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REVIEW ARTICLE

Mpox: Epidemiological, immunopathogenic aspects and pre- and post-infection management

Mpox: Aspectos epidemiológicos, imunopatogênicos e manejo pré e pós-infecção

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ABSTRACT

Mpox or Variola M is a zoonosis caused by viruses of the genus Orthopoxvirus, which also cause smallpox. It is a disease considered rare and self-limiting, being endemic in African countries. However, in 2022, it gained prominence due to the global outbreak that began when the world was still recovering from the COVID-19 pandemic. Thus, as it is an emerging disease, this review aims to point out general aspects of what is known so far about Mpox, from its immunopathogenesis to current forms of prevention and post-infection care.

PALAVRAS-CHAVE
Condições patológicas, sinais e sintomas
Transmissão de doença infecciosa
Vírus da Varíola dos Macacos

RESUMO

Mpox ou Varíola M é uma zoonose causada por vírus do gênero *Orthopoxvirus*, causadores também da varíola comum. É uma doença considerada rara e autolimitada, sendo endêmica em países africanos. Entretanto, no ano de 2022 ganhou destaque devido ao surto global que se iniciou, quando o mundo ainda se recuperava da pandemia da COVID-19. Dessa forma, por se tratar de uma doença emergente, a presente revisão visa pontuar aspectos gerais do que se sabe até o momento sobre a *Mpox*, desde sua imunopatogenia até as formas atuais de prevenção e cuidados pós-infecção.

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INTRODUCTION

After the global outbreak of transmission of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which claimed millions of lives worldwide, Mpox[1], formerly known as monkeypox, emerged as a new global health concern and was declared a public health emergency by the World Health Organization (WHO) in July 2022[2]. Although the transmissibility of Mpox is not as expressive as in cases of Coronavirus Disease 2019 - COVID-19, which occurs through droplets of saliva, the concern is, above all, about the behavior and evolution of the virus after it has spread globally since its transmission is made by close contact with body fluids such as saliva and coughing, which generates a state of less concern among the population[3].

Mpox is a zoonosis considered rare and self-limited, except in Central and West Africa, mainly in the Democratic Republic of Congo, where it is endemic due not only to the relatively close interaction between humans and wild animal reservoirs but also to the decline of cross-protective immunity after interruption of vaccination against smallpox, which had already been declared eradicated in the 1970s[4,5].

This disease was so named because researchers first detected it in laboratory monkeys in 1958, but it is believed to be transmitted to humans by wild animals such as rodents or other infected people[6]. Two viral phylogenetic branches cause this disease, the viral subtype associated with cases occurring in Central Africa (Clade I), which causes more severe symptoms, and the one related to West African cases (Clade II), which is less transmissible and less virulent, being more frequent in non-endemic countries[7]. Thus, as it is an emerging disease with pandemic potential, this review describes the general aspects of Mpox.

EPIDEMIOLOGY

The epidemiological importance of Mpox is reflected in the fact that this disease is the most relevant *Orthopoxvirus* infection in humans since the eradication of common smallpox. The first human case of Mpox was reported in a child from the Democratic Republic of Congo in 1970. Since then, sporadic cases have been identified in Cameroon, Central African Republic, Gabon, Côte d'Ivoire, Liberia, Nigeria, and Sierra Leone, where lethality was around 17%[4].

Epidemiological attention to Mpox began in 2003 when in the United States the virus was detected as causing an outbreak of exanthematous disease among humans and prairie dogs that had contact with rodents exported from Ghana. Subsequently, cases of infection were confirmed in humans in 23 states in Nigeria in 2017 and in the United Kingdom in 2018, again drawing the attention of the media, politicians, and scientists around the world[5,8,9]. Since then, thousands of cases have been reported, mostly in African countries[5,10].

In a systematic review, the epidemiological aspects mapped by Bunge et al.[11] demonstrated a higher prevalence of infection in the age group of 10 to 21 years in males from African countries, while in non-African countries, infection in adults was the most prevalent. The highlighted risk behaviors were sharing personal objects, contact with infected animals and family gatherings[12,13]. Based on 38 studies in 14 countries, the estimated lethality rate was 8.7%, with a concentration of 37.5% of deaths in children under 10 years of age between 2000 and 2019[11,12].

