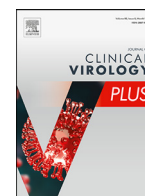


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Monkeypox: EpiMPX Surveillance System and Open Data with a Special Focus on European and Italian Epidemic



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ABSTRACT

Background: The current out-of-Africa 2022 outbreak of Monkeypox requires a coordinated, international response through the rapid sharing of data and research results, as we have seen with COVID-19 and the previous Ebola and Zika outbreaks, which demonstrated how important real-world data are to inform public health, to create surveillance systems, to determine policy decisions and to improve clinical trials.

Objectives: To support global response efforts by providing public access to real-time Monkeypox-related data for effective use of open data that could accelerate scientific knowledge and discoveries in terms of understanding, preventing, and treating the disease. In practice, to create a new surveillance system easy to consult and utilize.

Study design: This work aims to build a surveillance system, namely EpiMPX, that allows researchers and policymakers to monitor the impact of Monkeypox in Europe, with a special focus on the epidemic trends in the Italian regions, based on an open-access database containing information on the laboratory confirmed Monkeypox cases reported by EU/EEA countries and updated once a week. In addition, users will be provided open-access R codes to estimate key epidemiological parameters such as the reproduction number (updating the Serial Interval distribution when new estimates will be published) and produce real-time results on their devices.

Results: EpiMPX monitors the space-time distribution of cases and their characteristics, such as age, gender, symptoms, clinical status, and sexual orientation, when available. Even if it is currently too early for reliable calculation of epidemiological parameters, we estimated reproduction number R_t in European countries with more than 28 days of observed incidence, assuming that the Serial Interval (SI) early estimate in Italy is valid for other countries too. This provides a direct visual assessment of the geographic distribution of risk areas as well as insights into the evolution of the outbreak over time. Italian data were evaluated concerning gender, region prevalence and cumulative data.

Conclusions: The proposed EpiMPX surveillance system provides an overview of the European and Italian Monkeypox epidemiological situation with an open-access database to support epidemiological understanding of the origins and transmission dynamics of the disease with informative graphical outputs. These data confirmed the prevalent expression of Monkeypox within males, both in Europe and Italy. European MSM patients were affected by Monkeypox in a high percentage, confirming close sexual contact and possible sexual transmission. For the first time, Italian data on the regional distribution of cases and gender distribution were graphically evaluated. The data and research results are freely available and can be easily enriched to provide a prompt response to the scientific community and accelerate global efforts to contain the Monkeypox virus.

1. Background

Monkeypox (MPX) new outbreak of infections emerged on May 6, 2022, with the first case in the UK being reported to the WHO on May 7, 2022 [1]. Immediately after, new cases were reported in other European Countries [2] and worldwide. The first Italian case was reported on May 20, 2022.

On August 4, USA Government launched the “national emergency” for Monkeypox cases, 6,600, especially detected in New York and Florida, after the WHO Monkeypox alert as an “outbreak of international concern”. Starting from May 7, 2022, up to August 9, 2022, we have reached 17,897 cases in Europe as reported from 41 countries and areas to the ECDC/WHO Regional Office for Europe through the European Surveillance System (TESSy) [2]: 17,402 were laboratory confirmed. Importantly, when sequenced, 237 cases belonged to the West African clade [2]. Cases were between 31 and 40 years old (40%) and male (99.1%); according to ECDC [2] 7,470 out of 17,286 (43.2%) cases were

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men having sex with men-MSM. Excluding missing and unknown or undetermined sexual orientation MSM cases would represent 97.6% of the cases. When HIV status was known, 36% were HIV-positive. Prevalent symptoms were cutaneous rash (94.8%), systemic symptoms such as fever, fatigue, muscle pain, chills, or headache (65%). 455 cases were hospitalized (5.8%) of which 163 cases required clinical care. Three cases were admitted to ICU: two died of Monkeypox. 48 cases were health workers, with no occupational exposure [2].

