The Journal of Infectious Diseases

BRIEF REPORT

Accumulation of immunity in heavy-tailed sexual contact networks shapes mpox outbreak sizes

Hiroaki Murayama[a], Carl A. B. Pearson[b,c,d], Sam Abbott[b,c], Fuminari Miura[e,f], Sung-mok Jung[g], Elizabeth Fearon[c,h,i], Sebastian Funk[b,c], Akira Endo[b,c,j,1]

[a]School of Medicine, International University of Health and Welfare, Narita, Japan; [b]Department of Infectious Disease Epidemiology, London School of Hygiene & Tropical Medicine, London, UK; [c]Centre for Mathematical Modelling of Infectious Diseases, London School of Hygiene & Tropical Medicine, London, UK; [d]South African DSI-NRF Centre of Excellence in Epidemiological Modelling and Analysis (SACEMA), Stellenbosch University, Stellenbosch, Republic of South Africa; [e]Centre for Infectious Disease Control, National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands; [f]Center for Marine Environmental Studies (CMES), Ehime University, Ehime, Japan; [g]Carolina Population Center, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; [h]Department of Global Health and Development, London School of Hygiene & Tropical Medicine, London, UK; [i]Institute for Global Health, University College London, London, UK; [j]School of Tropical Medicine and Global Health, Nagasaki University, Nagasaki, Japan

Many countries affected by the global outbreak of mpox in 2022 have observed a decline in cases. Our mathematical model accounting for heavy-tailed sexual partnership distributions suggests that mpox epidemics can hit the infection-derived herd immunity threshold and begin to decline with less than 1% of sexually active MSM population infected regardless of interventions or behavioural changes. Consistently, we found that many countries and US states experienced an epidemic peak with cumulative cases of around 0.1–0.5% of MSM population. The observed

Corresponding author: Akira Endo. Address: London School of Hygiene and Tropical Medicine, Keppel Street, London, WC1E 7HT, United Kingdom. Email: akira.endo@lshtm.ac.uk. Phone number: +44 (020) 7299 4755

DOI: 10.1093/infdis/jiad254

decline in cases may not necessarily be attributable to interventions or behavioural changes primarily.

Keywords: mpox, herd immunity, depletion of susceptibles, men who have sex with men (MSM), heavy-tailed network

INTRODUCTION

Since May 2022, sustained local transmission of mpox (formerly monkeypox) has been confirmed in Europe, the Americas and other regions where the virus was not observed to circulate previously. The novel profile of this outbreak, i.e. the rapid spread predominantly among men who have sex with men (MSM) unlike previous outbreaks, can be explained by sexually-associated transmission and a heavy-tailed empirical distribution of sexual partners (i.e. a small number of people have disproportionately many partners) among MSM, which could lead to sustained human-to-human transmission in this population while not in others (1). However, by the end of 2022, many of those countries saw an apparent slowdown in growth of cases followed by a decline. In this study, we show that accumulation of immunity amongst individuals with highest numbers of partners can explain this decline, and thus should be accounted for when attempting to estimate the impact of interventions and behavioural changes.

METHODS

We developed a mathematical model of mpox transmission over the MSM sexual contact network that accounts for the accumulation of infection-derived immunity in a heavy-tailed MSM sexual contact network (see *Supplementary Materials* for methodological details). We represented the heavy-tailed distribution of sexual partners among MSM over the infectious period of mpox (assumed to be 14 days) as a left-truncated Weibull distribution parameterised in our previous study (1). We assumed that non-MSM transmission dynamics is negligible because transmission over MSM sexual networks could well approximate the overall dynamics of mpox in the current outbreak. The risk of an individual being in contact with an infectious sexual partner was modelled as proportional to the number of their sexual partners over 14 days. Upon recovery, infected individuals were assumed to develop long-term immunity and maintain their sexual behaviour without further risk of re-infection. To improve robustness of the model to uncertainties in time-related parameters such as generation time and reporting delay, we used cumulative incidence as a measure of epidemic progression instead of time—i.e. we directly modelled the relationship between the cumulative number of cases per MSM population and the effective reproduction number R_{eff}.

To compare our model outputs with observed mpox outbreak data (2,3), we identified the period during which reported cases likely peaked in different populations (European countries, the US,

Canada and US states). We fitted Gompertz curves to the cumulative reported case count over time in each of the included countries and US states and estimated the cumulative number of mpox cases per MSM population size by the apparent epidemic peak (cumulative incidence proportion at a peak of an epidemic; CIPP), where the estimated daily epidemic growth rate is consistent with a near-zero value (i.e. within ±0.01). We defined the "consensus range" as a set of values that lies within the CIPPs of at least 50% of included countries/states. That is, the consensus range represents the CIPP values shared by the majority of the countries/states.

