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Mini-Review

Re-emergence of monkeypox: a post-COVID-19 challenge

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ABSTRACT

While the world is grappling with the SARS-CoV-2 pandemic and striving to minimize the damage caused, another emerging virus called Monkeypox Virus (MPXV) has surfaced, capturing widespread attention and instilling panic among people. There is a fear that this new virus could lead to a scenario similar to, if not worse than, the ongoing COVID-19 crisis. Hence, the objective of this work is to provide an overview of the monkeypox disease to shed light on the characteristics and behavior of this emergent disease, to explore reliable and possible diagnostic methods, and delve into the available preventive and therapeutic measures, including viable drugs and approved vaccines, to mitigate the impact of the illness. Many enigmas still surround this emergent disease, which makes it crucial to emphasize the importance of clarifying its progression and establishing effective control measures; by doing so, we can learn from past experiences and avoid repeating the errors that occurred during the COVID-19 pandemic.

KEYWORDS: monkeypox virus, monkeypox disease, testing, treatments, vaccines.

INTRODUCTION

We live in a dangerous world, in which at any time, an emerging, lethal, and highly transmissible pathogen can appear [1, 2]. Whereas, at a time when the world is grappling with the mutant SARS-CoV-2 causing a respiratory syndrome in humans, and starting to recover from the negative repercussions of its pandemic, a new threat of Monkeypox virus has loomed ahead [3-5], after 42 years of eradication of the smallpox disease. The global battle against the Monkeypox virus (MPXV), a skin disease which is regarded as an ancient and one of the most lethal diseases that affects humans, has reignited, necessitating the health authorities and experts to unite in eradicating this rare yet highly contagious *Orthopoxvirus* [6, 7]. Its recent resurgence poses a significant challenge worldwide, leading to multiple outbreaks, particularly affecting men identified as homosexuals or bisexuals [4, 8]. The rapid spread of this emerging virus and its disease has once again highlighted the need to understand the true extent of all the symptoms of Monkeypox (Mpox) and its long-term effects [9]. Moreover, one can only control this disease by good hygiene practices, avoiding unsafe sexual intercourse, and more importantly, getting vaccinated [10]. In this mini-review, the broad range of Mpox clinical symptoms and its complications are elucidated, and the available tests for its diagnostic and treatments against it are comprehensively clarified.

Monkeypox disease

Incubation

The incubation period is defined as the period between the viral entry into the body and the appearance of the first symptoms [9, 11-13]. For Monkeypox disease, this asymptomatic period is

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estimated to be 7.4 days (ranging from five days to three weeks); (most likely 7 to 14 days) [10, 14-19].

Symptoms

This dangerous infection can be divided into two periods, the invasion period called prodromal phase, and the skin eruption period, known as rash phase [13]. The prodromal phase is estimated to be from 1 to 5 days [13, 20, 21], and is characterized by the onset of fever, restlessness, and unilateral or bilateral lymphadenopathy which is defined as enlargement of lymph nodes beyond their normal state in submandibular, cervical, post-auricular, axillary, and inguinal places that grow from 1 cm to 4 cm [17, 21-26]. Moreover, this invasion period can also be associated with other generic signs like severe headaches, muscle and back aches, chills, exhaustion, asthenia, and vomiting [27, 28]. Therefore, a high similarity is found between the symptoms of Monkeypox, smallpox, measles, and chickenpox, but lymphadenopathy is the only symptom that distinguishes MPX from the others [17, 29-31]. After the first period, the Monkeypox infection enters the rash phase, which progresses from 2 to 4 weeks [32, 33]. This phase is characterized by the onset of pleomorphic rash, which generally starts in the face and then spreads quickly to the whole body, including palms and soles of the feet, oral mucosa, genitals, and conjunctiva (Figure 1). Each lesion evolves through stages, beginning as a macule, advancing into papules, vesicles, pustules, and eventually forming scabs (Figure 2) [26, 31, 33]. Usually, the number of these lesions is between 1 and 100 while their diameter ranges from 0.5 cm to 1 cm [5, 17]. According to the results of some studies, scientists suggest that infected persons can suffer from the rash before other symptoms, or can only experience a rash [29, 34, 35]. Also, they suggest that this infection might be asymptomatic in some populations according to a serological study during the Cameron MPX outbreak where they find many individuals who did not show any symptoms had a high titer of *Orthopoxvirus* Immunoglobulin G (IgG) and Immunoglobulin M (IgM) antibodies [30].

