Estimates of mpox effective reproduction number in Spain, April-August 2022

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https://doi.org/10.1017/S0950268823000985 Published online by Cambridge University Press
Summary

We analyzed the transmission of human mpox virus in Spain by estimating the effective reproduction number of the disease from official surveillance data. Our computations show that this decreased steadily after an initial burst phase, dropping below 1 on July 12, and thus the outbreak was expected to reduce in the following weeks. Differences in trends were found across geographical regions of the country and across the MSM and heterosexual populations.
Introduction

Since April 2022, an increasing number of countries reported confirmed cases of mpox virus (also known as monkeypox virus) with transmission chains not linked to endemic countries [1,2]. On July 23, 2022, the WHO Director-General determined that the mpox outbreak constituted a public health emergency of international importance [3]. As of August 16, 16162 mpox cases had been reported in Europe [4].

In Europe, Spain was the most affected country, followed by Germany and France. The epidemic curve followed similar trends in these countries, peaking in the first week of July and starting to decrease during the second half of the month [5]. The basic reproduction number $R_0$ of the disease has been computed for some European countries [6,7,8], and estimates on the effective reproduction number and instantaneous growth rate are available as well for some countries [9,10,11].

The first case in Spain was identified retrospectively on April 25 2022 [12,13]. Since then, 6284 confirmed cases had been notified to the National Epidemiological Surveillance Network (RENAVE [14,15]) as of August 19 2022. This made Spain the non-endemic country with most confirmed cases in the European region at the time, reporting the second highest number of cases in the world [16]. The spatial distribution of these was not homogeneous: Madrid and Barcelona provinces hosted 35% and 28% of the total cases respectively (Fig. 1). To date, the disease is predominantly prevalent among men, with less than 2% of the cases being notified among women. Two patients under 3 years old have also been reported, as well as two deceased cases.

Even though the incidence of the disease decreased substantially in Europe after the autumn of 2022 winter of 2022, further epidemiological insights are still to be drawn from the outbreak [1,2]. While several studies in the country have addressed the clinical...
characteristics of the disease [17,18,19], assessments of the factors relevant for the containment of the disease at the population level are still in need. These are expected to provide valuable guidance in the design of effective public health policies, and improved preparedness for future outbreaks of the disease or other diseases sharing epidemiological features with it.

Here, we compute estimates of the effective reproduction number ($R_t$) during the mpox outbreak in Spain, to evaluate the evolution of its transmission and to investigate its possible differences across different subgroups of the population. In particular, we consider transmission across geographical regions of the country, and transmission across MSM and heterosexual individuals, as both the geographical setting [19,20,21] and sexual activity have been identified as relevant factors in the spread of the disease [1,18,22].

**Material and Methods**

We used confirmed cases notified to the National Epidemiological Surveillance Network (RENAVE) from April 25 to August 19 2022. These were used in the method of Cori et al [23,24,25] to estimate the $R_t$ of the disease. Several factors were taken into account for this:

- The date for new cases was chosen to be the date of symptoms onset, offset by the incubation period (see next item), as usual when computing $R_t$ estimates [26]. No asymptomatic transmission was assumed in the model. While some instances of transmission from individuals presenting no mpox-related symptoms have been observed [27,28], their occurrence has been rare. We thus assume that these do not represent a significant source of infection and that their possible effect on the model output can be disregarded.

- The output dates of the model were offset by an incubation time of 9 days [25], in agreement with several findings in the literature [3,6,29].
- The serial interval was assumed to be gamma-distributed with a 9.8 days average and a 3.875 days standard deviation, as estimated by WHO [3].
- We performed a descriptive sensitivity analysis for the choice of the smoothing window. We computed $R_t$ estimates for 3- to 13-day long smoothing windows (leaving the rest of the parameters fixed), and chose the value that seemed to provide a more balanced compromise between detail and variability in the estimate upon visual examination of the resulting curves.
- In total, 151 out of 6284 cases (2.4%) were notified as imported (a case is defined as imported in RENAVE if the probable place of infection was outside of the country). Although the information on this variable is not always complete, these were included as imported cases in the method of Cori et al. In addition to this, the first recorded case in each of the regions under study was also labelled as imported when performing region-specific $R_t$ estimates. This is a requirement of the method of Cori et al [23,24], that assumes that the first infection in each region was not caused by local transmission.

