



Monkey Pox Virus: A Re-Emerging Potential Healthcare Threat

A. C. Ifediora ^{a*} and V. O. Itaman ^a

^a Department of Microbiology, Michael Okpara University of Agriculture, Umudike, Abia State, Nigeria.

Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Monkeypox virus (MPXV) causes monkey pox infection which is a zoonotic disease with symptoms presentation similar to smallpox. The disease has a public health significance as it affects humans and animals worldwide. It is usually self-limiting but may be acute in some people. Transmission occurs via exposure to skin lesions, bodily fluids, or respiratory droplets of infected animals directly or indirectly. The clinical manifestation of the disease includes a prodromal illness with fever, malaise, swollen lymph nodes, characteristic rash, chills and/or sweats, headache, sore throat, cough, backache and shortness of breath. The incubation period is usually between 7 to 14 days with an upper limit of 21 days. Laboratory diagnosis is imperative and requires advanced technical skills and well-advanced laboratory methods. Monkeypox treatment is mainly supportive as there has been no proven treatment available over the years. Tecovirimat is a new antiviral which has received approval but still in limited supply, however, the use of smallpox vaccine, cidofovir, ST-246, and vaccinia immune globulin (VIG) have been recommended in the management of monkeypox outbreaks. Effective prevention depends on minimizing contact with infected patients or animals, practicing good hygienic habits after making contact with infected animals or humans, proper use of personal protective equipment (PPE) and the use of smallpox vaccination when unprotected exposure occurs. However, new therapeutics and vaccines offer hope for the treatment and prevention of monkeypox. There is therefore, a need for future researches to focus on identifying the virus and its host factors that regulate transmission between humans and animals.

*Corresponding author: E-mail: afoma20@yahoo.com;

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1. INTRODUCTION

Monkeypox is a known virus that is transmittable from animals to humans and a member of the poxviridae family. The virus has two known genetic clades; the central African (Congo Basin) clade and the West African clade [1]. Discovery of Monkeypox virus (MPXV) first occurred among laboratory monkeys in Denmark laboratory in 1958 while the first observed human case was detected in Democratic Republic of Congo in 1970 [1,2]. The virus is found in different parts of the world but is believed to be endemic in Central and West Africa [3]. Transmission occurs readily through close contact with body fluids, skin lesions, or respiratory droplets of infected animals directly or indirectly and also via contaminated fomites. Monkey pox virus causes monkey pox disease which is characterized with symptoms similar to those seen in the past in smallpox patients, although it is clinically less severe [3]. The disease is usually self-limiting but may be severe in immunocompromised, elderly and children. Diagnosis of monkeypox infection is achieved using advanced technical skills and well-advanced laboratory methods including cell culture, electron microscopy, polymerase chain reaction (PCR), enzyme linked immunosorbent assay (ELISA) or Western blotting with PCR being used for definitive diagnosis [4]. Treatment of Monkeypox (MPX) infection is mainly through symptomatic and supportive therapy. The smallpox vaccination is thought to protect against infection [5]. Newer vaccines have been developed and one received approval in 2019 for use in prevention of MPXV infection. Smallpox vaccination, antivirals, and vaccinia immune globulin (VIG) have also been implemented to suppress a MPX outbreak in the United States [6]. Those who are infected have a 3-6% chance of dying [3].

The increasing prevalence of this disease in non-endemic regions highlights the global importance of the disease and the need of increased public awareness. This review will highlight the current state of knowledge about human MPXV with emphasis on diagnosis, care, and control of this disease.

