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RESEARCH ARTICLE

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Spatiotemporal multiscale diagnosis model to proactively respond to the multi-country monkeypox virus outbreak in 2022

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Abstract

This research analyzes the spatiotemporal trend of 23,121 monkeypox virus cases in the multi-country outbreak that affected 82 countries from January 2022 to July 2022. The spatiotemporal trends analysis is developed using open data and GIS to model 3D bins and emerging hot spots globally (data by country) and nationally (data by region) for hardest hit countries, like the USA and Spain. The implemented methodology distinguishes between problem areas —as significant hot spots— and countries with no pattern. Results show consecutive hot spot patterns in Western Europe and high location quotients in North America. Factually, the countries with consecutive patterns record 16,494 cases, that is, 71.34% of the cases, where 7.63% of the world population live. At the national level, in the analysis of the USA and Spain, the results reveal regional differences with significative hot spots in California and on the East Coast of the USA and the Mediterranean coast of Spain. The proposed methodology facilitates the monitoring of the spatiotemporal evolution of monkeypox cases and is scalable and replicable using non-arbitrary and statistical parameters. The findings indicate problematic

zones in real-time, enabling policymakers to develop focused interventions and proactive strategies to mitigate the future risk of monkeypox.

1 | INTRODUCTION

The monkeypox virus (MPXV) outbreak is a new global health concern and has so far accumulated 23,121 confirmed cases in 82 affected countries during the study period, from January 31, 2022 to July 31, 2022. Society witnesses an unusual multi-country outbreak in non-endemic countries with no direct epidemiologic links to endemic countries or animal reservoirs (TLRH–Europe, 2022), in the context of declining global smallpox vaccination coverage. It is evident the global significance of the disease (Bunge et al., 2022) and the epidemic potential predicted by Grant et al. (2020) from mathematical models of historical data on smallpox and monkeypox transmission. MPXV is interpreted as a global epidemic potential since the number of cases and affected countries are increasing (Sklenovská & Ranst, 2018; Xiang & White, 2022), due to the combination of zoonotic spillover and human drivers (Nakoune & Olliaro, 2022). Considering that 75% of pathogens are of zoonotic origin, in the multi-country monkeypox outbreak scenario, the main risk is the pathogenic potential (Sklenovská & Ranst, 2018) or even that MPXV "might find an animal reservoir outside African endemic areas that can spread more easily in humans" (TLRH–Europe, 2022, p. 1).

Additionally, during the study period, society was still living under the international emergency of COVID-19, not revoked by the World Health Organization (WHO) until May 2023. As in the case of COVID-19, the WHO is a key actor in the global health concern of MPXV.

On May 16, 2022, the WHO issued its Disease Outbreak News (DONs) report on the evolution of MPXV. In the third such DONs report, the headlines referred to multi-country outbreaks in non-endemic countries (Figure 1). On May 29, 2002, the WHO classifies global public health risk as moderate, considering the first widespread reports of simultaneous cases of monkeypox in non-endemic countries. Then, the geographic scope of the disease becomes wider and the WHO expects more cases and further spread to other countries by human-to-human transmission.

One week later, the WHO provides a standard case investigation form (CIF) and minimum data set reporting form (CRF) with 40 fields organized into five sections: demographic (and geographic) data, medical history, clinical presentation, exposure, and laboratory information. On June 10, 2022, for the first time, the WHO includes the importance of working in coordination with summer event managers and planners in the northern hemisphere to ensure the safety of gatherings. References to vaccination were included on several dates as key steps in the public health response and the WHO shares a Go.data template encouraging member states to use this application to trace contacts, following Go.data's role during the COVID-19 pandemic.

In the last DON's report on MPXV (June 27, 2022), with more than 3400 cases and 50 countries affected at that time, the WHO requires urgent collective attention and coordinated action global–local to stop the further spread. They need the involvement of member states, health authorities at all levels, clinicians, and academics, among others, to respond quickly to contain cases locally. The only way to control the spread is to coordinate globally, but act locally (Adegboye et al., 2022; Salama, 2020) and analyze the spatiotemporal trend of MPXV cases using multiscale methods.

After the last DON's report, on July 27, 2022, the WHO Director-General announced that the Emergency Committee had not reached a consensus under the International Health Regulations (IHR) on whether the MPXV outbreak constituted an international public health emergency. They considered it to be a moderate risk worldwide, except in Europe, where the risk was high. On this basis, and bearing in mind that the outbreak spread

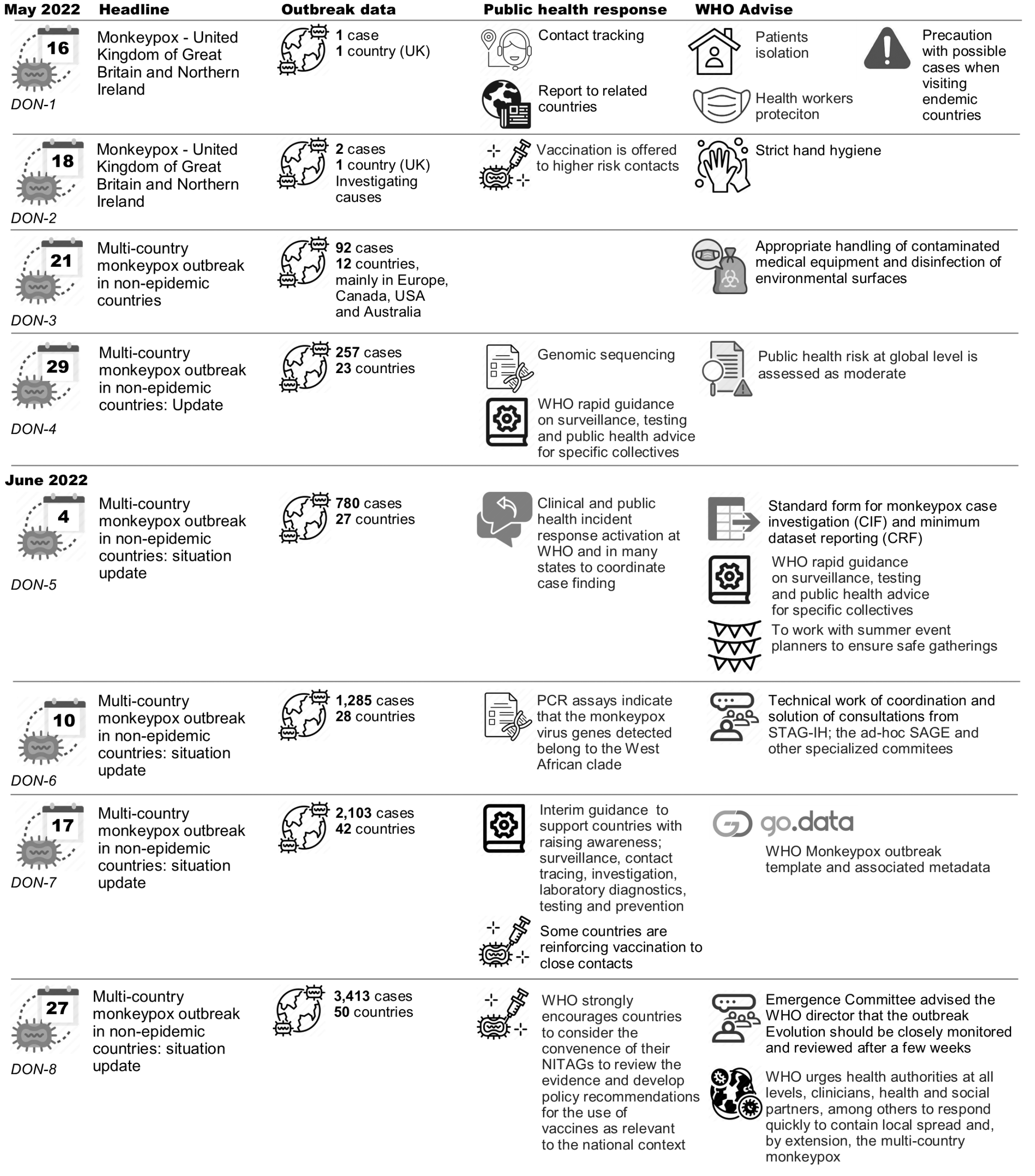

FIGURE 1 Synthesis of World Health Organization Monkeypox DONs. May–June 2022. Each date includes only new items. So, the calendar is cumulative. NITAGs, National Immunization Technical Advisory Groups; SAGE, Strategic Advisory Group of Experts on Immunization; STAG-IH, Strategic and Technical Advisory Group on Infectious Hazards.
Source: WHO (2022a), WHO (2022b), WHO (2022c), and WHO (2022d). Free icon images from Webpage Iconfinder. Authors' own elaboration.

rapidly in non-endemic countries through new modes of transmission, the WHO Director-General declared that the global monkeypox outbreak constituted a public health emergency of international concern (WHO-e, 2022).

