

The Global Resurgence of Monkeypox: A Review

Maimonah Qasim Yahya

Department of Clinical Laboratory Science, College of Pharmacy, Mosul University, Mosul, Iraq
Correspondence: pharm.maymona@uomosul.edu.iq

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ABSTRACT

Background: The World Health Organization led a program to eliminate smallpox, which was validated 40 years ago. According to estimates, most nations have stopped vaccinating their citizens against the disease on a regular basis. Cross immunity has been affected as a result, and a sizable section of the world's population no longer possesses protection to orthopox viruses that are directly connected to one another, such monkeypox and smallpox. These data raise the possibility that emerging or re-emerging human would fill the epidemiological gap left by smallpox, along with occasional instances of human pathogens with many orthopox viral infections.

Aim of this study: This review focused on the disease caused by the monkeypox virus and its significant modes of transmission, which has recently reemerged in some nations globally, as well as how to prevent the disease from spreading.

Conclusion: The monkeypox virus can spread in a variety of methods, all of which need intimate contact with ill people or infected animals. Small mammals are occasionally able to carry the virus without showing any symptoms. Monkeys, hedgehogs, rodents, anteaters, prairie dogs, dogs, and squirrels are just a few of the many animal species that can contract the monkeypox virus. Viral transmission between humans is less frequent than with infected animals, however, close contact either exposure to respiratory droplet, mouth contact to mouth or to skin, or skin contact with mucosal skin lesions of an infected person are the methods of transmission. Good personal hygiene and vaccination is recommended to build immunity against monkeypox. Further research is needed to clarify the role of host as well as viral components in the pathogenesis of serious and lethal infection, as well as to gain a better understanding of their risks, genes, and natural histories. This will enable global healthcare strategists to develop effective protection plans.

Keywords: Virus, monkeypox, antiviral, vaccines, orthopoxvirus.

عودة ظهور جدري القردة على مستوى العالم: مراجعة

ميمونة قاسم يحيى

فرع العلوم المخبرية السريرية، كلية الصيدلة، جامعه الموصل، الموصل، العراق

الخلاصة

الخلفية: قادت منظمة الصحة العالمية حملة للقضاء على الجدري ، والتي تم التحقق من صحتها قبل ٤٠ عامًا. وبحسب التقديرات ، فإن معظم الدول توقفت بشكل منتظم عن تطعيم مواطنيها ضد المرض. وقد أدى ذلك إلى أن نسبة كبيرة من سكان العالم لم يعد لديهم مناعة ضد فيروسات الأورثوبوكس التي ترتبط ارتباطاً مباشراً ببعضها البعض، مثل جدري القردة والجدري ، بسبب المناعة المتقاطعة. يتم حالياً الإبلاغ عن حالات جديدة من جدري القردة. تثير هذه البيانات احتمالية أن يؤدي ظهور البشري أو إعادة ظهوره إلى سد الفجوة الوبائية التي خلفها الجدري ، إلى جانب حالات متفرقة من الإصابات البشرية بفيروسات أورثوبوكس أخرى.

هدف الدراسة: ركزت هذه المراجعة على المرض الناجم عن فيروس جدري القردة وطرق انتقاله المهمة ، والتي ظهرت مؤخراً في بعض الدول على مستوى العالم ، وكذلك كيفية منع انتشار المرض.

الاستنتاج: يمكن أن ينتشر فيروس جدري القردة بعدة طرق ، وكلها تحتاج إلى اتصال مباشر مع الأشخاص المرضى أو الحيوانات المصابة. تستطيع الثدييات الصغيرة أحياناً أن تحمل الفيروس دون أن تظهر أي أعراض. القروود والقناذف والقوارض وأكل النمل وكلاب البراري والكلاب والسنجاب ليست سوى عدد قليل من أنواع الحيوانات العديدة التي يمكن أن تصاب بفيروس جدري القروود. الانتقال الفيروسي بين البشر أقل تواتراً منه مع الحيوانات المصابة ، ومع ذلك ، فإن طرق انتقاله تتضمن التلامس المباشر

إما بالتعرض للقطرات التنفسية ، أو ملامسة الفم للفم أو بالجلد ، أو ملامسة الجلد للآفات الجلدية المخاطية لشخص مصاب. يوصى بالنظافة الشخصية الجيدة والتطعيم لبناء مناعة ضد جدري القردة. هناك حاجة إلى مزيد من البحث لتوضيح دور المضيف وكذلك المكونات الفيروسية في التسبب في العدوى الخطيرة والقاتلة ، وكذلك لاكتساب فهم أفضل لمخاطرها وجيناتها وتاريخها الطبيعي. سيمكن هذا استراتيجي الرعاية الصحية العالميين من تطوير خطط حماية فعالة.