1.1 Biology

“Monkeypox virus belongs to the *Orthopoxvirus* genus in the family *Poxviridae* a large and varied family of double-stranded DNA viruses that

replicates in the cytoplasm of infected cells” [7,8]. It is an enveloped zoonotic virus with oval or brick-shaped structures measuring 200–400 nm when viewed under electron microscope [9]. The *Orthopoxvirus* genus also comprises of variola virus which is the agent of smallpox, vaccinia virus, and cowpox virus. The virus has a wide range of hosts including rodents, monkeys, and humans thus enabling the virus to remain in the wild host reservoir, occasionally causing periodic human diseases thereby making it difficult to be eradicated by vaccination [10]. The virus has been classified into two definite genetic clades: the Central African (Congo Basin) clade and the West African clade. The Central African clade has consistently caused more grave disease and was thought to be more contagious with higher morbidity and a case fatality ratio ranging between 8-13% while the West African clade, which is commonly associated with milder clinical symptoms has a case fatality ratio ranging between 0-6% [2,3]. The geographical distinction observed between the two clades has only been in Cameroon which is the only country where both virus clades have been detected [3,11].

1.2 The Historical Discovery of Monkeypox Virus

The first discovery of monkey pox virus was made when laboratory monkeys kept at a research institute in Copenhagen, Denmark developed a pox-like disease [1]. This occurred in 1958 while the first human case was on 1 September 1970, when a nine-month-old child was admitted to the Basankusu Hospital in the Democratic republic of Congo which was formally known as the Republic of the Congo. The boy exhibited symptoms similar to smallpox-like disease from which MPXV-like virus was isolated. Since 1970, there have been human cases of monkeypox recorded in some African countries including Benin, Cameroon, the Central African Republic, the Democratic Republic of the Congo, Gabon, Cote d'Ivoire, Liberia, Nigeria, Sierra Leone and South Sudan. However, the exact weight of monkeypox is unknown but most of the cases have been identified in Republic of Congo [3]. The first index MPXV case in Nigeria was recorded in 1971, and also between September and December 2017, Nigeria recorded 88 confirmed MPXV cases from 15 of the 36 states [6]. Since 2017, Nigeria has gone through a large outbreak, with over 500 suspected cases and over 200 confirmed cases

with a case fatality ratio of approximately 3%. Presently new cases are being observed [3].

2. EPIDEMIOLOGY

Monkeypox is majorly endemic in West and Central Africa, but cases also occur in other countries of the world. There was a major outbreak of monkey pox in the United States of America in 2003 and the incidence was the first major outbreak to occur outside of Africa. The incidence was attributed to contact with infected prairie pet dogs. The pet dogs were said to have been living together with Gambian pouched dormice and rats which had been imported from Ghana into the country. As a result, over 70 persons contracted the disease in the United States. Historically, Monkeypox has been reported in many countries of the world: in September 2018, travelers from Nigeria were implicated in different cases observed in different countries namely; the United Kingdom in September 2018, December 2019, May 2021 and May 2022, to Singapore in May 2019, and to the United States of America in July and November 2021. In May 2022, there were several cases of monkeypox disease that occurred in non-endemic countries. Currently a lot of research is being carried out to aid in the better understanding of the epidemiology, routes of infection, and transmission patterns [12].

Transmission can occur through contact with body fluids, skin lesions, or respiratory droplets of infected animals directly or indirectly via contaminated fomites. Monkeypox can spread during intimate contact between people, including during sex, as well as activities like kissing, cuddling, or touching parts of the body with monkeypox sores. At this time, it is not known if monkeypox can spread through semen or vaginal fluids. Additionally, MPX outbreaks occurs mostly among residents living together that engage in hunting and gathering, with close physical contact being the most significant risk factor for infection. Large respiratory droplets can harbor the virus [13].

Although, human-to-human transmission has previously been limited, mathematical modeling in the context of decreasing herd immunity to orthopoxviruses reflects an increasing threat of disease spread between humans [14,15]. The virus can also cross the placenta from the mother to her fetus. There is still some uncertainty as regards to the natural history of the monkeypox virus and more studies are being carried out to

trialify the exact reservoir(s) and how virus circulation is maintained in nature, however, there is a growing suspicion that African rodents have a part to play in monkeypox transmission to people [15].

Different animal species have been identified to be vulnerable to the monkeypox virus and the consumption of under-cooked meat and other biological products of infected animals is also possible risk factor [12].

The disease is normally self-limiting but may be severe in some people, such as children, pregnant women or immune-compromised due to other health challenges [12].