Complications

Monkeypox infection can be accompanied by a range of complications such as bronchopneumonia, cardiovascular involvement, extra-cutaneous manifestations like secondary skin soft tissue

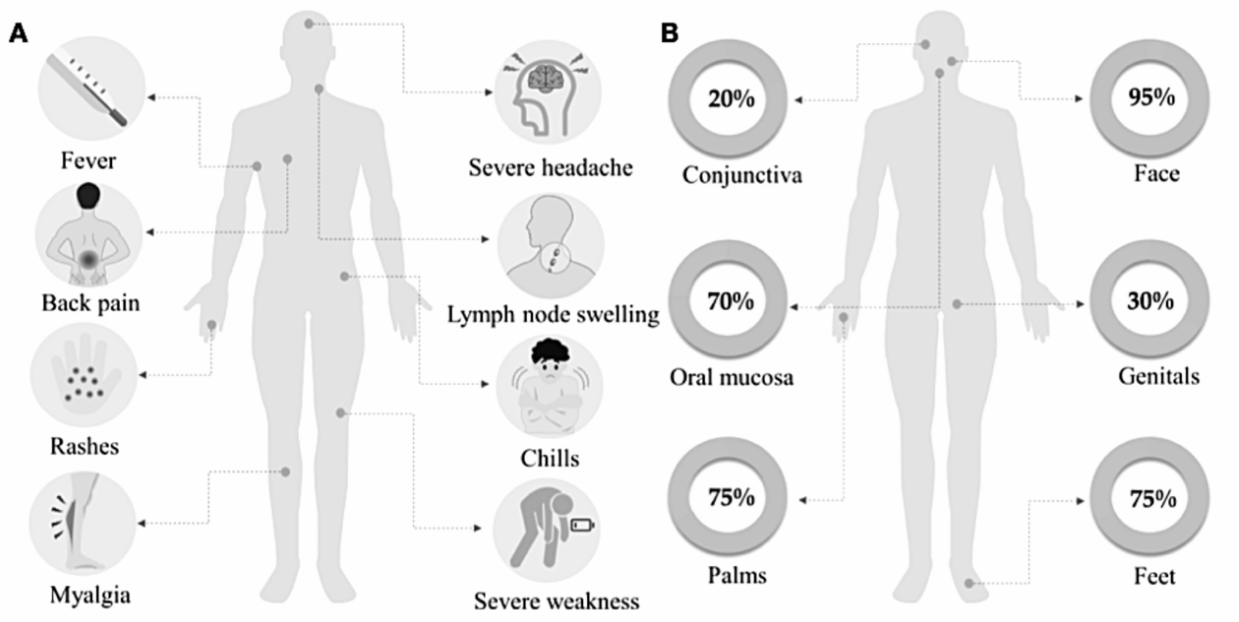

Figure 1. (A) Clinical Mpox symptoms. (B) Rash distribution (Reproduced from Wang *et al.*, 2023, Frontiers in Immunology, 14, 1174223 [72]).

