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Introduction to Monkeypox (MPOX) Virus Infection, Symptoms and Treatments

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Abstract

Monkeypox is zoonotic disease caused by the Monkeypox (MPOV) virus infect primate, rodents, and human. This enveloped virus is a large oval-shaped with double-stranded DNA, belongs to the genus Orthopoxvirus of the family Poxviridae. Monkeypox disease was first detected in 1970s in Central and West Africa. The infection usually spread from person-to-person contact or from the anhelation of infected person's lesions. These lesions found on the skin, eyes, mouth, throat, genitalia, and rectum. Monkeypox disease symptoms developed after the infection within five to twenty days incubation period and include rashes on faces that spread later across the body. Real-time Polymerase Chain Reaction (PCR) assay is the only reliable method to identify monkeypox virus infection. There are no special treatments for MPOX virus infection, but due to genetic similarity between Monkeypox (MPOX) virus, Smallpox (SPX) virus, and Vaccinia (VAC) virus, antiviral drugs for Smallpox (SPX) virus, and vaccinia (VAC) virus infections are used for the treatment from MPOX virus infection. In addition, the, developed vaccines for the protection from Smallpox (SPX) virus, and vaccinia (VAC) virus infection are used for the protection from Monkeypox (MOPX) virus infection. The global outbreak outside Africa occurred in the year 2022, and World Health Organization (WHO) declared endemic outbreaks of MPOX disease outside Africa after over 91,000 confirmed MPOX cases occurred in about 116 non-African countries with small number of deaths.

Keywords: Orthopoxvirus • Monkeypox (MPOX) Virus • Clad I • Clad IIa • Clad IIb • Central Africa • West Africa • Polymerase Chain Reaction (PCR) • Smallpox (SPOX) virus • Treatment • Vaccination • Global outbreaks • Intracellular Mature Virus (IMVs) • Extracellular Enveloped Virus (EEVs)

Introduction

The infection with Monkeypox (MPOX) virus was first identified in the year 1958 from two monkeys kept for research at the Staten's Serum Institute in Copenhagen. The first human case of MPOX disease was emerged in 1970s occurred in two African countries (Central and West African). Later and after over 50 years from the first case in Africa, MPOX disease was detected as endemic outbreaks in Europe and, United States of America [1]. Various epidemiology studies indicated that monkeypox disease clinically manifests as fever, fatigue, and a rash of smallpox-like lesions. Plus, the virus can cause various complications from second infection; include pneumonia, encephalitis, and sepsis, which might lead to death if the infection did not properly treat [2].

MPOX virus belongs to the genus Orthopoxvirus of the family Poxviridae and is related to the eradicated Smallpox (SPX) virus [3]. MPOX virus is a large, oval-shaped enveloped virus (Figure 1) comprising of a double strand DNA (dsDNA) genome. There are two distinct genomic types (groups) that were identified in Africa [4]. These are Clade I, present in Central Africa (Congo Basin) and Clade II, present in West Africa. Clade II is divided into two subleases Clade IIa and Clade IIb. Clade I that is present in Central Africa (Congo Basin) and is recognized to induce serious infection and can spread among humans with higher fatality rate that reached to about 11%. While Clade IIa, and Clade IIb present in West Africa displays lower fatality rate of infection less than 1% [5]. The early sign of MPOX virus infection (symptom) is the increase of the body temperature that is dangerous (pyrexia), followed by severe headache, myalgia, swelling of lymph nodes (lymphadenopathy), and fatigue (lethargy). After three days of these early symptoms dermal characteristics are developed such as rashes on facial region, and later spread on the chest, the back, the shoulders, and on the abdomen. These MPOX symptoms are quite similar to the eradicated Smallpox (SPX) virus symptoms [6]. MPOX symptoms are frequently self-determining disease; symptoms usually last for two to four weeks. Owing of MPOX disease originated in Africa, global outbreaks in the year 2022 with highest number of cases were detected at high rate in United States and Europe. Understanding the MPOX virus morphology, structure, mechanism of infection are important factors in developing special therapeutic drugs and vaccines to avoid future MPOX disease outbreaks.

