

Overview of case definitions and contact tracing indications in the 2022 monkeypox outbreak

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SUMMARY

Background: In 2022, a new outbreak of the Mpox virus occurred outside of Africa, its usual endemic area. The virus was detected in European, American, Asian, and Oceanian countries where Mpox is uncommon or had not been reported previously and where the spread was rapid. The study aims to compare the case definition and the indications for contact tracing in case of Mpox infection among the World Health Organization (WHO), the European Centre for Disease Prevention and Control (ECDC), and four European Countries.

Methods: From August 2022 to November 2022, we conducted research, first on the WHO and ECDC official websites and then on the official websites of the Ministry of Health or National Health Agencies of four European Countries (Italy, France, Spain, and Portugal). All reports found were compared to enlighten the differences in the definition of the case and indications for contact tracing.

Results: The WHO divides the case definition into four categories: suspected, probable, confirmed, and discarded, while the ECDC divides cases into confirmed and probable. The ECDC defines contact as close and others, while the WHO divides it into high, medium, and minimal risk. The four countries analyzed show heterogeneity in both the case definitions and the indications for contact tracing.

Conclusions: Our analysis revealed heterogeneity in the case definition between the WHO and ECDC. Different countries followed different indications or have given their indications for both the case definition and contact tracing indications. Harmonization strengthens public health preparedness and response and creates unified communication.

Keywords: Mpox outbreak, monkeypox, epidemiological and virological surveillance, public health authorities.

■ INTRODUCTION

While the new variants of COVID-19 still challenge the world, the emergence of a new outbreak caused by the Mpox virus, an orthopoxvirus close relative of variola virus (smallpox), has raised concern among public health authorities as to whether it would constitute a new threat [1-3]. It is transmitted between animals and humans and from human to human. Mpox disease results

in symptoms like those caused by the now-eradicated smallpox virus but is less clinically severe, usually only causing serious illness in young children and immunosuppressed persons [4].

The mortality rate ranged from 1% to 10% in occurrences, with the highest mortality rate in younger populations [5, 6]. Mpox's incubation period is typically about 6-16 days but can vary from 5 to 21 days. The main signs and symptoms in the first 5 days are fever, lymphadenopathy, back pain, extreme headache, myalgia, and serious asthenia. After 1-3 days from the onset of fever, a maculopapular rash grows into pus-filled vesicles. Finally, they become scabs in about 10 days [5].

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Mpox was first discovered in a monkey laboratory in Denmark in 1958, while the first human case was diagnosed in 1970 in a 9-month-old baby boy in Zaire (now Democratic Republic of the Congo, DRC). Since then, Mpox has become endemic in the DRC and has spread to other African countries, mainly in Central and West Africa [7, 8]. The first outbreak of Mpox outside of Africa was reported in 2003 in the United States. After that, Israel, the United Kingdom, Singapore, and other countries have reported Mpox cases among travelers returning from Nigeria since 2018 [9, 10]. In 2022, a new Mpox virus outbreak was occurring outside of its usual “endemic” base in Africa,

and the virus has so far been detected in 47 countries, including Europe, America, Oceania, and Asia, where Mpox is uncommon or previously unreported. On 25 June 2022, the World Health Organization (WHO) Emergency Committee declared that the outbreak does not currently constitute a Public Health Emergency of International Concern (PHEIC) but unanimously acknowledged the emergency nature of the event and that controlling further spread will require a vigorous response [11, 12]. After a rapid increase in cases on 23 July, the same WHO Emergency Committee declared that the current Mpox outbreak constitutes a PHEIC [13].

Table 1 - Reports reviewed.

