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Review

The outbreak of monkeypox 2022: An overview

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ABSTRACT

On May 6, 2022 an outbreak of monkeypox (MPX) was confirmed in the United Kingdom, originating from a British resident who had travelled to Nigeria. As of May 21, 2022, 92 cases have been confirmed worldwide, from 13 countries where monkeypox virus (MPXV) is not endemic. Reported cases thus far have mainly but not exclusively been identified among gay and bisexual men aged 20–50. MPXV is a viral zoonosis transmitted to humans via contacting or eating an infected animal, and direct connect with natural host's blood and body fluids. In addition to contacting with a patient's respiratory droplets, lesions, body fluids and polluted personal objects. Symptoms including shivers, headaches, fainting, backaches, and myodynia do not have any specific characteristics making it difficult to establish a proper diagnosis. Nevertheless, lymphatic hyperplasia, one of the most common symptoms of monkeypox, can be useful for diagnosing the disease. Clinical symptoms help establish the suspicion of monkeypox. However, in the absence of confirmed diagnostic tests it is very difficult to verify the disease and determine its cause based on clinical symptoms alone. There are numerous methods for detecting MPX, involving genetic, phenotypic, immunological methods, and electron microscopy. These tests require modern equipment and expert hands, which may not be available in developing countries where this disease is prevalent. Currently, there is no definite treatment for MPX. CDC recommends administering the smallpox vaccine within 4 days of exposure which may prevent the disease from happening, and within 2 weeks to reduce symptoms severity. To promptly identify patients and prevent further spreading, physicians should be aware of the travel or contact history of the patient with compatible symptoms.

1. Introduction

On May 6, 2022 an outbreak of monkeypox (MPX) was confirmed in the United Kingdom (UK), originating from a British resident who had travelled to Nigeria, where the disease is endemic, and while there, presented symptoms consistent with on April 29, 2022. This person returned to the UK on May 4, importing the index case of the outbreak into the country [1].

As of May 21, 2022, 92 cases have been confirmed worldwide, from 13 countries where monkeypox virus (MPXV) is not endemic (UK, Australia, Belgium, Canada, France, Germany, Italy, Netherlands, Portugal, Spain, Sweden, USA) [2]. As of May 22, 2022, the total number of countries have confirmed outbreaks has risen to 15. The United Arab Emirates (UAE) is the first Arab country to report an infected case on May 24 [3]. No deaths have been reported so far [2], and Belgium has become the first country to introduce a compulsory 21-day MPX quarantine [4].

MPXV was first isolated and identified in 1958 when monkeys transported from Singapore to Denmark for research purposes got a vesicular disease. Hence the name "monkeypox" [5]. However, rodents such as squirrels and giant pouched rats, which are hunted for food, represent the largest animal reservoirs for the virus [6].

The first human case was discovered in August 1970 when the virus was isolated from a 9-year-old child in rural areas of Democratic Republic of Congo (DRC) suspected of having smallpox [7].

Since 1970, human cases of MPX have been reported in 11 African countries [2,8], with a median age of 31 years [9].

A small number of cases have been recorded before outside of Africa [8]. In the current outbreak, the virus was found for the first time in some patients who had no clear link to West and Central Africa [2].

Reported cases thus far have mainly but not exclusively been identified among gay and bisexual men aged 20–50 [2], but it is uncertain if sexual behaviors making it easier to spread, or it is just a coincidence [10]. The vaccinia virus which is used to provide cross-protection

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against smallpox is proven to spread through sexual contact, this is largely due to direct contact with the infected rash [11].

2. Virology

MPXV is a lipoprotein membrane-enveloped double-helix DNA virus of the genus Orthopoxvirus, that belongs to the Poxviridae family and the chordopoxvirinae subfamily [8,9,12]. The Poxviridae is an ancient virus family that has been found in insects, reptiles, birds, and mammals, and is thought to form visible "pox" prior to vertebrate-invertebrate divergence [13,14].

Although the poxviruses genome contains all requirement proteins to replicate, transcribe, assembly and exit, it needs infected individuals' ribosomes to translate mRNA [12].

Along with MPXV, there are three more types of orthopoxvirus that also effect humans, including variola major virus -the cause of smallpox-, variola minor virus (Variola alastrim), and cowpox virus (vaccinia) [9].

MPXV is considered a large virus which measure about 200–250 nm with the appearance "brick-like" or ovoid shape [12].

MPXV has two distinguished hereditary subgroups, the West African and the Central African (Congo Basin) which motivates more serious infection and is believed to cause a higher infective possibility. In spite of the fact that there are different geographical incidence locations between the two virus categories, they both occurred in the same country "Cameroon" [8,9].

The virus's original source is wild animals. It can be found in a variety of mammals including squirrels, mangabey monkeys and Gambian rats. Even though the essential host continues to be not clear, the rodents are believed to be the host reservoir rather than monkeys [9,13,15].

