MONKEY POX VIRUS; A RE-EMERGING POTENTIAL HEALTHCARE THREAT

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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 is of global public health importance as it affects humans and animals worldwide. It is usually self-limiting but may be severe in some individuals. Transmission occurs via contact with bodily fluids, skin lesions, 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 typically lasts 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. Treatment of monkeypox 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 relies on limiting 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.

KEY WORDS: Monkey pox, Disease, Virus, Vaccine.

1. INTRODUCTION

Monkeypox is a zoonotic virus (a virus transmitted to humans from animals) that belongs to the family of poxviridae. The virus has two known genetic clades; the central African (Congo Basin) clade and the West African clade. Monkeypox virus (MPXV) was first discovered among laboratory monkeys in Denmark laboratory in 1958 while the first human case occurred 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. Transmission occurs readily through close contact with bodily 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

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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 diverse family of double-stranded DNA viruses that multiplies in the cytoplasm of infected cells [7; 8]. It is an enveloped zoonotic virus with brick-shaped or oval structures measuring 200–400 nm when viewed under electron microscope [9]. The *Orthopoxvirus* genus also includes variola virus (which causes smallpox), vaccinia virus (used in the smallpox vaccine), and cowpox virus. The virus has a wide range of hosts including rodents, monkeys, and humans thus enabling the virus to persist in wild host reservoir, causing sporadic human diseases thereby avoiding global eradication by vaccination [10]. The virus is known to have two distinct genetic clades: the central African (Congo Basin) clade and the West African clade. The Congo Basin clade has historically caused more severe disease and was thought to be more transmissible with higher morbidity and a case fatality ratio ranging between 8-13% while the West African clade, which is typically associated with milder clinical presentation has a case fatality ratio ranging between 0-6%. The

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geographical division between the two clades has so far been in Cameroon which is the only country where both virus clades have been detected [2; 11; 3].

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1.2. History 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 (at that time, known as the Republic of the Congo). The boy had a smallpox-like disease from which MPXV-like virus was isolated. Since 1970, there have been human cases of monkeypox reported in 11 African countries: Benin, Cameroon, the Central African Republic, the Democratic Republic of the Congo, Gabon, Cote d'Ivoire, Liberia, Nigeria, the Republic of the Congo, Sierra Leone and South Sudan. However, the true burden of monkeypox is unknown but the majority of 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 experienced a large outbreak, with over 500 suspected cases and over 200 confirmed cases and a case fatality ratio of approximately 3%. Presently new cases continue to be recorded [3].

2. EPIDEMIOLOGY

Monkeypox is a disease of global public health importance as it not only affects countries in West and Central Africa, but the rest of the world. In 2003, the first monkeypox outbreak outside of Africa occurred in the United States of America and was linked to contact with infected pet prairie dogs. These pets had been housed with Gambian pouched rats and dormice that had been imported into the country from Ghana. This outbreak led to over 70 cases of monkeypox in the U.S. Monkeypox was reported among travellers from Nigeria to Israel in September 2018, to 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, multiple cases of monkeypox were identified in several non-endemic

countries. Studies are currently underway to further understand the epidemiology, sources of infection, and transmission patterns [12].

Transmission can occur through contact with bodily 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].

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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. Uncertainty about the natural history of the monkeypox virus remains and further studies are needed to identify the exact reservoir(s) and how virus circulation is maintained in nature, although African rodents are suspected to play a part in monkeypox transmission to people [15].

Various animal species have been identified as susceptible to the monkeypox virus and eating inadequately cooked meat and other animal products of infected animals is a possible risk factor.

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Monkeypox disease is usually self-limiting but may be severe in some individuals, such as children, pregnant women or immune-compromised due to other health conditions [12].

2.1. Pathophysiology and Clinical Manifestation

Upon viral entry through any route (oropharynx, nasopharynx, or intradermal), the virus replicates at the inoculation site before spreading to local lymph nodes. There is an initial viremia followed by viral spread and seeding of other organs. This represents the incubation period and typically lasts 7 to 14 days with an upper limit of 21 days [16].

After the incubation period, prodromal illness with fever, malaise, and swollen lymph nodes appears in majority of the cases before rashes appear [Jezek *et al.,* 1988: Di Giulio and Eckburg. 2004]. 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. 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. The fatality rate is 10%, and death generally occurs during the second week of the disease [18].

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3. LABORATORY DIAGNOSIS OF MONKEY POX VIRUS

Preliminary diagnosis of monkeypox can be done if the characteristic skin lesions are present and there is a history of exposure; however, clinical cases can resemble chickenpox and may be difficult in distinguishing both clinically. During surveillance, this presumptive identification based on clinical symptoms is important for identification of suspected cases.

Definitive diagnosis of monkeypox 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].

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Specimen for laboratory diagnosis may be obtained from tonsillar tissue, oropharyngeal tissue or nasopharyngeal tissue swab, skin biopsy of the vesiculopustular rash, lesion fluid, a sample of the 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 crusts are stored in a dry, sterile tube and kept in cold temperature as viral DNA present in lesion material is stable for a long period of time if kept in a relatively dark, cool environment [19; 20; 13].