A summary of the chosen parametrization is shown in Table 1. We also estimated the $R_t$ in specific groups from the entire set of cases, in search for epidemiologically relevant differences. For this, we computed the $R_t$ considering as input data only those cases with particular features. The resulting curves describe how transmission evolves within distinct subgroups of the population. We then compared the resulting curves by visual inspection and looked for apparent differences between them. This was done for three different groupings of the population:

- **Madrid and Barcelona provinces.** These two provinces hosted most of the mpox cases in the country, especially during the initial burst phase of the outbreak. National transmission trends were thus expected to be dominated by cases residing in these provinces.
- **Mobility-based communities.** We divided the total population of the country in 7 “communities”, comprising several provinces. These communities were identified
using clustering algorithms on a large dataset of mobility data based on cellular network data, published by the Spanish Ministry of Transport, Mobility and Urban Agenda [30]. These communities should be understood as mobility clusters, in the sense that intracommunity movement is significantly more likely than intercommunity displacement. The role played by these communities in disease spread has been verified for other infectious diseases [31]. See Table S1 and Figure S2 for explicit descriptions of the communities.

- **MSM and heterosexual population**: transmission across individuals that identified themselves as heterosexual and men that have sex with men (MSM) was also computed. MSM that declared having a female sexual partner during the 21 days previous to symptom onset were removed from this grouping.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of new cases</td>
<td>Date of symptom onset, offset by incubation period</td>
<td></td>
</tr>
<tr>
<td>Incubation period</td>
<td>9 days</td>
<td>[3,6,29]</td>
</tr>
<tr>
<td>Serial interval</td>
<td>Average = 9.8 days Standard deviation = 3.875 days</td>
<td>Gamma-distributed [3]</td>
</tr>
<tr>
<td>Smoothing window</td>
<td>5 days</td>
<td>Chosen from sensitivity analysis (see Supplementary material)</td>
</tr>
<tr>
<td>Imported cases</td>
<td>Whenever the probable place of infection was not in Spain</td>
<td>Manually labelled first case in each region as imported (method requirement)</td>
</tr>
</tbody>
</table>

*Table 1. Model parametrization*. Summary of the parameter values used in the method of Cori et al [23] to estimate the effective reproduction number.
After a steady increase in the number of weekly declared cases of the disease, the outbreak seemed to stabilize and slightly decrease in July and August, by looking at the number of new daily cases (Fig. 1). The sensitivity analysis showed qualitatively similar results, with longer smoothing windows leading to estimates with smaller short-term variations, as expected (Fig. S1). We chose a 5-day long smoothing window after inspecting the resulting curves. The results reported in the article were consistent upon variations in this parameter and showed little or no change for different choices of it. In particular, we found a generally decreasing trend in $R_t$, with a decrease below 1 on July 12 when using a 5-day smoothing window (Fig. 2), and at most a 1-day variation on this date for 3- to 13-day long smoothing windows (Fig. S1).
Figure 1: Epidemic curve of MPX in Spain, Madrid and Barcelona. April 25 - August 19 2022.

The date of new cases was obtained as the date of symptom onset, offset by the incubation period.
Figure 2. MPX effective reproduction number ($R_t$) in Spain, April 25 2022 - August 10 2022.

Shaded area represents 95% the confidence interval.
The evolution of the $R_t$ for cases located in Madrid and Barcelona presented apparent

differences during the first month of the outbreak: transmission in Madrid seem to decrease
from an initial maximum peak, while transmission in Barcelona seemed to start at a low
point, then increased quickly and decreased again afterwards, although higher uncertainty
was found for the estimate in Barcelona (Fig. 3). After May 25, both curves seemed to
stabilize in a slowly decreasing trend.