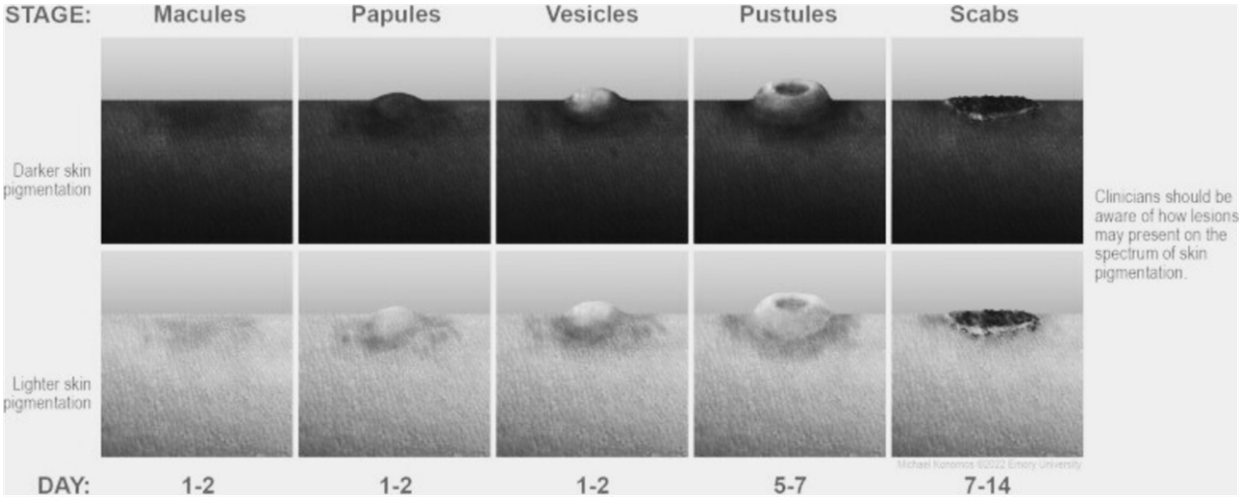

Figure 2. Stages of skin presentation and progression of monkeypox rash (Reproduced from Titanji *et al.,* 2022, Open Forum Infectious Diseases, 9(7), ofac310 [31]).

infection, bacterial superinfections and gastrointestinal involvement such as vomiting, and diarrhea with dehydration [33, 36, 37]. Additionally, ophthalmic manifestations like conjunctivitis, blepharitis, keratitis, or corneal lesions represent rare serious long MPX complications that can cause loss of vision [32, 38, 39]. Often, severe neurological complications such as encephalitis, seizures, cranial nerve palsy, Guillain-Barre syndrome, hemiplegia, and coma can be observed in some Monkeypox-infected cases [28, 40, 41]. These complications are more common in younger children (more than eight years) and adolescents, pregnant women, homosexual and bisexual males, and immunocompromised patients, particularity those with AIDS [42-45].

Tests and diagnostic

Diagnostic testing, which is currently performed at the Centers for Disease Control and Prevention (CDC) or State Health Departments (SHD) [21] is very important to detect the early stage of infection and to control actual outbreaks [41, 46]. Diagnostic efficiency is typically reliant on collecting specimens from skin exudates, vesicular lesions, or crusts, which must be promptly preserved in a sterile and dry tube, and on the type of laboratory test [13, 42]. Virological diagnosis and detection have many approaches (Figure 3) [47].

Electron microscopy observation

Electron microscopy can be used to visualize potential Poxvirus in a sample [13]. Unfortunately, this method is limited because it is expensive, the operation is extremely complex and takes time [33]. Furthermore, it faces challenges in distinguishing MPXV from other Poxviruses, given their significant morphological similarities [48].

Serology

The specific IgM and IgG antibodies in the serum of MPX patients after five and eight days of infection can be detected by the use of enzyme-linked immunosorbent assay (ELISA) technique [41, 48]. Scientifically, a positive IgM indicates a recent exposure to MPXV in both vaccinated and unvaccinated people, while a positive IgG indicates a previous exposure to the virus from either immunization or infection [20]. This serological technique should not be used alone for diagnosis [13] because of cross-reactivity between *Orthopoxviruses* and the possibility for false-positive results in those with prior smallpox vaccination [16, 21], but it is very useful for epidemiological purpose, especially for monitoring Monkeypox epidemics in non-endemic areas [49], and also useful owing to its advantages such as rapid detection, simple operation, lack of need for a special equipment, and low cost [50].