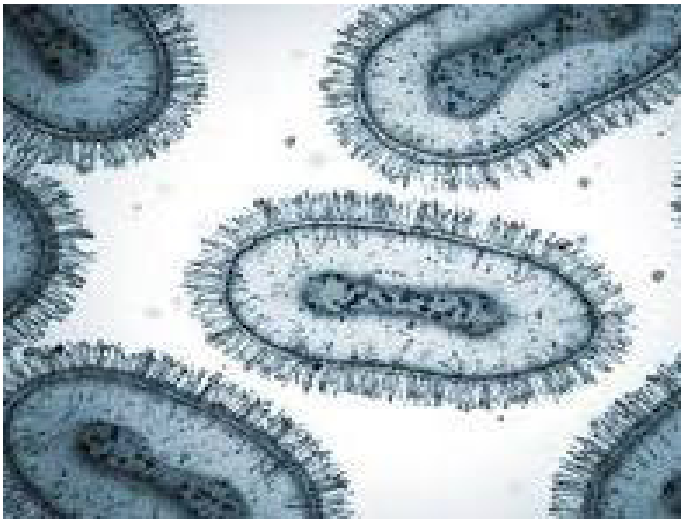

Figure 1. MPOX as a large, oval-shaped enveloped virus belongs to orthopoxvirus genus of the poxviridae family.

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Literature Review

Virus morphology and structure

MPOX virus is like other poxviruses morphology, it is oval-shaped highly complex virus that is not yet fully understood. In general, the virus structure has four components (Figure 2). These four components are outer lipoprotein envelop [7] outer membrane, lateral bodies, and the core. Outer lipoprotein, and outer membrane protects virus enzymes, DNA, and transcription factors from outside environments. The core which is the central part of the virus encompassed by core fibrils and double strand DNA (dsDNA) that are encircled by a rigid structure called the palisade layer [8]. The outer membrane accommodates the palisades layer, lateral bodies, and the central core [9]. On the surface on the outer membrane located a structure known by the name surface tubules.

MPOX replication, is known by the name Poxvirus replications, this replication occurs in the host cytoplasm in specific structures called Guarnieri bodies (also called factories) obtained from host infecting particles. The Guarnieri bodies (factories) are the site where virus dsDNA transcription, translation, and the assembly of virions are occurred [10]. Assembled MPOX Mature Virion (MV) inside the infected host cells cytoplasm form two separate infectious viral types (Figure 3). These infectious viral types are Intracellular Mature Virus (IMVs) and Extracellular Enveloped Virus (EEVs). Intracellular Mature Virus (IMVs) has single membrane, and Extracellular Enveloped Virus (EEVs), have additional outer membrane that is cleaved before the virus fusion into new host cell cytoplasm for new cell infection [11]. Both Intracellular Mature Virus (IMVs) and Extracellular Enveloped Virus (EEVs) are capable to infect human cells and hijack the host cell machinery.

Mechanism of infection

MPOX virus spreads from person-to-person when a healthy person contacts infected person by touching, kissing, sex, or *via* touching contaminated materials such as sheets, clothes, or needles. This virus can also spread *via* person contacts with infected animals, or through infected slaughtered animals skinning or cooking [12]. The infection initiated *via* the host skin cell, or as sometimes happened the virus inters the host body *via* respiratory tract to infect the epithelial cells such as ciliated cells [13]. There are a total of four viral proteins on the MPOX virus outer membrane surface helps the attachment of MPOX virus (EEV, and IMV) to the host cell [14]. These four virus proteins attached to non-glycosylated transmembrane proteins located on the host skin cells for the virus fusion into the host cell cytoplasm (Figure 4). MPOX replication (Provirus) occurs in the host cell cytoplasm inside specific structure known by the name Guarnieri bodies or factories that are obtained from host infected particles [15]. These Guarnieri bodies (factories) are the site where MPOX virus (virions) transcript, translate, and assemble is taken place. When the assembled MPOX became Mature Virion (MV) also known by the name Intracellular Mature Virus (IMV) enclosed within an endosomal membrane or trans-Golgi apparatus of the host infected cells, it is wrapped

