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Research Letter

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Reproduction number of monkeypox in the early stage of the 2022 multi-country outbreak

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Monkeypox is a sylvatic zoonosis, which is transmitted by close contact and droplet exposure via droplets[1] and is recognized as the most important orthopoxvirus infection after the eradication of smallpox.[2] Sporadic cases of monkeypox virus have been reported with travel to non-African areas before 2022. For example, from September 2018 to July 2021, 7 cases of travellers from Nigeria, which involved an outbreak of 118 confirmed cases during 2017–18, were exported into four countries outside Africa, with 4 cases arrived in the UK and each of the remaining 3 cases arrived in the USA, Israel and Singapore.[3] On 7 May 2022, the World Health Organization was informed of a confirmed case of monkeypox in the UK, an individual who travelled from the UK to Nigeria.[1] Eleven days later, Portugal, Spain and the USA, where outbreaks have rarely occurred, reported 14, 18 and 1 cases of monkeypox, respectively. The World Health Organization declared monkeypox as a public health emergency of international concern on 23 July 2022.[4] At that point, a rapid global response was quickly coordinated, including ring vaccination, following the atypical multi-country outbreak. Understanding the epidemiological metrics (e.g. transmissibility) of monkeypox virus is thus critical for guiding and optimizing public health and social measures required for preventing the spread of monkeypox virus.

The effective reproduction number (R_e) and the incubation period are key epidemiological metrics to adjusting the response against the outbreaks caused by pathogens. R_e is defined as the expected number of secondary infections per primary infection in a partly susceptible population. In this study, we performed a systematic review to synthesize the evidence from published estimates of the effective reproduction number and incubation period for the monkeypox virus. We further selected six countries and estimated the effective reproduction number for the ongoing outbreak between May and July 2022 in each of them (Supplement Methods). We included five countries with confirmed cases exceeding 1000, together with Portugal (i.e. one of the four countries with earliest reported monkeypox cases in 2022).

We identified 276 studies in total by searching PubMed, Embase and Web of Science for articles published until 24 July 2022 in which 172 irrelevant studies were removed and excluded through title and abstract screening (Figure S1). A total of 11 studies were finally included in this review, which provides six R_e estimates in five regions/countries (Congo, Central Africa, England, Portugal and Spain) and seven estimates of incubation periods in five regions/countries (Congo, Central and West Africa, the USA, Netherlands and Germany). Two distinct genetic clades of the monkeypox virus were reported: the west African clade and the central African (Congo Basin) clade. Before 2022, R_e was estimated to be 0.08 (95% CI: 0.02, 0.22) and in the range from 0.21 to 0.58, for the West African clade and the Congo Basin clade, respectively (Table S1). But R_e of the West African clade increased to 1.60 (95% CI: 1.50, 1.70) in England, 1.40 (95% CI: 1.20, 1.60) in Portugal and 1.80 (95% CI: 1.70,

