# Human Monkeypox Management and Strategies

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Monkeypox, a viral zoonosis caused by an Orthopoxvirus, is clinically characterized by fever, headache, lymphadenopathy, myalgia, rash and burdened by some complications that can be severe and life threatening. Monkeypox, endemic in some central and west African countries, in tropical areas near equator, rose to the headlines following its outbreak in non-endemic countries of Europe and the USA. Thus, the World Health Organization, worried about the growing dimension of the problem, declared monkeypox a global public health emergency.

COVID-19 epidemic human monkeypox therapy

## 1. Introduction

Monkeypox, a double-stranded DNA virus (genome size about 200 kilobases, seven times larger than SARS-CoV-2), has been known to belong to the Orthopoxvirus genus of the Poxviridae family since 1958 when, after two outbreaks of a generalized vesicular-pustular rash illness in colonies of Cynomolgus monkeys, it was identified at the Statens Serum Institute of Copenhagen [1][2][3] (hence the name monkey pox, although rodents would seem to be the main viral reservoir). In the years following the discovery, some outbreaks of pox infection were recognized in the United States of America (USA), Denmark and the Netherlands among groups of captive monkeys (of some species) (Cynomolgus, Rhesus, Macaca philippensis, Macaca mulatta, Macaca irus, Langur) coming from some regions of Asia (Singapore, India, Philippines, Malaysia) [4].

Monkeypox virus is not ancestral to variola virus (the causative agent of smallpox), but both have evolved independently of their common ancestor and the possibility of one becoming transformed into the other has been excluded, although they are closely related [5][6].

The presence of human monkeypox was first ascertained in September 1970 in a 9-month-old child in Basankusu district, on Equateur Region, in the Republic Democratic of the Congo [7]. The outcome of the disease was complicated by the onset of other infections leading up to child's death [7]. Since then, some outbreaks of human monkeypox, a few of which also causing death, have been identified in more than 50 years in several regions of the world. The incidence of monkeypox has risen almost tenfold, over the past few years, going from 0.63 to 5.53 in 10,000 people [8][9].

Clinically, human monkeypox has similar but milder features than those of smallpox; surely it has a different epidemiology [10]. Initially, two clades of monkeypox virus strains, with about 0.5% genomic sequence difference, were recognized in some regions of Africa, one of which (Congo basin MPXV-ZAI-V79) is more virulent than the other (West Africa) [11]. Now, in accordance with the World Health Organization (WHO), a novel classification of monkeypox virus strains was proposed based on three clades (clade I corresponding to Congo basin and clades IIa and IIb to West Africa) [12].

Although the WHO in 2018 still considered the monkeypox a rare viral zoonotic disease of remote areas of central and West Africa, near tropical rainforests [13], on 23 July 2022 deemed it a public health emergency of international concern, for the moment concentrated among men who have sex with men, especially those with multiple sexual partners, giving few necessary justifications to substantiate its decision [14][15]:

- the rapid spread of the virus to many countries never seen before and the new modes of transmission, largely unknown, meeting the International Health Regulations criteria.
- the risk for human health and its potential implication with the international traffic;
- the high risk in the European regions and the moderate risk worldwide.

## 2. Epidemiology

Monkeypox is a rare infectious zoonotic disease which is endemic in central and western Africa areas (especially in Democratic Republic of the Congo, Liberia, Sierra Leone, Nigeria and Ivory Coast) that are characterized by high mean annual precipitations and low altitude [16][17]. From its discovery to 2000, other regions in Benin, Cameroon, the Central African Republic, Gabon, Ghana, Sierra Leone and South Sudan were added to the list of the endemic areas for monkeypox, in Africa. However, the highest number of cases of monkeypox was reported in the Democratic Republic of the Congo with a case fatality rate of 11%, in smallpox unvaccinated patients, that reached 15% among children under 4 years [16].

In the Democratic Republic of the Congo in 1996–1997 and in 2003, the first outbreaks of human monkeypox have occurred in which it was observed that transmission of monkeypox virus took place from person to person [18][19].

In particular, during the 1996–1997 epidemic, the interhuman mode of transmission continued for two years in large areas of the Katako-Kombe and Lodja health-care zones [18].

On May 2003 there was the first documented human monkeypox case outside of Africa, in a 3-year-old girl from central Wisconsin in the USA [20]. An interesting epidemiological study showed that the monkeypox virus was present in African rodents arrived in a shipment from Ghana and responsible for transmitting the virus to animals destined for the pet trade [21]. In the human American outbreak that followed, involving six states (Illinois, Indiana, Kansas, Missouri, Ohio, and Wisconsin), fatal cases were not reported [21], probably because the West African

virus, the unique viral strain isolated in this outbreak, was less virulent than the other strain prevalent in the Congo [11][22]. Furthermore, in these states of the USA, most patients had performed vaccination against smallpox in the past [21].

