan, S. Bhagani, C. S. Brown, O. Carpenter, I. Cropley, K. Frost, S. Hopkins, J. Joyce, L. Lamb, A. Lyons, T. Mahungu, S. Mepham, E. Mukwaira, A. Rodger, C. Taylor, S. Warren, A. Williams, D. Levitt, D. Allen, J. Dixon, A. Evans, P. McNicholas, B. Payne, D. A. Price, U. Schwab, A. Sykes, Y. Taha, M. Ward, M. Emonts, S. Owens, A. Botgros, S. T. Douthwaite, A. Goodman, A. Luintel, E. MacMahon, G. Nebbia, G. O'Hara, J. Parsons, A. Sen, D. Stevenson, T. Sullivan, U. Taj, C. van N. tot Pannerden, H. Winslow, E. Zatyka, E. Alozie-Otuka, C. Beviz, Y. Ceesay, L. Gargee, M. Kabia, H. Mitchell, S. Perkins, M. Sasson, K. Sehmbey, F. Tabios, N. Wigglesworth, E. J. Aarons, T. Brooks, M. Dryden, J. Furneaux, B. Gibney, J. Small, E. Truelove, C. E. Warrell, R. Firth, G. Hobson, C. Johnson, A. Dewynter, S. Nixon, O. Spence, J. J. Bugert, D. E. Hruby, Clinical features and management of human monkeypox: a retrospective observational study in the UK. *The Lancet Infectious Diseases*. **0** (2022), doi:10.1016/S1473-3099(22)00228-6.

18. C. Dye, M. U. G. Kraemer, Investigating the monkeypox outbreak. *BMJ*. **377**, o1314 (2022).

19. D. Ogoina, M. Iroezindu, H. I. James, R. Oladokun, A. Yinka-Ogunleye, P. Wakama, B. Otike-odibi, L. M. Usman, E. Obazee, O. Aruna, C. Ihekweazu, Clinical Course and Outcome of Human Monkeypox in Nigeria. *Clinical Infectious Diseases*. **71**, e210–e214 (2020).

20. D. Ogoina, J. H. Izibewule, A. Ogunleye, E. Ederiane, U. Anebonam, A. Neni, A. Oyeyemi, E. N. Etebu, C. Ihekweazu, The 2017 human monkeypox outbreak in Nigeria—Report of outbreak experience and response in the Niger Delta University Teaching Hospital, Bayelsa State, Nigeria. *PLoS ONE*. **14** (2019), doi:10.1371/journal.pone.0214229.

21. Christian Happi, Ifedayo Adetifa, Placide Mbala, Richard Njouom, Emmanuel Nakoune, Anise Happi, Nnaemeka Ndodo, Oyeronke Ayansola, Gerald Mboowa, Trevor Bedford, Richard A. Neher, Cornelius Roemer, Emma Hodcroft, Houriiyah Tegally, Áine O'Toole, Andrew Rambaut, Oliver Pybus, Moritz U.G. Kraemer, Eduan Wilkinson, Joana Isidro, Vítor Borges, Miguel Pinto, João Paulo Gomes, Cheryl Baxter, Richard Lessells, Ahmed E. Ogwell, Yenew Kebede, Sofonias K. Tessema, Tulio de Oliveira, Urgent need for a non-discriminatory and non-stigmatizing nomenclature for monkeypox virus. *Virological* (2022), (available at https://virological.org/t/urgent-need-for-a-non-discriminatory-and-non-stigmatizing-nomenclature-for-monkeypox-virus/853).

22. A. Endo, H. Murayama, S. Abbott, R. Ratnayake, C. A. B. Pearson, W. J. Edmunds, E. Fearon, S. Funk, Heavy-tailed sexual contact networks and the epidemiology of monkeypox outbreak in non-endemic regions, May 2022. *medRxiv* (2022), doi:10.1101/2022.06.13.22276353.

23. A. Schneeberger, C. H. Mercer, S. a. J. Gregson, N. M. Ferguson, C. A. Nyamukapa, R. M. Anderson, A. M. Johnson, G. P. Garnett, Scale-Free Networks and Sexually Transmitted Diseases: A Description of Observed Patterns of Sexual Contacts in Britain and Zimbabwe. *Sexually Transmitted Diseases*. **31**, 380–387 (2004).