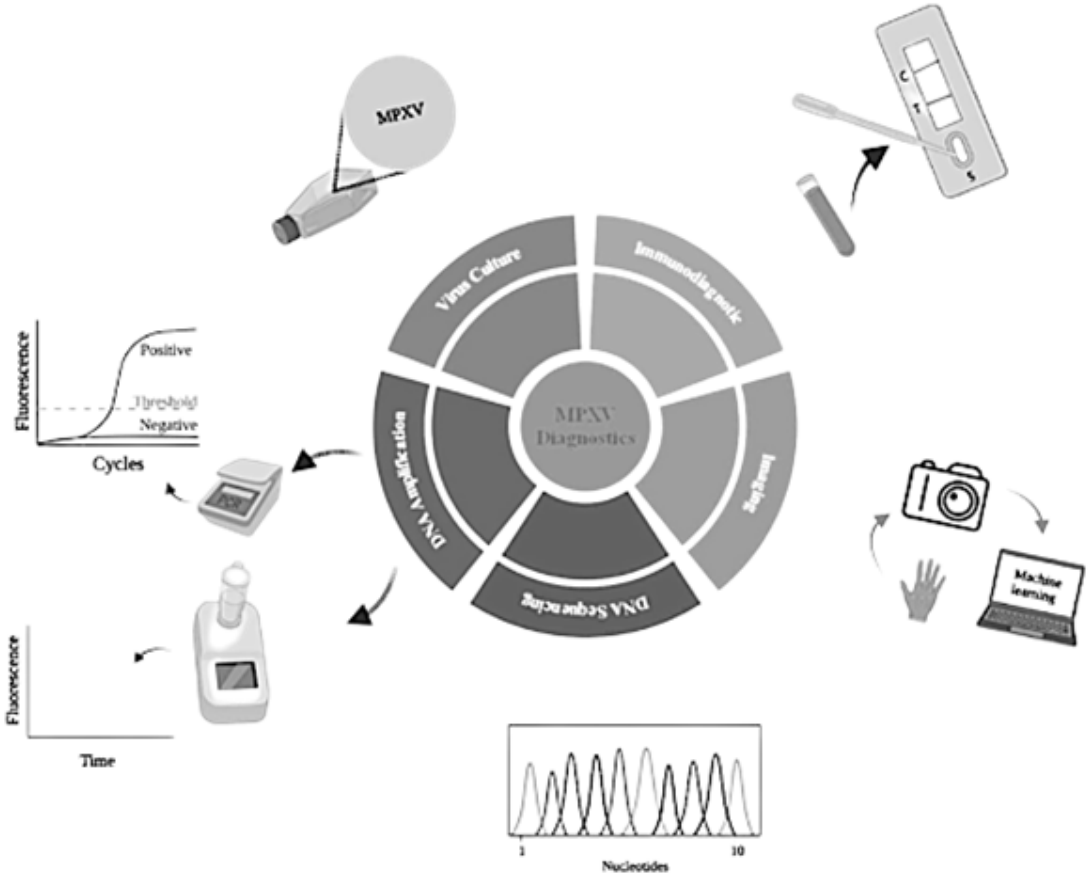

Figure 3. Schematic representation of current methods for the detection of MPXV (Reproduced from Gul *et al*., 2022. Bioengineering, 9(10), 571 [73]).