<i>Issued by</i>	<i>Title</i>	<i>Date</i>	<i>Key aspect</i>
WHO [15]	Surveillance, case investigation and contact tracing for monkeypox	24 June 2022	The aim of surveillance, case investigation, and contact tracing in this monkeypox outbreak is to stop human-to-human transmission to control it.
ECDC [16]	Monkeypox multi-country outbreak	23 May 2022	As of 23 May, cases of monkeypox have reported in nine EU member states (Austria, Belgium, France, Germany, Italy, Portugal, Spain, Sweden, and the Netherlands).
ECDC [17]	Considerations for contact tracing during the monkeypox outbreak in Europe, 2022	28 June 2022	This report shows considerations for the prioritization of efforts to identify and manage close contacts, as well as indicators for public health authorities in the EU/EEA that can be used for monitoring the efficacy of their contact tracing activities.
Italian Ministry of Health [18]	Monkeypox outbreaks in non-endemic countries: updates on case definition, reporting, contact tracing, and case management. Technical notes for laboratory diagnosis	2 August 2022	From the information provided by international health agencies on the outbreak of monkeypox in non-endemic countries, regarding the epidemiological situation, the new case definition for surveillance, contact tracing and case management, it is necessary to update the guidance provided.
France National Agency of Public Health [19]	Monkeypox cases in Europe, definitions and conduct	8 September 2022	This document specifies the definitions of Monkeypox cases adapted for this epidemic (suspected, possible, probable, and confirmed cases), the biological and epidemiological investigations around the cases, their management, the information of at-risk contacts, and the declaration of cases to the health authorities.
Spanish Ministry of Health [20]	Protocol for early detection and management of Monkeypox cases in Spain	2 November 2022	Since May 2022, more than 100 non-endemic countries have reported more than 68,000 cases of MPX. On 23 July 2022, the WHO Director-General, recognizing the complexities and uncertainties associated with this event, determined that the MPX outbreak constitutes a PHEIC.
Portuguese Directorate-General of Health [21]	Handling cases of human infection with the Monkeypox virus (MPX)	15 September 2022	Update several points throughout the guideline: case definition, clinical approach to pregnant women, case reporting, laboratory diagnosis, contact management, contact surveillance and vaccination.

Given the rapid evolution of Mpox and the global alert, and the lesson learned from COVID-19, where the transition from epidemic to pandemic was rapid, causing significant harm to society, early identification of cases and contact management became necessary to contain the outbreak. For this reason, the need to identify uniform definitions to detect cases and contacts has arisen. Several national and international health agencies have published their classification and criteria to define cases and contacts. Therefore, we set out to overview on the official websites of the main health agencies to compare the definition of the case and the indications contact tracing indications in case of Mpox infection. Then, we checked which indications were implemented in four European countries: Italy, France, Spain, and Portugal.

■ MATERIALS AND METHODS

From August 2022 to November 2022, we reviewed the available information about case definition and contact tracing indications of Mpox on the main health agencies' official websites. We looked at the WHO reports and, at the European level, the European Centre for Disease Prevention and Control (ECDC) publications. At the Euro-

pean level, we chose two countries with a high incidence of cases (France and Spain) and two countries with a lower incidence of cases (Italy and Portugal) [14]. We searched the ministry of health and national health authority websites of the European countries chosen to find the criteria to identify the case and contact tracing indications of Mpox. Table 1 shows the eligible reports to achieve our goal of WHO, ECDC, the circular letter of the Italian Ministry of Health, the procedure to be followed by the France National Agency of Public Health, the protocol of the Spanish Ministry of Health, and the guideline of Portuguese Directorate-General of Health [15-21]. Reports of these agencies and the four European Countries under study were compared to identify differences in the definition of the case and indications for contact tracing.

■ RESULTS

Table 2 shows the case definitions used by the WHO and ECDC. The WHO divides the case definition into four categories: suspected, probable, confirmed, and discarded. While the ECDC divides cases into only two categories, confirmed and probable. No difference emerged in the defi-

Table 2 - Case definitions used by the WHO and ECDC.

Case Definition	
WHO	ECDC
<p>Suspected: A person of any age presenting since 1 January 2022 with an unexplained acute rash or one or more acute skin lesions; AND one or more of these signs or symptoms*; AND for which the following common causes of acute rash or skin lesions do not fully explain the clinical picture.</p> <p>Probable: A person meeting the case definition for a suspected case AND (one or more): an epidemiological link to a probable or confirmed case of MPX in the 21 days before symptom onset; multiple or anonymous sexual partners in the 21 days before symptom onset; detectable levels of anti-orthopoxvirus antibody**; positive test results for orthopoxvirus infection.</p> <p>Confirmed: Laboratory confirmed monkeypox virus by detection of unique sequences of viral DNA by PCR and/or sequencing.</p> <p>Discarded: the suspected or probable case for which laboratory testing of lesion fluid, skin specimens or crusts by PCR and/or sequencing is negative for MPX.</p>	<p>Confirmed: A person with a laboratory-confirmed monkeypox infection, monkeypox virus-specific PCR assay positive result or orthopoxvirus-specific PCR assay positive result, which is then confirmed by nucleotide sequence determination of the detected virus as MPXV with symptom onset since 1 March 2022.</p> <p>Probable: A person with an unexplained rash on any part of their body AND one or more another symptom (s)* of monkeypox infection with symptom onset since 1 March 2022 AND one of the following: positive laboratory test result on orthopoxvirus infection; an epidemiological link to a confirmed or probable case of monkeypox in the 21 days before symptom onset; reports travel to MPX endemic countries in the 21 days before symptom onset; a person (of any sexual orientation) who had multiple or anonymous sexual partners in the 21 days before symptom onset; a man who has sex with men.</p>