Monkeypox has been so far considered a sylvatic zoonotic disease caused by an *Orthopoxvirus*, a genus of the family *Poxviridae* [3], similar to smallpox-like disease in humans. It's a self-limited disease; symptoms last from 2 to 4 weeks, occurrence of severe cases and case fatality rates are around 3–6% [3]. Monkeypox virus is transmitted from one person to another by close contact with lesions, body fluids, respiratory droplets, and contaminated materials such as bedding and fomites [3,4].

In humans was first diagnosed in 1970 in the Democratic Republic of the Congo (DRC), afterward, it has spread to other regions of Africa, primarily West and Central. Cases outside Africa have emerged firstly in the USA (2003), in several people due to contact with infected prairie dogs.

In recent years (2018-2021), seven Monkeypox cases were reported in the UK, prevalently connected to travels, except one: a hospital personnel infection. All these cases were well described in a retrospective observational study [4]. In particular, the family cluster of three MPX cases in the UK in 2021, studied in detail by Hobson et. al [5], showed the first pediatric case outside Africa, related to the family's travel from Nigeria, the country that observed the most considerable ongoing Monkeypox outbreak since 2007. According to genetic sequencing, this familial cluster has been linked to the West African clade, which has so far been less associated with human-to-human transmission. Other sporadic cases have been reported in Singapore, the US, Israel, and Europe, again linked to travel to endemic areas [1,3]. In May 2022 the simultaneous detection of several cases of Monkeypox in non-endemic countries defined the first out-of-Africa worldwide outbreak.

The 2022 epidemic outbreak is unique and shows a completely different pattern compared to previous cases seen outside Africa which had all been contained after a small number of cases with limited onward transmission. In fact, it is characterized by i) no relation to trips from endemic African nations; ii) a strict inter-human transmission; iii) a genetically defined and relatively homogeneous subclade related to the infection, the West African subclade IIb, according to the new classification proposed by WHO experts [6]; iv) different new clinic presentation with non-synchronic cutaneous lesions in the genital and perianal areas; v) variable temporal association between mucocutaneous and systemic presentation [7]; and vi) infected male prevalence, particularly men having sex with men (MSM), people with multiple partners, no condom use sex and people with social dating habits at gatherings and conventions.

This suggests that strict sexual contact can play a key role in current outbreak transmission. Additional new evidence supports the hypothesis that Monkeypox can be sexually transmitted via genital biological materials: viral DNA was reported in semen of several people during this 2022 outbreak, but virus infectiousness was very recently found only in longitudinal semen samples of one of the Italian Spallanzani hospital MSM cases [8], demonstrating a prolonged semen viral shedding and that infection acute phase semen contains a replication-competent virus, representing a potential source of infection. These data, taken all together, support a possible viral genital reservoir and infectious Monkeypox virus transmission via sexual route during this 2022 outbreak [8]. The prevalence and viral phylogenetic characteristics suggest that the West African Clade is now spreading mostly in non-endemic countries [2].

Information becomes essential because of the suspicion that the positive cases could be “the tip of the iceberg”: MPX virus could have run for a long time unidentified in the population as was asserted in early 2022 by Bunge and Coll. [9] showing an escalation of Monkeypox cases,

Table 1
Serial Interval's Gamma distribution parameters' early estimates 95% confidence interval (CI) [14].

	α	β^*	μ	σ
95% CI lo	6.86	1.10	7.55	2.88
95% CI up	5.67	3.05	17.29	7.26

especially in the highly endemic Democratic Republic of Congo-DRC, a spread to other countries, and a growing median age from young children to young adults. Causes were probably related to the cessation of smallpox cross-protecting vaccination, leading to increased human-to-human transmission.

2. Study design

Given the urgency of the situation, it is particularly important that scientists and the public have access to data and research results as soon as possible [10]. To support global response efforts in understanding and preventing the infection and spread of Monkeypox, this work proposes a surveillance system (namely EpiMPX) to i) collect high-granularity epidemiological data from reports from governments and public health organizations, and transform those data into a consistent open-access database; ii) make the data accessible and available in a machine-readable format for re-use by the global community for scientific research and public awareness; iii) enable governments for tracking virus spread in real-time and providing effective and timely responses by developing both short-term and long-term strategies to protect communities at greatest risk of contracting the disease.