Nucleic acid detection technology

Real-time reverse-transcription polymerase chain reaction (RT-PCR) principle is based on the detection of specific components of the MPXV genome like conserved regions of extracellular envelope protein gene (B6R), DNA polymerase-gene E9L, DNA-dependent RNA polymerase subunit 18 (RPO18) genes, and complement binding protein C3L, F3L, and N3R [33, 41]. According to the WHO, RT-PCR is the preferred method for the detection of this emerging virus [7] not only due to its efficiency and sensitivity but also because it shows positivity from 2 days to 20 days (median 5 days) after the onset of clinical symptoms [20, 42]. But the difficulties of RT-PCR lie in the need for high-quality labs which are hard to be found in low resource countries [17]. Moreover, some real-time PCR can discriminate between the two MPXV clades [Congo Basin or Central Africa (CA, Clade I) and West Africa (WA, Clade II)] [41], and it can be used in combination with others technique such as recombinase polymerase amplification (RPA), loop-mediated isothermal amplification (LAMP) technology, and restriction-fragment-length polymorphism (RFLP) [51, 52].

Preventive and therapeutic approaches

Disinfectants and antiseptics play a significant role in fighting emerging viruses that persist on surfaces and can transfer directly to susceptible individuals [53]. Moreover, boosting the immune system, which combats emerging viruses and diseases, using functional food and bioactive compounds such as Zinc would be a desideratum [54]. Furthermore, to fight the Monkeypox infection, it is necessary to find supportive care and symptomatic treatments [20]. To date, there are

no treatments specifically approved by the US Food and Drug Administration (US-FDA) for this contagious infection [31].

Drugs

Due to the genetic and antigenic similarity between *Orthopoxviruses* [55], smallpox antiviral drugs like Tecovirimat, Brincidofovir, and Vaccinia Immune Globulin Intravenous (VIGIV) might be beneficial for treating Monkeypox [56], although they can cause undesirable side effects (Table 1).

Tecovirimat (ST-246, TPOXX)

Tecovirimat is an oral intracellular inhibitor drug [9, 33] which was approved by the US-FDA for the treatment of smallpox in adults and children [13, 21]. Therefore, it was licensed in 2022, by the European Medicines Agency (EMA) to treat MPX infection. It blocks the final step of virus maturation by targeting the Vp37 viral protein which is responsible for the virulence through the formation of the viral envelope and the release of this mature virus into the outer environment [19, 57].

Cidofovir (Vistide)

Cidofovir is an acyclic nucleoside monophosphate (cytosine analogue) [32]. It was approved by the FDA in 1996, to treat Cytomegalovirus (CMV) retinitis in people with AIDS [12, 31]. Thus, the US-CDC allowed this drug to treat *Orthopoxviruses* during the outbreak [13, 58], and it gave positive results when scientists tested its ability to treat this virus in an animal model [21]. Hence, at the cellular level, this medicament was transformed into Cidofovir-diphosphate (CDV-PP) which inhibits the synthesis of viral DNA polymerase in the form of a substitute matrix and eventually blocks viral DNA synthesis at the DNA polymerase level [33].

Brincidofovir (CMX001, Tembexa)

CMX001 is a lipid conjugate of Cidofovir [59], characterized by a very long half-life and greater selective index (SI) (the relationship between the antiviral dose necessary to reduce viral replication by 50% (EC50) and cytotoxic dose (CC50); the value obtained in SI allows estimating drug safety level for use in animals) which was at least 25-fold higher than Cidofovir [19, 48, 60]. It was approved by the EMA and the US FDA to treat smallpox in adults and children, including newborns [13, 31]. In addition, it acts by inhibiting DNA polymerase after incorporation into viral DNA [19].

Vaccinia immune globulin intravenous (VIGIV)

VIGIV is licensed by the FDA for the treatment of complications due to vaccinia infection, including eczema vaccinatum, progressive vaccinia, and severe generalized vaccinia [31, 41]. This drug contains the pooled polyclonal immunoglobulins that have been purified from the plasma of thousands of healthy donors, where immunologically, it improves the immune response by decreasing macrophage activity, reducing endogenous antibody production, inhibiting auto-reactive T cells, and balancing cytokine profile [59]. The CDC has an expanded access protocol that authorizes the use

Table 1. Side effects of potential drugs for Monkeypox infection [31].