*Headache, acute onset of fever (>38.5°C), lymphadenopathy, myalgia, back pain and asthenia.

**IgM from 4 to 56 days after rash onset, or a four-fold rise in IgG antibody titer based on acute (up to day 5-7) and convalescent (day 21 onwards) samples; in the absence of recent smallpox/monkeypox vaccination or other known exposure to OPXV.

inition of a confirmed case between the two agencies.

Meanwhile, in the probable case definition, there are some differences between WHO and ECDC.

In the probable case, ECDC includes travel to MPX endemic countries in the 21 days before symptom onset, a person (of any sexual orientation) who had multiple or anonymous sexual partners in the 21 days before symptom onset, and man who has sex with men.

Instead, the WHO, in its definition of probable case, considers not only positive laboratory test results on orthopoxvirus infection but also detectable levels of anti-orthopoxvirus antibody [IgM from 4 to 56 days after rash onset, or a four-fold rise in IgG antibody title based on acute (up to day 5-7) and convalescent (day 21 onwards) samples; in the absence of a recent smallpox/monkeypox vaccination or other known exposure to orthopoxvirus].

Table 3 shows the definition of contact by the WHO and ECDC. The ECDC defines contact as

close and others, while the WHO divides it into high, medium, and minimal risk. The WHO estimates the permanence in the same room with a symptomatic MPX patient, without appropriate personal protective equipment (PPE) as a medium risk. It is impossible to determine whether the medium-risk contacts indicated by the WHO are close contacts or others for the ECDC.

Table 4 shows which indications for case definition and contact tracing indication were followed by four selected countries (France, Spain, Italy, and Portugal). There is heterogeneity in the case definitions and the indications for contact tracing. For case definitions, only Spain and Italy follow the precise indications of a major health agency (WHO), while France and Portugal give their definitions. Portugal seems to summarize the two case definitions (WHO and ECDC). As for contact tracing indications, Italy and Portugal follow the indications given by the ECDC, while Spain and France give their own indications without following either of the two main health agencies.

Table 3 - Definition of contact by the WHO and ECDC.

<i>Definition of contact</i>	
<i>WHO</i>	<i>ECDC</i>
<p>High risk: inhalation of droplets or dust from cleaning contaminated rooms; mucosal exposure due to bodily splashes; physical contact with someone with MPX, including direct contact during sexual activities. This includes face-to-face, skin-to-skin, or mouth-to-skin contact or exposure to body fluids or contaminated materials or objects; normally sharing a residence (permanently or occasionally) during the resumed incubation period with a person diagnosed with MPX, or a penetrating sharps injury from a contaminated device or through contaminated gloves.</p> <p>Medium risk: no direct contact but proximity in the same room or indoor physical space as a symptomatic MPX patient if not wearing appropriate personal protective equipment (PPE).</p> <p>Lower or minimal risk: contact with a person with confirmed, probable, or suspected MPX or an environment that may be contaminated with MPX virus while wearing appropriate PPE and without any known breaches of PPE or of donning and doffing procedures; community contacts, such as being in an outdoor setting with a symptomatic case without proximity or physical contact; no known contact with a symptomatic MPX case in the last 21 days, or laboratory personnel handling routine clinical blood samples or other specimens not directly related to MPX diagnostic testing.</p>	<p>Close: sexual partner; person(s) living in the same household or similar setting; person(s) sharing clothing, bedding, utensils etc., while the patient had a rash; caregivers of MPX case, while symptomatic; Healthcare worker (HCW) who had contact with MPX case (lesions or prolonged face-to-face contact) without appropriate PPE; HCW or another person who suffered a sharps injury or was exposed to MPX case body fluids or aerosol-generating procedure without PPE; laboratory staff suffering exposure to an occupational accident with the virus-containing sample; another prolonged physical or high-risk contact to be assessed on a case-by-case basis, for example, the person(s) sharing the same closed workspace/office for long periods; co-passenger seated one or two seats distance around the case while they were symptomatic, in an airplane, bus, or train.</p> <p>Others: brief social interactions; work colleagues not sharing the same office; persons sharing fitness equipment or sharing the same sauna or bath, without sexual contact; social encounters/ acquaintances; HCW contact with appropriate PPE.</p>