3. Results

We created an open-access database and made it available via a GitHub repository [12], using an automatic scraper which collects and manually maintains records from multiple sources. In particular, data are gathered from European Centre for Disease Prevention and Control (ECDC) reports [2] and aggregated by date of notification, symptom onset and country, demographic characteristics (i.e., age and gender), case profile (i.e., HIV status, health worker status, hospitalization, ICU, and death), sexual orientation and clinical description. In addition, to inform the general population about the impact and evolution of the outbreak and help health authorities make public health decisions in Italy, we continuously and systematically collect, compare, and analyze information twice a week (Tuesdays and Fridays) on the numbers of infected individuals with the Monkeypox virus at the regional level from the Italian Ministry of Health bulletins [11]. More details about the data are available in Technical Appendix.

To show how much the database can be useful, we estimated the effective reproduction number R_t from ECDC incidence (EpiCurves) by date of symptom onset and by country [12]. We used EpiEstim package [13] in R with "Serial Interval Uncertainty" method to estimate the effective reproduction number R_t on a weekly sliding time window in European countries with more than 28 days of observed incidence, assuming that the Serial Interval (SI) early estimate in Italy is valid for other countries too. With the "Serial Interval Uncertainty" method, useful in the first outbreak phases when SI is still uncertain, Gamma distribution parameters are normally distributed, and a Markov Chain Monte Carlo simulation is used to explore SI distributions (see Technical Appendix).

Fig. 1 shows the Serial Interval (SI) early estimate Cumulative Density Function (Fig. 1(A)) and Probability Density Function (Fig. 1(C)) Gamma distribution with 95% CI [14]; Fig. 1(B) and Fig. 1(D) show the normal distribution of SI Gamma distribution parameters (mean μ and standard deviation σ), respectively. As summarized in Table 1, SI early estimation has a mean that ranges from 7.55 up to 17.29 days [14].

