

1 **The roles of unrecognized monkeypox cases, contact isolation and vaccination in determining**
2 **epidemic size in Belgium. A modelling study**

3

4 Christophe Van Dijck, MD*

5 Niel Hens, PhD

6 Chris Kenyon, MD PhD *

7 Achilleas Tsoumanis, MSc

8

9 Author affiliations:

10 Institute of Tropical Medicine, Antwerp, Belgium (C. Van Dijck, C. Kenyon, A. Tsoumanis);
11 University of Antwerp, Belgium (C. Van Dijck, A. Tsoumanis, N. Hens); University of Cape Town,
12 Observatory 7700, South Africa (C. Kenyon); and Hasselt University, Hasselt, Belgium (N. Hens)

13

14 *Corresponding author. HIV/STI Unit, Institute of Tropical Medicine, Nationalestraat 155, Antwerp,
15 2000, Belgium. Tel: +32 3 345 58 65; Fax: +32 3 2480831; E-mail: cvandijck@itg.be

16 *Alternate corresponding author. HIV/STI Unit, Institute of Tropical Medicine, Nationalestraat 155,
17 Antwerp, 2000, Belgium. Tel: +32 3 2480796; Fax: +32 3 2480831; E-mail: ckenyon@itg.be

18

19 Running title: Monkeypox in Belgium: a network model

20 Keywords: Monkeypox, mathematical model, outbreak, vaccination, MSM

21 Word count: Text: 1328 words, Abstract: 50 words, References: 12

22 **Abstract**

23 We used a network model to simulate a monkeypox epidemic among men who have sex with men.

24 Our findings suggest that unrecognized infections have an important impact on the epidemic, and that

25 vaccination of individuals at highest risk of infection reduces epidemic size more than post-exposure

26 vaccination of sexual partners.

27 **Background**

28 Monkeypox is a viral zoonosis whose spread was, until recently, almost exclusively limited to Central
29 and West Africa. Since May 2022, over 15,000 cases of monkeypox have been confirmed from every
30 continent excluding Antarctica (<https://ourworldindata.org/monkeypox>, 24 July 2022). In this multi-
31 country outbreak, the number of cases resulting from human-to-human transmission is much higher
32 than ever reported, and unlike the outbreaks in Africa, many cases bore several hallmarks of sexual
33 transmission. Most cases were young men and where this information was available, typically men
34 who have sex with men (MSM) with high rates of partner change (termed higher risk-, or HR-MSM).
35 [1,2] Furthermore, monkeypox was frequently linked to sexual encounters and presented with
36 localized anogenital lesions compared to the generalized skin lesions typically associated with
37 monkeypox. [1,2] We and others have noted that a sizeable proportion of cases report few, atypical,
38 or absent symptoms. [3] This could have an important impact on transmission of the monkeypox
39 virus. Public health recommendations to contain the epidemic include isolation of cases, requesting
40 close contacts to abstain from sex and pre- or post-exposure (ring) vaccination of individuals at high
41 risk of infection with a smallpox vaccine. [4–6]

42 Previous modelling studies have estimated that monkeypox has epidemic potential in the general
43 population, but that such epidemics can generally be contained by case isolation, contact tracing
44 and/or ring vaccination. [7–10] These efforts have, thus far, been insufficient to contain the epidemic.
45 [8]

46 In this manuscript we evaluate the impact of undiagnosed infections on a sexually associated
47 monkeypox outbreak in an MSM sexual network, and we test the hypothesis that contact tracing or
48 vaccination reduce the epidemic. We do this using a network-based model, parameterized with
49 Belgian MSM behavioral data.

50 **Methods**

51 Network model

52 Building on a previously published separable temporal exponential family random graph model of a
53 Belgian MSM population, [11] we added a population of HR-MSM which was parameterized with
54 data from the cohort of HR-MSM that was included in the Preventing Resistance in Gonorrhea
55 (PReGo) study in Belgium [12]. The model was refined to include main and casual partnerships
56 among low-risk (LR) and HR-MSM in terms of number of partners and frequencies of sexual
57 encounters. Total size of the population was 10,000 MSM, 3,000 of whom were categorized as HR-
58 MSM.