As of May 2022, approximately 1,350 cases have been laboratory confirmed in 31 non-endemic countries. Of these, around 60% were reported to come from Portugal, Spain and the UK. Furthermore, in June of the same year, the Centers for Disease Control and Prevention (CDC) of the United States of America (USA) reported 45 cases in 15 states[12,13].

In the USA, around 94% of the identified cases occurred in Men who have Sex with Men (MSM), corroborating the hypothesis of transmissibility of the disease through the vertical route and direct contact with infected skin with mucocutaneous lesions[14]. Furthermore, the potential for transmissibility is also being investigated by respiratory droplets (possibly short-range aerosols) and indirectly via fomites such as towels, bed linen, and intimate objects[12,13]. In addition to the risk factors identified for Mpox infection, immunosuppressed patients were included, mainly People Living with HIV (PLHIV), sexual intercourse without barrier protection, and multiple sexual partners[13].

In Brazil, at the time of this review, the Brazilian Ministry of Health (MS) reported about 10,846 confirmed cases of Mpox infection via epidemiological bulletins, 50% of which were reported in the country's southeastern region, where the first case was also confirmed[15]. The epidemiological study by Pascom et al.[16] identified that young men and MSM were the most affected in Brazil with primarily mild symptoms of the infection.

From January 1 to March 2, 2023, 86,309 laboratory-confirmed cases and 1,087 probable cases, including 107 deaths distributed across 110 member states, were reported to WHO. The 10 non-endemic countries most affected by cases of infection were the USA, Brazil, Spain, France, Colombia, Mexico, Peru, United Kingdom, Germany and Canada[2]. The prevalence of infection was higher in males aged between 18 and 44 years[17]. WHO assessed the overall risk caused by Mpox as moderate, with the European and American regions classified as high risk, African, Eastern Mediterranean, and Southeast Asia as moderate, and the Western Pacific as low-moderate risk[2].

The actual number of documented cases is believed to be underestimated due to the lack of early clinical recognition and the limitation of epidemiological surveillance mechanisms given the short recognition period of Mpox by healthcare systems as a pandemic threat[13].

IMMUNOPATHOGENESIS

The natural reservoirs of Mpox are African squirrels, rodents and nonhuman primates[18]. Transmission occurs by a double-stranded linear DNA virus (197 kb) belonging to the *Orthopoxvirus* genus of the *Poxviridae* family and *Chordopoxvirinae* subfamily[19] (Figure 1). It has an oval or brick-shaped morphology, surrounded by a lipoprotein membrane, with a size range between 200 nm and 250 nm[10]. It has a densely packed

biconcave core containing enzymes, a double-stranded DNA genome, and transcription factors, which are protected by the outer membrane[20].

About 10 different viral strains from Nigeria, West Africa, and the Middle East or East Africa involved in the cases of infection were identified[21]. However, based on phylogenetic, geographic, and clinical characteristics correlating with the different epidemiological outbreaks, the Mpox virus has been divided into two main clades: Clade I and Clade II. Clade I, which is more virulent, clinically more severe, and has higher mortality rates, is linked to cases arising in Central Africa, specifically in the Democratic Republic of Congo. Clade II, on the other hand, is less virulent and causes milder symptoms and reduced mortality, being linked to cases originating in West Africa[22,23]. A third classification, in which Clade II is subdivided into IIa and IIb, correlates with the spread of the disease to non-endemic countries[22,24]. Phylogenetic analyses showed that the Mpox epidemic of 2022 was mainly caused by Clade IIb signaling an accelerated evolutionary path[25].

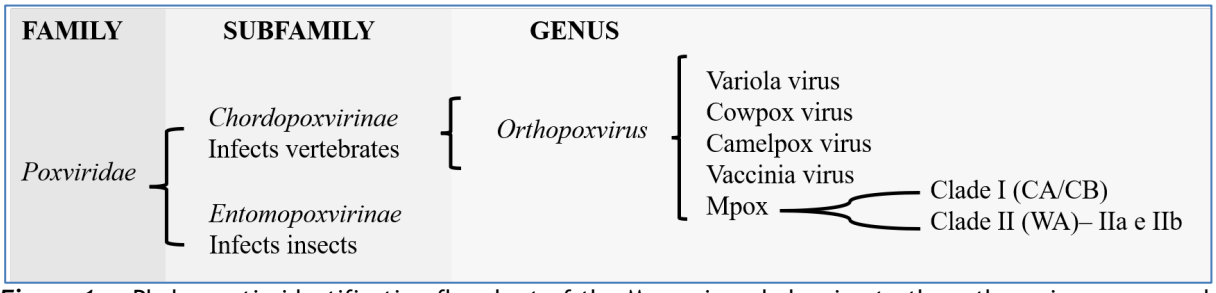

Figure 1 — Phylogenetic identification flowchart of the Mpox virus, belonging to the orthopoxirus genus and subdivided into Clade I (Central Africa/Congo Basin) and Clade II (West Africa)[19].