RESULTS

Using publicly available mpox outbreak data (2,3), we identified the period during which reported cases likely peaked in different populations (European countries, the US, Canada and US states) and estimated the peak level per MSM population size. The consensus range among the included countries suggested that their epicurves were generally consistent (though with some apparent outliers) with a saturation of growth when the cumulative case count reached 0.15–0.47% of the estimated MSM population size (Fig. 1A). Moreover, 22 out of 30 (73%) countries had their CIPP ranges overlapping at 0.24% (Fig. S5A). The consensus range among US states was 0.11–0.24% and CIPPs of 25 out of 43 (58%) states shared 0.16–0.18% in common (Fig. 1B, Fig. S5B).

As individuals with highest numbers of partners are most likely to be infected in the earliest phase of an epidemic, the effective reproduction number R_{eff} would rapidly decline as transmission progresses, even in the absence of any interventions or behavioural changes. Assuming SAR values of 10%, 20% and 30%, our model found that, while R_0 (the initial value of R_{eff}) is well above 1, R_{eff} rapidly decreases and crosses 1 after observing relatively few cases (< 1% of the MSM population) (Fig. 1C). The herd immunity thresholds given an SAR of 10%, 20% and 30% were estimated to be 0.15%, 0.43%, and 0.74% of the MSM population, respectively. These thresholds are substantially lower than the classical herd immunity threshold in a homogeneous population: $1 - \frac{1}{R_0}$ (55%, 78% and 85%, respectively, based on the values of R_0 in our model) and roughly align with estimated CIPP ranges. We showed in Fig. 1D that the observed consensus ranges of CIPPs are consistent with SARs of around 10–20% (global) or 10–15% (US states) if they are formed primarily by infection-derived immunity and our model assumptions are valid. We also estimated the final size of an epidemic driven by infection-derived immunity alone corresponding to different SAR values (Fig. 2). The estimated final epidemic size was generally more than double the size of CIPP, contrary to outcomes for a conventional homogeneously mixing transmission model (see *Supplementary Materials*). This suggests that the decreasing phase of an epidemic with highly heterogeneous transmission patterns may be more gradual than that of a homogeneous epidemic. The estimated final size relative to CIPP increased with SAR.

DISCUSSION

Many countries saw a dramatic decrease in mpox cases to which various reactions since the identification of the current outbreak could have contributed, including public health interventions such as contact tracing and vaccination (4,5) and heightened awareness triggering behavioural changes among high-risk populations (6). However, available evidence is overall insufficient to quantify the relative contribution of these responses to the decline in different countries and operational indicators suggest impact may have been blunted by practical factors. In some settings, contact tracing and ring vaccination have been hampered by difficulty identifying contacts and a limited consent rate for post-exposure vaccination among those traced (5). Vaccine supplies were initially limited, slowing rollout of mass vaccination and precluding many countries from achieving substantial coverage before observing a peak (7,8)—moreover, the time required for eligible individuals to complete the dosing schedule (e.g. 2 doses 4 weeks apart for JYNNEOS vaccine in the US (9)) and for immunity to be established (suggested to be up to two weeks by public authorities although evidence remains limited (10)) renders prompt epidemic control by vaccination more challenging. Providing a coherent explanation to the observed decline in growth in many affected countries at different times and outbreak sizes is not straightforward.

Another key mechanism that can shape epidemic trends is the accumulation of infection-derived immunity, known as (infection-derived) 'depletion of susceptibles' or 'herd immunity' (11). Highly heterogeneous contact patterns are known to lead to a high basic reproduction number (R_0) but lower the herd immunity threshold for immunising infections (12)—i.e. when a small fraction of individuals exhibit disproportionately high contact rates, the initial epidemic growth could be accelerated by transmission among these individuals but this growth would also be short-lived as these individuals become rapidly infected and immune and no longer contribute to the outbreak. The heavy-tailed nature of the sexual partnership distribution among MSM could create these conditions and thus explain the initial growth of mpox cases in many affected countries (1) but also their quick saturation. Britton et al. (13) showed in their illustrative example that introducing heterogeneity into a SARS-CoV-2 transmission model lowers the herd immunity threshold from 67% to 50%. However, compared with the context of respiratory infections, heterogeneity relevant to the transmission dynamics of mpox is more extreme due to the heavy-tailed nature of sexual contact patterns. As a result, our model assuming accumulation of infection-derived immunity but no interventions or behavioural changes replicated mpox epidemics over an MSM sexual contact network starting to decline even before 1% of MSM population experiences infection.