2.1 Pathophysiology and Clinical Manifestation

The viral route of entry may be the trialarynx, nasopharynx, or intradermal. Upon entry, there is viral replication at the inoculation site before spreading to the local lymph nodes. There is an initial viremia which is followed by virus spreading to other organs. This represents the incubation period and typically lasts 7 to 14 days with an upper limit of 21 days [16]. Following the incubation period, there is a prodromal illness occurring simultaneously with fever, malaise, and swollen lymph nodes is seen in most of the cases before rashes appear [17]. Other signs and symptoms of monkeypox include chills and/or sweats, headache, sore throat, cough, backache and shortness of breath. Lymphadenopathy (swelling of the lymph nodes), which has been observed in 90% of unvaccinated patients, is a key distinguishing feature of monkeypox [17]. The prodromal phase generally lasts 1–3 days before the commencement of the typical maculopapular rash. The patient is considered to be infectious during the first week of the rash and should be isolated until all scabs separate and results of throat swab PCR are negative. The mean diameter of the skin lesions is 0.5–1 cm, and the clinical progress resembles that of ordinary smallpox lesions. During a 2–4-week period, the lesions transform from macules to papules, vesicles, and pustules, followed by umbilication, scabbing, and desquamation [17]. Although, the rash starts mainly on the trunk, it can spread in a peripheral distribution to the palms and soles of the feet. Some pox lesions may become necrotic and destroy sebaceous glands, leaving a depression or pox scar that, with monkeypox, may gradually become less pronounced over a

few years. Lesions can be observed on mucous membranes, in the mouth and tongue, and on the genitalia. In addition to skin lesions, extracutaneous manifestations, such as secondary skin and/or soft-tissue infection, pneumonitis, ocular complications, and encephalitis have been observed in patients infected with MPXV [18]. The fatality rate is 10%, and death generally occurs during the second week of the disease [18].

3. LABORATORY DIAGNOSIS OF MONKEY POX VIRUS

Preliminary diagnosis of MPX can be done if distinctive lesions are present on the skin and there have been an exposure history; although, the clinical presentation often bear a resemblance to chickenpox making distinguishing both clinically a complicated task. During surveillance, this presumptive identification is essential for determining potentially infected cases.

“Definitive diagnosis of MPX infection requires advanced technical skills and well-advanced laboratory methods using cell culture, electron microscopy, polymerase chain reaction (PCR), enzyme linked immunosorbent assay (ELISA) or Western blotting with PCR” [4].

Laboratory specimen can be from trialllar tissue, oropharyngeal tissue or nasopharyngeal tissue swab, skin biopsy of the vesiculopustular rash, lesion fluid, roof of an intact skin vesicular lesion, whole blood, scab/crust of the lesion, acute and convalescent phase sera.

Samples obtained from skin lesions, exudate or scabs are maintained in cold chains to aid the stability of the viral DNA in the specimens [13,19,20].

Observation of MPXV using electron microscope usually reveals an intracytoplasmic brick-shaped particle measuring 200–300 µm; this help in determining the family (Poxviridae) the virus belongs to [21].

“Specimens analyzed using polymerase chain reaction (PCR) or real-time polymerase chain reaction (RT-PCR) is usually to investigate the presence of MPXV-specific DNA or Orthopoxvirus in the specimen” [13,22]. “The detection of viral DNA by PCR and RT-PCR are extremely delicate and effective. To achieve this, RT-PCR targets the conserved regions of

extracellular-envelope protein gene (B6R), DNA polymerase gene, E9L, DNA dependent RNA polymerase subunit 18, rpo18, and F3L gene” [22,23].

Immunological methods include using ELISA for the identification of IgG and IgM antibodies and immunohistochemistry for viral antigen. Immunochemistry assay uses polyclonal or monoclonal antibodies against all Orthopoxvirus (OPVs) to distinguish poxvirus infection from herpes virus. Reactions to MPXV and smallpox virus can be differentiated by the use of cross-adsorbed virus neutralization, immunofluorescence or hemagglutination inhibition assays, and immunoblotting (Western blotting). The use of transmission electron microscopy and PCR and further confirmatory analysis using ELISA, tissue culture and immunofluorescence assay for the discovery of MPXV in pustular swab has also been revealed in a recent study [4,24].

