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REVIEW ARTICLE

Monkeypox Disease with a Focus on the 2022 Outbreak; a Narrative Review

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Abstract: Monkeypox is a zoonotic disease caused by a double-stranded DNA virus belonging to the genus *Orthopoxvirus*. Despite being endemic in Central and West Africa, the disease has received relatively little research attention until recent times. As the Coronavirus disease 2019 (COVID-19) pandemic continues to affect the world, the rising number of monkeypox cases in non-endemic countries has further stoked global public health concerns about another pandemic. Unlike previous outbreaks outside Africa, most patients in the present outbreak had no history of travel to the endemic regions. The overwhelming majority of patients were initially identified amongst homosexual men, who had attended large gatherings. Mutations in the coding regions of the viral genome may have resulted in fitness adaptation, enhancement of immune evasion mechanisms, and more efficient transmissibility of the 2022 monkeypox virus. Multiple factors such as diminished cross-protective herd immunity (cessation of smallpox vaccination), deforestation, civil war, refugee displacement, farming, enhanced global interconnectedness, and even climate change may facilitate the unexpected emergence of the disease. In light of the increasing number of cases reported in the present outbreak, healthcare professionals should update their knowledge about monkeypox disease, including its diagnosis, prevention, and clinical management. Herein, we provide an overview of monkeypox, with a focus on the 2022 outbreak, to serve as a primer for clinical practitioners who may encounter the disease in their practice.

Keywords: Monkeypox; Disease Outbreaks; Diagnosis; Vaccination; Therapeutics

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1. Introduction

As the Coronavirus disease 2019 (COVID-19) pandemic continues to rage, a second public health threat is lurking in the shadows: a global outbreak of monkeypox. Emerging and re-emerging zoonotic diseases such as COVID-19, monkeypox, Ebola, and Zika still levy an unmercifully heavy toll upon human health worldwide (1). As previously thought to be confined to Africa, monkeypox is now causing a worldwide outbreak. The disease disproportionately has affected males who have had sex with males. In spite of being endemic in West and Central Africa, monkeypox has lately emerged in numerous non-endemic countries, evoking a great deal of concern. Only few cases had been detected outside of Africa prior to 2022. On 23 July 2022, the World Health Organization (WHO) declared monkeypox a public health emergency of international concern (2). Currently, healthcare professionals are learning about the clinical presentations and treatment of monkeypox infection as public health agencies strive to contain the ongoing outbreak.

Due to a lack of control over the spread of monkeypox in endemic African countries, the disease is now spreading to non-endemic countries. The 2022 monkeypox outbreak outside of Africa is currently the largest in history (3). Given the fact that the number of confirmed cases in the present outbreak is on the rise, clinicians ought to extend their knowledge of this disease, including prevention, clinical management, prophylaxis, and basic infection control (4). Furthermore, COVID-19 and monkeypox may occur coincidentally, which should be taken into account. As a result, both or one of the diseases may experience changes related to infection pattern, severity, management, or response to vaccination. Professionals need to update their knowledge of the monkeypox, including its prevention, clinical diagnosis, control, and management, to fully comprehend the consequences of the disease (5). In this paper, we intend to provide an overview of monkeypox virus infection with a focus on the 2022 outbreak.