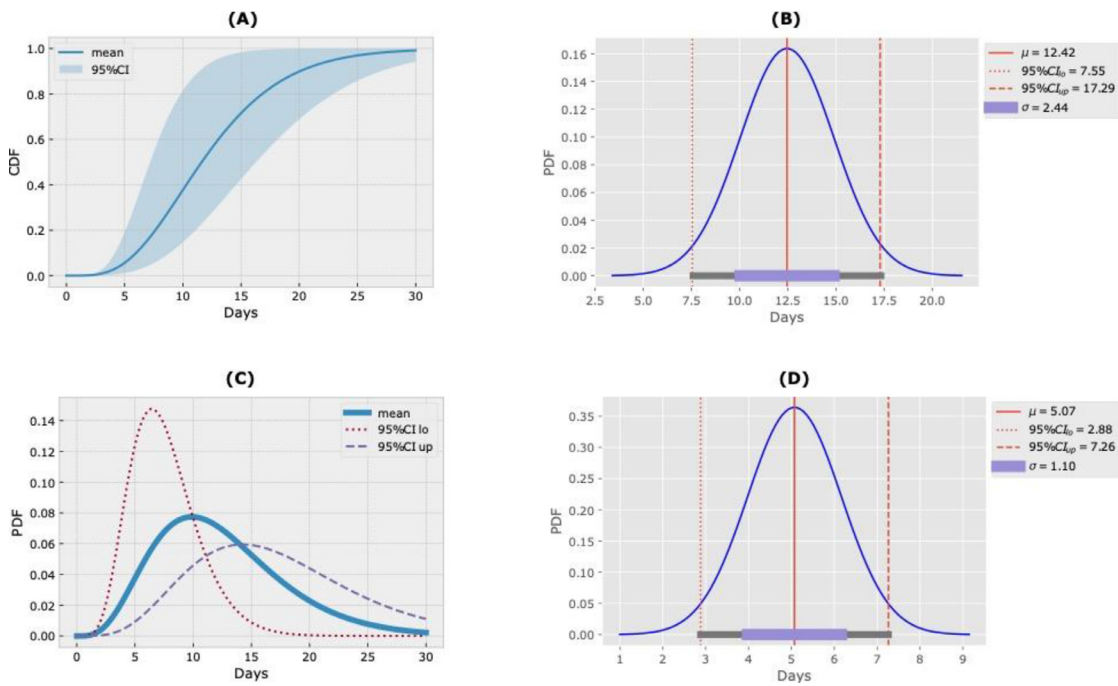


Fig. 1. Early estimate of Serial Interval [14]: (A) Cumulative Density Function with 95% CI; (B) Normal distribution of mean parameter μ ; (C) Probability Density Function mean and 95% CI; (D) Normal distribution of standard deviation parameter σ .

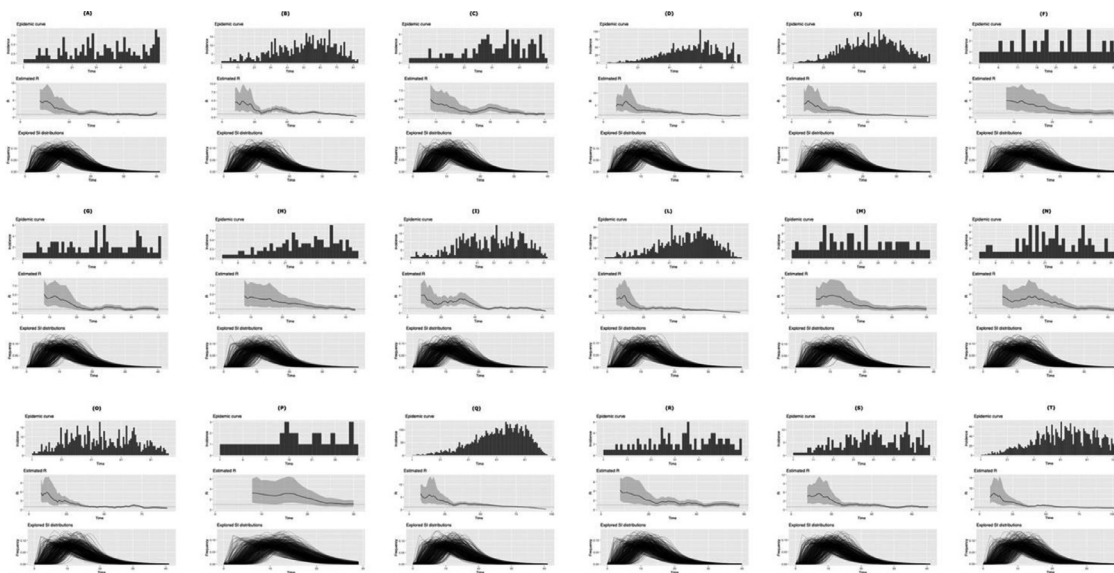


Fig. 2. Early estimate of effective reproduction number R_t in European countries with more than 28 days incidence: (A) Austria, (B) Belgium, (C) Denmark, (D) France, (E) Germany, (F) Hungary, (G) Ireland, (H) Israel, (I) Italy, (L) Netherlands, (M) Norway, (N) Poland, (O) Portugal, (P) Slovenia, (Q) Spain, (R) Sweden, (S) Switzerland, (T) United Kingdom.

Fig. 2 shows the results of early R_t estimation for each country: the panel 'Epidemic curve' shows observed incidence, the panel 'Estimated R' reports the R_t estimation, and the panel 'Explored SI distributions' describes Markov Chains Monte Carlo SI distributions. Most affected countries are Spain (4,942 confirmed cases), Germany (2,982 confirmed cases), United Kingdom (2,871 confirmed cases) and France (2,423 confirmed cases). In all other countries, less than 1,000 confirmed cases have been observed so far. Complete code in R, plots and research results can be found in the GitHub repository [12].