Actually, this is not the first time that MPXV cases have occurred outside of Africa, but it is the most severe outbreak in non-endemic countries in terms of number of cases and multi-country spread. In 2003, an outbreak occurred in the USA related to imported rodents, with no human-to-human transmission, and in 2018 a transmission from patient to health worker occurred in the United Kingdom. These were the first cases ever reported in the European Union —two patients who originally traveled to Nigeria and the healthcare worker—. Other cases had previously been identified in Israel and Singapore as a result of travel to Nigeria (Vaughan et al., 2020).

MPXV is not a new research topic. Many papers focus on MPXV from an ecological, epidemiological, and biological viewpoint since the first zoonotic MPXV transmission was reported in the 1970s in the African tropical rainforest areas (Breman et al., 1980). The peak of scientific publications on this topic coincides with the MPXV outbreak in the USA in 2003, and the authors hypothesize that this topic is more important when cases occur not only in endemic countries (Ihekweazu et al., 2020; Rodríguez-Morales et al., 2022). Regarding the MPXV genome, cases of non-endemic outbreak in Europe correspond to the West African clade, milder than the Congo clade from Central Africa (Kumar et al., 2022; WHO-c, 2022), also recently called clades 1 (Congo), 2 (prior West African) and 3 (West African 2017–2022), as per the novel proposal of monkeypox classification to avoid discriminatory and stigmatizing language (Happi et al., 2022).

The most relevant scientific concerns about MPXV are about its transmission (human-to-human and community), epidemiological data, outbreak surveillance, vaccine safety, and endemic regions (Cheng et al., 2022).

The latest research about the recent non-endemic multi-country outbreak theorizes on the possibility of new transmission patterns, such as sexual transmission, and more specifically in groups of men who have sex with men (Xiang & White, 2022). Nevertheless, the role of sexual fluids in MPXV transmission is still under investigation (Mahmoud & Nchasi, 2022; Simoes & Bhagani, 2022). In addition, factors such as globalization, travel, and global connections between people and products increase the risk of zoonotic diseases, and virus spread inevitable (Bhattacharya et al., 2022), as happened in 2015 with the Ebola epidemic, which went from a local outbreak to a global risk (Zumla et al., 2017).

In this context and considering the importance of “where” cases occur and “when” they are recorded, this research aims to implement a multiscale spatiotemporal analysis that integrates both components of the evolution of MPXV cases worldwide. To this end, the research proposes a methodological workflow conducted by Geographic Information Systems (GIS), integrating spatial statistics tools from ArcGIS Pro software (Esri). There is a large body of literature on methods of spatial statistics for analyzing spatial patterns and clusters of diseases (Kleinman et al., 2005; Kulldorff et al., 2005).

In this context, this study is original because, to the best of the authors' knowledge, it is the first to use 3D bins and emerging pattern analysis for real-time spatiotemporal monitoring of MPXV. Given the WHO's global warning, this research highlights the multiscale contribution to identify global and regional problem areas. Previous studies on global hotspots of MPXV reveal spatial pattern variations in the incidence of MPXV cases over time during the study period (Patwary et al., 2023). Therefore, it is crucial to adopt the proposed monitoring approach for repeatedly examining the spatiotemporal evolution of MPXV with high temporal resolution, such as on a weekly basis, taking into account the average MPXV incubation period of 7–14 days.

Emerging hot spots provide a spatiotemporal diagnosis of problem areas —as statistically significant hot spots— and location quotients (LQ) express the proportionality or over/under representation of MPXV cases in relation to population. Although this research is mainly based on country data, the methodology is replicable at more detailed levels, as this study demonstrates in the USA and Spain analysis, at the state and region levels, respectively. Then, multiscale replicated results report strategic spatiotemporal patterns to help institutions, such as WHO, to declare emergency alerts at the international level, and help policymakers implement proactive measures to stop further spread at the regional and local level when new challenges emerge for the public health system both globally and locally (Zumla et al., 2022).

2 | DATA AND METHODS

2.1 | Research based on open-access data

This study uses two sources of confirmed cases of MPXV: the Monkeypox data repository and Microdata Monkeypox. Data were collated by the Global. health team, who compiled publicly available information and provided real-time data in tabular format (Kraemer et al., 2022). Data are open access to users under the Creative Commons 4.0 License.

The Monkeypox data repository provides daily time series by country (Global.health, 2022). Data are updated many times a week and can be accessed as graphs, maps, tables, and downloadable files (CSV format) in the Monkeypox Data Explorer by Our World in Data (https://ourworldindata.org/monkeypox). CSV files record the combination of country and date as rows.

The data structure repeats each country as many rows as necessary, depending on the number of dates with new cases reported. The base file contains 4143 records with a total of 23,121 cases from January 31, 2022 to July 31, 2022. Fields refer to daily cases, cumulative cases, and deaths. In addition, other fields are added to the original data through GIS spatial joins to assign each country to the WHO region and disease endemicity.

Meanwhile, Microdata Monkeypox (Global.health GitHub, 2022; https://github.com/globaldothealth/monkeypox) includes fields for registered cases, classified by age, sex, symptoms, hospitalization/non-hospitalization, isolation, and travel history, among others. Although many fields may be unstandardized or null, microdata contain complete information on the regional location of cases in the country (mainly administrative areas, such as states, provinces, and occasionally cities).

2.2 | GIS methods

The multiscale GIS methodological workflow implemented by ArcGIS Pro (Esri) includes extended spatial statistics analysis (Gerber et al., 2009; Kulldorff, 2001) and widely used spatial methods linked to COVID-19 (Fatima et al., 2021; Franch-Pardo et al., 2021).

The research workflow involves two stages (Figure 2). The first encompasses an exploratory analysis of the global spatial pattern of MPXV cases and the second highlights spatiotemporal diagnosis trends. The method is mainly focused on country units with a global perspective; however, the implementation at the national level in the USA and Spain demonstrates the replicability and scalability of the methodological proposal.

2.2.1 | Exploratory analysis of global spatial patterns

Global Moran's (Moran, 1948) is explored taking the cumulative cases of MPXV in each location (country) in the study period as the weight (Equation 1). It reports the confidence level of probability of the pattern of distribution of MPXV cases being non-random, and the basic parameters, such as distance threshold, involved in the next method stage.

$$I = \frac{n}{S_0} \frac{\sum_{i=1}^{n} \sum_{j=1}^{n} w_{i,j} z_i z_j}{\sum_{i=1}^{n} z_i^2} \tag{1}$$

where z_i, is the deviation of an attribute for feature i from its mean value; $w_{i,j}$, is the spatial matrix weight between features i and j, n, is the total number of features, and S_0 is the normalization factor (aggregated spatial weights).

Note: features in our model correspond to countries, states, regions… and the attribute is the number of confirmed cases of monkeypox, or the volume of population, depending on the use context.