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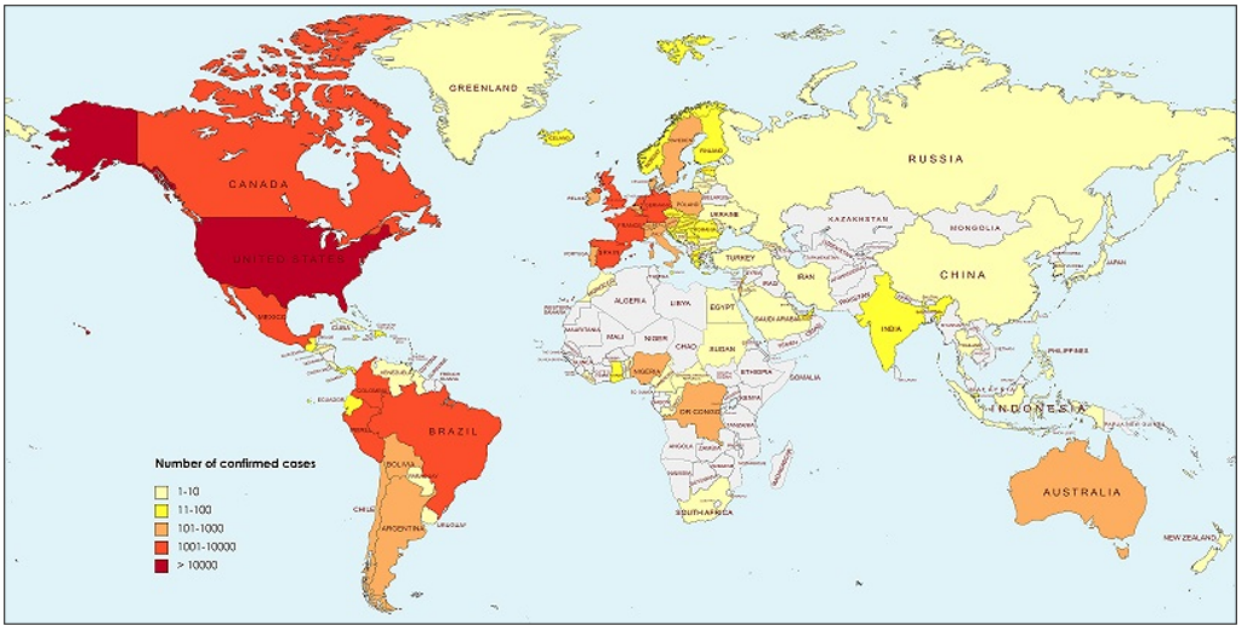

Figure 1: A global map of confirmed monkeypox cases as of September 26, 2022. Countries with confirmed cases are as follows: Andorra (n = 4), Argentina (n = 326), Aruba (n = 3), Australia (n = 135), Austria (n = 307), Bahamas (n = 2), Bahrain (n = 1), Barbados (n = 1), Belgium (n = 757), Benin (n = 3), Bermuda (n = 1), Bolivia (n = 164), Bosnia and Herzegovina (n = 3), Brazil (n = 7300), Bulgaria (n = 6), Cameroon (n = 8), Canada (n = 1389), Central African Republic (n = 8), Chile (n = 783), China (n = 1), Colombia (n = 1653), Costa Rica (n = 4), Croatia (n = 29), Cuba (n = 2), Curaçao (n = 3), Cyprus (n = 5), Czechia (n = 66), Democratic Republic of the Congo (n = 195), Denmark (n = 183), Dominican Republic (n = 31), Ecuador (n = 93), Egypt (n = 1), El Salvador (n = 4), Estonia (n = 11), Finland (n = 33), France (n = 3970), Georgia (n = 2), Germany (n = 3601), Ghana (n = 84), Gibraltar (n = 6), Greece (n = 72), Greenland (n = 2), Guadeloupe (n = 1), Guatemala (n = 18), Guyana (n = 2), Honduras (n = 6), Hong Kong (n = 1), Hungary (n = 77), Iceland (n = 12), India (n = 12), Indonesia (n = 1), Iran (n = 1), Ireland (n = 178), Israel (n = 250), Italy (n = 842), Jamaica (n = 14), Japan (n = 4), Jordan (n = 1), Latvia (n = 5), Lebanon (n = 11), Liberia (n = 3), Lithuania (n = 5), Luxembourg (n = 55), Malta (n = 33), Martinique (n = 1), Mexico (n = 1367), Moldova (n = 2), Monaco (n = 3), Montenegro (n = 2), Morocco (n = 3), Netherlands (n = 1221), New Caledonia (n = 1), New Zealand (n = 9), Nigeria (n = 277), Norway (n = 91), Panama (n = 13), Paraguay (n = 1), Peru (n = 2311), Philippines (n = 4), Poland (n = 173), Portugal (n = 917), Qatar (n = 5), Republic of the Congo (n = 5), Romania (n = 39), Russia (n = 2), Saint Martin (n = 1), Saudi Arabia (n = 8), Serbia (n = 40), Singapore (n = 19), Slovakia (n = 14), Slovenia (n = 46), South Africa (n = 5), South Korea (n = 2), Spain (n = 7083), Sudan (n = 7), Sweden (n = 186), Switzerland (n = 503), Taiwan (n = 3), Thailand (n = 8), Turkey (n = 1), Ukraine (n = 3), United Arab Emirates (n = 16), United Kingdom (n = 3585), United States (n = 25161), Uruguay (n = 6), Venezuela (n = 5). [according to the data obtained from https://www.cdc.gov/poxvirus/monkeypox/response/2022/world-map.html].

