Global Mpox spread due to increased air travel

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Abstract

Mpox is an emerging, infectious disease that has caused outbreaks in at least 91 countries from May to August 2022. We assessed the link between international air travel patterns and Mpox transmission risk, and the relationship between the translocation of Mpox and human mobility dynamics after travel restrictions due to the COVID-19 pandemic had been lifted. Our three novel observations were that: i) more people traveled internationally after the removal of travel restrictions in the summer of 2022 compared to pre-pandemic levels; ii) countries with a high concentration of global air travel have the most recorded Mpox cases; and iii) Mpox transmission includes a number of previously non-endemic regions. These results suggest that international airports should be a primary location for monitoring the risk of emerging communicable diseases. Findings highlight the need for global collaboration concerning proactive measures emphasizing real-time surveillance.

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Introduction

Mpox (previously known as monkeypox) is an infectious disease caused by the monkeypox virus, a member of the *Poxviridae* family (Damaso, 2023). The infection generally gives only mild symptoms and typically self-resolves except in at-risk patient groups with limited cellular immune response, children under 8 years of age, pregnant women, and immunocompromised individuals (Guarner *et al.*, 2022). In the latter group, Mpox severity is significant and includes conjunctivitis, encephalitis, pneumonia, death, and fetal mortality (Burki, 2022; Guarner *et al.*, 2022). Fatality rates are greater in patients infected by the human immunodeficiency virus (Simpson *et al.*, 2020).

Mpox is transmitted through body fluids or skin lesions, as (Falendysz et al. 2017) during close physical contact with infected people or animals, such as African rodents, mice, prairie dogs, or non-human primates (Li *et al*., 2023). In non-endemic areas, such as Europe and North America, preliminary genomic sequencing studies have identified the West African variant as the main virus lineage that has a case fatality rate of 1% (Burki, 2022). Currently found only in Africa, the Congo Basin variant of the monkeypox virus has a fatality rate of up to 10% (Simpson *et al*., 2020; Burki, 2022). The differences in virulence among monkeypox virus lineages highlight the outbreak risk of Mpox and its global health relevance.

Before 2018, Mpox infections rarely occurred outside of West Africa, where the disease was endemic (Vaughan *et al.*, 2020; Burki, 2022). Endemic countries, such as Nigeria and Ghana, have served as sources of Mpox for international outbreaks through the travel of infected people or live animal exports (Vaughan *et al.*, 2020; Guarner *et al.*, 2022). A significant turning point came in 2018 when the first confirmed case of human-to-human transmission outside Africa was reported in the United Kingdom. The transmission involved a healthcare worker who cared for a patient who had traveled from Nigeria (European Center for Disease Control and Prevention, 2018). In May 2022, the first Mpox outbreak was reported in the United Kingdom, linked to a British resident recently returning from a trip to Nigeria (Kraemer *et al.*, 2022). This coincided with the international relaxation of COVID-19 restrictions, which limited the number of flights and individuals traveling between countries (post-COVID-19 pandemic). The reduction of travel restrictions increased international air passenger flow *via* airline transportation, immediately returning to 68% of pre-COVID-19 pandemic levels (Kazda *et al.*, 2022; Kinoshita *et al.*, 2023). Understanding the dynamics of Mpox transmission, especially in the context of international travel, is crucial for effective outbreak control and prevention. Global changes facilitate the appearance of emerging diseases (Jones *et al.,* 2008), and the constant increase in connectivity (Baker *et al.*, 2022) amplifies the risk of future international epidemics and pandemics. This project examined the spread of Mpox during the 2022 outbreak period, with a focus on temporal incidence, patterns of international travel, and global hotspots of transmission risk. This study aimed to enhance our understanding of how the translocation of emerging diseases is influenced by international human mobility patterns. We hypothesized that international air passenger flow positively correlates with the translocation of Mpox infections. To test this hypothesis, we assessed the geographical and temporal patterns of airline networks and Mpox spread. We expect that our findings on global Mpox spread can help inform the formulation of public health measures within the airline networks.