Several transmission patterns were found for the transmission in mobility-based
communities (Fig. 4). Three communities (Central East, Central West and Canary Islands)
showed a general decrease with some oscillations after an initial peak, similarly to Madrid.
The transmission dynamics in two communities (Northeast and South) were similar to that
found in Barcelona, following an initial increase and subsequent decrease, with another mild
increase in transmission before the final decrease. Two communities (North and Northwest)
seemed to follow a different, more variable pattern, probably due to the smaller number of
cases declared in these regions (see Table S1 and Fig. S3).

While transmission across MSM resembled closely the global dynamics (as expected, since
75% of the patients identified themselves as MSM), the dynamics of infection over the
heterosexual population seemed to be qualitatively different, with several peaks and valleys
in the curve before the final decrease (Fig. 5).
Figure 3. MPX effective reproduction number ($R_t$) in Madrid and Barcelona, April 25 2022 - August 10 2022. Shaded areas represent 95% confidence intervals.
Figure 4. MPX effective reproduction number by mobility-based community in Spain, April 25 – August 10, 2022. Shaded areas represent 95% confidence intervals.
Figure 5. MPX effective reproduction number across the MSM and heterosexual populations in Spain, April 25 – August 10, 2022. Shaded areas represent 95% confidence intervals.
Discussion

Several factors might have contributed to the decrease in $R_t$. Since July, institutional and NGOs campaigns have also been launched in order to increase awareness over the LGTBIQ community and to promote preventive measures, which may have caused changes in behavior of the at-risk population. The reduction of the susceptible population due to natural or acquired immunity may also be a relevant factor for reducing the transmission. Indeed, contact networks among men who have sex with men are known be governed by a smaller number of individuals that concentrate a larger proportion of contacts [32]. This relatively small group of the population may have been more exposed to the disease during the first weeks of the outbreak, acquiring immunity at a higher pace. Post-exposure vaccination to close contacts of confirmed cases was prioritized in Spain on June 9 [33], and this recommendation was extended to pre-exposure vaccination of the most-at-risk population on July 12 [34]. However, the expected time required to develop immunity makes it unlikely for vaccination to have contributed significantly to a reduced transmission.

Transmission in Madrid and Barcelona seemed to follow different initial trends. In Madrid, it steadily decreased from an initial peak, while in Barcelona a bell-shaped curve was found for the first month of the outbreak. In addition to the different infection dynamics that may have taken place in the two provinces, the substantially higher estimates for the first days in Madrid may represent an overestimation due to the new incorporation of the disease in the surveillance system [25]. No apparent relations between the variations in these curves and the dates of events expected to be associated to higher risk of infection was found (for instance, Madrid Pride during July 1-10 2022), hinting towards the role of continued transmission in the spread of the outbreak (see below, however, for the limitations of this estimate).
As with any surveillance system, delays and incomplete information may occur and distort our estimates. This is particularly relevant for the first few days of the outbreak, where an exceptionally high $R_t$ is obtained, possibly due to an accumulation of cases of a previously non-prevalent disease and the known initial overestimation of the $R_t$ [26]. A smaller value should be expected during these days, close to the basic reproduction number of the disease $R_0$ [6,29]. A slightly lower value for the $R_t$ may also be found in the last few days due to possible reporting delays during a holiday period, as usual when using the method of Cori et al [25]. Finally, some cases during the last observed days may be missing due to delayed updates in the database, as the final date of update of the dataset was August 23, 2022.

The estimates for the different groupings of the population should also be interpreted with care, due to the following limiting factors. First, the notification of imported cases is not always complete. In addition to this, geographical mixing is expected to occur between the regions considered in the analysis (both between Madrid and Barcelona and the mobility-based communities). These facts could cause variations in the estimates, in particular overestimations of the effective reproduction number during the first stages of the outbreak. Finally, the variable recording the sexual orientation of the cases is subject to considerable underreporting (23% empty records, only 149 out of 6284 cases identified as heterosexual), which manifests the possible inaccuracy of the estimate found for the heterosexual population, seen also in the large confidence intervals found for this estimate. Possible mixing between the MSM and the heterosexual populations could also be overlooked in our analysis due to incomplete declaration of the previous sexual partners.