2. Virology

Being an enveloped double-stranded DNA virus, monkeypox virus belongs to *Orthopoxvirus* genus of the *Poxviridae* family. Several different poxviruses have been proven to cause infections in human beings including, but not limited to, Variola (smallpox), Cowpox, Monkeypox, Vaccinia, and Molluscum contagiosum virus (6). Small mammals and rodents are the natural hosts of monkeypox virus. As a result of its wide spectrum of potential hosts, monkeypox virus circulates for long periods in the wild, while occasionally causing disease in humans by spillovers (7).

Monkeypox virus exhibits a brick-like structure of around 200 nm × 200 nm × 250 nm, with a genome size of approximately 197 kbp (8). While most of the genes encoded by the viral genome are not indispensable for multiplication in cell culture, they may bestow upon the virus the ability to defend against host immunity (4). Virus replication takes place in the cytoplasm of infected cells through complex molecular pathways. At each end of the viral genome, there exist identical but oppositely oriented terminal reads of around 6 kbp, with a set of short tandem repeats and terminal hairpin loops. Moreover, the monkeypox genome encompasses approximately 190 non-overlapping open reading frames of >180 bp in length, encompassing ≥60 amino acids (9). Housekeeping genes, including those contributing to transcription, replication, and assembling virus particle, are all encoded by the central conserved region (8). As with other orthopoxviruses, the monkeypox DNA has a low G/C content (about 31%) (9). Monkeypox virus has been divided into at least two distinct genetic clades, Clade 1 (the former Congo Basin or Central African clade) and Clade 2 (the former West African clade).

Geographic, clinical, genomic, and epidemiological characteristics also differ from clade to clade (10). Genomic analyses indicate that a new strain is associated with the ongoing outbreak. This strain is diverged from Clade 2 by almost 50 single nucleotide polymorphisms (SNPs) (11). In other words, the current circulating virus is phylogenetically close to Clade 2, but it differs enough from Clade 2 to be classified as Clade 3. As opposed to Clade 1, Clade 2 exhibits reduced pathogenic characteristics and less transmissibility with lower case fatality rates (12). Recent phylogenetic studies divulged that the 2022 outbreak cluster (lineage B1) diverged from the lineage A1 during microevolutionary changes following the virus exportation from Nigeria to Britain, Israel, and Singapore in 2017–2019 (11).