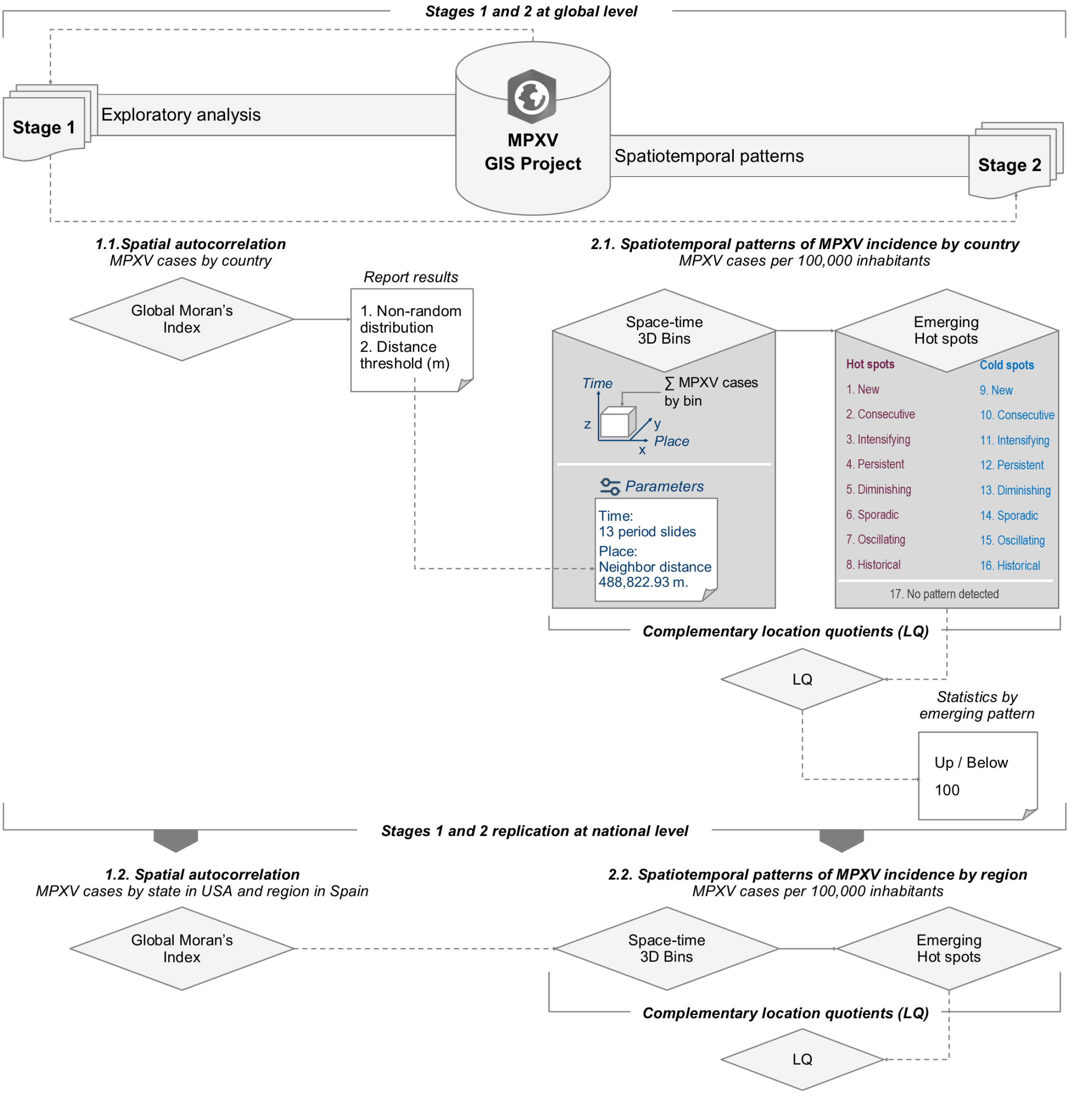

FIGURE 2 Methodological workflow of the research and GIS spatial analysis tools.

2.2.2 | Spatiotemporal diagnosis of problem areas based on 3D bins and emerging hot spot analysis

This method examines spatiotemporal incidence patterns of MPXV through the use of 3D bins and hot spot identification. It determines if there is spatial clustering of high or low MPXV values based on significant spatiotemporal trends. Similarly, it was applied to COVID-19 spread analysis, using polygons as defined locations (Chunbao et al., 2020; Syetiawan et al., 2022) and, more detailed spatially, using points of geocoded microdata (De Cos et al., 2021, 2022; Tokey, 2021).

3D bins represent a regular structure by country with both dimensions of MPXV cases: where (*x*, *y*: country, region...) and when (*z*: time).

Depending on the time parameter defined by the researcher, 3D bins represent a regular location where MPXV incidence rates are aggregated over time in a 3D structure.

The ArcGIS Pro tool for creating 3D bins requires a minimum of 10 slices. The study period covers 25 weeks and 6 days from January 31, 2022 to July 31, 2022. Here, the relative time parameter is based on the average MPXV incubation period of 7–14 days between infection and onset of symptoms, because transmission occurs after symptoms, primarily through fluid secretion, respiratory droplets, and skin rashes (Grant et al., 2020). On this basis, the time parameter is 14 days, and therefore there are 13 internal period slices. This analysis required another parameter, the neighbor distance (ND), which includes a risk of subjectivity, as other cluster methods with geometric windows (Kulldorff, 2001).

The method parameters, including spatial size and time slices, are determined through objective measures to ensure replicability and scalability. So, the temporal discretization of the global period is adapted to the timing of MPXV from infection to symptom onset, and the spatial size of each bin is determined by the expected distance obtained from the previous Global Moran's Index results. The distance threshold and the z-score (standard deviation) ensure that there are multiple neighboring countries. In the global analysis, ND is 488,822.93 m, calculated from the Moran's distance threshold/4 times the z-score, that is, 5,081,979.1135/(4 $\times$ 2.599090). In this regard, the subsequent analysis of emerging hot spots is not distorted by an arbitrary radius in a study window.

Emerging hot spots are based on Getis-Ord Gi* statistics, and trends are determined by Mann-Kendall statistics (Ogneva-Himmelberger, 2019). Trends refer to the evolution of the MPXV incidence in each bin over time.

The diagnosis of emerging hot spots complements Moran's local and global indices by uncovering the statistical significance attributed to spatiotemporal trends. This yields a maximum of 16 noteworthy patterns: 8 hot spots, with a significant increase in MPXV incidence rate, and 8 cold spots, with a significant decrease in MPXV incidence rate. Finally, one type of no pattern detected corresponds to countries with no significant trend.

Problem areas correspond to hot spot patterns, while no pattern and cold spots are secondary, less risky. The significant patterns of hot and cold spots have differences depending on whether they are significant in the last period, whether they were significant in at least 90% of the time analyzed, etc. (Table 1). Recent hot spots (new and consecutive types) have level 1 as problem areas (minimum). The intensifying type has the maximum level as problematic areas, regarding last time, at least 90% of the time as hot spots and trend up. Some types are characterized by significative hot or cold spots alternately along time, as sporadic and oscillating. In contrast, historical hot and cold spots are of secondary importance because they are not hot spots in the last time slice.

TABLE 1 Main characteristics of hot spot patterns.

Pattern	<u>Last time</u>	<u>At least 90%</u>	<u>Trend up</u>	Trend down	Alternating	Level
New	*					1
Consecutive	*,[a]					1
Intensifying	*	*	*			3
Persistent	*	*				2
Diminishing	*	*		*		2
Sporadic	*				*	1
Oscillating	*				*,[b]	1
Historical		*				1

Note: **Characteristics:** "Last time" is * when the pattern in last time slice is hot; "At least 90%" is * when the pattern is hot at least 90% of the time slices; "Trend up" is * when the pattern presents trend up; "Trend down" is * when the pattern is becoming less hot over time; "Alternating" is * when the pattern is not hot in some time slices. **Underlined characteristics** contribute to problem areas. **Level** counts the number of characteristics that contribute to problem areas.

[a]In consecutive pattern is hot in the last time slice and the previous one.

[b]In an oscillating pattern some of the time slices are hot, but others are cold.

Indeed, this approach may monitor the clustering daily evolution of MPXV cases to rapidly identify the location and type of problematic areas like hot spots. Furthermore, the conducted research adapts this method from global to national level, using monkeypox time series data at a state level for the USA and by region for Spain, selected as the two countries with the highest MPXV cases when this research was conducted.

To complement this, location quotients (LQ) are considered a relative measure to reveal whether the cumulative cases per entity (country, state, etc.) were proportional to population size (Equation 2). We adapted this extended index in the social sciences, particularly the economy (degree of specialization) and geography (degree of concentration) (Wheeler, 2005).

$$LQ = \frac{X_i \,/\, \sum_{i=1}^{n} X_i}{N_i \,/\, \sum_{i=1}^{n} N_i} \cdot 100 \tag{2}$$

where (at world level): X_i, is the value of a variable (monkeypox confirmed cases) in the country i; $\sum_{i=1}^{n} X_i$, is the world value of the variable (total of monkeypox confirmed cases); N_i, is the total of population in the country i; $\sum_{i=1}^{n} N_i$, is the total population in the world.