الكلمات المفتاحية: جدري القردة ، مضاد فيروسات ، لقاحات ، فيروس أورثوبوكس.

INTRODUCTION

There are still many new and reemerging diseases caused by viruses, as well as a large variety of infectious illnesses that can harm both people and animals. Now, they represent a significantly bigger hazard to international public health than they did a century ago. Monkeypox virus (MPXV), which is currently causing outbreaks outside of Africa, is genetically related to the variola virus (smallpox) and is phylogenetically linked to the West African lineage¹. Because of their rapid expansion and ability to produce the most dreadful and terrible diseases in humans, viruses are a major cause of infectious disease death and morbidity worldwide. Many viruses can also be employed as both bioweapons and mass-destruction weapons². Significant international attention has been raised by the monkeypox (MPX) outbreak in 2022 that will affect numerous nations in both endemic and nonendemic regions. In particular since scientists have been worried about the possibility of a monkeypox outbreak for well over a decade³. As the world commemorates forty years of smallpox elimination, Nigeria and other countries have recently had an epidemic of a serious skin rash illness with monkeypox virus (MPXV) as the causative agent³. This review focused on the disease caused by monkeypox virus and its significant methods of transmission globally, which has recently reemerged in some countries around the world, as well as how to prevent the spread of the disease and other details.

METHODS

Data from reputable and trustworthy sources, including the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC), as well as publications in peer-reviewed journals, were analyzed. Several previously published studies from various countries were gathered and summarized in this review from the occurrence of monkey pox disease until November 2022. For pertinent information, reports from global and national scientific and governmental organizations were gathered. The search was then modified to look for other pertinent articles on Scopus. All observational and intervention studies including people who

displayed MPX were included, along with both systematic and nonsystematic reviews were also included. Studies that provided data on the number of affected individuals in each nation were eliminated.

Background Information and Taxonomy

The term "monkeypox" originated when the virus was discovered in monkeys for the first time in Copenhagen, Denmark, 1958⁴. The first individual instances of this uncommon viral zoonosis were discovered in a youngsters category from the Republic of the Congo in Africa in 1970⁵. With a rash resembling smallpox but being clinically less severe, monkeypox is the most common in the west and central African tropical rainforest areas⁶. In the past, the smallpox vaccine has been proven to offer cross-protection towards MPX³. Vaccination against smallpox was halted after the World Health Organization (WHO) declared the disease eradicated around 1980. So it is currently thought that over 70% of people worldwide no longer have immunity to the disease⁷. International travels or importing animals have been connected to MPX infections found in nations outside of Africa (such as Europe and North America). Scientists were disturbed by the virus' abrupt and unanticipated development in many populations throughout the world in non-endemic regions. The WHO issued a Public Health Emergency of International Concern (PHEIC) regarding the spreading monkeypox outbreak on July 2022⁸.

Poxviruses have an enclosed, brick-like shape and are big (200–250 nm) dsDNA viruses⁵. A double DNA virus known as the human MPXV is a member of the Poxviridae family, the Chordopoxvirinae subfamily and the Orthopoxvirus genus^{5,9}. It was divided into two clades: the West African variation, with an estimated case fatality ratio (CFR) of less than 4% and a higher frequency in HIV patients, and the Congo Basin (Central African) form, with a CFR of 10%⁵. Both aforementioned virus clades were just found in Cameroon. In the European / North American 2022 outbreaks, a third strain believed to be related to Branch 2 was found^{6,8}. As a result of the enormous number of infections reported in previous and present outbreaks in the Congolese

Democratic Republic, more instances of the central African clades have been recorded overall than those associated to the West African clades¹⁰. The West African clade's patients in non-endemic countries have been isolated as a result of the multi-country outbreaks in May 2022¹⁰.

Transmissions Pathways and Pathogenesis

The MPXV can spread in a variety of methods, all of which need intimate contact with ill people or animals, as listed below:

1. Transfers from Animals to Humans:

Human viral infections have been linked to animal interaction, although it can be challenging to determine the exact exposure of an infected human in regions where contact with animals is frequent. Small mammals are occasionally able to carry the virus without showing any symptoms, but non-human primates can contract monkeypox and have symptoms similar to those seen in humans¹¹. Monkeys, hedgehogs, rodents, anteaters, prairie dogs, dogs, shrews, and squirrels are just a few of the many animal species that can contract the monkeypox virus. Bunge *et al*¹² listed the factors associated with monkeypox infection which includes the putative ways of transmission. Close contact with or exposure to potential pathogens present mainly in the body secretions of diseased animals including feces, saliva, pulmonary excretions (typically include inhaling droplets after long exposure to infected body), communicate directly with fluids secreted from dermatological or gastrointestinal lesions^{12,13}. In areas where resources like food are scarce, households are compelled to kill and cook small mammals, which increase their likelihood of getting MPX¹⁴.