The epidemiological situation of Monkeypox in Italy is shown in Fig. 3. From 20 May through 16 August 2022, a total of 662 laboratory-confirmed cases of Monkeypox have been reported to Ministry of Health, of which 46 in the South and Islands, 156 in the Centre, 131 in the North-East, and 329 in the North-West. Currently, Lombardy has been the most affected region with 291 cases (Fig. 3(A)), followed by Lazio (121 cases), Emilia-Romagna (70 cases), Veneto (46 cases), Toscana (31 cases), Piemonte (25 cases), and Campania (21 cases), whose daily and cumulative trends are described in Fig. 3(C) and Fig. (D), respectively.



Fig. 3. Epidemiological curve of weekly confirmed cases of Monkeypox (MPX) in Italy, from 20 May 2022 to 16 August 2022. (A) Total MPX cases by region. (B) Distribution of MPX cases by gender. (C) New cases and (D) cumulative cases of MPX in the most affected Italian regions.

Other key epidemiological results were obtained from our open data repository and derived from Italian bulletins: 99.53% (652/662) of the reports concerned males, as shown in Fig. 3(B); the median age of the reported cases is 37 years (range: 18-71); 28% (185/662) are traveler-associated cases.

4. Discussion

The sudden outbreak in May 2022, which spread beyond Africa into non-endemic countries, highlighted the uniqueness, distinctiveness, and global relevance of this Monkeypox epidemic. For this reason, it is important that data are open and rapidly available to the international scientific community and governments for informing public health policy decisions and improving clinical trials.

Since the start of the Monkeypox outbreak, a total of 17,897 cases have been reported from 41 countries and areas throughout the European region up to 9 August 2022. About 40% of the European cases were between 31 and 40 years and were male (99%). In addition, among the cases with known HIV status and sexual orientation, 36% were HIV positive and 43% MSM (97.6% excluding unknown or undetermined orientation and missing data), confirming strict sexual contacts and a possible sexual transmission.

To accelerate global efforts to prevent and treat the Monkeypox (MPX) outbreak, this work proposes EpiMPX, an open-access database to generate new insights to i) track virus spread in real-time; ii) estimate key epidemiological parameters such as the reproduction number; and iii) monitor the most recent trends of the disease with informative graphical outputs at European and Italian levels.

Considering the Italian situation, as of 16 August 2022 a total of 662 laboratory confirmed cases of Monkeypox have been reported in the weekly bulletins, with the North-West being the most affected area with 291 cases in Lombardy alone. Epidemiological data evaluation confirmed male prevalence of the cases (99.53%), in agreement with the European percentage. Total MPX cases were detailed by Italian region and cumulative incremental cases are described in five regions. To the best of our knowledge, this is the first study to detail the Italian epidemiological situation, providing regionally disaggregated data in a machine-readable format, for informing the general population on the impact and evolution of the epidemic, helping health authorities make public health decisions, ensuring that the epidemic is monitored throughout the country.

We have shown that EpiMPX, with all its publicly available and machine-readable data from European countries and details in Italian regions, can help researchers and decision-makers easily to perform epidemiological analysis, comparisons, estimations, and forecasts about the Monkeypox outbreak.

However, the study may have some limitations. We assumed that the Serial Interval (SI) early estimate in Italy is valid for other countries too. This is a limitation because a more reliable SI estimate is needed, in more countries and with more subjects. Another limitation is that the ECDC dataset does not detail imported and locally acquired confirmed MPX cases and, at least, data of the last 2 weeks could be incomplete or unconsolidated.

Despite these estimates are preliminary, uncertain (due to SI uncertainty too) and too early in the epidemic curve, they show how much this machine-readable dataset can be useful, providing a simple, fast, costless, and publicly available method for important epidemiological indexes estimation, such as R_t . As soon as new and less uncertain SI distributions will be estimated and published (in other countries too), more reliable R_t estimations could be performed with EpiMPX, which could help Monkeypox international surveillance.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcvp.2022.100114.

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