Human MPXV transmission happens in two ways, either from animal-to-human or human-to-human. Aerosol transmission has been demonstrated between animal populations [9]. Contacting with a patient's respiratory droplets, lesions, body fluids and polluted personal objects support the virus spreading among peoples. Furthermore, hospital-acquired transmission has been confirmed, whereas intercourse transmission is suspected for the patient with genital MPXV lesions. However, zoonotic transmission can exist if people contact or eat an infected animal, In addition to direct connect with natural host's blood and body fluids [8,13].

3. Clinical manifestations

MPXV has an incubation period ranging from five days to three weeks [9,16], and the symptoms can last for nearly 2–5 weeks. Early symptoms include shivers, headaches, fainting, backaches, and myodynia, but they are not specific [9].

The most common symptoms observed before the the rash development are fever, restlessness and lymphadenopathy [16]. Human MPX has similar clinical features to ordinary and modified smallpox [16,17], but generally more moderate [18]. As swollen lymph nodes are not a common sign of smallpox and are seen in 90% of MPX patients [9]. They are considered a distinctive hallmark of MPX. These enlargements can be observed in the neck, the groin and submandibular areas [16].

During the five days following the fever, various sizes of rashes develop, initially on the face and then spreading across the trunk area and extremities. The rashes often appear on the palms and soles of the feet [9]. These lesions measure approximately 0.5 cm in diameter, and some can reach up to 1 cm [18]. Exanthems progress through different developmental phases, resolving into crusts that fall off during the healing phase [9]. Lesion co-infection is recurrent and plays a major role in future skin marking [17].

While MPX symptoms are less severe than those of smallpox, it is still considered a fatal disease, that causes death at a fluctuating rate of up to 10% [9]. Death usually occurs within the second week of the infection [16]. The risk is higher in children and young adults, and the disease can take a severe course in immunocompromised patients [19]. The disease can present with numerous complications, such as co-infections, respiratory disorders, encephalitis, blindness-related keratitis, and gastrointestinal symptoms like vomiting and diarrhea [9].

Smallpox vaccination can offer some protection against MPX and can alter the course of the disease. Studies between 1980 and 1990 indicated a change in the pathogenesis of human MPX, because more people without immunity to smallpox developed the disease. Moreover, the pathological picture was less severe in the vaccination group, and the skin infection was milder. This was in contrast to the unvaccinated, whose skin infection was more severe, with multiple forms and a higher probability of death [20–23].

Since the symptoms of MPX are varied and non-specific, many diseases can be included in a differential diagnosis. The differential diagnoses are: chickenpox (the most clinically similar disease), water warts, red measles, rickettsia disease, staphylococcus skin infections, bacillus anthracis, itch mites, syphilis, and drug reactions for non-infectious causes of rashes [24].

Since lymphatic adenopathy is one of the most frequently observed symptoms, which is a differential sign from other diseases, it is imperative to emphasize its importance in the initial examination of a suspected patient.

4. Diagnosis

In order to diagnose monkeypox, health providers should collect a proper specimen and send it carefully to a capable lab. Verifying human MPX virus relies on the sample type and the available laboratory tests [2].

As the illness symptoms are still difficult to identify and hard to minimize in low-income countries. It poses a world challenge since these areas are considered endemic with this disease [23].

The confirming techniques that are used for analyzing specimens and determine MPX include genetic, phenotypic and immunological methods [13]. Table 1 lists the diagnostic methods that can be used to identify human MPX. These approaches work better when are combined with the medical and epidemiological information including the patient's immunization history [23].

A detailed medical history with focus on specific information, such as recent traveling to an endemic area, vaccinating with the smallpox vaccine, along with linking clinical information to the existing symptoms, can be extremely directing to the disease diagnosis, but it is not sufficient to establish a definitive one. The golden test to establish the diagnose is the polymerase chain reaction. Beside its high accuracy and sensitivity, the viral DNA within the lesion persists constant for a long time if kept in a dark and comparatively cool atmosphere [23].

As Real-time PCR needs high quality labs which are hard to be found in low-resources countries. The upcoming technologies are reliable on to develop the PCR and qPCR to overcome their consequences and become available outside the large laboratories, which allows to have an accurate diagnostic tool within the reach of all medical staff, even those in poor countries.

Establishing the conditions source requires an antibody-based diagnosing. Immunological tests against orthopoxviruses have a cross-reactivity with other Orthopoxviruses. Still, these tests may be valuable when there is previous indication to explain the disease cause.

Although IgG alone cannot provide a definitive diagnosis to a patient who has been exposed to orthopoxvirus during his life through vaccination, IgM is considered more effective in diagnosing newly infections patients retrospectively [23,25].