Two different estimates for the mean generation interval are available in the literature [3,6,9], to our best knowledge. These were computed from 17 and 16 identified pairs of a secondary case and its primary case from the UK and Italy, respectively, and both report a wide 95% confidence interval. Interestingly, we found that the $R_t$ decreased below 1 on the same date (July 12th) when using both of these parametrizations. It would be desirable to further support
our computations when estimates for this parameter computed from a larger amount of data are available. While estimates based on a larger number of cases are available for the incubation period [3,6,17,29], a more accurate description of this parameter’s distribution is still of need.

Acknowledgements

We are grateful to all Members of the National Monkeypox Response Group:

Coordinating Centre for Health Alerts and Emergencies, Directorate General of Public Health, Ministry of Health: Fernando Simón, Berta Suarez Rodríguez, Bernardo R. Guzmán Herrador, Eduardo Javier Chong Chong, Sonia Fernández Balbuena, Andrés Mauricio Brandini Romersi, Cristina Giménez Lozano, Alberto Vallejo-Plaza, Gabriela Saravia Campelli, Patricia Santángueda Balader, Lucía García San Miguel, Esteban Aznar Cano; División de control de HIV, STI, Hepatitis y Tuberculosis, Ministerio de Sanidad, Madrid, Spain: Julia del Amo, Rosa Poló, Javier Gómez Castellá, Ana Koerting; National Centre of Epidemiology, Carlos III Health Institute: Pedro Arias; National Centre for Microbiology, Carlos III Health Institute: Maria Paz Sanchez Seco (second affiliation: CIBER in Infectious Diseases, CIBERINFEC, Ana Vázquez (second affiliation: CIBER Epidemiología y Salud Pública, CIBERESP), Patricia Sánchez (second affiliation: CIBER in Infectious Diseases, CIBERINFEC), Laura Herrero, Francisca Molero, Montserrat Torres; Immunization Programme Area, Directorate General of Public Health, Ministry of Health, Madrid, Spain: Aurora Limia, Laura Sánchez Cambronero Cejudo; Andalucía: Ministry of Health and Families of Andalusia: Nicola Lorusso, Virtudes Gallardo García, Isabel Maria Vazquez Rincon; Aragón: Dirección General de Salud Pública: Juan Pablo Alonso Pérez de Agreda, Alberto Vergara Ugarriza, Carmen Montaño Remacha;
Asturias: Dirección General de Salud Pública; Gobierno de Asturias: Mario Margolles

Martins, An Lieve Boone, Marta Huerta Huerta;

Islas Baleares: Dirección General de Salud Pública. Antonio Nicolau Riutort, Teresa González Cortijo;

Canarias: Dirección General de Salud Pública, Servicio Canario de la Salud: Álvaro Luis Torres Lana, Araceli Alemán Herrera, Isabel Falcón García, Laura García Hernández, Oscar-Guillermo Pérez Martín;

Cantabria: Public Health Observatory of Cantabria, Cantabria, Spain: Adrian Hugo Aginagalde Llorente

Cataluña: Public Health Agency of Catalonia: Ana Martinez Mateo, Jacobo Mendioroz Peña, Manuel Valdivia Guijarro, Gemma Rosell Duran;

Ceuta: Consejería de Sanidad, Consumo y Gobernación: Ana Isabel Rivas Pérez, Violeta Ramos Marín;

Castilla la Mancha: Servicio de Epidemiología de Castilla la Mancha: Pilar Peces Jiménez, M. Remedios Rodolfo Saavedra;

Castilla y León: Dirección General de Salud Pública: Maria del Carmen Pacheco Martínez, Socorro Fernández Arribas, Henar Marcos Rodríguez, Nuria Rincón Calvo, Virginia Alvarez Rio, Natalia Gutierrez Garzón, Isabel Martínez-Pino (second affiliation: CIBER in Epidemiology and Public Health, CIBERESP, Madrid, Spain), M. Jesús Rodríguez Recio;

Comunidad Valenciana: Subdirección General de Epidemiología, Vigilancia de la Salud y Sanidad Ambiental: Francisco Javier Roig Sena, Rosa Carbó Malonda;

Extremadura: Dirección General de Salud Pública, Servicio Extremeño de Salud: Juan Antonio Linares Dópido, María del Mar López-Tercero Torvisco;

Galicia: Dirección Xeral de Saúde Pública, Consellería de Sanidade, Xunta de Galicia, Santiago, Spain: Maria Teresa Otero Barrós; Sección de Epidemioloxía; Xefatura Territorial de Sanidade, A Coruña: M. del Carmen García Bañobre, Sección de Epidemioloxía.