Interestingly, it was noted that the outbreak occurred in the USA was strictly related to the domestic use of exotic wildlife which pushed the Food and Drug Administration to ban the import of all rodents from Africa and the sale, distribution, transport, and release into the environment of prairie dogs and six African rodent species [21]. However, the spread of monkeypox virus through human contact during this outbreak could not be excluded although the exposure to infected prairie dogs was the main invoked mechanism of transmission to humans [20].

The analysis of another outbreak of monkeypox that began in South Sudan in 2005, confirmed the role of importation into the area from a place where monkeypox is endemic (the Congo) both through infected animals and humans entering in that area, thus supporting the hypothesis of person-to-person transmission [23].

However, a different epidemiology distinguished the African from the American outbreak.

Indeed, in Africa, human monkeypox primarily affected children younger than 10 years (80% of cases) that were part of rural populations (residents of villages of less than 1000 people), and the transmission was both via contact with infected small mammals obtained for food or through infected animal bites and person-to-person contact (28% of cases) with a case fatality ranging from 10% to 17% [24]. In the USA, an equal number of males and females was affected, infected prairie dogs were the main vehicle of transmission, whereas person-to-person transmission was infrequent and no death was observed [23].

Some conditions make possible the epidemic outbreak of monkeypox [25][26][27][28][29][30]:

- today, 70% of the world population and 75% of young individual have never received the smallpox vaccine resulting unimmunized against the monkeypox virus;
- re-emergence of monkeypox in Africa (epidemic in Nigeria 2017–2018 and in Central African Republic in 2018) due to endemicity favored by climate change, rain forest exploitation, geopolitical and armed conflicts, without neglecting the possibility of intrafamilial infections;
- travel-associated monkeypox (case worldwide).

It has become clear that Monkeypox may spread from human to human through close contact with skin lesions or lesions on internal mucosal surfaces, body fluids and respiratory droplets, but cases of airborne transmission were not reported [31][32]. An indirect transmission through contaminated objects is also mentioned [31].

Recently, in the course of the monkeypox epidemic in Nigeria in 2017–2018, the sexual transmission in several patients with genital ulcers was also hypothesized [33].

Travel associated monkeypox was reported in 2018 in men who returned from Nigeria to Israel, Singapore and United Kingdom [34][35][36][37][38] with the peculiarity, in the latter country, of the first nosocomial and household transmissions to be reported outside of the African continent [36].

They were also the first-time international travelers implicated in the spread of monkeypox outside of an outbreak setting [39].

Coming to the present day, the Democratic Republic of the Congo would be the greatest responsible for epidemic resurgence, with 1356 cases of monkeypox and 64 deaths from January to July 2022 [40][41].

In the first months of the current year, the sudden appearance of the monkeypox virus in non-endemic areas and the high risk of human-to-human transmission attracted the attention of the scientific and institutional world. This led to increase the amount of research and number of publications on this matter.

From January 2022 to June, a great number of cases of monkeypox have been reported also in several non-endemic countries of Europe, in the United Kingdom, USA, ASIA (Singapore, South Korea) Australia and Republic of China (Taiwan) (**Table 1**).

**Table 1.** The number of cumulative confirmed monkeypox cases reported to the WHO, in non-endemic Regions, from 1 January 2022 to July 2022.

| WHO | NON-ENDEMIC COUNTRIES | CASES REPORTED |
|---|---|---|
| EUROPEAN REGION | Austria | 12 |
| | Belgium | 77 |
| | Czechia | 6 |
| | Denmark | 13 |
| | Finland | 4 |
| | France | 277 |
| | Georgia | 1 |
| | Germany | 521 |
| | Gibraltar | 1 |
| | Greece | 3 |
| | Hungary | 7 |
| | Iceland | 3 |

| WHO | NON-ENDEMIC COUNTRIES | CASES REPORTED |
|---|---|---|
| | Ireland | 24 |
| | Italy | 85 |
| | Latvia | 2 |
| | Luxembourg | 1 |
| | Malta | 2 |
| | Netherlands | 167 |
| | Norway | 4 |
| | Poland | 7 |
| | Portugal | 317 |
| | Romania | 5 |
| | Serbia | 1 |
| | Slovenia | 8 |
| | Spain | 520 |
| | Sweden | 13 |
| | Switzerland | 46 |
| | The United Kingdom | 793 |
| | Argentina | 3 |
| | Brazil | 11 |
| | Canada | 210 |
| MAINLAND OF THE AMERICAS | Chile | 3 |
| | Mexico | 11 |
| | United States of America | 142 |
| | Venezuela | 1 |
| MEDITERRANEAN REGION | Israel | 13 |
| | Lebanon | 1 |

| WHO | NON-ENDEMIC COUNTRIES | CASES REPORTED |
|---|---|---|
| | Marocco | 1 |
| | United Arab Emirates | 13 |
| | Australia | 9 |
| ASIA | Republic of Korea | 1 |
| | Singapore | 1 |
| REPUBLIC OF CHINA | Taiwan [43] | 1 |

Important research across 16 countries [44] provided further support for this.