3. A brief history of monkeypox

Monkeypox is endemic to tropical rainforests in Central and West African countries. The disease has received relatively little research attention in spite of being endemic in these regions. The monkeypox virus was first identified in the late 1950s in Danish primate research facilities. Later, a child in the Democratic Republic of Congo (DRC) became the first human case in 1970. Since 1970s, there have been cases reported from 10 African countries (13). A detailed discussion of the previous outbreaks is beyond the scope of this paper. The epidemiology of these cases and outbreaks between 1970 and 2019 is summarized in a systematic review by Bunge et al. (2022) (14). Most cases occur sporadically or in connection with localized outbreaks. In the Congo basin, nearly 30,000 cases of monkeypox, with a few hundred deaths, have been reported since the 1970s. In the 1980s, the most common source of infection was animal contact (72%), while human contact explained 78% of cases in the 1990s. Before the 1990s, almost all deaths occurred in children under 10 years of age. Since then, this rate has decreased to 35%. There is a possibility that this change may be due to the waning of cross-protective effects provided by previous smallpox vaccinations (15). Transmission is thought to occur through inhalation of respiratory droplets, direct contact with skin lesions, exposure to contaminated body fluids (e.g. breastmilk, seminal fluid, blood, respiratory droplets), and even through contaminated fomites (16).

Monkeypox affects the DRC more than any other country, and no other country has reported cases continuously over the past 50 years. Cases outside of endemic countries are usually associated with international travel or importations of infected animals (14). As a result of the 2003 outbreak in the United States, linked to infected pet prairie dogs, the disease has grown to become a global public health concern. Infected individuals became sick when they came into contact with pet prairie dogs that were initially kept with rodents imported from Ghana in Western Africa (17). Over the past few years, Nigeria has been the source of several travel-associated monkeypox cases. In this respect, three cases were reported in the United Kingdom (UK) in 2018 and 2019, one in Israel (2018) and one in Singapore (2019). There was a fourth case in the UK (2018) caused by nosocomial transmission (14). Many different theories have been put forward as to why monkeypox cases have been on the rise in the last few decades. It seems that factors such as diminished cross-protective herd immunity (cessation of smallpox vaccination), deforestation, civil war, refugee displacement, farming, enhanced global interconnectedness, and even climate change contribute to these outbreaks (18).

4. The ongoing global outbreak

There was a monkeypox case reported in the UK on 6th May 2022, a traveler who had recently returned from Nigeria. Since then, an increasing number of patients were identified in over 100 countries (Figure 1) across the globe (19). As of September 26, 2022, more than 65900 confirmed cases were reported worldwide (Figure 2a), 26 of whom succumbed to death (Figure 2b). Following reports of racist and stigmatizing language surrounding the name of the disease, the World Health Organization (WHO) has changed the name of monkeypox to mpox in November 2022 (20). Unlike previous outbreaks outside Africa, the majority of patients in the present outbreak had no travel history to the endemic countries. The disease is primarily observed among men who had sex with men attending large gathering events. It is speculated that an undetected chain of infections may have been responsible for the unpredictable resurgence of outbreaks across the globe (21). The outbreak dynamics are therefore complicated by this, which enlightens the need for urgent global surveillance. Besides, non-synonymous mutations in the coding regions of the viral genome (e.g. B21 protein; an important antibody target with several key immunodominant epitopes) may have resulted in fitness adaptation, enhancement of immune evasion mechanisms, and more efficient transmissibility of the monkeypox virus (11). Researchers also noticed that certain mutation patterns in the 2022 monkeypox viruses matched the types of mutations that apolipoprotein B mRNA-editing catalytic polypeptide-like 3 (APOBEC3) enzymes would introduce (12).

5. Clinical features and differential diagnosis

Although most cases of monkeypox are self-limited (lasting between 2 and 4 weeks), severe cases do occur, with a fatality rate of 3–10%. The median incubation period for monkeypox infection is usually 7 days (22). Typically, the disease is