Note: A value of 100 indicates that there is the same proportion of confirmed cases as population. Less than 100 corresponds to the countries that registered fewer cases than "expected" compared to the population volume. In contrast, values greater than 100 indicate a higher proportion of monkeypox cases than "expected" compared to the population who live in those countries.

3 | RESULTS

3.1 | The unusual distribution of the multi-country MPXV outbreak in 2022

During 2022, the world accumulated 23,121 MPXV cases up to 31 July, as a result of the remarkable increase in cases during the last 2 months (Figure 3a). The number of confirmed cases from May 2022 increased progressively (Figure 3b). In fact, the health authorities reported 5540 confirmed cases in June, that is, 23.9% of cases during the entire period covered, reaching 16,916 in July, that is, 73.2%.

Nevertheless, the multi-country MPXV outbreak shows important contrasts in its evolution. Considering the WHO regions, the European Region led the way with a large increase from the end of May, followed by the Region of the Americas, with the same trend, although with fewer cases and a time lag of one week (Figure 4a). The evolution of the African Region differs from the others, increasing slowly and progressively while the other regions

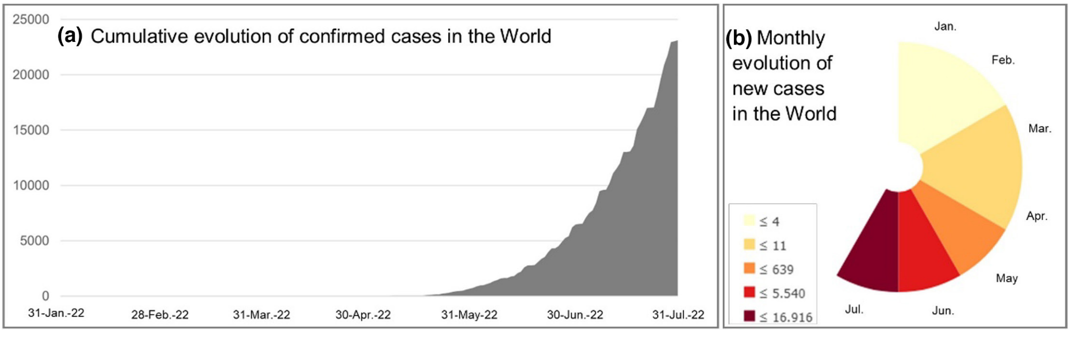

FIGURE 3 Evolution of MPXV cases in the World. January–July 2022. (a) Cumulative bar chart of confirmed MPXV cases worldwide. (b) Plot of confirmed cases of MPXV reported by month (January-July 2022). *Source*: Global.health Monkeypox Daily time series by country (accessed on 2022-08-04) *published online at* OurWorldInData.org (Monkeypox Data Explorer) and Kraemer et al. (2022). Authors' own elaboration.

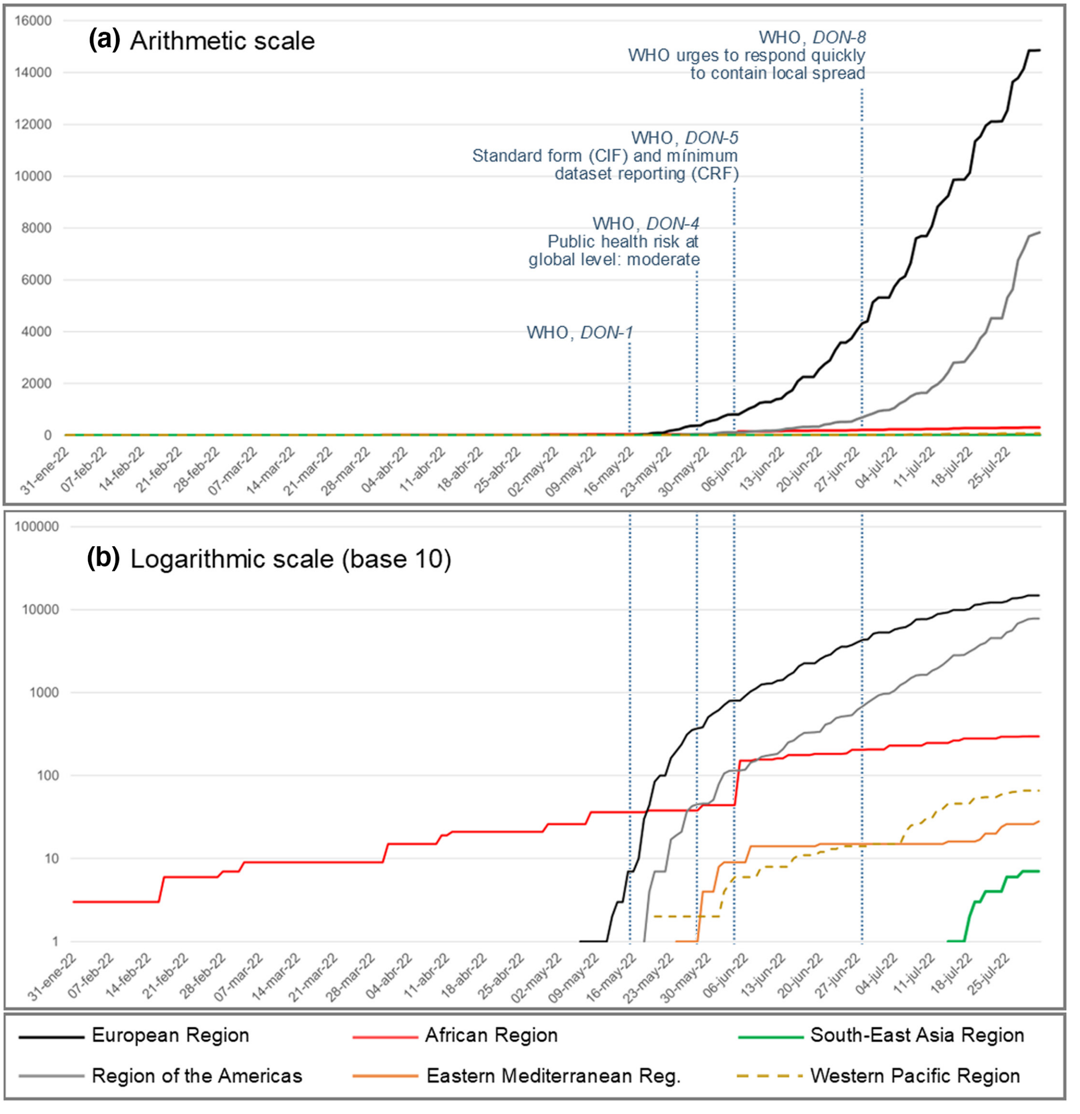

FIGURE 4 Arithmetic and logarithmic evolution of cumulative cases of MPXV by WHO Regions. January–July 2022. (a) Progression of MPXV cases using arithmetic scale. (b) Progression of MPXV cases using logarithmic scale (base 10).

show a very steep climb at the beginning of the period of increase (Figure 4b). Another difference is that cases were only present in endemic countries in the African region during the early months, prior to the multi-country outbreak in non-endemic countries.

Cases show an unusual distribution by WHO region, considering that only 297 cases were reported in endemic countries, while 22,824 cases were reported in non-endemic countries, that is, 98.72% (Table 2). The European Region, with 14,866 cases, made up 64.30% of the total, followed by the Region of the Americas, where 7827 cases represented 33.58% of world cases. Both are non-endemic areas with an over-representation of MPXV cases, according to the LQ > 100.00% with 539.96% and 258.48% respectively. Although there are reported cases in endemic countries, the African Region presents low infections (297 cases, i.e., 1.28%), and the LQ is very low 8.77%.

TABLE 2 Distribution of monkeypox cases and LQ by WHO Regions. January–July 2022.