Table 4 - The difference in case definition and contact tracing indication between France, Spain, Italy, and Portugal.

Country	Case Definition	Contact tracing indication
France	Divides it into three categories: possible, probable, and confirmed	Divides it into two categories: at-risk and negligible risk
Spain	Follows WHO's criteria	Only the definition of close contact is given, but it is different from ECDC's criteria
Italy	Follows WHO's criteria	Follows ECDC's criteria
Portugal	Divides it into three categories: suspected, probable, and confirmed	Follows ECDC's criteria

■ DISCUSSION

Our study aimed to compare the case definitions and the indications for contact tracing in the 2022 Mpox outbreak through an overview of reports issued by the main health agencies and by four European countries.

The emergence and re-emergence of new and old infectious diseases have been widely linked to poverty, vulnerability, malnutrition, and poor health behavior, which is more common in low-income countries, such as sub-Saharan Africa and some Asian countries [22-24].

The current Mpox outbreak also involved middle- and high-income countries, and its rapid spread in Europe has generated intense scientific, political, and media activity [25]. In this context, surveillance systems are essential to create a fair epidemiological and virological view, to stop an epidemic before it can explode and become uncontrollable. The consequences of large-scale viral infection can be severe for persons healthcare systems still facing the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic [26-28]. The WHO and ECDC agree on the definition of a confirmed case; in fact, the infectious agent must be identified by culture or PCR, but in the classification of the non-confirmed case (probable, suspected, discarded), there are some differences [29]. The problem of case definition, as identified in our study, of an infectious disease is already known in Europe, which could lead to incomplete epidemiological data [30]. As already suggested, the case definition should be homogenized between the main health agencies [13]. This would make epidemiological surveillance more effective and give the countries clear guidance for managing the Mpox outbreaks with the same criteria. The current case definitions of

Mpox given by the WHO and ECDC would miss the case of a heterosexual patients with a characteristic vesicular-pustular rash but no travel history or contact with confirmed infection [31]. Mpox, unlike SARS-CoV-2, is rarely thought to spread asymptotically. Therefore, more information on the Mpox infection in asymptomatic high-risk persons would be needed to determine whether any screening in persons without skin lesions is justified [32]. The outbreaks in several countries raise concerns that potential genotypic mutations could change the phenotype of the virus. This could be a sign of increased transmissibility of the virus or of a progressive and slow transmission which is more difficult to trace, making contact tracing, in this case already challenged by the high number of anonymous sexual partners, even more challenging [33, 34]. In addition, contacts, once traced, may have generated other cases: contact tracing strategies should also consider a pre-symptomatic infectious period when trying to find the contacts of confirmed cases [35]. Given this Mpox outbreak in non-endemic countries, which now seems to manifest itself as a sexually transmitted infection, it is highly concerning, not least because of possible new transmission routes [36]. This makes it crucial for contact tracing services to identify people at risk quickly and subsequently curb super-diffuse transmission events [37].

■ CONCLUSIONS

Our analysis has revealed heterogeneity in the case definition and in the definition of contacts between the main health agencies. Certainly, harmonizing case definition is important to strengthen public health preparedness and response and create unified communication. Moreover, uniform

contact tracing is a key public health measure to control the spread of infectious diseases, such as Mpox. Each of the four countries followed different directions or provided its own directions for case definitions and contact tracing. Italy was the only country to stringently follow the case definitions and contact tracing directions of the main health agencies. Given this, the lessons learnt from SARS-CoV-2 should teach us that its early spread could have been mitigated if the initial case definitions had been less strict and if extensive community-based testing had been carried out earlier.

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Conflict of interest

The authors declare no conflict of interest.

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