3.1 Treatment of Monkey Pox Virus

The treatment of MPX is mainly supportive as there has been no proven treatment obtainable over the years. However, the use of smallpox vaccine, cidofovir, tecovirimat (ST-246), and vaccinia immune globulin (VIG) have demonstrated anti-MPXV viral activity and are therefore used in the management of MPV outbreaks.

The use of smallpox vaccination is recommended within 14 days of exposure to MPX [13]. Smallpox vaccination have been reported to confer protection of up-to 85% from MPXV disease [13,25] but it is currently not in use in endemic areas to treat MPX disease and not made available to the public because of its severe adverse effects in immunocompromised populations and the risks associated with the vaccine as it is comprised of live vaccinia virus.

Also, cidofovir and brincidofovir (CMX- 001) have been reported to possess anti-MPX viral activity both in animal and *in vitro* studies. Patients with severe MPX disease are urged to use cidofovir for treatment [5].

Currently there is a new antiviral agent (tecovirimat) that was developed for smallpox by the European Medicines Agency (EMA) for MPX in 2019 based on statistics obtained from non-human and human studies. However, it is not readily accessible [12].

It is advised that when tecovirimat is to be used for patient care, it should be kept under surveillance using clinical research studies. There is a new vaccinia-based vaccine known as Modified vaccinia Ankara (MVA), which was approved by WHO for MPXV prevention in 2019. This vaccine is a two-dose and the accessibility is still restricted [12].

There is an on-going development of various anti-viral agents that will help in alleviating the spread of the disease. There is also, evolving research to produce and authenticate the efficacy of LC16m8 vaccines and other vaccines for the prevention of MPX [26,27].

4. PREVENTION AND CONTROL OF MONKEY POX VIRUS

To prevent the spread of MPXV in endemic areas, it is imperative to refrain from making contact with rodents, primates, any material or substance that have been exposed to MPXV infected animal, eating improperly cooked meats as well as restricting contact with secretions and biofluids. The practice of good hygiene habits after contact with infected humans or non-humans restrict the possibility of having and spreading the disease [13].

Animals with suspected MPX infection should be quarantined and their contacts traced, isolated and monitored for the signs and symptoms of MPX for about 30 days. The habitat of these animals should be thoroughly washed and fumigated. Infected patients should be isolated, contact with humans and pets should be limited, droplet precautions should be taken and good disease control procedures should be implemented to curb the spread of the infection [4].

As a routine preventive measure, injuries or breaks in the skin should be properly treated and covered while working with potential animal hosts for MPXV or anyone infected. Increased awareness campaigns on the proper use of personal protective equipment (PPE), training of staff and care-givers on proper infection control measures and isolation practices when handling sick animals or in contacts with infected patients or their samples will help prevent transmission from human-to-human and animal-to-human [5,28,29].

If an triale contact with an infected animal or a confirmed human case occurs, smallpox

vaccination is recommended. Since there is currently no commercially available MPX vaccine, the centers for disease control and prevention (CDC) endorses immunization or pre-exposure smallpox vaccination of healthcare workers and healthy persons in high risk professions. Also, post-exposure smallpox vaccination given to individuals who have been in contact with MPX-infected person or animal within 14 days of exposure (ideally before 4 days) provide 85% cross-protection against the infection [5,30,31]. Vaccination with Smallpox (vaccinia virus) vaccine could help protect animals at risk. This vaccine cannot be used in an entire population because of the risk of complications in those who are immunocompromised.

5. RECENT ADVANCES IN THE KNOWLEDGE OF MONKEYPOX VIRUS

The existence of a gene coding for Golgi-associated retrograde protein (GARP) complex in an infecting MPXV strain which can lead to severe infection have been observed in a recent study. It is important to note that, there is no precise tissue tropism of MPXV as it has been discovered in various tissues in a wide variety of animals. The understanding of tissue tropism gives a clue about the immunologic responses of the virus and how it spreads between its hosts. Therefore, it is essential to identify the definite typical MPXV host and their target cells necessary for viral proliferation as this could facilitate the advancement of anti-viral remedy [24,32].