Attributing the observed decline in cases to interventions or behavioural changes without accounting for rapid accumulation of infection-derived immunity can bring a risk of misleading policy assessment. While these factors may also have had effects, our analyses without assuming them find plausible scenarios in which infection-derived immunity alone could explain the observed peak sizes. The observed CIPPs in the global outbreak in 2022 ranging around 0.1–

0.5% as opposed to the classical herd immunity threshold of > 50% for an R_0 of > 2 underscore the role of heavy-tailed sexual contact networks. Our model suggests that accumulation of infection-derived immunity among high-contact individuals in those networks is likely to have played a key role in limiting peak outbreak sizes. Meanwhile, we also observed variations in CIPPs that may reflect other factors including interventions, behavioural changes and differences in case ascertainment. Although we did not find a clear correlation between CIPPs and allocated vaccine doses in US states, we found that later epidemic onset was associated with lower CIPP (Fig. S2). This may indicate possible impacts of interventions and behavioural changes because places with later epidemic onset may have had more lead time to implement these early in their outbreaks. However, interpreting these observed correlations requires caution because of possible confounding—states with more cases may be more likely to be allocated more vaccines, while countries and states with more active MSM populations may have been more likely to see mpox cases in the earlier phase of the outbreak. More direct and robust evidence would be required to draw conclusions regarding the effects of interventions and behavioural changes in lowering epidemic peaks. Even given a role for accumulation of infection-derived immunity in reaching epidemic turnover, it is still essential to characterise the influence of behavioural changes and public health interventions. Our model projected that, in the absence of behavioural changes and interventions, the declining phase of an epidemic in a heavy-tailed contact network may be gradual especially if the SAR is high. This means that, regardless of the factors driving peak incidence, promoting and providing effective and sustainable means of prevention, particularly vaccination, to those at risk—not only in newly affected countries but also in countries where mpox has long been endemic—serves as key operations to bring the disease spread under control and to minimise the disease burden. Ensuring access to prevention for individuals at the centre of sexual networks is crucial as the acceptance and effectiveness among this group would contribute most to epidemic control. This is further emphasised by the reported severe forms of mpox among cases with advanced HIV infection (14) because the sexual network core groups and people living with HIV often overlap (15). Sustained resourcing despite the declining trend is particularly important given that there might be waning of immunity or incomplete protection, or turnover in the population of MSM with the most partners, which would lead to the replenishment of susceptible individuals and therefore of epidemic potential.

Our simulations suggest that accumulation of infection-derived immunity can plausibly reproduce the observed decline in mpox cases, but with a number of key limitations, especially uncertainty in characterising the transmission network and SARs (see *Supplementary Materials* for details). Our model provides a parsimonious explanation of the observed decline in mpox cases but future work with more detailed data may discriminate the role of interventions and behavioural change from saturation of infection. Such future work would help better understand the determinants of mpox epidemic trends and also assess the risk of future resurgence.

References

1. Endo A, Murayama H, Abbott S, Ratnayake R, Pearson CAB, Edmunds WJ, et al. Heavy-tailed sexual contact networks and monkeypox epidemiology in the global outbreak, 2022. Science (1979). 2022;eadd4507.
2. Global.health. Monkeypox 2022 global epidemiology; Report 2022-09-23 [Internet]. 2022 [cited 2022 Nov 10]. Available from: https://www.monkeypox.global.health/
3. Centers for Disease Control and Prevention. 2022 Outbreak Cases and Data [Internet]. 2022 [cited 2022 Oct 18]. Available from: https://www.cdc.gov/poxvirus/monkeypox/response/2022/index.html
4. UK Health Security Agency. Monkeypox vaccination recommendations [Internet]. 2022 [cited 2022 Oct 18]. Available from: https://www.gov.uk/government/publications/monkeypox-vaccination
5. Vivancos R, Anderson C, Blomquist P, Balasegaram S, Bell A, Bishop L, et al. Community transmission of monkeypox in the United Kingdom, April to May 2022. Eurosurveillance [Internet]. 2022 Jun 2 [cited 2023 May 17];27(2):2200422. Available from: https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2022.27.22.2200422
6. Delaney KP. 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. 2022;71.
7. Centers for Disease Prevention and Control. Monkeypox Vaccine Administration in the U.S. [Internet]. 2022 [cited 2022 Oct 18]. Available from: https://www.cdc.gov/poxvirus/monkeypox/response/2022/vaccines_data.html
8. UK Health Security Agency. Investigation into monkeypox outbreak in England: technical briefing 8 [Internet]. 2022 [cited 2022 Oct 19]. Available from: https://www.gov.uk/government/publications/monkeypox-outbreak-technical-briefings/investigation-into-monkeypox-outbreak-in-england-technical-briefing-8
9. Centers for Disease Control and Prevention. Monkeypox Vaccination Basics | Monkeypox | Poxvirus | CDC [Internet]. 2022 [cited 2022 Nov 10]. Available from: https://www.cdc.gov/poxvirus/monkeypox/vaccines/vaccine-basics.html
10. Zaeck LM, Lamers MM, Verstrepen BE, Bestebroer TM, van Royen ME, Götz H, et al. Low levels of monkeypox virus-neutralizing antibodies after MVA-BN vaccination in healthy individuals. Nat Med [Internet]. 2022; Available from: https://doi.org/10.1038/s41591-022-02090-w
11. Ashby B, Best A. Herd immunity. Current Biology [Internet]. 2021 Feb 22;31(4):R174–7. Available from: https://doi.org/10.1016/j.cub.2021.01.006
12. Kiss IZ, Green DM, Kao RR. Infectious disease control using contact tracing in random and scale-free networks. J R Soc Interface [Internet]. 2006 Feb 22;3(6):55–62. Available from: https://doi.org/10.1098/rsif.2005.0079
13. Britton T, Ball F, Trapman P. A mathematical model reveals the influence of population heterogeneity on herd immunity to SARS-CoV-2. Science (1979). 2020;369(6505):846–9.