MPX patients often pursue medical help at countryside health centers or hospices which are not provided with electricity [23]; therefore, it is requirement to improve the current tests so it can be used in developing countries where there is lack in resources and human performing.

Table 1
The diagnostic methods that can be used to identify human MPX.

	Genetic Methods	Phenotypic Methods	Immunological Methods	Electron Microscopy
Based on	PCR or qPCR [23].	Clinical diagnose [13].	• Sensitive detection of IgG or IgM antibodies against MPX using Elisa test. • Immunohistochemical (IHC) to spot virus antigens [13].	Electron microscopy (EM).
Pros	• PCR is the standard test for detecting MPX-specific DNA sequences due to its high accuracy and sensitivity [2]. • For genetic testing, the recommended diagnostic samples are from cutaneous lesions (a smear from the surface of the lesion and/or exudate, or crusts of the lesion) or from a biopsy when possible [2,9].	• possible diagnosing based on clinical signs is essential in order to expose suspected cases during examination [26].	• Increased antiviral antibodies and T-cell activation against MPX have been documented with disease onset [13]. • When a rash develops, IgM and IgG can be detected in serum about 5 days and more than 8 days in a row [13]. • If both IgM and IgG are present in unvaccinated persons with a history of rash and symptoms of severe disease, then an indirect diagnosis can be founded [13].	• Can distinguish Orthopoxvirus from herpes simplex virus. • It gives evidence that mpx may belong to the Poxviridae family [13].
Cons	• Highly sensitive examinations where there are justified concerns about sample contamination [23]. • These tests demand high-cost tools, reagents, and expert techniques [23].	• According to a study conducted on a group of 645 individuals whose clinical diagnosis of MPX was not accompanied by a laboratory confirmation, it had a high sensitivity (93–98%) but low specificity (9%–26%) [24].	• The above methods are not considered qualitative for human MPX [13].	• Orthopoxviruses are indistinguishable from each other. • Orthopoxviruses are indistinguishable from each other. Hence, it requires more specific testing diagnose [13].

5. Prevention

Ever since the SARS outbreak in 2003 and even earlier, experts have realized the grave threat of zoonotic infections rising from constant remodeling of ecosystems, as per a report issued by the Institute of Medicine back in 2003 as a follow up to their 1992 report [27]. MPX is one such infection that is portrayed by the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) as an emergent disease [28]. Preventing the spread of MPX is a war fought on many fronts:

On the ecological front, limiting humans' exposure to suspect host animals must be the first step as available evidence indicates that human-to-human transmission cannot sustain the continuance of an endemic without repeated zoonotic introductions [15]. This can be achieved by limiting people's dependence on hosts, in particularly rodents, as protein sources and instead relying on vegetarian alternatives [15]. In addition, urban expansion into reclaimed forest lands must be studied as to prevent displacement of reservoir animals [29]. Ecological prevention is especially important as future strains may not need repeated introductions if their transmissibility among humans increased [29]. Another front would be to protect at risk groups, which include health care workers, contacts of MPX patients, and workers in rural areas. CDC recommends that this protection can be achieved through small pox vaccines [9], As data shows that the smallpox vaccine provides 85% protection against MPX via cross-immunity [30]. The problem regarding this approach is that first and second generations of smallpox vaccines can cause adverse side effects, which promotes the importance of developing third generation vaccines like INVAMUNE, which as for now, have proved efficient and safe in people infected with HIV or atopic dermatitis [31]. This is especially important in areas endemic to MPX as no accurate estimations of HIV infections exist in these countries [31].

In hospital settings, the CDC recommends that patients are to be isolated in negative pressure rooms and that health care professionals take adequate contact and droplet precautions [12]. This is the standardized response for a patient presenting with fever and disseminated vesicular or pustular rash [32]. Data shows that MPX is less transmissible among humans in comparison with smallpox, and the longest chain of infected individuals is around 6 patients [33].

6. Treatment

There is no specific treatment for MPX as to date [12]. CDC recommends administering the smallpox vaccine within 4 days of exposure which may prevent the disease from happening, and within 2 weeks to reduce symptoms severity [12]. In immunocompromised patients, first and second generations smallpox vaccines are contradictive, and are replaced with vaccinia immune globulin [32]. FDA approved Smallpox antivirals tecovirimat and brincidofovir can be used to treat MPX but there are no studies that prove their efficacy [12,32]. Other antivirals that show promise are Cidofovir, CMX-001, and ST-246 [33].

In conclusion, we should ask whether the virus has developed new properties that allow it to spread rapidly, and we should reconsider the decision to discontinue the national smallpox vaccination programs in many countries. Moreover, the most important questions are: Is this synchronization in the spread of the current hepatitis in children and MPX just a coincidence? Is there any possible connection with the COVID-19 Pandemic?

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This article is a narrative review.

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