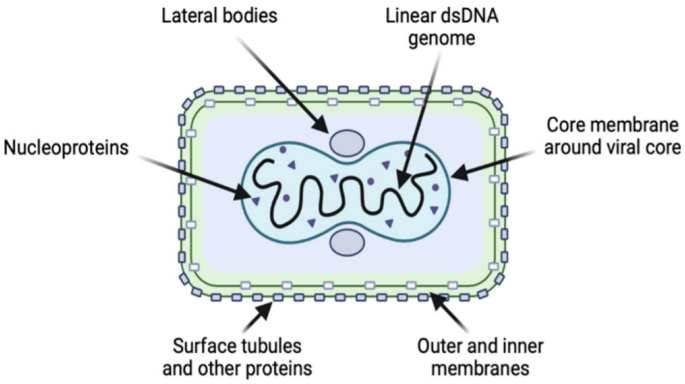

Figure 2. The virus contains four components of outer lipoprotein envelop, outer membrane (outer, and inner membranes), lateral bodies, and core. The core contains a linear double-stranded DNA (dsDNA) encodes the majority of proteins required for the virus replication inside host cell cytoplasm (Graphic created using BioRender).

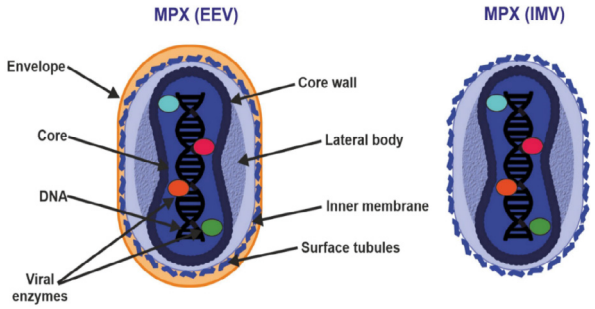

Figure 3. Poxvirus particles have two mature infection forms, Extracellular Enveloped Virus (EEV) and the Intracellular Mature Virus (IMV) that are released during infected host cell lysis. The most difference between IMV and EEV is IMV lack the additional outermost membrane layer that known by the name envelope [35].

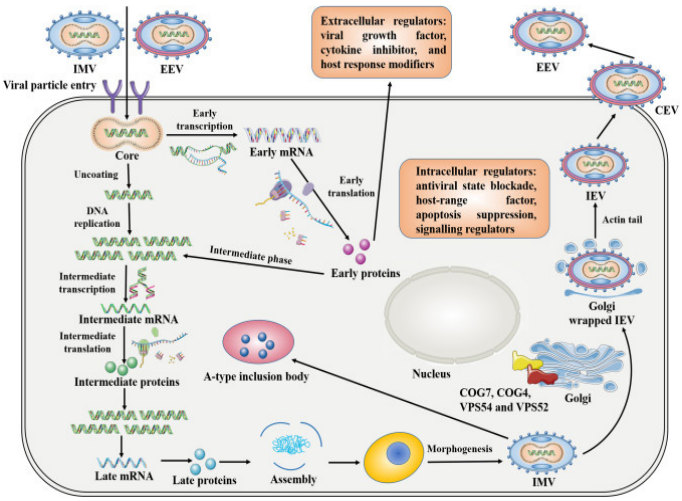

Figure 4. Monkeypox EEV and IMV virions (virus) bind to the unknown host cell receptors or to extracellular matrix components. MPOX replication involves viral mRNA, and protein synthesis, followed by the assembly of infectious virions (EEV and IMV). IMV is wrapped by a double membrane derived from the host cell Golgi to form an Intracellular Enveloped Virus (IEV). Developed IEV lose its outer membrane wrappings by Actin-tall and subsequently fuse with the host cell membrane to form Cell-associated Enveloped Viruses (CEVs). These CEVs can be released from infected host cell in the form of the infectious EEV [36].