Clades I and II showed a similar nucleotide identity in about 95% of the cases with the identification of nine proteins with conserved differences between the two clades. Five of the nine proteins showed geographically associated differences and were involved in immune evasion. Thus, the nucleotide difference between the two clades was sufficient to produce different clinical pictures[25].

Orthopoxviruses generate cross-reactive humoral and cellular immune responses, sharing antigenic genetic characteristics. Thus, inoculating an agent of this genus can confer immunization against another species of virus of the same genus[26,27]. For example, the Vaccinia virus protects against diseases caused by smallpox, monkeypox and cowpox, with the main immunological component responsible for cross-protection being the neutralizing antibodies produced by the primary infection[28].

Infection occurs via the oropharyngeal, nasopharyngeal, or intradermal route. The virus replicates locally at inoculation, spreading to regional lymph nodes and later to other organs in the body. They enter the host cell by macropinocytosis endocytosed dependent on low pH that releases its viral nucleus into the cytoplasm where its life cycle occurs[10].

In the later stages of replication cycle, a complex of late gene products and a collective of viral membrane assembly proteins act to dismantle the surrounding endoplasmic reticulum membranes and produce crescent-shaped structures as substrates for the assembly of immature virions that will be further processed into mature intracellular virus[29].

All proteins necessary for replication, transcription, virion assembly, and viral DNA output are encoded by the Mpox virus genome. Genes that encode maintenance functions are highly conserved among *Orthopoxvirus* and are present in the central region of the genome, while those that encode virus-host interactions are less conserved and are located in the terminal region[30,31].

Early gene expression occurs in the viral core and DNA replication, followed by intermediate and late gene expression. Viral particles formed go through long stages of maturation until they reach the infectious stage where they have two forms: 1) extracellular enveloped virus that has a fragile outer membrane and mediates viral dissemination in the infected organism, being released from cells through interaction with the actin tails and 2) intracellular mature virus, more stable, mediates the transmission between hosts, being released only in cell lysis[20,28,32].

In *Poxvirus*, the intracellular mature virus is enveloped by a membrane derived from an endosomal component and forms an intracellular envelope that breaks before fusion[28]. Cell-to-cell spread occurs by microtubule-mediated transport of the intracellular enveloped virus to the cell periphery, where its outer membrane fuses with the host cell's plasma membrane and remains attached to the cell surface. It is believed that the same may occur for VPM[33].

Orthopoxviruses use a set of intracellular and extracellular proteins encoded by virulence genes that act as modulators of the host's immune system. Intracellular virotransducer proteins interfere with the cell's ability to respond to infection, and virostealth proteins negatively modulate pathogen recognition via molecular histocompatibility complex class 1 (MHC-1)[5,34].

Extracellular proteins are divided into viroreceptors, which are glycoproteins that compete for cytokine and chemokine receptors, and virokines, which mimic host cytokines, chemokines, and growth factors that are effective in subverting host responses that are harmful to virus survival and in promoting appropriate responses for viral replication and dissemination[34,35].

Thus, the Mpox virus, specifically Clade I, can nullify local T cell responses through the T cell receptor (TCR) 36-38, inhibiting CD4+ and CD8+ after interactions

with infected cells, avoiding systemic immunosuppression while protecting the viral reservoir from immune surveillance. The variola virus M inhibitor of complement enzymes (a gene that inhibits complement enzymes) is absent in clade II strains and has been implicated as a critical immunomodulatory factor contributing to the increased virulence of clade I strains[35,38].

CLINICAL ASPECTS AND DIAGNOSIS

The Mpox outbreak that began in May 2022 has current evidence of human-to-human transmission[39]. Most commonly, the described mechanism of viral transmission in this outbreak is close contact related to the context of sexual intercourse with infected individuals. However, in July 2022, a series of cases linked to piercings and tattoos were identified, whose infection was attributed to sanitary irregularities, poor hygiene conditions, and asepsis in the studio location, with a high viral load being identified in sharps and work instruments that were used in the detected individuals[40]. Due to the different possibilities of infection mechanisms, new virological evaluation studies are expected about the transmission routes regarding the presence of Mpox in humans[41].