14. Mitjà O, Alemany A, Marks M, Lezama Mora JI, Rodríguez-Aldama JC, Torres Silva MS, et al. Mpox in people with advanced HIV infection: a global case series. Lancet [Internet]. 2023 Mar 18;401(10380):939–49. Available from: https://doi.org/10.1016/S0140-6736(23)00273-8
15. Rosenberg ES, Sullivan PS, DiNenno EA, Salazar LF, Sanchez TH. Number of casual male sexual partners and associated factors among men who have sex with men: Results from the National HIV Behavioral Surveillance system. BMC Public Health [Internet]. 2011;11(1):189. Available from: https://doi.org/10.1186/1471-2458-11-189

Statement Ethical statement: Not applicable to this study.

Funding statement: AE is supported by JSPS Overseas Research Fellowships. AE and FM are supported by Japan Society for the Promotion of Science (JSPS) *KAKENHI* (to AE, grant number: 22K17329 and to FM, 20J00793). AE and HM are supported by foundation for the Fusion Of Science and Technology (to AE) and Japan Science and Technology Agency Precursory Research for Embryonic Science and Technology (PRESTO; to AE, JPMJPR22R3). SF and SA are supported by Wellcome Trust (to SF, 210758/Z/18/Z). CABP is supported by the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement EBOVAC3 (800176); this Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA. S-mJ is supported by the Centers for Disease Control and Prevention (CDC) SHEPheRD (200-2016-91781). EF is supported by the Medical Research Council, United Kingdom Research and Innovation (MRC-UKRI; MR/S020462/1).

Data and code availability: All data used in this study is publicly available. The analysis codes are available from a GitHub repository: https://github.com/hiroaki-murayama /MPX_depletion_susceptibles.

Conflict of interest: AE received a research grant from Taisho Pharmaceutical Co., Ltd. for research outside this study. FM receive a research grant from AdvanSentinel Inc. for research outside this study.

Authors' contributions: AE conceived of the study. AE and HM collected the data and developed the mathematical model. AE, CABP and HM designed the study. HM implemented the methods. AE and HM wrote the first draft of the manuscript with feedback from all other authors. All authors read and approved the final version of the manuscript.

Corresponding author: Akira Endo. Address: London School of Hygiene and Tropical Medicine, Keppel Street, London, WC1E 7HT. Email: akira.endo@lshtm.ac.uk. Phone number: +44 (020) 7299 4755

FIGURES

Fig. 1. The observed and modelled number of cumulative mpox cases per MSM population. (A, B) Estimated range of cumulative incidence proportion at the peak of an epidemic (CIPP) (A) by country and (B) by US state. We fitted Gompertz curves to the cumulative reported case count over time in each of the included countries and US states and estimated the cumulative number of mpox cases per MSM population size by the apparent epidemic peak, where the estimated daily epidemic growth rate is consistent with a near-zero value (i.e. within ±0.01). Some countries or US states have not clearly passed the peak as of available data (last updated on 15 October 2022 for countries and 15 March 2023 for US states) and therefore the upper limit of CIPP is undetermined (blue bars); others have apparently passed the peak and have both limits for CIPP (red bars). The consensus range of CIPP (values consistent with at least 50% of included countries/states) is shown with light blue shades. (C) Modelled trajectory of the effective reproduction number (R_{eff}) over the course of an epidemic. The reproduction number was computed for three possible values of SAR (0.1, 0.2, and 0.3). (D) Estimated relationship between CIPP and SAR. Thick and thin green areas represent the global and US consensus ranges of CIPPs, respectively.