59 The next paragraphs briefly summarize the main characteristics of the inter- and intra-host processes
60 in the model for each scenario. In every scenario, ten cases of monkeypox were introduced among
61 HR-MSM on day 1. All scenarios were run 100 times for 720 days. For further details, references and
62 explanations for the assumptions made, please see Supplement 1.

63 Baseline scenario

64 Scenario A was the baseline scenario to which the remaining scenarios were compared (Table 1).
65 During each sexual encounter between an infectious and a susceptible individual, we assumed a 20%
66 transmission probability of monkeypox. After a uniform incubation period of 7 days, exposed
67 individuals became infectious for 21 days. Fifty per cent of infectious individuals were diagnosed
68 with monkeypox after an average patient delay plus diagnostic delay of 14 days since the start of the
69 infectious period. Diagnosed individuals ceased sexual activity for the next 28 days. The remaining
70 undiagnosed individuals continued having sexual encounters. All cases recovered on day 21, after
71 which lifelong immunity against reinfection was assumed.

72 Undiagnosed infections

73 To evaluate the impact of undiagnosed infections on the epidemic, scenario Z provided an alternative
74 to scenario A in which 0% of infections remained undiagnosed.

75 Per-encounter transmission probability

76 Scenarios X and Y were identical to scenario A, except for the per-encounter monkeypox
77 transmissibility probability, which was set to 10% and 30%, respectively.

78 Partner notification, post-exposure vaccination and pre-exposure vaccination

79 In scenarios B to I, individuals diagnosed with monkeypox notified 10% of their partners of the last
80 21 days prior to diagnosis. All notified partners ceased sexual activity for the next 28 days.
81 Additionally, in scenario C, notified partners of the last seven days prior to the index partner's
82 diagnosis were vaccinated (post-exposure vaccination). In scenarios D to I, pre-exposure vaccination
83 was done at day 1 of the model, in 1% to 50% of HR-MSM. Both pre- and post-exposure vaccination
84 were assumed to prevent infection in 85% of vaccinees and have a lifelong effectiveness against
85 infection. Childhood smallpox vaccination was not taken into account in the model.

86 Sensitivity analysis

87 In a sensitivity analysis, we repeated all scenarios, while introducing one additional monkeypox case
88 per week among HR-MSM, which represents an infection imported by travel.

89 **Results**

90 The baseline scenario, in which half of the monkeypox cases remained undiagnosed, resulted in a
91 median of 1,442 (IQR 1,073 - 1,650) cases by day 720 (Table 1 and Figure S1 in Supplement 2). This
92 was almost eight-fold higher than scenario Z, in which all cases were diagnosed (median of 185, IQR
93 113 – 296 cases). Simulations with 10% and 30% transmission probability per sexual encounter
94 resulted in unrealistically small (median 71, IQR 56 – 86 cases) or large (3,812, IQR 3,660 – 3,932
95 cases) epidemics, respectively.

96 If 10% of contacts of diagnosed cases abstained from sex (scenario B), the median number of cases by
97 day 720 was reduced to a median of 943 (IQR 636 – 1,284), which represents a 35% reduction
98 compared to baseline (Table 1 and Figure S2 in Supplement 2). Post-exposure vaccination of 10% of
99 contacts (scenario C) had relatively limited additional impact (40% reduction compared to scenario A,
100 to a median of 867, IQR 591 – 1,168 cases). It also required a median of 68 (IQR 46 – 82) contacts to
101 be vaccinated and did not reduce epidemic duration compared to scenario B. Pre-exposure vaccination

102 of a comparable number of HR-MSM ($n = 75$, scenario E) at day 1 was slightly more effective than
103 post-exposure vaccination (reduction of 43% of cases compared to scenario A). Pre-exposure
104 vaccination of 5%, 25% and 50% of HR-MSM resulted in a 56%, 91% and 95% reduction in number
105 of cases, respectively. The epidemics in the sensitivity analysis were much larger and more protracted,
106 with much lower impact of all interventions on epidemic size. None the less in this analysis, pre-
107 exposure vaccination of 150 HR-MSM reduced the epidemic size to a greater extent than post-
108 exposure vaccination of a similar number of contacts (Table S1 in Supplement 2).