2. Transfers from Humans to Humans:

It is less frequent than animals-to-humans transmission, however, close contact either exposure to respiratory droplet, mouth contact to mouth or to skin, or skin contact with mucosal skin lesions of an infected person are the main methods of transmission. All these ways lead to the transfer of droplets or body exudate secreted from an infected patient to other person or contact with contaminating things or surfaces¹⁵. Using dishes that have been used by an infected individual or sharing a home is two instances of contaminated objects or surfaces that are considered to enhance the likelihood of outbreaks among family members¹³. Air transmission may occur for unknown reasons, and research is being done to find out more⁸. Also, it has been found that guys who have sex with other males are more likely to become ill; this was learned during the current recent monkeypox outbreak¹⁶. While the

WHO is unsure if monkeypox may be transmitted sexually, it is known that it can be transferred by close contact^{16,17}.

The virus is transmitted either from individual to individual or from animals to peoples, this leads to the etiology and pathophysiology of monkeypox. The stages of disease development go through two stages, the first of which is called the incubation stage and is marked by the absence of symptoms and contagiousness in the patient, It can continue up to 21 days but is typically 7 to 14 days long. The second stage is referred to as the prodromal stage when disease symptoms such as mucocutaneous infections, lymphadenitis, or even other non-specified abnormalities become apparent in infected individuals and the individual in this stage is considered to be the most contagious¹⁸. Starting with exposure to the patient's nasopharyngeal or bronchial mucosal, the MPXV distributes similarly to smallpox. In the event of transmission between individuals, the pulmonary and nasopharyngeal mucosal serve as the injection site where the MPXV replicates after getting into the body. Following viral replication, the first viremia causes the viral burden to migrate to the nearby lymph nodes. Via the bloodstream, the second viremia's viral load spreads to faraway lymph nodes and tissues¹⁹. Secondary viremia, which affects the skin and tertiary organs including the respiratory system, digestive system, etc., develops from the lymphoid organs during the prodromal stage.

Monkeypox Multicounty Outbreak 2022

Several countries are endemic for monkeypox especially in Central and West Africa, including Cameroon, Cote d'Ivoire, Central African Republic, Gabon, Liberia, Nigeria, Congo, Democratic Republic of the Congo (DRC), and Sierra Leone. The majority of cases appears sporadic or takes place in the midst of small-scale outbreaks^{12,18}. Cases even outside the endemic regions are frequently related to the foreign travels or the importing animals infected with the MPX virus. A significant rise has been noticed in monkeypox outbreaks in comparison to the preceding three decades. The DRC has experienced the most outbreaks, with Central African Republic and Nigeria coming in second and third place, respectively¹¹. A number of injuries were recorded in Republic of the Congo, South Sudan, Cameroon, Liberia, United Kingdom, United State, Sierra Leone, Israel, Singapore etc.¹¹. According to the WHO study "2022 Monkeypox Outbreak: Worldwide Trends," the total number of new MPX reported cases worldwide is declining^{20,21}. However, the number of recorded incidents climbed slightly (2.4%), from week 43 (24–30

October 2022) to week 44 (31 Oct. 2022 to 6 Nov. 2022)²⁰.

Clinical Manifestations and Consequences

Monkeypox has a wide range of signs and symptoms. While some people have milder symptoms, others may have more serious illnesses that call for in-facility care²². Individuals with weakened immune systems, pregnant women, and children are often at a greater risk²³. The incubation period of MPX is usually seven to fourteen days, although it may vary. Serum antibodies can be detected during the second week after exposure¹⁹. Monkeypox virus infection begins with initial manifestations such as increase body temperature, shiver, headache, muscle aches, backaches, and exhaustion, followed by the development of lesions from oropharyngeal origins throughout the body. After the commencement of fever, the infected person often develops a dermatitis that extends to other areas on their body. The skin sores can range from a single sore to numerous ones. Initially, the skin sores are flat, but they later fill with fluid, crust over, dry up, and eventually fall away, revealing a fresh skin layer beneath⁸.