Materials and Methods

Data sources

Mpox data were downloaded from the GLOBAL.HEALTH monkeypox data repository (https://www.monkeypox.global.health/) for May and August 2019 (pre-COVID-19) and 2022 (post-COVID-19) (Kraemer *et al.*, 2022). This repository indicates the emergence and rapid spread of the Mpox outbreaks and provides aggregated information for cases reported by the World Health Organization, the Centers for Disease Control and Prevention in the United States and the European Center for Disease Control and Prevention (websites accessed on August 22, 2023). We collected international flight travel information from the OpenSky Network project (https://opensky-network.org/) on the number of flights including origin and destination data (Schafer *et al.*, 2014). This network is a product of the Automatic Dependent Surveillance-Broadcast, which contains information directly transmitted by an aircraft, such as arrival and departure records, identification number, coordinates, altitude, and ground speed (Chevallier *et al.*, 2023). Analyzing Mpox incidence data during the May-August 2022 period allowed us to capture major epidemiological signals of the outbreak, including its geographical patterns, early detection of cases, and the impact of international air travel during the summer months of the northern hemisphere, with special reference to changes in COVID-19 travel restrictions.

Data analysis

We performed a descriptive analysis of Mpox cases to depict the cumulative and monthly case reports from each country and month, as well as the travel history involved (origin and destination) using R statistic software version 4.1.2 (R Core Team, 2021). The Mpox incidence was calculated by dividing the cumulative confirmed cases by the population size of each country downloaded from the World Population Prospects 2022 (UNDESA, 2022), and we used log-transformation to ensure a standardized measure of Mpox cases per million inhabitants. We used the 'sf' package of R (Pebesma, 2018) to conduct analyses of the number of cases imported *via* flights between countries. The 'raster' package (Hijmans & Van Etten, 2021) was applied to visualize the spatial distribution of overlap with confirmed Mpox cases reported and detect hotspot areas with a high frequency of Mpox transmission around the world. Finally, we compared the international air travel patterns to investigate air travel pre- and post-COVID-19 pandemic in each country. Air travel was then related to Mpox cases using generalized linear models to examine the relationship between the number of incoming flights and the number of confirmed Mpox cases.

Results

During the period between May and August 2022, Mpox outbreaks were reported in 91 countries, encompassing all continents except Antarctica. There was a total of 41,304 confirmed Mpox cases reported, and 89% of affected countries had not historically reported Mpox outbreaks. High Mpox case counts were observed in the United States, Spain, Brazil, and Germany (Figure 1). When controlling Mpox incidence by a country's population size, Spain had the highest incidence per million inhabitants (0.12 cases), followed by the Netherlands (0.06 cases) and the United Kingdom (0.05 cases) (Figure 2).

According to international air travel data in the summer of 2022, after the COVID-19 mobility restrictions had been lifted, passenger flow surpassed pre-pandemic levels of air travel reported in 2019. Mpox patient flight histories revealed a biased origin of the outbreak, originating from patients returning from Europe and spreading to the rest of the world (Figure 3). Indeed, air travel