24. L. K. Whittles, P. J. White, X. Didelot, A dynamic power-law sexual network model of gonorrhoea outbreaks. *PLoS Comput Biol*. **15**, e1006748 (2019).

25. R. Pastor-Satorras, A. Vespignani, Epidemic Spreading in Scale-Free Networks. *Phys. Rev. Lett.* **86**, 3200–3203 (2001).

26. National Centre For Social Research, A. Johnson, K. Fenton, A. Copas, C. Mercer, A. McCadden, C. Carder, G. Ridgway, K. Wellings, W. Macdowall, K. Nanchahal, National Survey of Sexual Attitudes and Lifestyles II, 2000-2001. [data collection] (2005), , doi:10.5255/UKDA-SN-5223-1.

27. A. Johnson, Centre for Sexual and Reproductive Health Research, London School of Hygiene & Tropical Medicine, NatCen Social Research, National Survey of Sexual Attitudes and Lifestyles, 2010-2012 [data collection] (2015), , doi:10.5255/UKDA-SN-7799-1.

28. University of Glasgow, MRC/CSO Social and Public Health Sciences Unit, University College London, London School of Hygiene and Tropical Medicine, National Survey of Sexual Attitudes and Lifestyles COVID-19 Study, 2020. [data collection]. (2015), (available at http://doi.org/10.5255/UKDA-SN-8865-1).

29. H. Stigum, W. Falck, P. Magnus, The core group revisited: the effect of partner mixing and migration on the spread of gonorrhea, Chlamydia, and HIV. *Math Biosci*. **120**, 1–23 (1994).

30. Z. Jezek, B. Grab, M. Szczeniowski, K. M. Paluku, M. Mutombo, Clinico-epidemiological features of monkeypox patients with an animal or human source of infection. *Bull World Health Organ*. **66**, 459–464 (1988).

31. A. M. McCollum, I. K. Damon, Human Monkeypox. *Clinical Infectious Diseases*. **58**, 260–267 (2014).

32. D. B. D. Giulio, P. B. Eckburg, Human monkeypox: an emerging zoonosis. *The Lancet Infectious Diseases*. **4**, 15–25 (2004).

33. O. Diekmann, J. A. P. Heesterbeek, M. G. Roberts, The construction of next-generation matrices for compartmental epidemic models. *J R Soc Interface*. **7**, 873–885 (2010).

34. D. Verreault, S. Z. Killeen, R. K. Redmann, Chad. J. Roy, Susceptibility of Monkeypox virus aerosol suspensions in a rotating chamber. *J Virol Methods*. **187**, 333–337 (2013).

35. World Health Organization, "2022 Monkeypox Outbreak: Global Trends," (available at https://worldhealthorg.shinyapps.io/mpx_global/) (Accessed 11 August 2022).

36. K. P. Delaney, Strategies Adopted by Gay, Bisexual, and Other Men Who Have Sex with Men to Prevent Monkeypox virus Transmission — United States, August 2022. *MMWR Morb Mortal Wkly Rep*. **71** (2022), doi:10.15585/mmwr.mm7135e1.

37. J. Badham, R. Stocker, The impact of network clustering and assortativity on epidemic behaviour. *Theor Popul Biol*. **77**, 71–75 (2010).

38. A. Endo, H. Murayama, S. Abbott, R. Ratnayake, Carl A. B. Pearson, W. J. Edmunds, E. Fearon, S. Funk, *akira-endo/monkeypox_heavytail: Heavy-tailed sexual contact networks and the epidemiology of monkeypox outbreak in non-endemic regions* (Zenodo, 2022; https://zenodo.org/record/6984338).

39. C. H. Mercer, S. Clifton, J. Riddell, C. Tanton, L. Freeman, A. J. Copas, E. Dema, R. B. Pérez, J. Gibbs, W. Macdowall, D. Menezes, M.-C. Ridge, C. Bonell, P. Sonnenberg, N. Field, K. R. Mitchell, Impacts of COVID-19 on sexual behaviour in Britain: findings from a large, quasi-representative survey (Natsal-COVID). *Sex Transm Infect* (2021), doi:10.1136/sextrans-2021-055210.

40. B. Davoudi, J. C. Miller, R. Meza, L. A. Meyers, D. J. D. Earn, B. Pourbohloul, Early Real-Time Estimation of the Basic Reproduction Number of Emerging Infectious Diseases. *Phys. Rev. X*. **2**, 031005 (2012).