Drug	Side effects and adverse vents
Tecovirimat	Intravenous use: pain and swelling at infusion site, extravasations at infusion site, headache. Oral use: headache, abdominal pain, nausea, vomiting.
Cidofovir	Nephrotoxicity, neutropenia, decreased intraocular pressure, nausea, vomiting.
Brincidofovir	Abdominal pain, nausea, vomiting, diarrhea, elevated liver transaminases and bilirubin.
VIGIV	Infusion reaction; local injection-site reaction (contraindicated in persons with IgA deficiency and possible IgA hypersensitivity).

of VIGIV to treat *Orthopoxviruses* during an outbreak, but to date, there is no evidence that VIG is effective against Monkeypox [12].

Vaccines

To date, vaccines are the most effective method to prevent and fight emerging viruses and diseases [61, 62], since the discovery of vaccination by Edward Jenner in 1769, after finding the possibility to vaccinate against smallpox [63]. Sadly, the different nature of emerging virus, limited resources, the long time to develop and test vaccines, and manufacturing problems cause the lack of vaccine availability for most emerging pathogens [62, 64, 65]. Yet, even if they exist, they would not be available for everyone [66].

Monkeypox vaccines represent the second and third generation of smallpox vaccines [67]. The US and the UK were the first countries to pursue vaccination to close contacts of MPX cases in the 2003, 2018 and 2019 outbreak. Afterwards, more and more countries like Canada, decided to offer vaccination to people exposed to MPXV or at risk of acquiring it [38, 68].

Second-generation vaccine (ACAM 2000)

ACAM 2000 is a live vaccinia virus preparation [26] that was demonstrated in the US, in 2003, to reduce MPXV symptoms during the outbreak [33]. Subsequently, its use was licensed by the FDA in August 2007, [69]. The strategic national stockpile (SNS) has over 100 million doses of ACAM2000 that are immediately available in its inventory [57]. This vaccine involves one dose and peak vaccine protection is conferred within 28 days [41]. It can cause lesions in injection sites which can spread to other sites or peoples, while also carrying the potential for adverse outcomes like progressive vaccinia, eczema vaccinatum, and myopericarditis [12]. As a result, it is not available to the public, especially for individuals with immunodeficiency such as atopic dermatitis and AIDS, and in MPXV endemic areas [33, 59].

Third generation vaccine (JYNNEOS and IMVAMUNE)

JYNNEOS is a live viral vaccine produced from the modified vaccinia Ankara-Bavarian Nordic (MVA-BN strain) [69]. It can cross-react and generates immune protection against MPXV [57]. In 2019, the US FDA approved the use of this vaccine against emerging diseases [70]. As a result, the U.S. recently distributed 1200 doses of the JYNNEOS vaccine from its national stockpile across the U.S. for people who have had high-risk exposures to Monkeypox [57]. This vaccine involves two vaccine doses 28 days apart, and vaccine protection is not conferred until two weeks after receipt of the second dose [41], and it can be used in patients with atopic dermatitis and immunodeficiency persons [33]. Finally, in June 2022, over 300,000 doses were distributed mainly, among males aged 25-39 years [71].

CONCLUSION

Lessons learned from the COVID-19 pandemic must be followed, including conducting epidemiological investigations, understanding the first cases of outbreaks, ensuring large availability of testing points and treatment options, as well as disseminating correct information, all of which are essential focal points for combating and averting extensive global outbreaks. Unfortunately, after more than two years of COVID-19 devastating impact on our lives, the perpetual concern over potential viral epidemics remains ever-present, especially for the Monkeypox disease. Will history repeat itself with another COVID-19 pandemic? Only time holds the answer to this uncertain future.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

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AUTHORS' CONTRIBUTIONS

Ilyes Zatla: Conceptualization, manuscript editing, manuscript review, supervision of the project.

Lamia Boublenza: Manuscript review, supervision of the project.

Wafa Abid: Literature search, manuscript writing, manuscript editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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