During the prodromal stage, an individual may experience lymphadenitis, muscle aches, and other immune system-stimulating symptoms. As these symptoms are non-specific, an infected person may mistake them for those of a common cold or flu. However, as the immune system is activated, fever sets in, and lymph nodes in the cervical, maxillary, and inguinal regions become enlarged^{18,19}. The death rate varies from one to ten percent depending on the clade of the virus strain causing the infection and the accessibility of contemporary healthcare²⁴. One to three days following the commencement of the elevated body temperature and lymphadenopathy, rashes would frequently begin to manifest. The fever frequently subsides the next day, or even up to three days after the rash first emerges²⁵. The rash began on the face and quickly moved across the body²⁵. The symptoms in chickenpox are superficial rather than deep and occur in groups of virions (up to 10 in each cluster) of the same stage, with less intense manifestations on the face and upper and lower limbs than on the abdomen and the rest of the body^{26,27}.

Significant skin disruption caused by the skin lesions raises concerns about bacteria severe infection, which has been reported in 19% of monkeypox individuals who have not gotten the vaccine^{19,28}. The rash seen in those who have been infected has a highly specific presentation, including bacteremia, dehydration, encephalitis, ocular inflammation, cellulitis, persistent scarring,

respiratory distress, inflammation of lungs and bronchioles, sepsis, and septic shock. The protective barriers of the mucosal and skin surfaces could be compromised, a severe focal inflammation would be elicited in the lymphatics, and lung congestion could result from monkeypox²⁹. Exfoliation can be crucial in cases of substantial rash burden, exposing patients to dehydration and protein losses. The willingness and/or capacity of a patient to take nourishment and drink water may be reduced by severe illness and bronchopneumonia. Severe clinical symptoms of sickness can also be influenced by co-infections (like malaria, HIV, varicella) as well as comorbidities (such as malnourishment). An optimum treatment strategy for low-resource settings should consider the likelihood of each of these outcomes for a given patient³⁰.

Laboratory Diagnosis

The non-specific nature of monkeypox symptoms necessitates consideration of a broad range of differential diagnosis, such as molluscum contagiosum, chickenpox, scabies, syphilis, rickettsia infections, bacterial skin infections, measles, anthrax, and other non-infectious causes of rash. Monkeypox can be differentiated and distinguished clinically from chickenpox and smallpox by the existence of enlarged lymph nodes (lymphadenopathy), especially in the submental, cervical, inguinal, and submandibular nodes⁴. The best clinical specimens for laboratory testing are those obtained from skin infections, such as pus or scabs. A nasopharyngeal or oropharyngeal swab should be used to collect viral cultures. Biopsies obtained from skin rash or from the top of an intact lesion are useful for diagnosis^{4,27}. Serologic tests require samples from both acute and chronic patients. Immunoglobulin M or G specific for the monkeypox virus should be detected after 5 or 8 days of presentation, respectively. In the lacking of confirming the diagnosis, it can be confirmed using serological techniques including ELISA, polymerase chain reaction (PCR), electron microscopy (EM), and morphological and clinical illness presentation. However, the specificity of identification depend solely on clinical examination is limited^{30,31}.

Therapy and Vaccination

In most cases, symptoms will go away by themselves or with effective care, such as fever-relieving drugs. However, depending on how well a person's immune system responds to the illness, an infection in some people might cause serious health issues or even death. At present, there is no evidence-based medication for MPX infections; simply a symptomatic medication and supportive therapy are the primary options for patient management³². Another point to mention is the possibility of adopting countermeasures tested in clinical trials of smallpox in the developed countries to the management of MPX in Africa. Despite there are currently no anti-virus medications against virus available used to treat MPX, there are two experimental chemical substances (ST-246®, SIGA Technologies, Inc., New York, NY, USA; and CMX-001®, Chimerix, Inc., Durham, NC, USA) taken orally that have just demonstrated promise in combating orthopoxvirus illnesses^{30,33}. Both drugs can be administered orally and have successfully completed phase 2 human effectiveness trials. None, however, has been put to the test in a carefully managed clinical study as a therapy for human monkeypox. In such trials, enormous resources would be needed to make sure that sick people were well controlled and able to give Prior approval³⁰.

