Risk assessment of cross-border transmission of infectious diseases: an example of a multi-country monkeypox outbreak in 2022

**Introduction**

Since the 19th century, with the advent of rapid transportation such as ships, trains, and airplanes, the movement of people around the world has accelerated, and the era of globalization has also been the era of global disease transmission. Global trade and travel have facilitated infectious disease transmission, from the plague in the 14th century, smallpox in the 16th century, to SARS, a novel influenza virus or COVID-19 in the 21st century (2–4). Dynamic monitoring and assessment of the extent of the global public health risk of an epidemic is important for the prevention and control of the spread of the epidemic. The largest risks tend to occur when novel diseases appear or when familiar diseases appear in novel geographic locations. Assessing disease-related health risks thus necessitates understanding where they might arise and how it might transmit. 【ref1】

A public health emergency of international concern (PHEIC) is a formal declaration by the World Health Organization (WHO) of "an extraordinary event which is determined to constitute a public health risk to other States through the international spread of disease and to potentially require a coordinated international response".[ref2] Monkeypox was declared as a PHEIC by the WHO on July 23, 2022, which is the seventh declaration of a PHEIC[[1]](#endnote-1). Monkeypox virus (MPXV) was first isolated in 1958 in monkeypox lesions in cynomolgus monkeys [2]. In 1970, nine months after the Democratic Republic of the Congo (DRC) declared smallpox eradicated, the monkeypox virus was first isolated from a child, the same year monkeypox was recognized as zoonotic [3]. Although there have been sporadic cases of monkeypox in non-endemic countries historically, the transmission chain is clear and the impact is small. Since the first case of the monkeypox outbreak was detected in the United Kingdom in early May this year, monkeypox cases have appeared in many continents and countries in a short period of time. Up to October 17, 2022, WHO reported 73,437 laboratory confirmed cases and 29 deaths, which involved 109 countries/areas/territories, which caused a tremendous impact on human health and public health security. Moreover, this batch of cases has shown a different "unspecific manifestation" in epidemiological and clinical characteristics than in previous years, which has aroused global attention.

Currently, most countries reported only a few imported cases without community transmission, such as China, which were at risk of cross-border transmission of monkeypox. The availability of risk assessment indicators and tools for countries with predominantly imported cases is essential to monitor the occurrence and progression of the epidemic as well as to develop related plans in advance. In this study, we provide index to assess the risk of cross-border transmission in Monkeypox and a nowcast of the probable size of the epidemic. It can provide decision-making basis for the prevention and control of the current monkeypox epidemic, and also provide risk assessment methods and scientific support for the cross-border spread of infectious diseases for the prevention and control of imported infectious diseases in the future.

**Methods**

To assess the risk of cross-border transmission of Monkeypox, we constructed an Monkeypox Risk Assessment model , where is the inbound flight dataset (Table S1 in the Supplement), is the WHO publicly available Monkeypox dataset (Table S2 in the Supplement), and is the evaluation time. Given inbound flight data and local epidemic data , describes the risk of epidemic import from the region to China at time . The larger the, the greater the risk of epidemic importation.

Inbound flights are the main channel for cross-border infectious disease import under the impact of current COVID-19 epidemic prevention and control measures. Based on air travel flows data for May, June and July, we calculated the average daily inbound flights from countries around the world to major cities in China.

Assuming that the epidemic time-series data observed in a region is , we define the Local Epidemic Risk Index as follows:

Where is a priori indicator related to the source area itself before the monkeypox epidemic (e.g., the sanitary status of the region, the state of sanitation facilities, etc.), and is the risk index of the region at time assessed based on, reflecting the posterior knowledge derived from the quantitative measurement and assessment of the data after the occurrence of the epidemic.

Considering the recent global COVID-19 pandemic and the various initiatives and policies of countries in response to the epidemic, we chose the stringency index (Table S3 in the Supplement) derived from Oxford COVID-19 Government Response Tracker to measure the ability of regions to prevent and control the spread of infectious diseases. The stringency index records the strictness of “lockdown style” policies that primarily restrict people’s behavior, taking values between 0 and 100.