by a double membrane derived from the host cell Golgi apparatus to form an Intracellular Enveloped Virus (IEV). Golgi-wrapped Intracellular Enveloped Virus (IEV) loses its outer membrane wrappings by Actin-tall and subsequently fuses with the cell membrane to form Cell-Associated Enveloped Virus (CEV). CEV is eventually released from infected host cell in the form of Extracellular Enveloped Virus (EEV). The unenclosed IMV outside endosomal membrane or trans-Golgi apparatus of the infected host cells remain free until the infected host cell is lysed [16]. Both released EEV and IMV is infectious virus that can spread the disease form person- to- person [17]. The stable EEV transmits the infection between hosts based on person-to-person contact, while the fragile IMVs spread the disease within the infected host cells. This stable EEV is capable to infect and replicate in the host lymph nodes, and cause viraemia causing the infection of the host large organs such as spleen and liver allowing EEVs to infect and replicate in distance organs such as lungs [18]. EEV also Infect host Antigen-Presenting Cells (APCs) such as dendritic cells and macrophages (Mø) present in the host blood calculation. It is important to highlight, that the developed virion inside host cell cytoplasm known by the name Cell-Associated Enveloped Virus (CEV) stays affixed to the infected cell surface. This CEV cannot spread into neighboring cells before developing actin tails below the plasma membrane to form sable EEV to be release from infected host cell surface to infect neighboring cells, plus causing viraemia, infect distance host organa, and spread form person-to-person contact.

Immune system response to MPOX virus infection

MPOX virus infection, trigger host cytokines response such as T-helper

cells (Th2) response, and a weakened T-helper cell (Th1) response. This result in the elevation of anti-inflammatory cytokines (IL-5, and IL-6, IL10) linked to Th2-mediated immune response, while down regulate cytokines (TNF-α, IFN-α, IFN-γ, and IL-2) linked to Th1 mediated immune response. In general, this virus has special mechanism to evade the host innate and adaptive immunity system. In addition, this virus has a set of modulated proteins encoded by the virus virulence genes to avoid the host immune response [19]. These modulated proteins are classified based on its function into intracellular proteins, and extracellular proteins (Figure 5). Intracellular proteins include viotransducers protein interfere with the infected host cell to respond to the infection, and virostealth protein decrease the virus detection by the host immune response *via* downregulating the function of immune molecules such as MHC class I and T cells-CD4 in recognizing the virus infection. Extracellular virus modulated proteins include two types of viremic proteins (viroeceptors, and virokines). Viroreceptors protein secreted as cell surface glycoproteins competitively bind to the host cytokines and chemokines of the infected host, while, Virokines protein mimic, the host cytokines, chemokines, and growth factors. In summary, this MPOX virus modulated proteins allow the virus to replicate while evading the host immune response. It is important to highlight that without this MPOX virus modulated proteins the virus will not be able to avoid the host immune response [20].

Infection symptoms

MPOX virus infection leads to skin lesions followed by sepsis, deep tissue abscess, severe respiratory disease, and injuries to immune organs such as, bone marrow, thymus, lymph nodes, spleen, tonsils, and mucous membranes [21]. Infection symptoms are usually started with fever, and rashes. The common site for first rashes is on the face (Figure 6). These rashes can also develop on the palm of hands, soles on the feet, mouth, genitalia, and eyes (conjunctivae and cornea). Other common symptoms are sore throat, headache, muscle aches, back pain, low energy, and, swollen lymph nodes. Most of the time the patient recovers from these symptoms on his/ her own within few weeks. But in some cases, a patient with week immunity became very sick and could die from the infection.