Xefatura Territorial de Sanidade, Pontevedra: M. del Pilar Sánchez Castro, Sección de Epidemioloxía. Xefatura Territorial de Sanidade, Ourense: Miriam Rebeca Martínez Soto;
Financial support
This research was partially supported by CIBER (Strategic Action for Monkeypox) - Consorcio Centro de Investigación Biomédica en Red- (CB 2021), Instituto de Salud Carlos III, Ministerio de Ciencia e Innovación and Unión Europea - NextGenerationEU.

Conflict of interest

None declared.

Authors’ contributions

DG-G, DG-B, VH, AD drafted the manuscript. DG-G, DG-B conducted the analysis, MR-A, LS, VH, MS were responsible for the management of the mpox surveillance, data collection and quality control. PG, MJS revised the manuscript. All authors read, revised and approved the final manuscript.

Data availability statement

Data was collected by routine surveillance systems. Information available at Instituto de Salud Carlos III’s official mpox site:

https://www.isciii.es/QueHacemos/Servicios/VigilanciaSaludPublicaRENAVE/Enfermedades Transmisibles/Paginas/Resultados_Vigilancia_Viruela-del-mono.aspx

The dataset analysed during the current study is available upon reasonable request from vigilancia.cne@isciii.es
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Supplementary material for

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https://doi.org/10.1017/S0950268823000985 Published online by Cambridge University Press
Sensitivity analysis

Figure S1 shows the variations in $R_t$ estimate for different choices of smoothing window. As expected, wider windows lead to smoother curves, while shorter curves yield noisier estimates.

Figure S1. $R_t$ curves resulting from a sensitivity analysis on the length of the smoothing window, ranging from a 3- to a 13-day long window.
Mobility-based communities

$R_t$ estimates were computed for “communities” in Spain, based on a mobility-based analysis [30]. Table S1 shows the cumulative number of mpox cases reported at each of these communities during the study period. Figures S2 and S3 show the geographic distribution of the communities and their epidemic curves, respectively. Figure 4 shows $R_t$ estimates for each of these communities, computed from the series of cases shown in Figure S3.

<table>
<thead>
<tr>
<th>Community</th>
<th>Provinces</th>
<th>Number of MPX cases, April 25 – August 19, 2022</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canary Islands</td>
<td>Las Palmas, Santa Cruz de Tenerife</td>
<td>143</td>
</tr>
<tr>
<td>Central East</td>
<td>Albacete, Alicante, Ciudad Real, Cuenca, Guadalajara, Illes Balears, Madrid, Soria, Toledo, Valencia</td>
<td>2796</td>
</tr>
<tr>
<td>Central West</td>
<td>Asturias, Ávila, Cáceres, León, Palencia, Salamanca, Segovia, Valladolid, Zamora</td>
<td>113</td>
</tr>
<tr>
<td>North</td>
<td>Araba, Bizkaia, Burgos, Cantabria, Guipuzkoa, Navarra, La Rioja</td>
<td>264</td>
</tr>
<tr>
<td>Northeast</td>
<td>Barcelona, Castellón, Girona, Huesca, Lleida, Tarragona, Teruel, Zaragoza</td>
<td>1925</td>
</tr>
<tr>
<td>Northwest</td>
<td>A Coruña, Lugo, Orense, Pontevedra</td>
<td>98</td>
</tr>
<tr>
<td>South</td>
<td>Almería, Badajoz, Cádiz, Córdoba, Granada, Huelva, Jaén, Málaga, Murcia, Sevilla</td>
<td>824</td>
</tr>
</tbody>
</table>

Table S1. Mobility-based communities in Spain, provinces in each of these communities, and cumulative number of MPX cases during April 25 – August 19, 2022.
Figure S2. Mobility-based “communities” in Spain, based in the results in [30].

Figure S3. MPX cases by mobility-based community in Spain, April 25 - August 19, 2022.