Due to the serious potential for spreading the disease, the WHO established, in the aforementioned provisional guideline manual, an instruction for determining cases based on the clinical characteristics of suspicion, probability, or confirmation (Figure 2)[39].

SUSPECTED CASE	PROBABLE CASE	CONFIRMED CASE
Contact with a probable or confirmed case 21 days before symptoms **AND** Non-specific symptoms **OR** Unexplained acute skin rash, mucosal lesion or lymphadenopathy	Unexplained acute skin rash, mucosal lesion or lymphadenopathy **AND** Contact with an infected individual within the last 21 days **OR** MSM, multiple sexual partners, increased IgG without recent vaccination, detection of anti-orthopoxvirus IgM, positive test for orthopoxvirus infection	Detection of viral DNA or PCR

Figure 2 — Determination and classification of Mpox cases as suspected, probable or confirmed, based on the expression of symptoms and associated factors, according to the WHO interim guidance manual[39].

The viral incubation period varies between 5 and 21 days, and the prodromal stage lasts from 1 to 4 days, characterized by nonspecific symptoms that include fever with a variable temperature from 38.5 ºC to 40.5 ºC, chills, headache, lethargy, fatigue, myalgia and low back pain[5,41,42]. The first case described in Brazil involved itching and burning in the glans penis 43. The prodromal phase can also be asymptomatic[44].

After this phase, skin eruptions and lymphadenopathy appear, the latter not characteristic of smallpox. The lymph nodes are firm, increasing between 1 and 4 cm in diameter and may be hypersensitive and painful. It is considered that lymphadenopathy may indicate an effective immune response to infection by the virus; however, further studies regarding this hypothesis are needed[45].

The rash of varying sizes tends to appear within 1 to 5 days after the onset of fever, with centrifugal dissemination, starting on the face with subsequent involvement of the hands, legs, and feet. It may go through different stages of evolution, from macules, papules, vesicles, and pustules, followed by crust formation in the period of resolution and recovery[5] (Figure 3).

It was found that the lesions tend to appear at the site of inoculation, which may explain the fact that there are lesions located in the perineal and perianal regions in the current outbreak, in addition to the coexistence of lesions in different stages of progression of the eruptions[12]. In a series of 528 cases in 16 countries, skin lesions were observed in 95% of those infected, with the most affected anatomical sites being the anogenital region (73%), trunk, arms or legs (55%), face (25%) and palms and plants (10%); the maximum number of lesions was 10 or less[42] (Figure 4).

Mpox infection and common smallpox are significant, so the distinction for diagnostic determination can be difficult for the health professional when faced with a similar clinical picture[30,47]. Other differential diagnoses include syphilis, chickenpox, measles, herpes zoster, human immunodeficiency virus (HIV) infection, chancroid,

chlamydia, scabies, and allergic reactions[41,48].

The disease is usually self-limiting, lasting between 2 and 4 weeks, but severe cases can result from associated complications. Complications were described mainly among the unvaccinated (74.5%) compared to those vaccinated (39.5%) against smallpox, and among the most susceptible groups are those with risk factors for having underlying immune deficiencies, younger age, co-infection with HIV or other chronic diseases[11,45].

Lethality varies between 1% and 10% according to host factors, access to care, intervention, and early support in cases of complications. A study of 282 cases identified no deaths among individuals who received smallpox vaccinations, with a 11% death rate among non-vaccinated individuals[49]. In a recent study with 23 individuals with a confirmed diagnosis of Mpox, no deaths were identified, only complications that included one epiglottitis and two myocarditis[2].