41. S. Watanabe, A Widely Applicable Bayesian Information Criterion. *Journal of Machine Learning Research*. **14**, 867–897 (2013).

42. A. E. Raftery, Bayesian Model Selection in Social Research. *Sociological Methodology*. **25**, 111–163 (1995).

43. Investigation into monkeypox outbreak in England: technical briefing 4. *GOV.UK*, (available at https://www.gov.uk/government/publications/monkeypox-outbreak-technical-briefings/investigation-into-monkeypox-outbreak-in-england-technical-briefing-4).

44. G. Millward, *Vaccinating Britain: Mass vaccination and the public since the Second World War* (Manchester University Press, Manchester (UK), 2019; https://www.ncbi.nlm.nih.gov/books/NBK545998/).

45. Office for National Statistics, "Population and household estimates, England and Wales: Census 2021," (available at https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/bulletins/populationandhouseholdestimatesenglandandwales/census2021).

46. UK Health Security Agency, Investigation into monkeypox outbreak in England: technical briefing 7. *GOV.UK*, (available at https://www.gov.uk/government/publications/monkeypox-outbreak-technical-briefings/investigation-into-monkeypox-outbreak-in-england-technical-briefing-7).

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Data and materials availability: The underlying data (National Survey of Sexual Attitudes and Lifestyles, UK) is available from UK Data Service (serial numbers: SN 5223, SN 7799 and SN 8865) provided the End User Licence Agreement. The analysis codes are available

from a GitHub repository: https://github.com/akira-endo/monkeypox_heavytail. Archived version is available at Zenodo (*38*).

Ethical review

This study was approved by the London School of Hygiene & Tropical Medicine ethics committee (reference number: 27985).

Supplementary Materials

Materials and Methods

Supplementary Text

Figs. S1 to S6

Tables S1 to S4

References (*39*–*46*)

Table 1. Likelihood of an outbreak over MSM or non-MSM sexual contact network given different numbers and profiles of introduction events.

SAR	Likelihood of 728+ cases in MSM given 1 introduction event			Likelihood of 10000+ cases given multiple introductions	
	S-A event (MSM)	Non-S-A event (MSM)	Non-S-A event (Gen. pop.)	728 S-A events in MSM	1000 non-S-A events in non-MSM
5%	10%	0.25%	0.003%	100%	< 0.001%
10%	20%	0.9%	0.02%	100%	< 0.001%

20%	31%	2.6%	0.04%	100%	< 0.001%
50%	45%	7.3%	0.16%	100%	< 0.001%

SAR: secondary attack risk; MSM: men who have sex with men; S-A: Sexually-associated; Gen. pop.: general population.