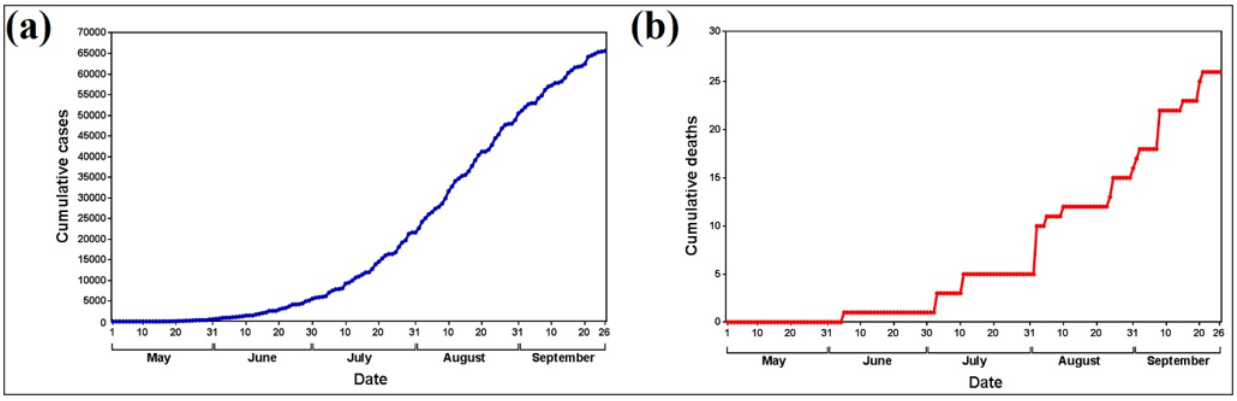

Figure 2: Cumulative number of confirmed cases (a) and deaths (b) related to the monkeypox as of September 26, 2022 [according to the data obtained from https://www.cdc.gov/poxvirus/monkeypox/response/2022/world-map.html].