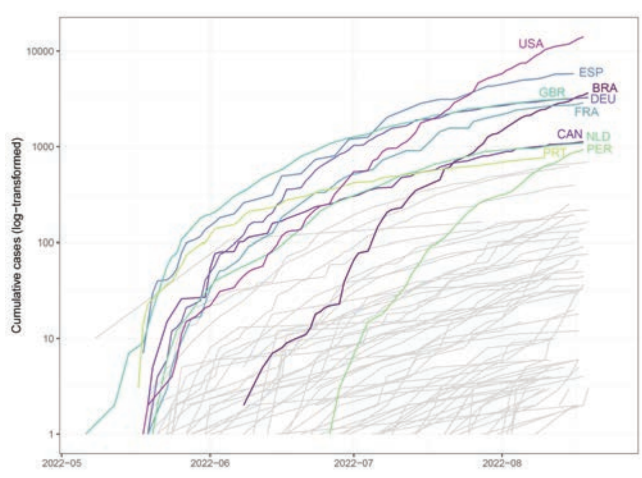

Figure 1. Log-transformed, cumulative cases (y-axis) in 91 countries during May-August 2022 (x-axis). Mpox cases by August 24, 2022, denoting the countries with a particular high number of cases: the United States [(USA)14,052 cases], Spain [(ESP) 5792 cases], Brazil [(BRA) 3658 cases], Germany [(DEU) 3266 cases], the United Kingdom [(GBR) 3193 cases], France [(FRA) 2737 cases], Canada [(CAN) 1109 cases], the Netherlands [(NLD) 1087 cases], Peru [(PER) 889 cases] and Portugal [(PRT) 770 cases]. Gray lines denote cases in all other affected countries.

resumed in most countries (~79%) with numbers often exceeded pre-pandemic travel (Figure 4).

However, a decrease in air travel was detected in Russia, Thailand, and Canada, which reported less than 100 Mpox cases, while Sweden, Italy, and the Czech Republic had air travel close to pre-pandemic levels and reported more than 100 Mpox cases. Importantly, the great majority of countries with increased travel reported more than 100 Mpox cases during the international Mpox outbreak.

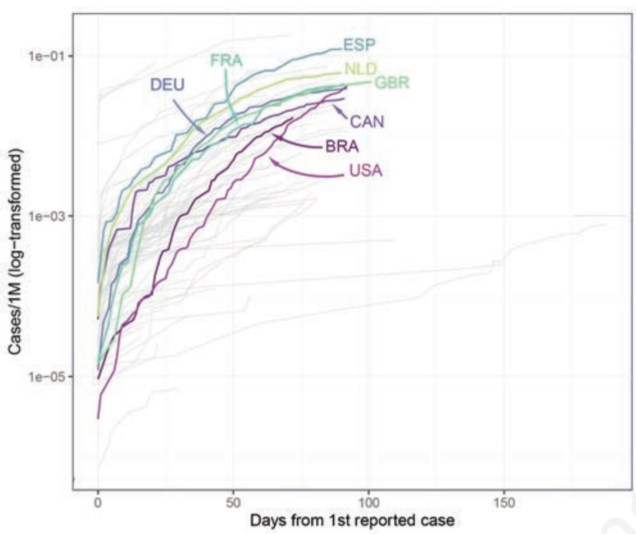

Figure 2. Log-transformed number of confirmed Mpox cases per million inhabitants (y-axis) in 91 countries since the first case detected (x-axis). Mpox case numbers/million inhabitants in countries with high infection rates, including Spain [(ESP) 0.12], the Netherlands [(NLD) 0.06], the United Kingdom [(GBR) 0.05], France [(FRA) 0.05], Germany [(DEU) 0.05], the United States [(USA) 0.05], Canada [(CAN) 0.04], Brazil [(BRA) 0.02]. Gray lines denote cases in all other affected countries.

Figure 3. Mpox transmission hotspots. The number of cases imported via flights between countries is shown in different colors: one case (yellow), two cases (green), three cases (blue), and four cases (purple).

International airports in the United States, Spain, and Portugal became Mpox transmission hubs for the export of cases to the rest of Europe, the Americas, Australia, and Africa, while Germany played a key role in facilitating the spread to Asia. The amount of air travel was a strong predictor of Mpox cases in non-endemic countries, with higher passenger flow linked to larger Mpox outbreaks (Figures 4 and 5). The levels of air passenger flow identified hotspot areas of likely Mpox outbreaks around the world, as shown in darker shades in Figure 5A. Most Mpox cases during the global outbreak were concentrated in the United States, Spain, Brazil, the United Kingdom, Germany, and France, with secondary clusters of cases in Canada, the Netherlands, Peru, and Portugal (Figure 5A). The heavier international connectivity by air travel led to significant global hotspots of Mpox emergence and spread, while countries exceeding pre-pandemic levels of air-passenger flow also reported the highest Mpox incidence (Figure 5B). The number of incoming flights was a strong, significant predictor of Mpox cases (*i.e.*, R^2=0.63) (Figure 5B).