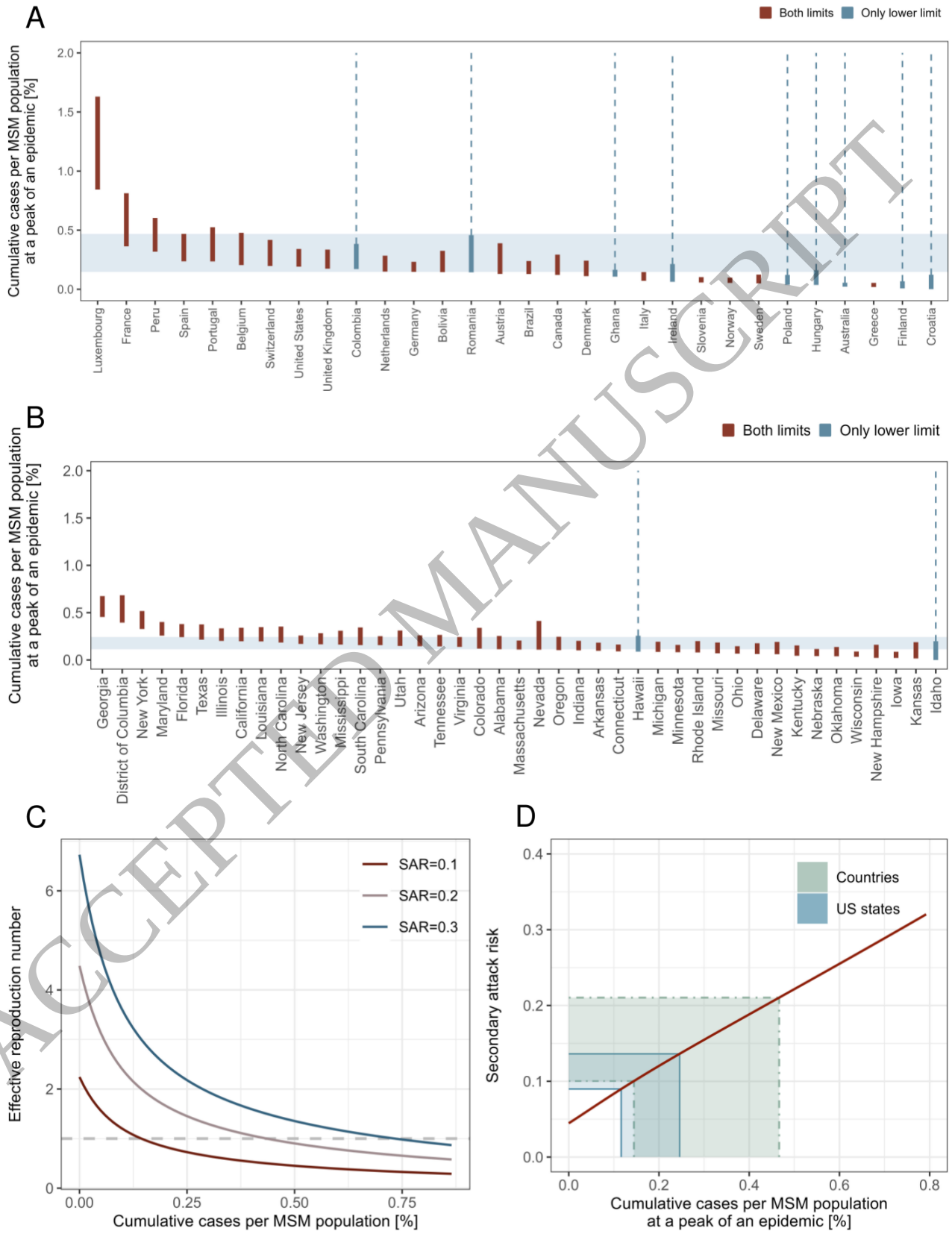

Fig. 2. Estimated peak and final sizes by secondary attack risk in the absence of effective interventions or behavioural changes. Cumulative numbers of cases per MSM population at the peak and at the end of an epidemic estimated by our model accounting for heavy-tailed sexual partnership distribution and infection-derived immunity are shown. For comparison, a dotted line representing the double the outbreak size at the peak is also included.