Denote , where is the weight vector and is the n-dimensional vector associated with the epidemic, describing the risk level of the epidemic in a particular region in different dimensions, such as the number of infections, the rate of disease growth, etc. We construct a simplified but reliable epidemic transmission model to obtain explicitly from the time-series data . Let denote the number of infections in a region at time t, following the idea of the SEIR model, we can express as an ordinary differential equation as follows:

Where is a pooled coefficient used to describe the change in the number of infections over time, taking into account the basic regeneration number, growth rate, and containment intervention. Take a first-order approximation to :

We can solve the above differential equation and obtain:

The parameters and can be estimated from the time-series data , and according to , the inflection point of the epidemic can be deduced as follows:

Here, the parameter actually describes the acceleration of the infection rate under the combined influence of various factors, which is difficult to be estimated directly by the original SEIR model.

In addition to the above derivation that provides us with chronological information on the development of the epidemic, we need to consider statistics related to the epidemic itself. Available studies suggest that the basic regeneration number of monkeypox is approximately 2.4 in the MSM population and 0.8 in the non-MSM population. To better characterize the population transmission of monkeypox, we divided the infected individuals at time into MSM population (denoted as ) and non-MSM population (denoted as ) according to the proportion of case statistics provided by WHO (Table S4 in the Supplement).

Denoting the total population of the source country as (Table S5 in the Supplement), we select the following five-dimensional vector to describe the epidemic risk situation in the region:

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where the first two dimensions incorporate the main time-series information, i.e., the assessed epidemic inflection points and growth coefficient, and the last three dimensions incorporate the main epidemic-related vital statistics, namely the number of MSM infections, the number of non-MSM infections, and the infection rate. We use min-max normalization to linearly map the data values of each dimension into the interval [0, 1] and calculate the risk index of the region by the weight vector . Multiplying by the priori knowledge of a region and the number of flights at time, the risk of epidemic import from the region to China can be estimated.

All analyses were conducted in RStudio software using R version 4.2.1. The code used for this study is available online. Data were analyzed from May to October 2022, and the results were calculated from 100 randomized experiments with different infectious periods.

Limitation:

我们选取的五维向量v(t)中有两个维度与传染病的的流行过程密切相关，但是一些国家的病例数极少，仅有少数天零星几例，不足以体现疫情流行的变化趋势，因此难以直接应用我们的风险指数评估模型。对于此类情况，我们主要考虑epidemic-related vital statistics，并将时序相关因素的影响置于最低。

~~In order to assess the epidemic risk more accurately, we need to consider multiple dimensions of epidemic data.~~ Two dimensions of our selected five-dimensional vector are closely related to the epidemic process of infectious diseases, but the number of cases in some countries is extremely small, with only a few sporadic cases on a few days, which is insufficient to reflect the changing trend of the epidemic, so it is difficult to directly apply our risk index assessment model. For such cases, we mainly consider epidemic-related vital statistics and place the influence of time-series related factors at a minimum. In addition, there are multiple routes of cross-border transmission of infectious diseases, and this outbreak of monkeypox is mainly human-to-human transmission. The assessment model mainly takes into account the risks associated with cross-border flights, and other risks such as ground travel, animal and food transmission risks are not included.

1. Monkeypox as a PHEIC: implications for global health governance DOI:https://doi.org/10.1016/S0140-6736(22)01437-4

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   Ref1：Suk JE, Van Cangh T, Beauté J, Bartels C, Tsolova S, Pharris A, Ciotti M, Semenza JC. The interconnected and cross-border nature of risks posed by infectious diseases. Glob Health Action. 2014 Oct 10;7:25287. doi: 10.3402/gha.v7.25287. Erratum in: Glob Health Action. 2015;8:27635. PMID: 25308818; PMCID: PMC4195207.

   Ref2: WHO. World Health Organization; Geneva: 2005. Article 1, International Health Regulations (2005) UNTS 2509. [↑](#endnote-ref-1)