The Mpox incidence varied temporally and geographically (Figure 6). In May 2022, the highest number of confirmed cases was reported in Europe, including the United Kingdom (n=183), Spain (n=122), Portugal (n=94), Germany (n=38) and the Netherlands (n=26). In June 2022, Germany reported a substantial increase in confirmed cases (n=888), and the number of cases increased by more than 300% in the United Kingdom (n=745), Spain (n=678), France (n=497) and Portugal (n=308). In July 2022, a high number of cases was reported in the United States (n=4369) and Brazil (n=1239). In August 2022, the United States accumulated the highest number of confirmed cases (n=14,140), followed by Brazil (n=3780), Spain (n=2245), France (n=1593),

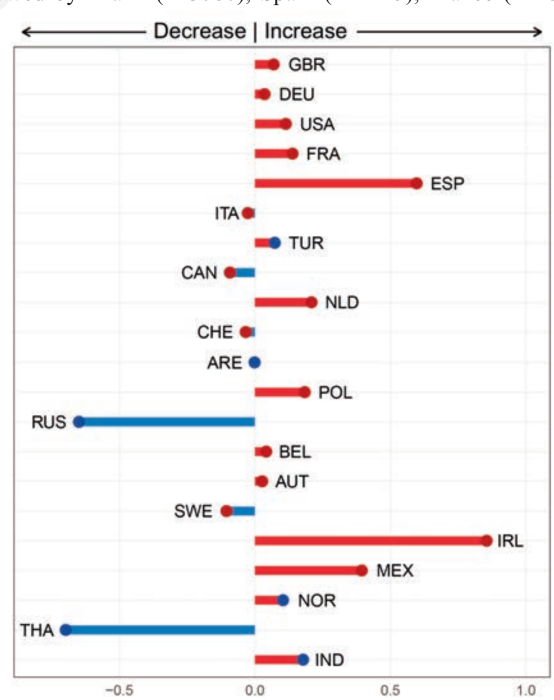

Figure 4. Change in international air travel patterns before (2019) and after (2022) the COVID-19 pandemic and Mpox cases in 2022. Red points denote countries reporting more than 100 Mpox cases; blue points those reporting less than 100 Mpox cases; red bars those with increased air travel; blue bars those with decreased air travel. The vertical line (0.0) denotes no change in air passenger flow.

and the United Kingdom (n=1395). In May 2022, 38.9% of the Mpox confirmed cases had a history of travel from Spain and only 5.6% from Nigeria, which was the only incidence reported from Africa (Figure 7). In June 2022, 36.8% of the Mpox confirmed cases had a history of travel departing from Spain, with 15.9% of all cases linked to departures from the United States, Australia, Singapore, and Mexico (Figure 8). At least 25% of Mpox imported cases in South America originated in Spain and France (Figure 9). In August 2022, 17.6% of confirmed cases had a history of travel from the United States. Late in the outbreak, Europe played a limited role in exporting Mpox cases, with six cases linked to a European origin in August 2022, the lowest compared with previous months (Figure 10).

Discussion

Our findings regarding the Mpox outbreak of 2022 with European countries, especially Spain, playing a key role in its international spread, indicate that the number and direction of flights were associated with the fast spread in non-endemic localities (Betancort-Plata *et al.*, 2022; González-Val & Marcén, 2022). The relaxation of COVID-19 restrictions for international air travel in 2022 resulted in air travel exceeding pre-pandemic levels, which correlated with higher Mpox spread to non-endemic countries. Therefore, there is a need for effective global health strategies to prevent and control the international spread of infectious diseases, informed by international air travel data.