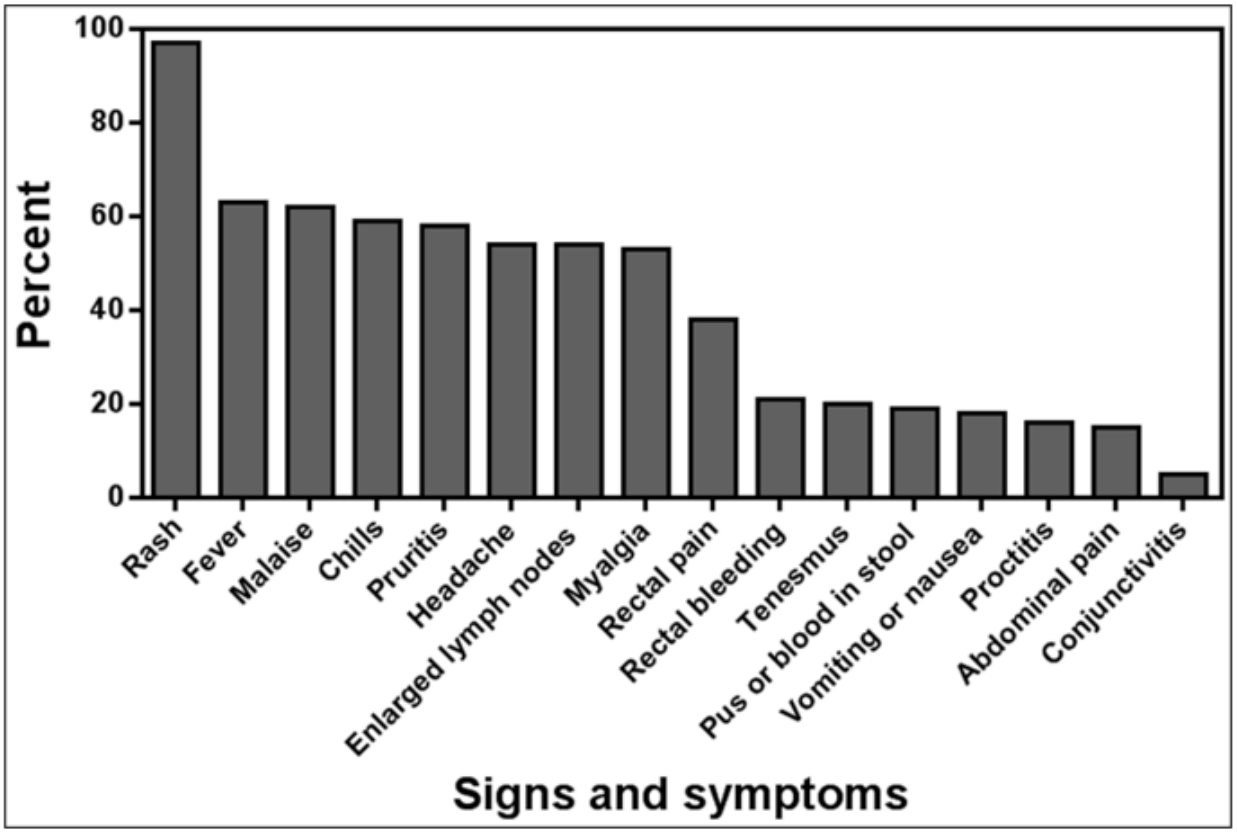

Figure 3: Clinical symptoms of the 2022 monkeypox disease. [according to the data obtained from https://www.cdc.gov/poxvirus/monkeypox/response/2022/demographics.html].

associated with a febrile prodrome phase (characterized by fever, headache, malaise, fatigue, and lethargy), followed by a rash that may appear anywhere on the body (Figure 3). The rash starts on the face and then spreads centrifugally to other parts of the body (23). The majority of them occur on the face and extremities, affecting palms, oral mucosa, genitals, and conjunctiva. The rash progresses through four morphological stages: macular, papular, vesicular, and pustular. At any given time, the lesions are in the same stage of progression (a useful characteristic for distinguishing chickenpox from this condition). Pustules eventually form crusts that desquamate after a couple of weeks (22). That said, many homosexual men have reported painless anogenital lesions associated with the monkeypox during the present outbreak, often with-

out a prodrome, after close contact with an infected individual (24).

A bewildering array of infectious diseases can imitate the symptoms of monkeypox. In the early stages of the infection, the signs and symptoms are analogous to those of smallpox; however, unlike smallpox, lymphadenopathy is a prominent feature. Lymphadenitis occurs primarily in sub-mental, submandibular, cervical, and inguinal regions. In clinical practice, genital sores could easily be mistaken for lesions caused by certain sexually-transmitted diseases including syphilis, genital herpes, chancre, and lymphogranuloma venereum (25). Physicians should also be cognizant of co-infection with other viral diseases such as varicella-zoster or human immunodeficiency virus (HIV). As a result of the monkeypox disease, complications such as secondary bacterial infections, sepsis, myocarditis, bronchopneumonia, encephalitis, sight-threatening keratitis may also occur (26). The risk of experiencing severe illness is higher in children, especially those who have eczema, pregnant women, and individuals who have immunocompromising conditions (27). The gold standard for its diagnosis is PCR assay of lesion specimens, and this is the first test that should be performed. Fluid from vesicles and pustules, along with dried crusts, are the best diagnostic samples. Additionally, a biopsy is an option when possible (28). Viral DNA may also be found in saliva, blood, urine, feces, and nasopharyngeal swabs (29). PCR amplification usually targets the conserved regions of extracellular envelope protein (B6R), DNA polymerase E9L, DNA-dependent RNA polymerase subunit 18 (RPO18), and complement binding protein C3L, F3L, and N3R genes (30).

Specific confirmation of monkeypox cannot be achieved via antibody and antigen detection methods, because members of the *Orthopoxvirus* are serologically cross-reactive. After 5 and 8 days of infection, monkeypox patients can be tested for IgM and IgG specific antibodies using enzyme-linked immunosorbent assay (ELISA). However, these procedures are not recommended for diagnosis or case investigation when resources are limited (31). Overall, serological tests are helpful in epidemiologic investigations, retrospective diagnosis of past infections, and diagnosis of late clinical manifestations (e.g. encephalitis). Although serology tests may cross-react with a prior smallpox vaccination, unvaccinated individuals should not be concerned (4).