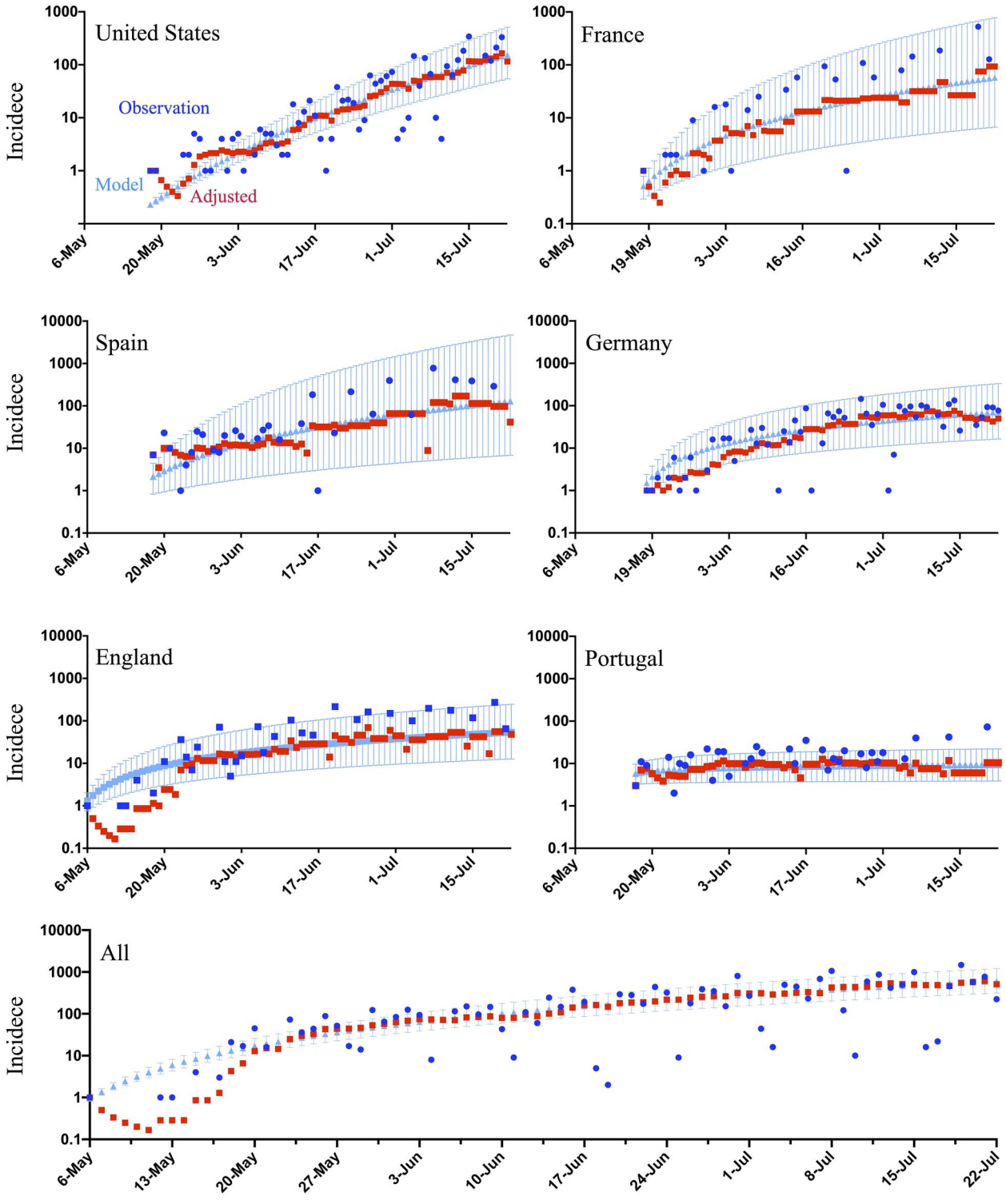

Figure 1. Estimated daily confirmed cases during the period between 6 May and 22 July 2022; we estimate the mean and 95% CI of daily confirmed cases using the sub-exponential model informed by the adjusted (smoothed) observation from the actual observation across five countries and globally; the *X*-axis and *Y*-axis denote the reporting date and the daily cases, respectively.

2.00) in Spain in May to June of the 2022 outbreak.[5] The incubation period ranged from 5 to 41 days and from 8 to 14 days for the West African clade and the Congo Basin clade, respectively (Table S2).

We further estimate the effective reproduction number in outbreaks as of 22 July 2022 (Figure 1, Table S3). For those six countries with increasing confirmed cases, the USA has the highest R_e estimated as 1.95 (95% CrI: 1.82, 2.10), followed by

1.40 (95% CrI: 1.31, 1.56) in France, 1.38 (95% CrI: 1.27, 1.56) in Spain, 1.24 (95% CrI: 1.20, 1.28) in Germany, 1.18 (95% CrI: 1.15, 1.21) in England and 1.02 (95% CrI: 1.01, 1.03) in Portugal (Table S3). We aggregate all cases in 70 countries and estimate R_e as 1.39 (95% CrI: 1.37, 1.42), which is larger than four of the six countries with increasing confirmed cases. Compared with earlier R_e estimates (Tables S1 and S2), transmission may have slowed down recently with increased awareness of the monkeypox epidemic (Table S3), though with $R_e > 1$, further spread is likely without more stringent containment measures. In addition, we conduct a sensitivity analysis of R_e by using unadjusted daily confirmed case data (Table S4) or adjusted cases before peaking incidence for four study countries (Table S5). The incubation period is reported to be 8.5 days (95% CrI: 3.6, 19.9) in the Netherlands,[6] 5 days (range: 0, 20) in Germany[7] and 7.6 days (95% CrI: 6.2, 9.7) in the USA[8] during May 2022 (Table S2).