This global outbreak demonstrated a concerning trend in the emergence of wildlife diseases of pandemic potential (World Health Organization, 2022). The first case confirmed on May 6, 2022, in the United Kingdom was linked to recent travel history from Nigeria, an endemic country for Mpox (Kraemer *et al.*, 2022). The human Mpox cases confirmed by six laboratories in the United Kingdom between May 13 and 15 in 2022 lacked travel links to endemic countries, suggesting human-to-human community transmission in non-endemic localities (Burki, 2022; Guarner *et al.*, 2022; World Health Organization, 2022). Community transmission was further supported by the fact that over 5000 Mpox

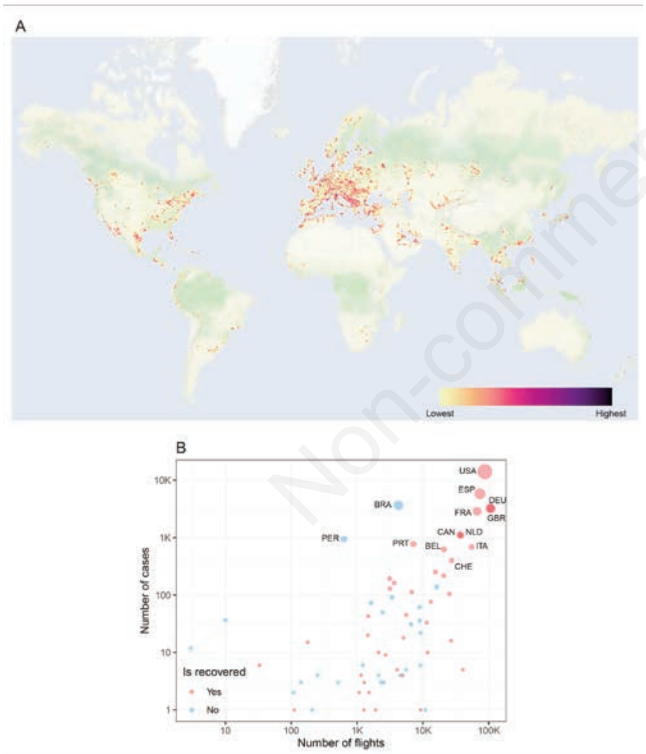

Figure 5. Mpox transmission hotspots predicted based on international air passenger flow. **A**) Mpox super spreader airports estimated from the Generalized Linear Model coupling passenger flow and Mpox transmission. Map denotes sites (airports) of high (red) and low (yellow) disease spread potential. **B**) Relationship between air travel and Mpox cases: blue points indicate countries having not returned to pre-pandemic levels of passenger flow (not recovered); red points indicate countries having exceeded pre-pandemic levels of passenger flow (recovered); point size denote the amount of Mpox cases.

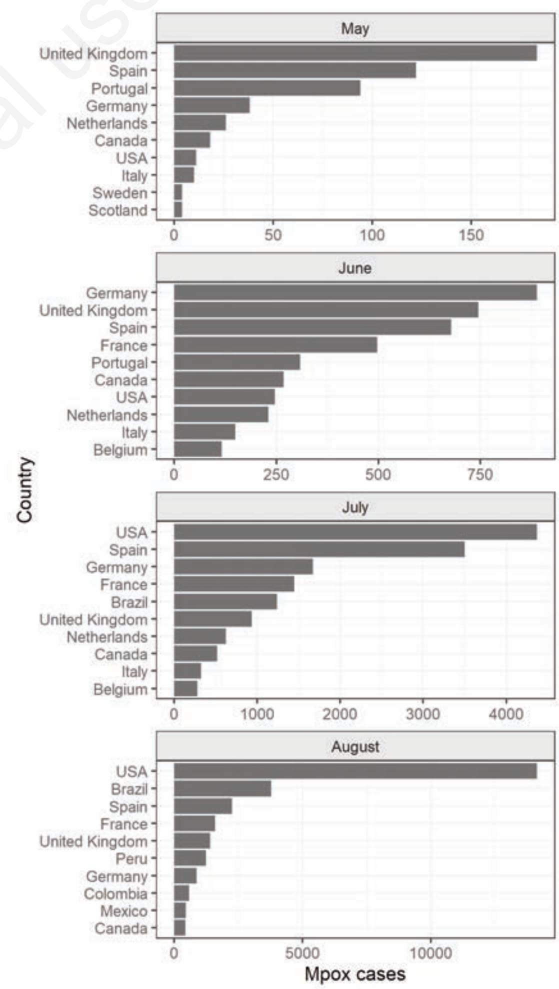

Figure 6. Count of confirmed Mpox cases detailed for the ten countries with the highest transmission during the period May-August in 2022.