WHO regions	Countries with cases		Confirmed cases		Population 2021	LQ
	Total	%	Total	%		
European Region	36	67.92	14,866	64.30	931,389,984	539.96
Region of the Americas	16	45.71	7827	33.85	1,024,381,811	258.48
African Region	8	17.02	297	1.28	1,145,310,300	8.77
Western Pacific Region	8	28.57	66	0.29	1,931,250,942	1.16
Eastern Mediterranean Region	6	28.57	28	0.12	739,378,959	1.28
South-East Asia Region	2	18.18	7	0.03	2,041,216,533	0.12
Non-WHO countries	6	11.32	30	0.13	8,811,628	115.18
Regions without endemic countries	74	36.81	22,824	98.72	6,676,429,857	115.65
Regions with endemic countries[a]	8	17.02	297	1.28	1,145,310,300	8.77
Total world	82	33.06	23,121	100.00	7,821,740,157	–

Note: Decreasing order by number of cases.

[a]The endemic countries are part of the African Region.

Source: Global.health Monkeypox Daily time series by country (accessed on 2022-08-04) *published online at* OurWorldInData.org (Monkeypox Data Explorer) and Kraemer et al. (2022). United Nations, Population Division, World Population Prospects (Accessed in the World Bank via Web, 2022). Authors' own elaboration.

3.2 | The clustered spatial pattern of the multi-country MPXV outbreak

The resulting Global Moran's Index of 0.1007 shows that MPXV cases follow a non-random and clustered pattern, with a z-score (standard deviation) of 2.5991 (z-score > 2.58 is the higher interval of clustered pattern), and a p-value of 0.0093. There is less than 1% probability that this clustered pattern is the result of random chance (p-value < 0.010).

The overall clustering pattern shows important differences at the national level, particularly in relation to population size. Location quotient map confirms an over-cumulation of cases (LQ > 100.00%) in European countries—Spain with the highest level, followed by Portugal and the Netherlands—and North America—the USA and Canada (Figure 5). By contrast, the endemic countries in Africa, and the other WHO regions record fewer cases than expected compared to their population volume (LQ < 100.00%).

3.3 | Spatiotemporal trends and emerging hot spots of confirmed cases of MPXV to identify problem areas in the world

The density map of MPXV cases shows that countries in the WHO European Region have higher densities than those in the Americas. Africa has very low densities, and cases are reported only in endemic countries (Figure 6a).

3D bin analysis reports a global upward trend in number of cases (trend statistic 3.5781) and temporal aggregation (trend statistic 4.8176). Considering 3D bin model by country and the number of MPXV cases during the study period, the emerging hot spots model of MPXV distinguishes problem areas—12 countries as significant hot spots in the WHO European Region—from no pattern countries (Figure 6b), secondary in terms of the risk level due to the absence of an upward trend.

Results show two types of hot spots: consecutive and new. Consecutive hot spots appear in 7 countries (Spain, Germany, the Netherlands, Portugal, Belgium, Luxembourg, and Iceland). As shown in Table 3, more than 170

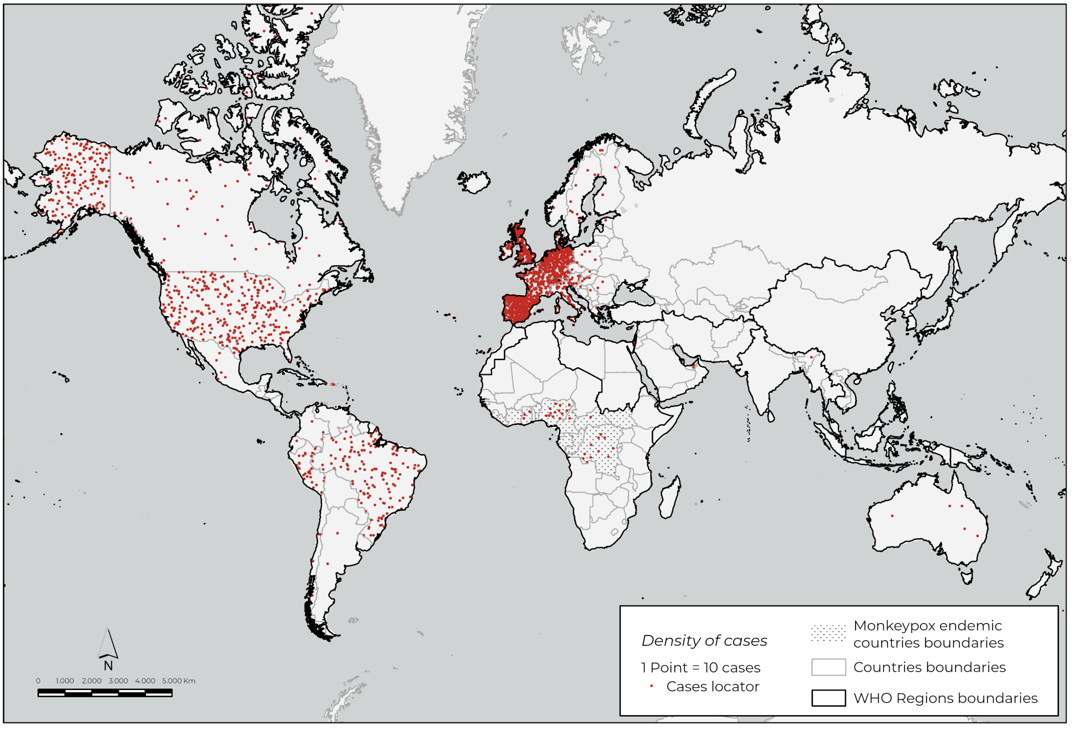

FIGURE 5 Location quotients of confirmed cases of MPXV by country. January–July 2022. Discretization criteria of natural breaks adapted by the user in intervals 1 and 2 according to the interpretation level 100. *Source*: *Esri, Garmin, CIA World Factbook—ArcGIS Living Atlas of the World: World Country Boundaries* (*2019*). Global.health Monkeypox Daily time series by country (accessed on 2022-08-04) *published online at* OurWorldInData.org (Monkeypox Data Explorer) and Kraemer et al. (2022). United Nations, Population Division, World Population Prospects (Accessed in the World Bank via Web, 2022). WHO regions and List of endemic countries from WHO-b (2022). Authors' own elaboration.

million habitants live in countries with a consecutive pattern (i.e., 2.19% world population) and these accumulated 8837 cases of MPXV (i.e., 38.22%).

On the contrary, new hot spots correspond to 5 countries (United Kingdom, France, Switzerland, Malta, and Andorra). New hot spots, where almost 145 million habitants live, accumulated 4716 cases (i.e., 20.40%). With the approach of responding proactively, new hot spot could represent countries with increasing or consecutive patterns in the near future.

In both significant patterns (consecutive and new) there is a higher concentration of monkeypox cases than expected in regard to the volume of population: LQ > 100.00 (1749.06% in consecutive pattern countries and 1106.06 in new hot spot countries).

3.4 | Spatiotemporal trends and emerging hot spots of the countries with most cases of MPXV: The USA and Spain

In the multiscale approach, the methodology is applied at the national level in the two countries with the highest number of confirmed cases during the period studied.