Under electron microscope, Monkeypox virus appears as intracytoplasmic brick-shaped with lateral bodies and a central core of about 200–300 nm; 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 assess the presence of Orthopoxvirus or Monkeypox virus in a lesion sample [13; 22]. These assays are highly sensitive and efficiently detect viral DNA. This is accomplished by RT-PCR targeting 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 enzyme-linked immunosorbent assay (ELISA) for IgG and IgM antibodies detection and immunohistochemistry for viral antigen detection. Immunochemistry analysis uses polyclonal or monoclonal antibodies against all Orthopoxvirus (OPVs) to differentiate between poxvirus infection and herpes virus. Reactions to monkeypox virus and smallpox virus can be differentiated by the use of cross-adsorbed virus neutralization, immunofluorescence or hemagglutination inhibition assays, and immunoblotting (Western blotting). The detection of monkeypox virus in pustular swab through transmission electron microscopy and polymerase chain reaction (PCR) and confirmatory diagnosis by Enzyme-Linked Immunosorbent Assay (ELISA), tissue culture and immunofluorescence assay has been revealed in a recent study (4; 24].

3.1. Treatment of Monkey Pox Virus

Treatment of monkeypox is mainly supportive as there has been no proven treatment available over the years. However, the use of smallpox vaccine, cidofovir, ST-246, and vaccinia immune globulin (VIG) have been recommended in the management of monkeypox outbreaks.

The use of smallpox vaccine is best administered within two weeks of exposure to monkeypox. Scientific data reveals that smallpox vaccination confers 85% protection from the disease [13; 25] but it is currently

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not in use in monkeypox-endemic areas and not made available to the public because of its severe adverse effects in immunocompromised populations and the safety of the vaccine containing live vaccinia virus.

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Currently there is a new antiviral agent known as tecovirimat that was developed for smallpox by the European Medicines Agency (EMA) for monkeypox in 2019 based on data in animal and human studies however, it is not yet widely available [12].

It is advised that when used for patient care, tecovirimat should be monitored in a clinical research context with prospective data collection. There is a new vaccinia-based vaccine known as Modified vaccinia Ankara (MVA), which was approved for MPXV prevention in 2019. This is a two-dose vaccine and the availability is still limited [12].

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There is an on-going development of various anti-viral agents that will help in alleviating the spread of the disease. There is also, an ongoing study to produce and validate the effectiveness of LC16m8 vaccines and other vaccines for the prevention of monkeypox [26; 27].

4. PREVENTION AND CONTROL OF MONKEY POX VIRUS

In order to prevent the spread of monkey pox virus in endemic areas, it is imperative to avoid contact with rodents, primates, any material that have been in contact with infected animal, exposure to body fluids and secretions and eating improperly cooked meats. The practice of good hygiene habits after contact with infected animals or humans limits the risk of infection and its spread [13].

Animals with suspected monkeypox infection should be quarantined and their contacts (animals that might have come in contact with an infected animal) traced, quarantined and observed for monkeypox symptoms for about 30 days. Places where these animals have been kept should be thoroughly cleaned and disinfected. Infected patients should be isolated, contact with humans and pets should be limited, droplet precautions should be taken and good infection control measures should be put in place 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 monkeypox virus 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 exposed to patients with monkeypox or their samples will help prevent human-to-human and animal-to-human transmission [5; 28; 29].

If unprotected exposure to an infected animal or a confirmed human case occurs, smallpox vaccination is recommended. Since there is currently no commercially available monkeypox vaccine, the centers for disease control and prevention (CDC) recommends immunization or pre-exposure smallpox vaccination of healthcare workers and healthy persons in occupations at high risk of exposure. Also, post-exposure smallpox vaccination given to people who are exposed to a monkeypox-infected person or animal within two weeks of exposure preferably within 4 days of exposure provide 85% cross-protection against the infection [5; 30]. 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 presence of a gene coding for Golgi-associated retrograde protein (GARP) complex in an infecting monkeypox virus strain which could contribute to serious infection have been observed in a recent study. It is important to note that, there is no specific or definite tissue tropism of monkeypox virus because it has been detected in a number of tissues in a wide variety of animals. The knowledge of tissue tropism will give a clue about the spread and the immune responses of the virus between the hosts. Therefore, it is essential to identify the definite natural host of monkeypox virus and the host target cells which are required for viral multiplication as this could pave way for the development of anti-viral remedy [24; 31].

The spread of monkepox virus to humans is not exactly known as there is no known reservoir for the virus. A recent study suggested that, through bites from close association with wild animals, unhygienic practices of humans with animals and consumption of bush meat could serve as potential risk factors in acquiring this infection [25; 32]. It is imperative for future researches to focus on identifying the virus and its host factors that regulate transmission between humans and animals.

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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 nonhuman primates

such as monkeys [31; 25]. The development of an on-site laboratory diagnostic test known as ABICAP (Antibody Immuno Column for Analytical Processes), which is an immune-filtration technique and can be used both in humans and animals have been recently reported to aid in the complex identification of monkeypox virus 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. Based on currently available information, cases have mainly but not exclusively been identified amongst men who have sex with men (MSM) seeking care in primary care and sexual health clinics [12].

To date, all cases whose samples were confirmed by PCR have been identified as being infected 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 expanding. WHO expects to receive more reports from these areas as surveillance expands. Available information suggests that human-to-human transmission is occurring among people in close physical contact with cases who are symptomatic.

Table 1: Cases of monkeypox in non-endemic countries reported to WHO between 13 to 21 May 2022 as at 13:00

Country	Confirmed	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

Country	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].

6. CONCLUSION

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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. There is therefore an urgent need to carry out researches and enlightenment programs for effective control and to avoid a pandemic.

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