Several antiviral drugs that may be act as anti-MPXV were currently available. Tecovirimat inhibits p37, a conserved protein throughout all orthopoxviruses, which blocks the formation of viral membrane. Tecovirimat was granted FDA agreement in 2018 for smallpox management³⁴. The CDC has an EA – IND(Enhanced Access - Investigational New Drug) protocol which allows tecovirimat to be used in MPXV infections (non-variola orthopoxviruses). Cidofovir, DNA polymerase inhibitor, indicate therapeutic benefits against orthopoxvirus types. Because cidofovir induces kidney damage, a modified variant of this drug-CMX-001, an oral medication that functions by blocking DNA polymerase-is in the early stages of research³². Brincidofovir (BCV, CMX001) is a pro-drug of cidofovir has a broad spectrum long-acting oral antiviral medication (e.g. against cytomegalovirus retinitis in patient with AIDS), it has demonstrated an in vitro efficacy against smallpox (variola) virus, and is being developed as a smallpox management according to the US FDA's 'Animal Rule'^{33,34}. Brincidofovir, which the FDA approved as a therapeutic treatment of smallpox in 2021, may be safer than cidofovir because it has not been linked to serious renal toxicity or other significant side effects when used to treat CMV infections, though there is limited clinical evidence to support this^{32,34}. ST-246,

another orally administered medication, blocks the release of internal viruses and has demonstrated promising efficacy against variola (orthopoxviruses) virus. It has also been used to treat the MPXV in non-human primates and small vertebrates with success³².

A person is infectious up to the point at which all of the wounds have crusted over, all of their dead skin has peeled off, and a new skin layer has grown over everything³². Whether this mode of transmission plays a significant role in the epidemic's continuous expansion is currently being investigated by experts. The vast majority of MPX cases were seen in youngsters under ten years and individuals with no previous vaccination mark had a considerably greater assault rate (7.2%) than those with a vaccination mark. (0.9%)³⁵. Because the vaccination provides cross-protection against the monkeypox virus, the rate of fatal cases in people who were not inoculated against smallpox is 11%³⁶. The lifetime of smallpox immunization is uncertain, however it is expected to even provide up to 85% cross-protection from MPX³⁷.

Some health professionals believe the reemergence of MPX is partly due to the discontinuation of regular MPX immunization following illness was declared eliminated in 1980³⁸. In the United States, two licensed vaccines available for the protection against smallpox have been approved by the FDA: JYNNEOS® (Imvanex® in Europe and Imvamune® in Canada) and ACAM2000® (Acambis, Inc.) , both contain a live virus, while the first one has replication incompetent vaccinia virus in comparison to other that has replication competent vaccinia virus^{2,34,39}. They could provide protective immune responses to monkeypox. The WHO declared the global elimination of smallpox as a result of widespread immunization programs; such two vaccines are given for individuals who were high-risk of infection, rather than universal vaccination. It is recommended that people who are occupationally exposed to orthopoxviruses, such as researchers, should receive vaccinations as pre-exposure prophylaxis. Close contacts of infected patients can also receive a post-exposure vaccine³⁴.

Control and Prevention

To prevent human contraction of monkeypox, the following measures can be taken^{40,41}:

1. To avoid the propagation of virus through droplets, it is recommended that close contact with infected individuals be avoided. Touching the skin of people with monkeypox-like symptoms such as rash, blisters, or scabs should be refrained from, and it is also recommended that kissing, embracing, cuddling,

or engaging in sexual activity with monkeypox sufferers be avoided.

2. After handling anything that might be infectious, it is advised to practice good personal hygiene and clean hands immediately.
3. Things touched by a person infected with MPX, such as drinking or eating utensils, bedding, towels, or clothing, should be avoided.
4. Vaccination is recommended to build immunity against monkeypox.
5. Infected animals, especially in endemic areas, such as rodents, primates, and monkeys, which are usually the species that can transmit the monkeypox virus, should be avoided.
6. In endemic areas, maintaining potent airways also contributes to avoiding respiratory infections, atelectasis, and pulmonary compromise.

CONCLUSION

Monkeypox virus infection is associated with significant skin degeneration. The majority of people didn't involve hospitalization as a result. Like other viral diseases, the common manifestation of monkeypox is a progressive onset of fever, while lymphadenopathy is a key differentiating feature. Isolation precautions should be initiated by clinicians and lab confirmation should be obtained if patients report recent travel to regions where the new virus is still spreading or touch with a confirmed MPX case. Further research is needed to clarify the role of both host and virus components in the pathogenicity of serious and life-threatening illness, as well as to gain a better understanding of their risks, genes, and natural histories. This will enable health care strategists to develop successful preventive measures.

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Observance of Ethical Principles

Not relevant. There are no studies by any of the authors in this article that used animals. There are no studies by any of the authors in this article that used human subjects.

Competing Interests

This study's authors confirm the absence of conflicts of interest.

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