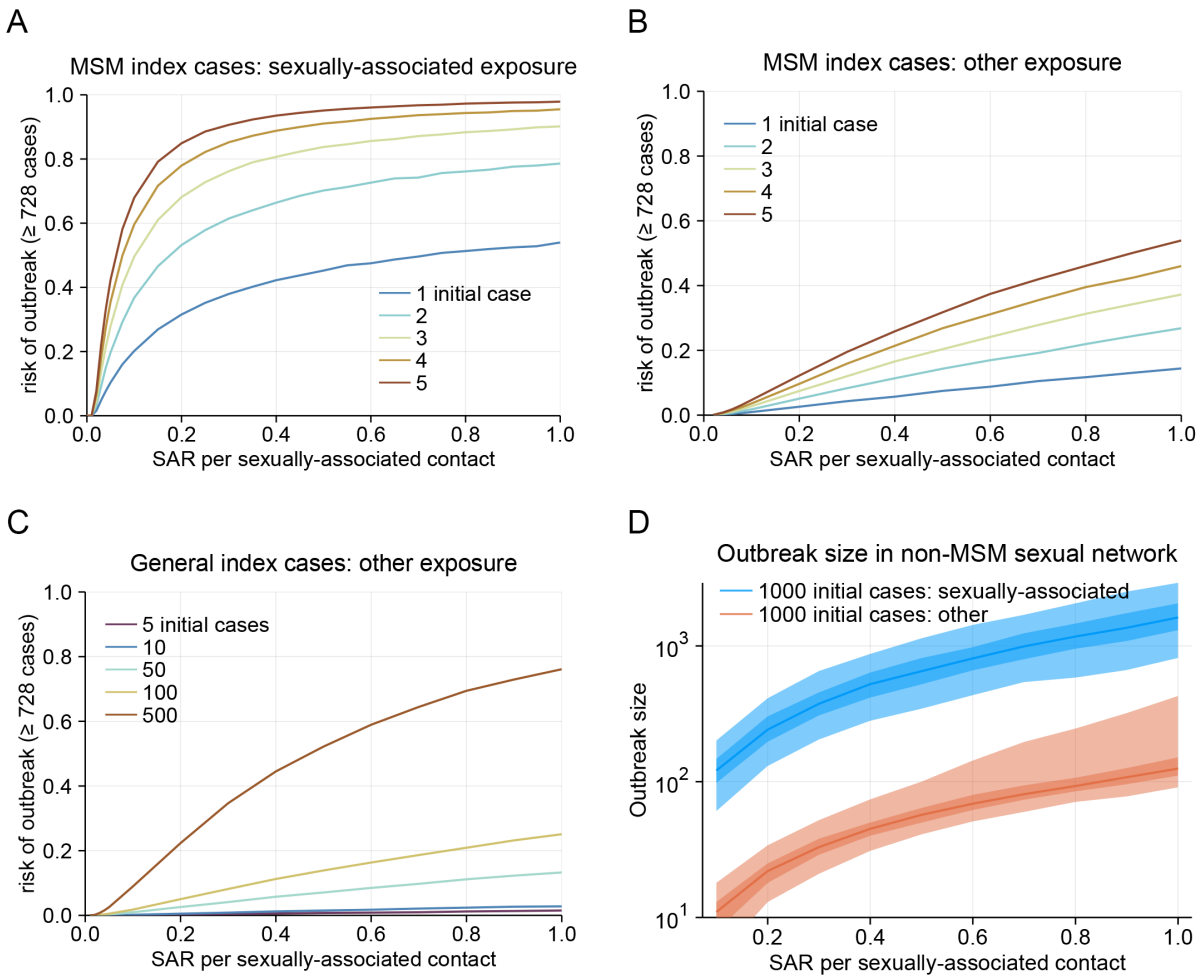

Fig. 1. Likelihood of observing an outbreak given introduction events of different profiles. **(A–C)** The likelihood of observing an outbreak of the current size (728 cases) or greater over the MSM sexual contact network given initial cases who are: (A) MSM with sexually-associated exposure; (B) MSM with non-sexually-associated exposure; (C) random cases from the general population with non-sexually-associated exposure. The likelihood was computed from 100,000

simulations for each value of SAR varied between 0% and 100%. **(D)** Simulated outbreak sizes over non-MSM sexual contact network given 1,000 non-MSM initial cases who have had sexually-associated exposure (blue) or non-sexually-associated exposure (red).