In the 2022 global outbreak, the multi-country monkeypox virus from the West African clade has a R_e that is a dozen times higher than that in the 1970s (Table S1). It may have found its global march outward into highly interconnected men who have sex with men (MSM) networks, where it can spread via a unique behavioural pattern that is different from the general population. For example, in the UK, there were 54 confirmed cases of monkeypox virus reported in London between 14 May and 25 May 2022, all of which occurred among MSM networks.[9] Male sexual encounters may play a role in transmission of monkeypox viruses, perhaps due to high viremia, local inflammation, imperfection of the blood–testis barrier, testis as an immunologically privileged site and replication in accessory glands. Increased propensity to seek healthcare among MSM may also contribute to increased diagnoses in this group to date. The heterogeneous R_e over regions and its increases may be attributed to the population susceptibility to monkeypox infection due to phasing out of smallpox vaccination in the 1980s, together with waning immunity,[10] which could be validated by further seroprevalence studies.

While we believe that our qualitative findings are robust, our estimates have several limitations. We may overestimate the infection risks in the 2022 outbreaks. The modes of transmission in the reviewed studies are mainly in a general population, which is different from that in the ongoing outbreak in 2022. The estimated R_e has a value >1 across countries; however, it would not denote a risk for the general population; but instead, it would reflect the risk faced by the MSM community.

In conclusion, multiple estimates of the reproduction number have been published for monkeypox. Reliable estimates of its reproduction numbers in an epidemic will aid in the accurate assessment of the impact of control efforts and the potential need to curtail the spread of monkeypox in both the MSM community and the general population.

Supplementary data

Supplementary data are available at *JTM* online.

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Conflict of interest

B.J.C. reports honoraria from AstraZeneca, Fosun Pharma, GlaxoSmithKline, Moderna, Pfizer, Sanofi Pasteur and Roche. The authors report no other potential conflicts of interest.

Authors' contributions

Z.D., Z.S., Y.B., L.W. and B.J.C. conceived the study, designed statistical and modelling methods, conducted analyses, interpreted results, wrote and revised the manuscript; J.L.H.-D., S.J.F., Z.E. and E.H.Y.L. interpreted results and revised the manuscript.

References

1. World Health Organization. Disease Outbreak News. *Monkeypox - United Kingdom of Great Britain and Northern Ireland*. 2022. https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON381 (24June2022,datelastaccessed).
2. World Health Organization. *Monkeypox: Epidemiology, Preparedness and Response for African Outbreak Contexts*. https://openwho.org/courses/monkeypox-intermediate (24 June 2022, date last accessed).
3. Rao AK, Schulte J, Chen T-H *et al*. Monkeypox in a Traveler returning from Nigeria - Dallas, Texas, July 2021. *MMWR Morb Mortal Wkly Rep* 2022; **71**:509–16.
4. Second Meeting of the International Health Regulations. *(IHR) Emergency Committee Regarding the Multi-Country Outbreak of Monkeypox*. 2005. https://www.who.int/news/item/23-07-2022-second-meeting-of-the-international-health-regulations-(2005)-(ihr)-emergency-committee-regarding-the-multi-country-outbreak-of-monkeypox (24 July 2022, date last accessed).
5. Kwok KO, Wei WI, Tang A, Shan Wong SY, Tang JW. Estimation of local transmissibility in the early phase of monkeypox epidemic in 2022. *Clin Microbiol Infect* 2022. https://doi.org/10.1016/j.cmi.2022.06.025.
6. Miura F, Ewijk CE, Backer JA *et al*. Estimated incubation period for monkeypox cases confirmed in the Netherlands, May 2022. *Euro Surveill* 2022; **27**:2200448.
7. Berlin MPX study group, Selb R, Werber D *et al*. A shift from travel-associated cases to autochthonous transmission with berlin as epicentre of the monkeypox outbreak in Germany, may to June 2022. *Euro Surveill* 2022; **27**:2200499.
8. Centers for Disease Control and Prevention. *Technical Report: Multi-National Monkeypox Outbreak, United States, 2022*. 2022. https://www.cdc.gov/poxvirus/monkeypox/clinicians/technical-report.html (10 August 2022, date last accessed).
9. Girometti N, Byrne R, Bracchi M *et al*. Demographic and clinical characteristics of confirmed human monkeypox

virus cases in individuals attending a sexual health centre in London, UK: an observational analysis. *Lancet Infect Dis* 2022; **22**:1321–8. https://doi.org/10.1016/S1473-3099(22)00411-X.

10. Taube JC, Rest EC, Lloyd-Smith JO, Bansal S. The global landscape of susceptibility to orthopoxviruses: the legacy of smallpox vaccination bioRxiv. 2022. https://www.medrxiv.org/content/10.1101/2022.07.29.22278217v1.full.