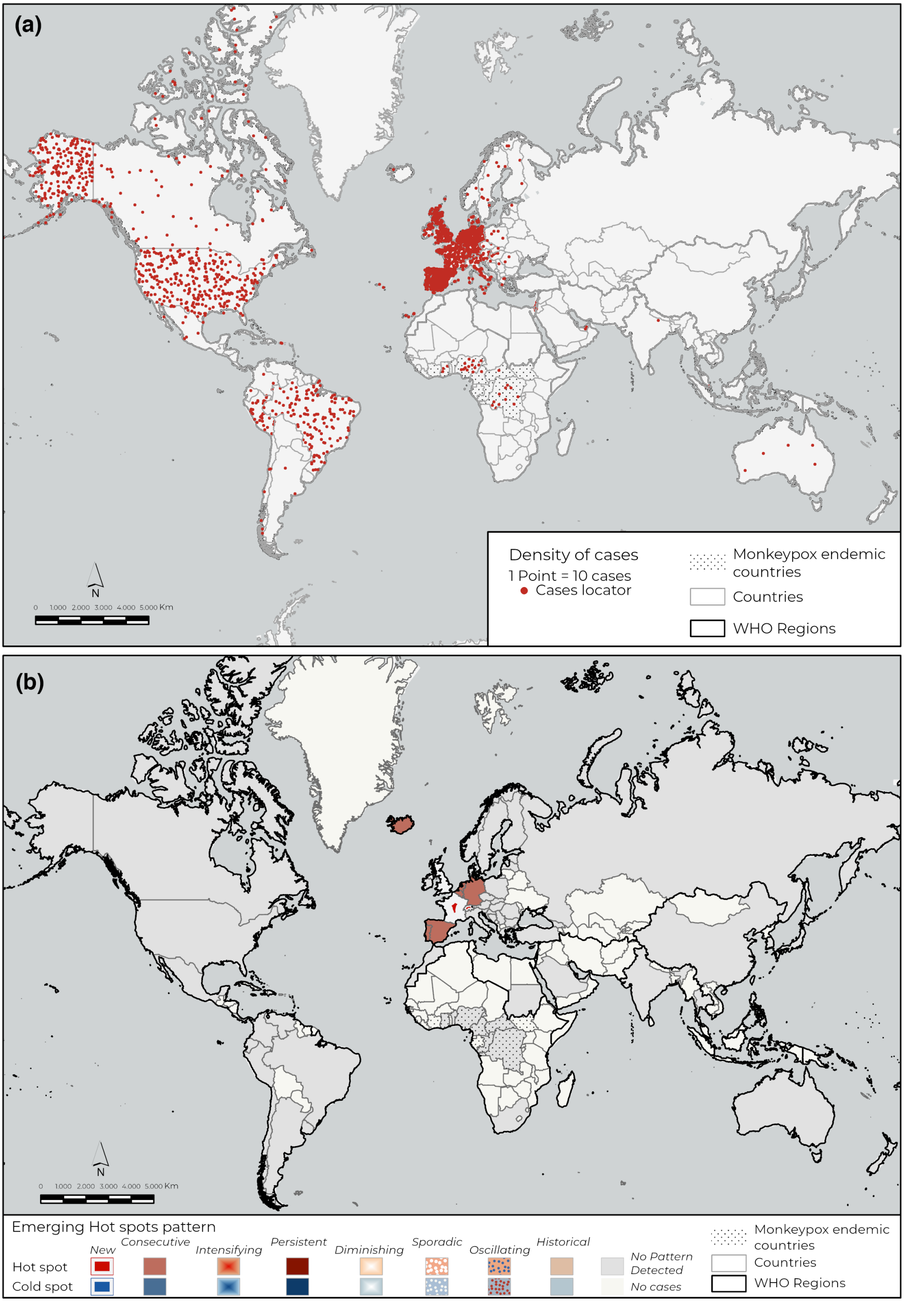

FIGURE 6 Density points map of confirmed cases of MPXV (a) and emerging hot spots (b) by country. January–July 2022. 3D bins model of MPXV by country is available in the 3D scene cartographic visor at: https://bit.ly/Monkeypox3DBins.
Source: *Esri, Garmin, CIA World Factbook—ArcGIS Living Atlas of the World: World Country Boundaries* (*2019*). Global.health Monkeypox Daily time series by country (accessed on 2022-08-04) *published online at* OurWorldInData.org (Monkeypox Data Explorer) and Kraemer et al. (2022). WHO regions and List of endemic countries from WHO-b (2022). Authors' own elaboration.

TABLE 3 Size of emerging hot spots of MPXV by pattern in the world.

Spatiotemporal pattern	MPXV Cases	MPXV %	Average % time hot spot	Average Trend z	Population Total 2022	Population %	LQ (%)	IR*
Consecutive hot spot	8837	38.22	19.64	2.13	170,921,738	2.19	1749.06	5.17
New hot spot	4716	20.40	7.14	1.77	144,241,522	1.84	1106.06	3.27
No pattern detected	9568	41.38	0.00	−1.65	5,209,787,847	66.61	62.13	0.18
No cases	0	0.00	0.13	–	2,296,789,050	29.36	–	0.00
World	23,121	100.00	–	–	7,821,740,157	100.00	–	0.30

Note: *IR is the incidence ratio of MPXV cases per 100,000 inhabitants.
Source: Global.health Monkeypox Daily time series by country (accessed on 2022-08-04) *published online at* OurWorldInData.org (Monkeypox Data Explorer) and Kraemer et al. (2022). United Nations, Population Division, World Population Prospects (Accessed in the World Bank via Web, 2022). Authors' own elaboration.

In the USA there is a concentration of cases in the urban east coast states around New York and southeast Florida (Figure 7a). On the west coast, California has a large number of cases, concentrated around San Francisco and Los Angeles. Chicago and Texas also have notable densities of cases.

Emerging hot spots show a continuous corolla of 14 states around New York with a consecutive pattern that accumulates 2854 cases (i.e., 43.25%) along the east coast from Massachusetts in the north to South Carolina in the south (Figure 7b).

As shown in Table 4a, states with consecutive patterns have more MPXV cases than expected by population volume, with LQ > 100.00 (145.72%). These states were significant hot spots in 26.67% of the study period and are hot spots in the most recent period slices. Therefore, if the trend continues these states should be surveilled.

In the case of the Spanish regions, 3D bins show internal disparities, with higher densities in the main metropolitan regions (Madrid and Catalonia) and secondary Mediterranean regions of Valencia and Andalusia (Figure 8a). Nevertheless, the emerging hot spot model distinguishes only five regions with significant hot spot patterns. There are two hot spot areas: one around the Madrid metropolitan region—and the neighboring regions of Castilla y León and Castilla La Mancha—and the other around the Barcelona metropolitan region (Catalonia). In an intermediate position, the region of Aragon is a new hot spot among consecutive hot spots (Figure 8b).

Consecutive hot spot regions accumulate 3285 cases, that is, 71.77%, with LQ > 100.00 (180.36%). Therefore, consecutive hot spots have more MPXV cases than expected by population volume (Table 4b). With the approach of responding proactively, the new hot spot in Aragon is an incipient problem area in terms of increasing trends in the last slice of the period. New hot spots are regions where surveillance is particularly important to stop the spread.

4 | DISCUSSION

4.1 | Main findings, strengths, and comparison with other studies

Approaching spatiotemporal diagnosis, the 3D bins and emerging hot spots method demonstrates that the 2022 multi-country outbreak was unusual—as other authors have concluded from other approaches (Kumar et al., 2022)—due to the number of cases in non-endemic countries, and the statistical significance of non-endemic countries as hot spots, in contrast to no pattern detected in endemic countries.