The spread of MPXV to humans is not exactly known as the virus does not have a known reservoir [25].

A recent study suggested that, through bites from close association with wild animals, unhygienic practices of humans with animals and eating of bush meat could serve as possible threats in acquiring this infection [25,33]. It is imperative for future researches to focus on identifying the virus and its host factors that regulate transmission between humans and animals.

Study have shown that vaccination with vaccinia virus (smallpox vaccine) have been proven to be beneficial to healthy humans for up to 6 weeks after vaccination and protective in non-human primates such as monkeys [32,25].

“Recently developed is an on-site laboratory diagnostic test known as ABICAP (Antibody Immuno Column for Analytical Trialsses), which is an immune-filtration approach that can be employed in humans as well as animals have been recently reported to aid in the complex identification of MPXV infection” [13,27].

5.1 Outbreaks in Non-Endemic Countries

As of 21 May 2022, the World Health Organization (WHO) reported a total of 92 laboratory confirmed cases, and 28 suspected cases of monkeypox from 12 member States that are not endemic for monkeypox virus, across three WHO regions (Table 1). As at that date no associated deaths have been reported from these regions. Reported cases have not been directly linked to any endemic area. “According to the recent available information, there has been an increasing number of cases involving men who have sex with men (MSM) looking for health

care in primary care and sexual health clinics” [12].

“As at the time of this review, all PCR confirmed cases were as a result of infections contracted with the West African clade. Genome sequence from a swab sample from a confirmed case in Portugal, indicated a close match of the monkeypox virus causing the current outbreak, to exported cases from Nigeria to the United Kingdom, Israel and Singapore in 2018 and 2019” [12].

Surveillance to date in non-endemic areas which had previously been limited, is now on the increase. WHO expects to receive more reports from these areas as surveillance expands. From the information available, it is highly probable that human-to-human transmission now occurs when symptomatic people come in close contact with other people.

Table 1. Data on Monkeypox cases in non-endemic countries between 13 to 21 May 2022 as at 13:00

Country	Oey iei-se	Suspected
Australia	1-5	-
Belgium	1-5	1-5
Canada	1-5	11-20
France	1-5	1-5
Germany	1-5	-
Italy	1-5	-
Netherlands	1-5	-
Portugal	21-30	-
Spain	21-30	6-10
Sweden	1-5	-
United Kingdom	21-30	-
United States of America	1-5	-
Total	92	28

Table 2. Cases of monkeypox in endemic countries between 15 December 2021 to 1 May 2022

	Time period	Cumulative cases	Cumulative deaths
Cameroon	15 December 2021 to 22 February 2022	25	<5
Central African Republic	4 March to 10 April 2022	6	<5
Democratic Republic of the Congo	1 January to 1 May 2022	1238	57
Nigeria	1 January 2022 to 30 April 2022	46	0

Adapted from [12]

“It is on record that betrial 1 January to 15 June 2022, an increasing total of 2103 laboratory confirmed cases, one probable case, and one death from Nigeria have been reported to WHO from a total of 42 countries in five WHO Regions. Most of the cases (98%) occurred since May 2022 indicating an increasing prevalence” [30]

6. CONCLUSION

MPXV infection is a reemerging disease that shares similarities with smallpox disease. The identification of confirmed and suspected cases of monkeypox having no direct travel links to endemic area presents a disturbing scenario. The rate of emergence in these regions coupled with lack of immunity due to stoppage of smallpox vaccine portends a great threat to the health care system. This disease should be regarded as a possible health care threat as this is the first time that many cases and clusters are reported concurrently in different countries. Though mortality is low, the burden on health-care system may become burdensome and overwhelming especially in developing countries which some are coincidentally endemic for the virus. There is therefore an urgent need to carry out researches and enlightenment programs for effective control, treatment and to avoid a pandemic.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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