confirmed cases in non-endemic countries were reported, denoting the fast spread of the outbreak (Kozlov, 2022; Kraemer *et al.*, 2022). The Mpox outbreak revealed an exponential growth of community transmission globally (Kozlov, 2022), which was not immediately obvious due to delayed identification, tracing, and isolation of patients.

Effective distance of contagion

The recent availability of air travel data has facilitated epidemiologic applications of air travel models to predict disease arrival times and sites of origin. For instance, Brockmann and Helbing (2013) proposed the "effective distance" concept to denote air travel connections as a more effective distance to anticipate disease spread compared to geographic distance. This pioneering approach was employed to successfully anticipate the sites of origin and international spread of the H1N1 influenza, the 2003 severe acute respiratory syndrome, and the 2016 Chikungunya epidemic (Brockmann & Helbing, 2013; Escobar *et al.*, 2016). We employed a network modeling approach to identify nodes with the highest likelihood of spreading cases to new regions. We used this information to map airport-level hotspots of transmission risk, which can inform future Mpox containment in view of the risk of future Mpox emergence (Figure 5).

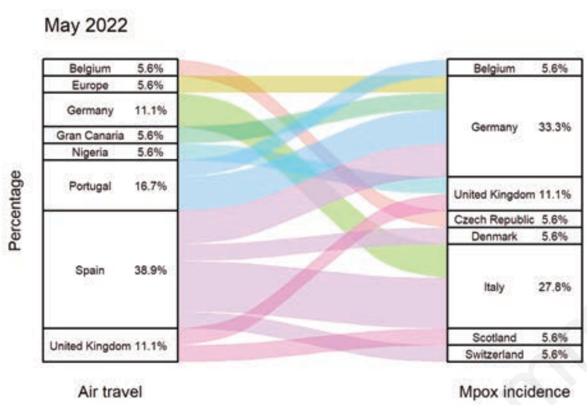

Figure 7. Air travel and Mpox spread globally in May 2022. Left: percentage of air travel between countries and their connectivity to other countries (color lines); right: Mpox incidence in May 2022.

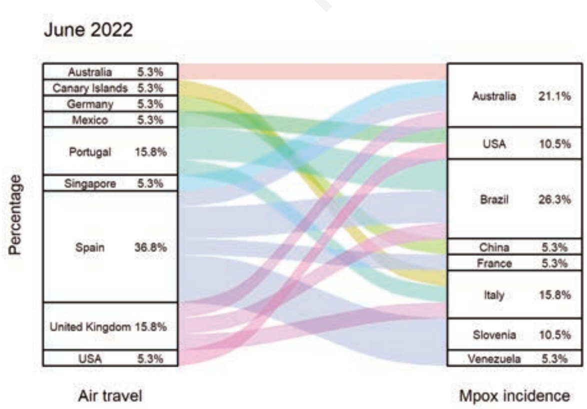

Figure 8. Air travel and Mpox spread globally in June 2022. Left: percentage of air travel between countries and their connectivity to other countries (color lines); right: Mpox incidence in June 2022.