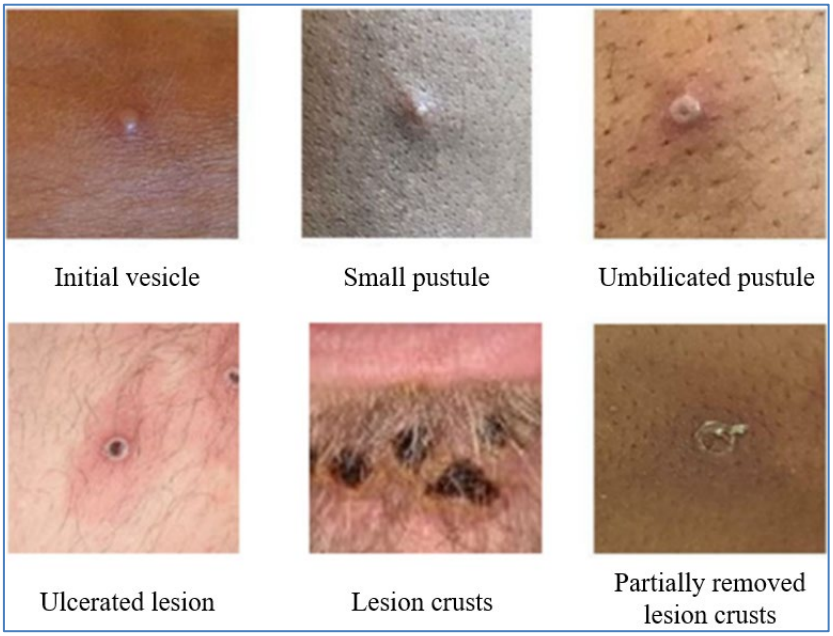

Figure 3 — Stages of evolution of skin eruption described by the WHO in patients affected by Mpox, starting as a vesicle, with pustular evolution, until the formation of crusts[46].

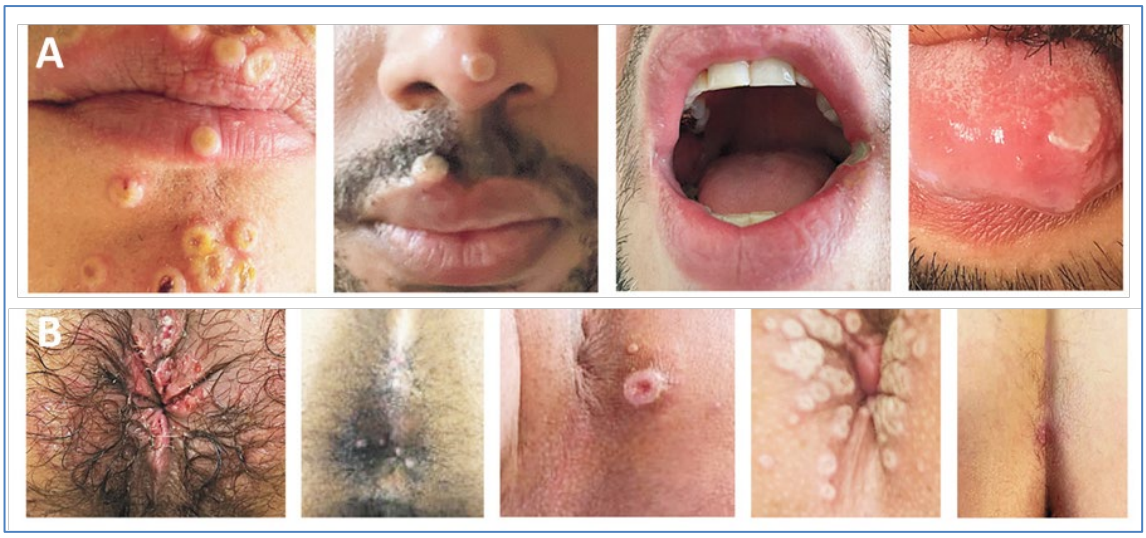

Figure 4 — Characteristics of the lesions and most affected anatomical sites in people infected with Mpox. Distribution and evolution of lesions in the oral cavity (A) and quantitative and evolution of anogenital lesions (B). Extracted from Thornhill JP et al.[42].

PREVENTION AND POST-INFECTION MEASURES

Preventive measures against Mpox focus mainly on containing the spread of the virus. Current research suggests that prior immunization with the vaccine against common smallpox may confer a protective effect against the Mpox virus in addition to milder signs and symptoms[38,50]. Regarding the cases after infection, measures support and control symptoms such as rehydration in cases involving vomiting and diarrhea[12,51,52].

According to the Advisory Committee on

Immunization Practices (ACIP), pre-exposure prophylaxis is recommended for individuals who are at risk of occupational exposure to *Orthopoxvirus*, such as research laboratory or clinical workers, health teams, family members, and caregivers of people with Mpox, considering the clinical decision and absence of contraindications[51,53,54].