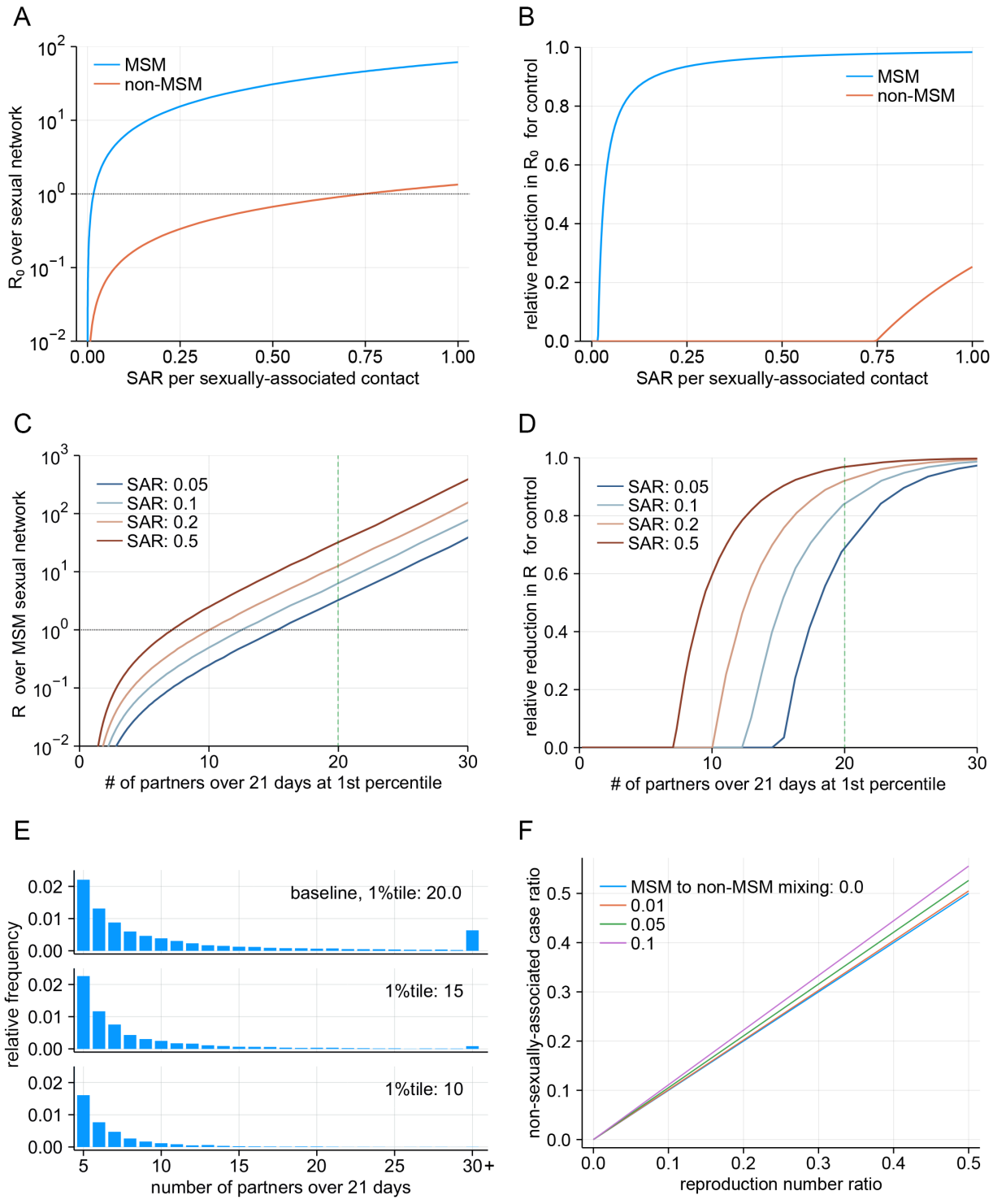

Fig. 2. Basic reproduction number (R_0) of monkeypox over sexual contact networks and control. (A) Projected R_0 over the MSM and non-MSM sexual contact networks based on the Natsal sexual partnership datasets. The dotted horizontal lines denote the epidemic threshold (R_0 = 1). **(B)** Relative reduction in R_0 required to bring the outbreak under control. **(C)** Projected reproduction number (R) over the MSM sexual contact networks with different levels of the partnership distribution tail. Holding the body shape of the distribution (see *Supplementary materials* for details) constant, we adjusted the parameter of the Weibull distribution to reduce the weight of the distribution tail, which we assume reflects the effect of interventions for those with highest numbers of partners. The degree of reduction in the distribution tail was represented by the upper 1st percentile of the resulting (effective) number of 21-day sexual partners (among MSM with at least one partner over 21 days). Dashed green lines indicate the upper 1st percentile of the original Weibull distribution fitted to the Natsal datasets (baseline). Colours denote different assumptions for the baseline SAR, i.e. risk of infection per contact without interventions. **(D)** Relative reduction in R required for control with different levels of the partnership distribution tail. Using the R corresponding to the adjusted Weibull distribution as the baseline, additional relative reduction required to bring the outbreak under control is shown. **(E)** Modelled 21-day effective sexual partnership distributions among MSM with different levels of distribution tail. Histograms represent modified Weibull distributions under interventions focusing on those with highest numbers of partners (with the upper 1st percentile of 15 and 10). The original distribution fitted to the Natsal datasets (upper 1st percentile: 20.0) is shown as a baseline. Only the range $x \geq 5$ is shown for readability; see Figure S6 for the range $1 \leq x \leq 4$. **(F)** The relationship between the reproduction number ratio and the asymptotic proportion of non-sexually-associated cases among total cases. The reproduction number ratio is defined as the ratio between the reproduction number via non-sexually-associated routes of transmission and

that of the sexually-associated route. The “MSM to non-MSM mixing” parameter denotes the average proportion of non-MSM sexual partners a typical sexually-associated MSM case would have. The mixing parameter of 0.0 corresponds to the 1:1 line.