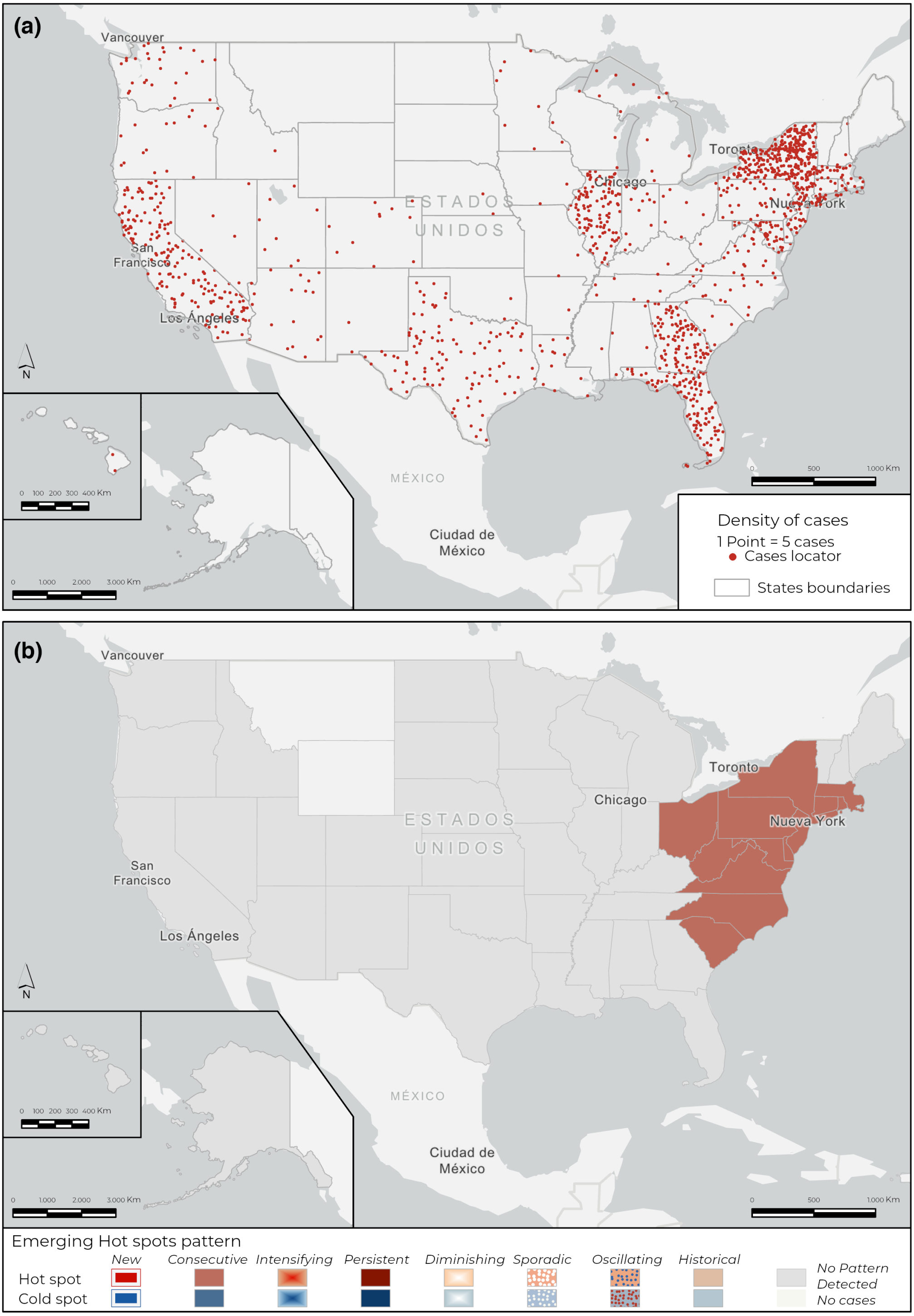

FIGURE 7 Density points map of confirmed cases of MPXV in the United States (a) and emerging hot spots (b) by state.
Source: U.S. Census Bureau, The TIGER/Line Shapefiles April 1, 2020 to July 1, 2021 (NST-EST2021-CHG). Global.health Monkeypox Microdata (accessed on 2022-08-04) and Kraemer et al. (2022). Authors' own elaboration.

TABLE 4 Size of emerging MPXV hot spots by pattern.

Spatiotemporal pattern	MPXV		Average		Population		LQ (%)	IR*
	Cases	%	% Time hot spot	Trend z	Total 2022	%		
a. The United States								
Consecutive hot spot	2854	43.25	16.67	2.13	99,538,709	29.70	145.62	2.87
No pattern detected	3745	56.75	0.00	−0.07	23,0671,962	68.82	82.46	1.62
No cases	0	0.00	0.00	–	4,946,658	1.48	0.00	0.00
Total USA	6599	100.00	–	–	335,157,329	100.00	–	1.97
b. Spain								
Consecutive hot spot	3285	71.77	31.82	2.84	18,875,338	39.79	180.36	17.40
New hot spot	45	0.98	9.09	1.56	1,314,586	2.77	35.47	3.42
No pattern detected	1247	27.24	0.00	0.26	27,077,153	57.09	47.73	4.61
No cases	0	0.00	0.00	0.00	165,729	0.35	0.00	0.00
Total Spain	4577	100.00	–	–	47,432,806	100.00		9.65

Note: *IR is the incidence ratio of MPXV cases per 100,000 inhabitants.

Source: Census Bureau, Population Division, Annual and Cumulative Estimates of Resident Population Change for the United States (July 1, 2021). Global.health Monkeypox Microdata (accessed on 2022-08-04) and Kraemer et al. (2022). Authors' own elaboration.

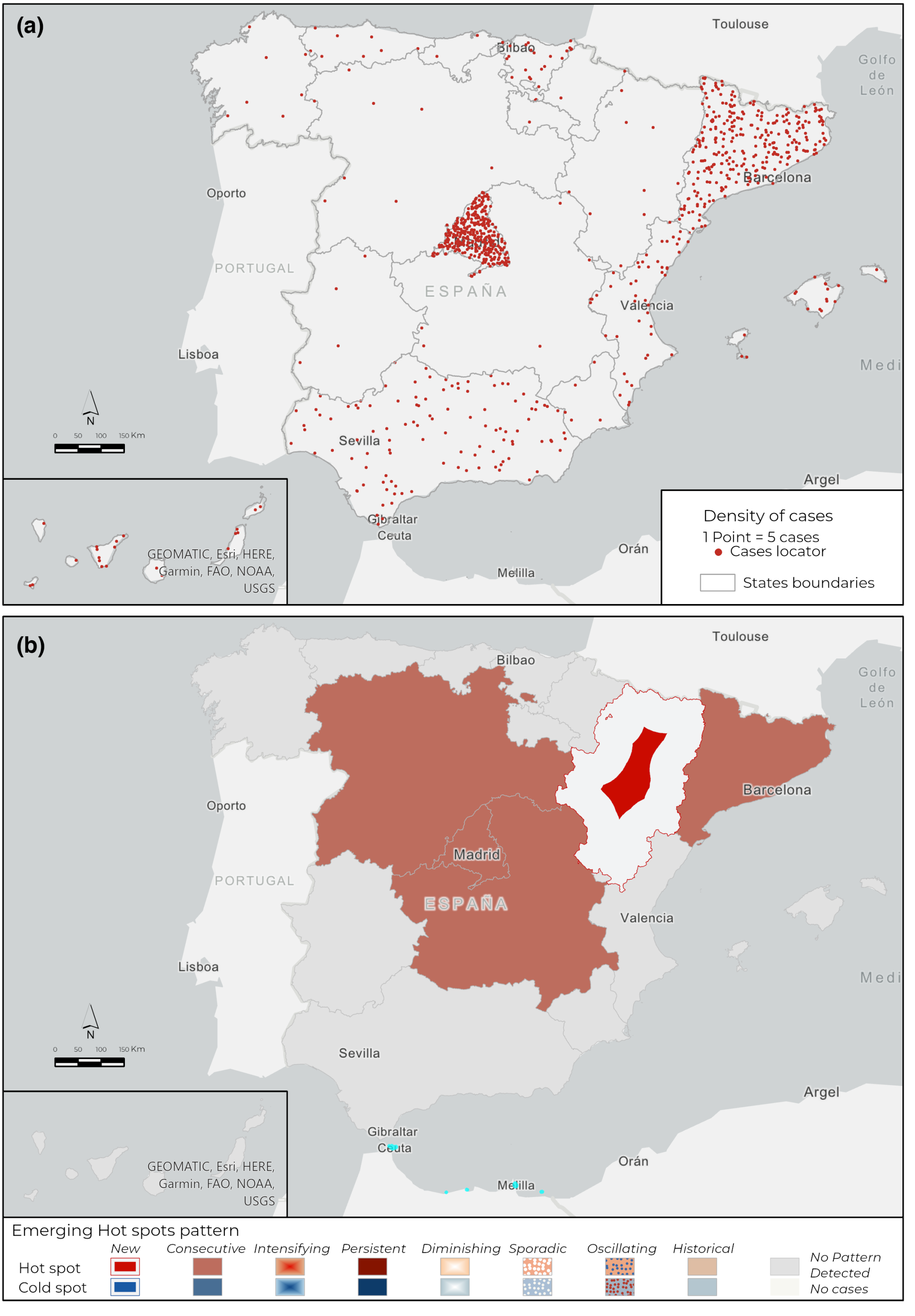

FIGURE 8 Density points map of confirmed cases of MPXV in Spain (a) and emerging hot spots (b) by region. *Source*: National Geographic Institute, Boundary lines (File shape). Global.health Monkeypox Microdata (accessed on 2022-08-04) and Kraemer et al. (2022). Authors' own elaboration.

According to Global Moran's, MPXV cases showed a non-random and clustered pattern internationally, as obtained by other authors for the global distribution in the 2022 multi-country outbreak (Patwary et al., 2023). New outbreaks of MPXV outside of Africa underscore the global significance of the disease, with unrelated clusters associated with human-to-human transmission in non-endemic countries (Hakim & Widyaningsih, 2023).

In this regard, emerging hot spots of MPXV incidence reveal problem areas from a spatiotemporal perspective.