There are two smallpox vaccines in the US Strategic National Stockpile: Jynneos® (also known as Imvamune®, Imvanex®, and MVA-BN®) and ACAM2000®. In addition, the Aventis Pasteur Smallpox Vaccine (APSV) can be used, but only under the Investigational New Drug (IND) protocol.

Jynneos vaccine is a live viral immunizer produced from the modified *Vaccinia* virus, strain Ankara-Bavarian Nordic, an attenuated, non-replicating *Orthopoxvirus*[55]. In September 2019, it was licensed by the US FDA and is currently recommended for the prevention of common smallpox and Mpox in people aged 18 years or older who are considered at high risk for infection with the disease[56]. The vaccine was used as an off-label treatment in response to cases of Mpox in the United Kingdom[57], and recent evidence has shown that vaccination with the *Vaccinia* virus was 85% effective. MS has already received an exemption from registration to import and use the vaccine in Brazil[58].

Similarly, ACAM2000® is also composed of live Vaccinia virus and was licensed by FDA in August 2007 when it replaced the previous Orhtopoxvirus vaccine Dryvax® withdrawn by the manufacturer[59]. Immunization is indicated for people at a high risk of smallpox infection. The CDC has an emergency access IND protocol that allows the use of ACAM2000® for non-smallpox orthopoxvirus infection, which includes Mpox during an outbreak[56].

Aventis Pasteur Smallpox Vaccine (APSV) is a replication-competent Vaccinia vaccine. However, it is restricted under an investigational new drug protocol or an emergency use authorization if already licensed vaccines are unavailable or contraindicated due to the scarcity of studies to attest to the effectiveness of APSV, specifically against Mpox[52].

Medications such as antivirals are being used, but studies attesting to their effectiveness as a treatment for Mpox are still scarce. Tecovirimat has been studied by National Institutes of Health (NIH) and approved since January 2002 by Food and Drug Administration (FDA) as the drug of choice to abbreviate and improve the resolution of Mpox[36,60].

In addition to Tecovirimat, Brincidofovir, and Trifluridine can be considered in the presence of ocular involvement. In cases where smallpox vaccination is contraindicated, intravenous vaccinia immunoglobulin can be evaluated[12,51,52].

ACAM2000 vaccine and antiviral Tecovirimat in the post-exposure control of Mpox reported that the isolated use of the vaccine did not impact the evolution of the disease or the reduction of mortality, but the antiviral associated or not with the vaccine obtained good results even 6 days after exposure[61]. In a series of cases from 2018 to 2021 in the United Kingdom, it was reported that Brincidofovir induced an increase in liver enzymes, while tecovirimat did not have adverse effects, better controlling the symptoms[62]. Considering that the effectiveness of these measures is not well established, physicians should access public health authorities and current protocols to support the prescription of such medications[12,51,52].

Regarding postexposure prophylaxis, the risk of transmission associated with the interaction time with a symptomatic individual must be considered. In cases of rapid interactions and acceptable use of personal protective equipment (PPE) are not considered for post-exposure prophylaxis, individuals must be monitored and instructed to call health services in case of symptoms. In situations of exposure at an intermediate level or suspicion of a high degree of contact, the recommendation for post-exposure immunization must be individualized according to the analysis of the benefits to the detriment of the risks[63,64].

Immunization is considered in direct contact with the patient without using PPE, contact with lesions, body fluids, contaminated materials, personal items, and resuspension of dry exudates[63]. Jynneos and ACAM2000 are the vaccines used, and the CDC recommends the first dose within 4 days of exposure. If given 4 to 14 days after exposure, it can reduce disease symptoms but not prevent its onset[64].

CONCLUSION

The general aspects presented about Mpox, also known as Variola M, demonstrate that although it is a zoonosis with self-limiting clinical characteristics, its pandemic potential is correlated with the rapid evolution of the virus and its variants. Furthermore, it is worth noting the geographical factor in the spread of the disease, as the variant exported to non-endemic countries results in a milder and less lethal clinical picture, which can engender a false sense of security regarding the risk of infection.

The Mpox infection is not limited solely to its pandemic potential but also highlights the fragility in the realm of healthcare regarding immunization policies and campaigns in both endemic and non-endemic countries, due to the resurgence of an already eradicated disease. Its global dissemination still persists with substantial remnants following the COVID-19 pandemic, where the capacity of healthcare units to manage, a global crisis was pushed to the extreme.

Further clinical research is essential to deepen the therapeutic response of already available antiviral drugs and vaccines that show potential for Mpox treatment.

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