Furthermore, even in the USA the transmission of monkeypox was prevalent in communities of gay, bisexual, and other men who have sex with men and in racial and ethnic minority groups, as well [45].

Physical contact, sexual transmission in men who have sex with men, or transmission via fomites were the infection routes indicated in a prospective cross-sectional study performed by experienced dermatologists in multiple medical facilities during the monkeypox epidemic in Spain in the 2022 outbreak [46].

Person-to-person transmission of monkeypox within the United Kingdom was also demonstrated in a retrospective observational analysis of patients between May and July 2022 in a south London High Consequence Infectious Diseases Centre [47].

Even in Germany, France and Portugal the analysis of the first monkeypox outbreak showed a clear human-to-human transmission among a susceptible demographic group (especially men who have sex with men) [48][49][50]. A probable importation of the virus in Portugal from other European countries, in which it circulated without being detected, was suggested [48].

The absence of connection between the current monkeypox outbreak and travels in the endemic areas strengthens the impression of an undetected spread of monkeypox virus in Europe through human-to-human transmission [51].

Indeed, the hypothesis of a mutation in the monkeypox virus able to explain the recent outbreak worldwide has been denied by the absence of major mutations in the viral genome [52].

## 3. Prevention

Various practical preventive measures should be taken and, among them, interrupting the virus transmission from animals to humans might greatly hamper the monkeypox epidemic from spreading [53]. For example, pets belonging to individuals with monkeypox should be kept at home and away from other animals and people up to 21 days after the most recent contact [53].

However, since as previously said, the human-to-human transmission is the prevalent route during this epidemic, it is essential to avoid [54]:

- close physical contact (including sexual activity) with persons affected by monkeypox rash;
- contact with body fluids of infected animals;
- bites of infected animals;
- processed meat from infected animals;
- become in touch with fomites.

Contact tracing is a desirable measure to identify exposed persons, isolate them and prevent further cases. However, it should be remembered that previous smallpox vaccination may give false positive results [55].

Since men who had sex with men, bisexual and also ethnic and racial minority groups are affected by monkeypox, the efforts of public health should, rather, be focused on these groups for infection prevention and testing [56].

Furthermore, it would be important to give medical staff any information such as to pay close attention to hand hygiene, ensure a proper cleaning of contaminated surfaces and, in addition, provide them with protective devices for full safety of health (for example, eye protection in the event of procedures that expose to the risk of contact with body fluid) [53][57].

## 4. Management and Strategies

No specific Food and Drug Administration (FDA) approved treatment exists for monkeypox disease, but some recommendations should be followed, especially with the aim to prevent or better manage the development of possible complications [58].

The symptomatic management of fever and respiratory distress, with antipiretics and supplemental oxygen, is desirable where necessary [59].

Encephalitis accompanying monkeypox, depending on symptoms and causes, needs to be treated with intravenous fluids, supplemental oxygen, steroids, antiseizure medicine, antiviral or antibiotics.

Secondary bacterial infections (pneumonia, abscess, other infections of the skin) should be treated with empirical oral or parenteral cephalosporins or beta-lactam antibiotics [60].

No FDA approved antivirals exist to treat monkeypox, although tecovirimat is FDA approved for treating smallpox, being able to prevent viral release from cells via inhibition of the viral envelope protein p37. However, even if

current studies have not proven the effectiveness of tecovirimat in human monkeypox, a recent report supports the continued recourse to treatment with tecovirimat in the current monkeypox outbreak, also taking into account that it is generally well tolerated [61]. Moreover, other authors suggest that it may be useful in patients with weakened immune systems without age limits [33][62]. Finally, CDC guidelines advise its use in patients with severe disease, or in those at high risk for severe disease, or with aberrant infections [45]. However, headache, nausea, abdominal pain, vomiting, neutropenia and infusion site reaction are some side effects that patients might experience after the antiviral administration [62].

Although the use of monoclonal antibodies is approved to treat severe cases of monkeypox and subjects affected by T cell lymphopenia, divergent views exist on their safety. Indeed, they are burdened with some problems in the production methods, including the one of being exposed to the risk of contamination with blood-borne infectious agents [62][63].

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