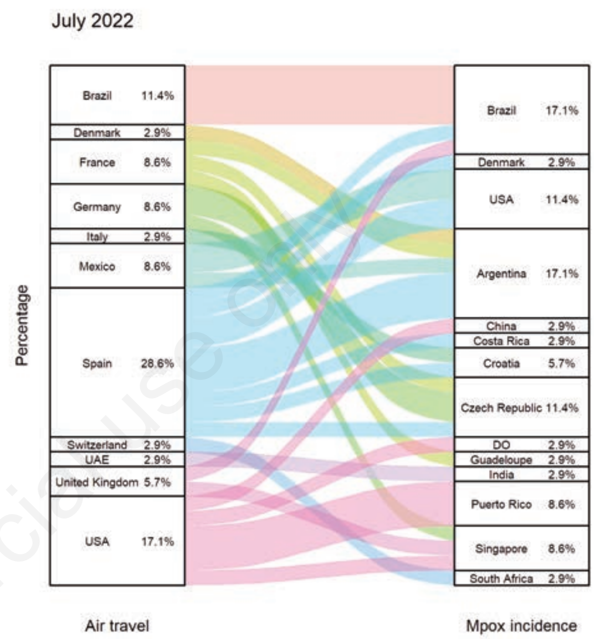

Figure 9. Air travel and Mpox spread globally in July 2022. Left: percentage of air travel between countries and their connectivity to other countries (color lines); right: Mpox incidence in July 2022. Dominican Republic (DO); United Arab Emirates, (UAE).

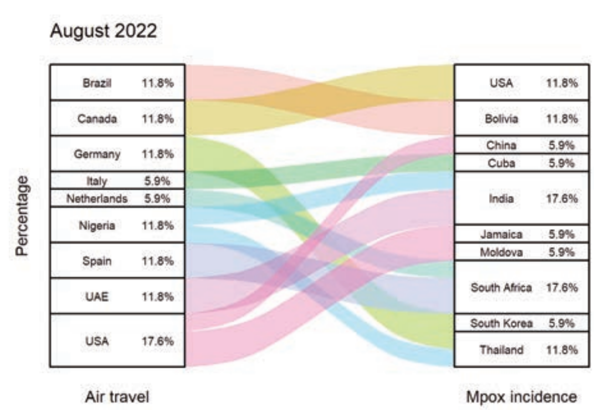

Figure 10. Air travel and Mpox spread globally in August 2022. Left: percentage of air travel between countries and their connectivity to other countries (color lines); right: Mpox incidence in August 2022.

The emergence of the 2022 Mpox outbreak and the introduction and spreading of Mpox to new countries, including specific super-spreading hotspots across Europe, the Americas, and South Asia, is in line with previous suggestions of the likely contribution of the relaxation of COVID-19 prevention measures to disease spread (Thornhill *et al.*, 2022). Previous studies have centered on local-level air travel data to estimate local Mpox spread risk (Kinoshita *et al.*, 2023). Our global-level studies combining air travel data with Mpox importation data generated a data-driven, empirical estimate of Mpox spread (Figure 5). As shown in Figures 1 and 2, our results overcame other assessments that identified the United States as a source of cases driven mainly by the volume of passengers from this country. That is, by controlling for air travel and Mpox incidence *per capita*, we found other countries having a key contribution to the global spread of Mpox (Escobar *et al.,* 2016; Del Valle *et al.,* 2018).

We detected specific countries, cities, and airports with the highest likelihood of Mpox spread risk (Figure 5), which could help inform future travel restrictions to reduce epidemic spread. Grépin *et al.* (2021) found that implementing travel restrictions that reduce international travel by 40-90% could likely have a positive impact on reducing the risk of infectious disease importation through airline networks. Nevertheless, Kinoshita *et al*. (2023) argue that the potential efficacy of travel restrictions to reduce the importation risk of Mpox through airline networks may have different magnitudes of effect among countries. We found that Brazil and Peru had higher Mpox incidence than expected, which could be explained by public health systems with limited capacity to block transmission. For instance, Brazil's public health system dramatically worsened during the COVID-19 pandemic, leading to a slow recovery when the Mpox outbreak occurred (Sott *et al.,* 2022).