109

110 **Discussion**

111 The results of this model suggest that undiagnosed monkeypox infections may have an important
112 impact on the epidemic. Secondly, our findings suggest that contact tracing helps to reduce epidemic
113 size even if only 10% of contacts effectively ceased sexual activity. Finally, if only a small proportion
114 of partners can be traced, post-exposure vaccination of those partners may be less effective than
115 vaccinating a random proportion of individuals at highest risk of infection, and in our model this
116 effect became more pronounced in scenarios with a weekly influx of new cases from other
117 endemic/epidemic regions via travel.

118 The data presented here should be interpreted in the context of the design of the model and the
119 assumptions made to parameterize it. We currently do not have accurate estimates of key parameters
120 such as the proportion with unrecognized infections and the per-encounter transmission probability
121 and how this varies according to type of (sexual) contact. In addition, our model did not capture
122 superspreading events, which may have played an important role in the current outbreak. Finally, we
123 modelled a relatively limited set of parameters.

124 Network-based models such as the one used here are particularly suitable to study transmission of an
125 infectious disease in a densely connected sexual network of MSM. They have a proven utility in
126 modelling other STIs such as gonorrhoea and HIV, [11] and are likely to provide a more accurate
127 representation of the sexual networks responsible for STI spread than the branching process models
128 previously used to model monkeypox transmission among MSM. [6,8]

129 In conclusion, our model emphasizes the need to quantify key parameters such as transmission
130 probability and the proportion of monkeypox infections that are unrecognized. A key finding is that
131 pre-exposure vaccination of individuals at highest risk of infection may be more effective than post-
132 exposure contact vaccination.

133

134 **Notes**

135 Acknowledgements

136 Nil

137 Potential conflicts of interest

138 None to declare. All the authors declare that they have no conflicts of interest

139 Availability of data and materials

140 The code used for the model is available from the corresponding author

141 Funding

142 This research did not receive any specific grant from funding agencies in the public, commercial, or
143 not-for-profit sectors.

144 Authors' contributions

145 CK, AT and CVD conceptualized the study and, CVD and AT analyzed the data and drafted the
146 manuscript, CK and NH revised the manuscript. All authors reviewed and approved the final
147 manuscript.

148

149 **References**

- 150 1. Vivancos R, Anderson C, Blomquist P, et al. Community transmission of monkeypox in the
151 United Kingdom, April to May 2022. *Euro Surveill* **2022**; 27:1–4.
- 152 2. Thornhill JP, Barkati S, Walmsley S, et al. Monkeypox Virus Infection in Humans across 16
153 Countries — April–June 2022. *N Engl J Med* **2022**;
- 154 3. Asymptomatic monkeypox virus infections among male sexual health clinic attendees in
155 Belgium. *medRxiv* **2020**; :19.
- 156 4. UK Health Security Agency (UKHSA). Monkeypox contact tracing classification and