Infection diagnostics

Real-time Polymerase Chain Reaction (PCR) is regarded to be the best technique for accuracy and sensitivity in MPOX virus species differentiation. There are several PCR protocols that are available in the market to identify and differentiate between Smallpox (SPOX) virus, vaccinia (VAC) virus, and Monkeypox (MPOX) virus from other poxviruses family [22]. Serological and antigen detection methods do not provide reliable specific confirmation for MPOX virus infection due to cross-reactivity with another genus of Orthopoxviruses. These serological and antigen detection methods are not recommended for the diagnostic of MPOX virus infection [23]. Enzyme-linked immunosorbent assay (ELISA) methods for the detection of IgM and IgG antibodies in the infected host serum after 5 to 8-days of MOPX virus infection also does not provide reliable diagnostics due to antigenic cross reactivity between MPOX virus and other Orthopoxviruses. Therefore, these ELISA methods are not recommended for MPOX virus infection diagnostics as well. The only reliable

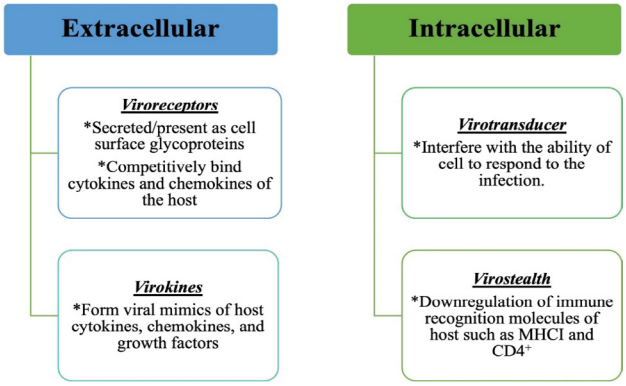

Figure 5. MPOX virus modulatory proteins can be classified into extracellular and Intracellular proteins. Extracellular proteins include viroreceptors and virokines. Intracellular proteins include virotransducers and virostealth [37].

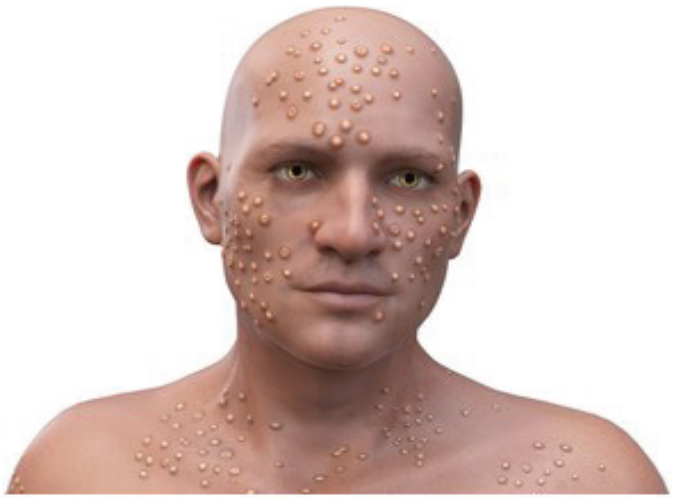

Figure 6. Common site for skin lesions (rashes) is on the face, but gradually spread over the infected person's body to cover the palm of hands, soles on the feet, mouth, genitalia and eyes.