This contribution is innovative in the specific study of MPXV spatial patterns. It differentiates between countries that recorded cases (significant hot spots versus no pattern detected) and the specification of significant patterns—mainly consecutive and new, for the incipient MPXV multi-country outbreak. The study was conducted at the beginning of the multi-country outbreak, so it reports only two types of emerging hotspots—consecutive hot spots and new hot spots—although this method can yield a maximum of 16 types. Furthermore, the absence of cold spots in the results reveals the increasing and active stage of MPXV around the world, against results obtained using this methodology in the COVID-19 study, where many cold spots appeared (De Cos, 2022).

However, research for a later period states that the spatial correlation of cases changed over time and increased shortly after our study period (Patwary et al., 2023). Thus, the methodological workflow is particularly relevant for future MPXV surveillance.

Here, transmission methods should be considered as drivers of spatial patterns. Although there is a wide knowledge about transmission factors in endemic countries, there is only nascent literature about monkeypox spread and transmission factors in non-endemic countries. In endemic countries, infections mainly occur in contact with animal reservoirs, facilitated by deforestation, hunting, and demographic characteristics, among others (Durski et al., 2018; Sklenovská & Ranst, 2018). By contrast, ongoing research hypothesizes that viral transmission in non-endemic outbreaks began at social public events in some European countries, such as Spain and Belgium (TLID, 2022). New ways of transmission are being researched, such as sexual contact (Heskin et al., 2022). The first study to assess the global risks of MPXV spread in the 2022 multi-country outbreak shows that risk factors have changed from relatively simple in endemic countries to multiple in non-endemic outbreaks, where mobility, population of men who have sex with men or socioeconomic factors drive the virus spread worldwide (Gao et al., 2023).

Emerging hot spot results demonstrate the multiscale ability of the method to identify spatiotemporal problem areas through national analyses of the USA and Spain. In fact, this method is exportable and replicable for other areas, scales, diseases, or time periods because the only risk of subjectivity (parameters of spatial size and time slices) responds to non-arbitrary and statistical criteria.

LQ results are relevant and novel. Countries with higher LQ values (>1000%) coincide with high-risk countries in Western Europe and North America identified by Gao et al. (2023). Clearly, location quotients show that there is no proportionality between the volume of population and cumulative MPXV cases by country at a global scale, while other health geography and epidemiologic research found a concentration of cases at the local scale in most populated and metropolitan areas (Polidoro et al., 2023).

4.2 | Public health challenges and opportunities

An interdisciplinary approach is essential to address future challenges in the study of emerging diseases. The spatial approach to the study of MPXV is present in epidemiological and ecological models, as the extended niche modeling (Peterson, 2006). Spatial models implemented by GIS are essential to analyze the distribution of MPXV cases at different scales (Ellis et al., 2012). Even more, spatial vision is important, even when studying and tracking the origin of each case (Mauldin et al., 2022). To this end, Brown (2022) states that geography has a clear challenge, framed by the public health emergency of MPXV 2022, to contribute across sub-disciplinary boundaries to explain the spread of MPXV. In fact, GIScience research and multiscale spatial methods can use health geography to complement the expert approaches of priority disciplines such as epidemiology, ecology, or biology, among others (Rosenkrantz et al., 2020). Here, the contribution of the emerging hot spot method to model spatiotemporal problem areas is remarkable.

On the base of hot spot surveillance, some authors suggest proactive actions linked to joint efforts by governments, scientists, industries, and healthcare systems to tackle monkeypox outbreaks in the future, under the expectation of an increasing trend (Yang, 2022).

Challenges are related to horizontal multi-country collaborations and vertical multiscale coordination (Durski et al., 2018). Additionally, targeting proactive measures seems necessary to address the spread of the virus. The global diagnosis results reveal key countries on which to provide advice on surveillance and targeted vaccination led by international organizations, such as the WHO, and national governments. In this line, Petersen et al. (2019) proposed targeting vaccination in more affected areas, as in our revealing significant problem areas. National emerging hot spots are strategic for planning strategies coordinated by national and regional health authorities. Focusing on vertical coordination in public health, MPXV data are essential to monitor spatiotemporal problem areas using emerging hot spots analysis. Factually, regional authorities need spatiotemporal diagnosis at the regional level to stop the spread.

Taking into account the previous COVID-19-related challenges for policymakers, society, and health authorities and systems, many authors consider that valuable lessons have been learned about contact tracing, rapid and coordinated responses, and information sharing, among others (Kumar et al., 2022; TLRH—Europe, 2022) to tackle a new global spread of MPXV in the context of a public health emergency of international concern (WHO, 2022e). Other authors argue that the focus of policymakers and researchers on COVID-19 may be a disadvantage in designing strategies against other diseases, such as monkeypox (Adegboye et al., 2022). Consequently, the COVID-19 pandemic may have a bipolar effect (positive and negative) when tackling new public health challenges. In any event, health authorities need to be proactive and consider that the greatest risk of MPXV is the possibility of becoming a major human pathogen (Xiang & White, 2022).

4.3 | Limitations

Despite the contributions, this research has some limitations. The study is based on data from reported cases, but some authors consider that data may be underreported, particularly in some endemic African countries where the prevalence of smallpox vaccination is higher and asymptomatic cases may not be reported (Levine et al., 2007; Nguyen et al., 2021). Obviously, this possible under-reporting of data could have a biasing effect on the spatiotemporal patterns.

In contrast, the study period began to consider previous cases in endemic countries on January 31, 2022, before the multi-country outbreak. However, it was not adjusted for the specific period of May–July for non-endemic countries affected, and our method reports some bias >70% in first-period slices.

There is a significant scientific history of applying spatial clustering methods to health research. However, one of the limitations of the presented research is that we cannot compare our results with those from other studies on MPXV using the same diagnosis method in the 2022 multi-country outbreak. Nevertheless, similarities were found in the results at the global level with other research based on other methodologies, such as risk models (Gao et al., 2023).

Finally, this study has been applied at the global and national levels, but it lacks replication at the local level, which is essential to help health authorities design targeted measures to proactively contain the spread and hot spots.

5 | CONCLUSION

In the context of a new world threat and after methodological advances in analyzing the spatial patterns of the recent COVID-19 pandemic, emerging hot spots reveal multiscale problem areas considering the spatiotemporal trends of MPXV cases. Indeed, results show relevant knowledge and expressive multiscale maps and reports to help international health institutions, as WHO, and regional policymakers to design efficient containment and mitigation strategies from a geoprevention perspective.

Using this approach, this contribution is replicable over time and is valuable for monitoring spatial patterns. Knowing problem areas in real-time is useful for taking targeted and efficient decisions. Replicating the same method at different scales contributes to coordinating the actions of different institutions and governments and standardizing the results at international, national, and local levels.

The results provide clear interpretations for policymakers; hot spots are considered to be spreading areas, while cold spots, if any, and no pattern detected are secondary in terms of geoprevention.

In addition, this methodology can be applied on a continuous time scale (daily, weekly, etc.) and on a multiscale spatial analysis to monitor the MPXV problem areas. Thus, at the international level, emerging hot spots report countries with increasing trends; secondly, in these countries, the replicated national methodology reports hot spots in regions, and thirdly the replicated regional methodology can report municipalities with increasing trends of MPXV cases, and so on. The use of non-arbitrary and statistical parameters is crucial for achieving replicability and scalability in emerging hotspot analysis.

Definitely, this study proposes a replicable and scalable methodological workflow based on emerging hot spot analysis to monitor the spatiotemporal evolution of MPXV in real-time, using GIS methods and open data. This study is the first to examine MPXV spatial patterns in this way. It provides a unique contribution to the existing literature by complementing other studies based on local and global Moran indices at the global level.

On this basis, proactive and preventive strategies based on the differences between regions could be viable.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

Our research is based on open-access data produced by Global.health. We have shown the links to where these data are available from Global.health GitHub and Our World in Data. Additionally, we have shared tables of results for emerging hot spots by countries (world), by states (USA), and by regions (Spain). Access data in the link: https://tinyurl.com/39jwbb4j. Users can join our research results to external databases or mapping datasets by ID fields. Additionally, 3D bins model of MPXV by country is available in the 3D scene cartographic visor at: https://bit.ly/Monkeypox3DBins. Here, users can interact with the map by panning, zooming in, zooming out, and opening pop-ups by bin.

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