Consequently, despite passenger flow in this country not returning to pre-pandemic levels, Mpox effectively spread through community transmission, particularly among domestic travelers participating in mass gathering events (Luques *et al.,* 2023). Practical implementation of air travel interventions across airline networks may not be feasible in most areas after the detection of an emerging pathogen with pandemic potential due to the strong economic and social impact of travel restrictions (Meier *et al.,* 2022; Kinoshita *et al.*, 2023). Therefore, focused efforts to reduce air travel in high-risk airports would be more effective (Shi *et al.,* 2020), especially if combined with enhanced capacities and infrastructure for early disease detection, rigorous contact tracing, and effective isolation of first cases.

Caveats

Important challenges during the international outbreak were likely delayed case identification and the lack of resources designated for early pathogen detection in some countries (Cui *et al.*, 2023). Delayed detection could potentially result in an underestimation of the burden of Mpox. The rapid infection rate of Mpox requires large-scale screening and real-time monitoring for an accurate reconstruction of the numbers and spread of cases (Pliakos *et al.*, 2018; Cui *et al.*, 2023). Rapid, affordable, and accessible diagnostic methods could significantly improve outbreak response and containment, reducing the potential public health impacts of Mpox in endemic and non-endemic countries (Bhatia *et al.*, 2021; Chang *et al.*, 2021). Furthermore, the primary lesson derived from the Mpox outbreak was the evident need for proactive global health collaboration (Kading *et al.*, 2018). Global collaboration should start by sharing, incorporating, analyzing, and publishing economic and social data fundamental for decision-making during outbreak responses (Meier *et al.*, 2022; Kinoshita *et al.*, 2023). Global data sharing is needed considering that active infectious disease surveillance requires international cooperation among researchers, policymakers, and public health officers (Bhatia *et al.*, 2021). Given the challenges of the Mpox outbreak, the global health community should push for active data sharing, enhanced public health infrastructure, global health diplomacy, and the generation of novel tools in digital epidemiology for more effective and timely outbreak response.

Future directions

The rise of Mpox in ten African countries over the last five decades, totaling 1347 confirmed cases and an additional ~28,800 suspected ones from the Democratic Republic of Congo, is likely tied to increased human-wildlife interaction with subsequent monkeypox virus spill-over to humans (Han *et al.,* 2020; Bunge *et al.,* 2022; Burki, 2022). Unlike smallpox, the monkeypox virus may exhibit both animal-to-human (spill-over), human-to-human (community), and human-to-animal (spill-back) transmissions (Henderson & Moss, 1999; Simpson *et al.*, 2020; Seang *et al.*, 2022). Current hypotheses suggest that spill-over leading to Mpox occurred in response to climate change, rainforest exploitation, and highly mobile human populations (Simpson *et al.,* 2020). Nevertheless, the mechanisms behind the wildlife-human spill-over of monkeypox virus and posterior community spread are poorly understood (Glidden *et al.,* 2021).

The limited knowledge of the patterns of Mpox transmission increases the risk of this virus becoming endemic where it currently circulates in wildlife. Our results suggest that international air travel modulates the likelihood of international disease spread. As such, international airports could play a crucial role by serving as places for monitoring the risk of emerging diseases. Future research should explore the effects of domestic flights on the spread of emerging diseases and the role of terrestrial and maritime human movement in the spread of infectious pathogens. Finally, the low transmissibility of the monkeypox virus, as compared with airborne infections, allowed for a reliable recovery of case numbers in this international outbreak, which contributed to providing the epidemic signals that could help inform future models of emerging diseases.

Conclusions

Our project delved into the global spread of Mpox, emphasizing temporal incidence, international travel patterns, and transmission risk hotspots. The summer of 2022 indicated a rapid global spread of Mpox, particularly affecting non-endemic countries, with increased air travel identified as a contributing factor. The recent Mpox international outbreak has clear geographical patterns, which were used to delineate hotspots of importation risk, aiming to inform its prevention, control, and epidemiological surveillance. Air passenger flow is a predictor of hotspot areas of Mpox spread, which suggests the potential role of international airports as the first front to monitor the risk of disease emergence. This study underscores the need for proactive public health measures, emphasizing real-time epidemiological monitoring and global collaboration at the airport level.

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