diagnostic protocol for MPOX virus infection detection is the real-time PCR. This real-time PCR method is capable to identify the two MPOX virus types (Clade I, and Clade II), but does not differentiate between the two subleases of Clade II (Clade IIa and Clade IIb). The only differentiation between these two subclasses is by DNA sequencing. It is important to highlight that epidemiolocal studies demonstrated that 2022 -2023 MPOX virus infection outbreaks in U.S. and Europe were identified and classified by PCR, and DNA sequencing methods to be from type Clade II, specifically, from Clade IIb subclass that is rarely fatal. However, patients with weakened immune system, and a history of eczema, pregnant women, and one year of age children, are more likely to have serious illness from MPOX infection that could end to death. Other accepted method for this virus diagnostic for characterization at the level of subclasses is cell culture method. This cell culture methods are only restricted for the use of biosafety level 3 reference laboratories [24]. Clinical specimens for MPOX virus infection diagnostics are by skin lesion swab. Skin lesion from infected patient contains high MPOX virus titer for real-time Polymerase Chain Reaction (PCR), and for DNA sequencing methods. In some rare cases the patient does not develop external skin lesion, and in such cases the MPOX lesion is internal and clinical specimens are usually from nasopharyngeal, and oropharyngeal swabs [25].

Infection treatments

There are no special treatments for MPOX virus infection, and during the 2022-2023 MPOX outbreaks, antiviral drugs to treat MPOX virus infection became urgently needed. Monkeypox (MPOX) virus and Smallpox (SPX) virus are genetically similar, suggested that antiviral drugs used for the treatment from SPX virus infection, and vaccines used for the protection from POX virus infection can be used for the treatment from MPOX virus infection, and for vaccination for protection from MPOX virus infection [26]. Antiviral drug Tecovirimat (trade name TPOXX) used for SPX infection treatment demonstrated to have strong inhibition efficacy on MPOX virus infection [27]. Tecovirimat mechanism is the inhibition of virus envelops proteins that are essential for the virus assembly. Such virus envelop proteins inhibition preventing the virus from assembly and release from infected cell, hindering the virus spread to infect more healthy cells in the infected host. In addition, antiviral drug Cidofovir that has a broad-spectrum as antiviral agent to treat a variety of viral infections include poxviruses family demonstrated to provide treatment efficacy against MPOX virus infection. This antiviral drug Cidofovir acts through the selective inhibition of viral DNA polymerase resulted in the inhibition of virus DNA synthesis [28]. In the case of vaccination for the protection from MPOX virus infection, Smallpox (SPX) vaccine ST-246, and vaccinia (VAC) immune globulin (VIG) are currently used for vaccination to control MPOX virus infection outbreaks [29]. In addition, there are two vaccinia (VAC) virus vaccines that are available in United States to reduce the risk and severity of MPOX virus infection. These two vaccines are JYNNEOSTM (live, replication-incompetent

vaccinia virus), and ACAM2000® (live, replication-competent vaccinia virus). These two vaccines used in U.S. are made from vaccinia (VAC) virus which is a poxvirus related to MPOX virus [30]. Centers for Disease Control and Prevention (CDC) recommend the use of JYNNEOSTM as the primary vaccine to protect from MPOX virus infection. This JYNNEOSTM vaccine is less associated with potential side effects comparing to ACAM2000® vaccine. This JYNNEOSTM vaccine is recommended for people vaccination within 4 to 14 days after the exposure to MPOX virus. This window of vaccination after exposure to MPOX virus can help the person to prevent the infection. All these approved vaccines for the protection from MPOX virus infection are strongly recommended to vaccinate specially gays, and bisexual groups of people, that are considered to be at high risk for this virus infection [31].

Infection prevention

The first priority of prevention is to treat infected patient by approved antiviral drugs and vaccinate high risk groups of people for the protection from MPOX virus infection. This first priority of treatment and infection prevention will prevent MPOX virus from infecting and spreading into large population causing serious outbreaks. The second priority for infection prevention is to educate people and increase population awareness to these virus methods of infection and symptoms. Such education will minimize virus infection rates and reduce future outbreaks [32].