- 157 vaccination matrix. V10. 2022: 2–3. Available at:
158 [https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/f](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1087450/monkeypox-contact-tracing-classification-and-vaccination-matrix-version-10-1-july-2022.pdf)
159 [ile/1087450/monkeypox-contact-tracing-classification-and-vaccination-matrix-version-10-1-](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1087450/monkeypox-contact-tracing-classification-and-vaccination-matrix-version-10-1-july-2022.pdf)
160 [july-2022.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1087450/monkeypox-contact-tracing-classification-and-vaccination-matrix-version-10-1-july-2022.pdf). Accessed 1 July 2022.
- 161 5. Robert Koch-Institut. Epidemiologisches 2022 Bulletin. **2022**; :1–148.
- 162 6. European Centre for Disease Prevention and Control (ECDC). Considerations for contact
163 tracing during the monkeypox outbreak in Europe, 2022. Stockholm: 2022.
- 164 7. Bisanzio D, Reithinger R. Projected burden and duration of the 2022 Monkeypox outbreaks in
165 non-endemic countries. *The Lancet Microbe* **2022**;
- 166 8. Endo A, Murayama H, Abbott S, et al. Heavy-tailed sexual contact networks and the
167 epidemiology of monkeypox outbreak in non-endemic regions, May 2022. *medRxiv* **2022**;
168 :2022.06.13.22276353.
- 169 9. Grant R, Nguyen LBL, Breban R. Modelling human-to-human transmission of monkeypox.
170 *Bull World Health Organ* **2020**; 98:638–640.
- 171 10. Jezek Z, Grab B, Dixon H. Stochastic model for interhuman spread of monkeypox. *Am J*
172 *Epidemiol* **1987**; 126:1082–1092.
- 173 11. Buyze J, Vanden Berghe W, Hens N, Kenyon C. Current levels of gonorrhoea screening in
174 MSM in Belgium may have little effect on prevalence: a modelling study. *Epidemiol Infect*
175 **2018**; 146:333–338.
- 176 12. Van Dijck C, Tsoumanis A, Rotsaert A, et al. Antibacterial mouthwash to prevent sexually
177 transmitted infections in men who have sex with men taking HIV pre-exposure prophylaxis
178 (PReGo): a randomised, placebo-controlled, crossover trial. *Lancet Infect Dis* **2021**; 21:657–
179 667.
- 180

182 **Table 1: Model scenarios and results**

Scenario	Probability of transmission per sexual encounter (%)	Proportion of undiagnosed cases (%)	Proportion of Contacts Traced (%)	PEP vaccination	PrEP vaccination = Proportion of HR-MSM vaccinated at day 1 (%)	Proportion of ongoing epidemics at day 720 (%)	Number of cases by day 720, median (IQR)	Epidemic duration, median (IQR) ^a	Number of people vaccinated, median (IQR)	Reduction in number of cases compared to scenario A (%)
A	20	50	0	No	0	55	1,442 (1,073 – 1,650)	720 (621 - 720)	0	REF
B	20	50	10	No	0	47	943 (636 – 1,284)	690 (566 - 720)	0	35
C	20	50	10	Yes	0	49	867 (591 – 1,168)	714 (557 - 720)	68 (46 - 82)	40
D	20	50	10	No	1	43	924 (533 – 1,229)	682 (558 - 720)	30 (30 - 30)	36
E	20	50	10	No	2.5	37	824 (493 – 1,044)	631 (494 - 720)	75 (75 - 75)	43
F	20	50	10	No	5	29	632 (327 - 865)	595 (409 - 720)	150 (150 - 150)	56
G	20	50	10	No	10	13	321 (188 - 525)	408 (280 - 596)	300 (300 - 300)	78
H	20	50	10	No	25	0	136 (95 - 195)	235 (171 - 314)	750 (750 - 750)	91
I	20	50	10	No	50	0	72 (57 - 86)	131 (105 - 157)	1,500 (1,500 – 1,500)	95
X	10	50	0	No	0	0	71 (56 - 85)	138 (114 - 190)	0	-
Y	30	50	0	No	0	2	3,812 (3,660 – 3,932)	532 (503 - 585)	0	-
Z	20	0	0	No	0	0	185 (113 - 296)	277 (198 - 404)	0	-

183 ^a this number represents an underestimation as epidemics that were still ongoing at day 720 were assumed to last 720 days

184 IQR = interquartile range; MSM = men who have sex with men; HR-MSM = high-risk MSM; PEP = post-exposure prophylactic (vaccination); PrEP = pre-exposure prophylactic (vaccination)

185