General steps for the prevention from MPOX virus infection and spreading through the large population are:

- Avoid close contact with patients have rashes that looks like MPOX virus infection symptoms.
- Avoid handling clothes and other materials that have been used with infected person.
- Wash hands with disinfectants if contacted with infected person.
- Isolate patients that are infected with MPOX and showed symptoms from the community.
- Avoid contact with animals that are susceptible to carry this virus.

Discussion

Monkeypox (MPOX) virus is a rare skin infection disease caused by a dsDNA enveloped virus belongs to Proxviridae family, and to the genus Orthopoxvirus. This Proxviridae family include Smallpox (SPX) virus, Cowpox (CPX) virus, and Vaccinia (VAC) virus. Monkeypox (MPOX) virus is Zoonotic diseases Infect primates, rodents, and humans. The infection spread from person-to-person contact or from the anhelation of infected person's lesions. These lesions may be located on the skin or as mucous on the surface of eyes, mouth, throat, genitalia, and rectum. Symptoms after the infection with MPOX virus usually developed within five to twenty days and include fever, headaches, muscle or back aches, swollen lymph nodes, and exhaustion. These symptoms followed by rashes on the face that quickly spread across the body. This enveloped dsDNA monkeypox virus is quite similar in mechanism of infection, treatments, and vaccination to viruses belongs to Proxviridae family. Mechanism of infection by these viruses require first the uncoating of virus envelop after fusing in the host cell, and reaching host cell cytoplasm for DNA replications, virus proteins synthesis, and new viruses' assembly steps to be released from infected host cell cytoplasm to infect neighboring host cells, or to infect new person *via* person-to-person contact. Developed antiviral drugs mechanism for these Proxviridae family are based on blocking the uncoating of the virus envelope inside infected host cell cytoplasm, or inhibiting virus DNA synthesis (replication) inside the host infected cell cytoplasm. Currently there are no specific antiviral drugs for the treatment of Monkeypox (MPOX) virus infection. However, due to the similarity in mechanism of infection for Smallpox (SPX) virus, and Vaccinia (VAC) virus to Monkeypox (MPOX) virus, FDA approved antiviral drugs used for the treatment from Smallpox (SPX) virus infection, and antiviral drugs for the treatment from vaccinia (VAC) virus infections to be used for the treatment from Monkeypox (MPOX) virus infection. Also, FDA approved vaccines used for the protection from Smallpox (SPX) virus infection, and from vaccinia (VAC) virus infection to be used for vaccination from Monkeypox (MPOX) virus infections.

For over 50 years MPOX virus infection and disease were restricted to Africa especially in West and Central Africa, plus to a rare case outside Africa linked to international travel to these African countries or through import animals from these countries. African rodents and primates such as monkeys believed to be the initial source of infection to the people in West and Central Africa. Global outbreaks outside Africa were declared by World Health Organization (WHO) in the year 2022 after over 91,000 confirmed MPOX virus infection cases in about 116 non-African countries with small numbers of death [33]. The most affected countries by these global outbreaks are UK, Australia, Belgium, Canada, France, Germany, Italy, Netherlands, Portugal, Spain, Sweden, and U.S. The most MPOX virus type circulated in these global outbreaks is belong to the clade IIb type that has lower fatality rate of infection (less than 1%). Due to the low rate of Monkeypox virus infection World Health Organization declared on May 2023 an end to MPOX disease endemic outside Africa citing steady progress in controlling the spread of the disease. It is important to highlight as of 20 January 2024, there have been a total of 93,275 confirmed cases and 177 deaths in over 113 countries outside Africa [34]. This rate of infection is concern that ending MPOX disease endemic on May 2023 was too early.

Conclusion

The risk from the infection with Monkeypox (MPOX) virus is still moderate. However, it appears that this zoonotic monkeypox virus is adaptive to be suited globally to human. Developing specific antiviral drugs and vaccines especially for monkeypox virus infection are in demand for potential new outbreaks outside Africa in years to come.

Acknowledgement

None.

Conflict of Interest

None.

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