6. Clinical management

Most monkeypox cases, particularly in the ongoing outbreak, are mild and self-limited. Thus, supportive care usually suffices without any medical intervention (32). Nevertheless, the prognosis is affected by a number of factors such as the initial clinical presentation, the presence of comorbidities, and the status of previous vaccinations. The main objective of supportive care is to maintain an adequate fluid balance. If necessary, other measures should be considered, including hemodynamic support, supplemental oxygen, and treatment of bacterial secondary infections (4).

Currently, there is no specific monkeypox treatment approved by the US Food and Drug Administration (FDA). Nevertheless, several drugs including tecovirimat, brincidofovir, and cidofovir may be considered for anti-viral therapy in patients suffering from severe diseases (e.g. hemorrhagic disease, confluent lesions, sepsis, encephalitis, or other conditions requiring hospitalization) or in individuals who are at a high risk of severe diseases or complications (e.g. immunocompromised patients, children, people with severe skin conditions, and pregnant or breastfeeding women) (31, 33). The antiviral drug of choice is tecovirimat. The drug blocks the final maturation and release of virions by inhibiting the viral envelope protein VP37. Brincidofovir, an analogue of the intravenous drug cidofovir, is a new medication for the treatment of human smallpox disease in adult and pediatric patients. It acts as a viral DNA polymerase inhibitor (30). A prophylactic intravenous dose of vaccinia immune globulin (VIGIV) may also be beneficial for patients with severe monkeypox infections or individuals with T-cell immunodeficiency when smallpox vaccination is contraindicated (34).

7. Prevention

In order to prevent the infection, vaccination is the first line of defense (31). However, the high rates of adverse events associated with live, attenuated virus vaccination limit their general use, in spite of providing effective protection (31). Post-exposure prophylaxis (vaccination following monkeypox exposure for those at risk) and pre-exposure prophylaxis (vaccination against monkeypox for those at high risk of exposure, such as laboratory workers performing monkeypox diagnostic testing) can be considered after a careful assessment of the risks and benefits (35).

There are currently two smallpox vaccines licensed in the United States: ACAM2000® (Emergent Product Development Gaithersburg, MD, USA), and JYNNEOS™ (Bavarian Nordic, Hellerup, Denmark). JYNNEOS™ is an attenuated, non-replicating *Orthopoxvirus* vaccine derived from modified vaccinia Ankara-Bavarian Nordic (MVA-BN strain). It was licensed by the US FDA in September 2019 and is now indicated for prevention of smallpox and monkeypox disease (36, 37). ACAM2000® is a live, replication-competent vaccinia virus. These two vaccines differ significantly. There is a risk of serious adverse events associated with ACAM2000® (e.g. eczema vaccinatum, myopericarditis, and post-vaccine encephalitis) because it is replication-competent. In contrast, there are fewer contraindications with JYNNEOS™,

and there is no risk of inadvertent inoculations and auto-inoculations (31, 37). In JYNNEOS^{TM}, two vaccine doses are administered 28 days apart, with vaccine protection conferred after two weeks. On the other hand, vaccination with ACAM2000® involves one dose and provides peak protection within 28 days (30).

8. Conclusions

As global cases of monkeypox continue to rise in many countries, it is possible that the virus has evolved to become more transmissible during this outbreak. Although the COVID-19 pandemic is not yet expected to be exacerbated by the outbreak of monkeypox, it is imperative for the public healthcare authorities to establish a nationwide surveillance system as well as taking appropriate pre-cautionary measures before the ongoing monkeypox outbreak creates a critical situation. In order to control the disease, regional capacity should be strengthened for early detection, prevention, and management in developing countries, because vaccines and drugs are not readily available. Currently, all efforts should be concentrated on preventing the entry of monkeypox into healthcare facilities that are still dealing with the effects of the ongoing COVID-19 pandemic. Finally, physicians need to keep a high index of clinical suspicion for the monkeypox disease and follow the standard protocols for diagnosis, reporting, and isolation.

9. Declarations

9.1. Acknowledgments

Not applicable.

9.2. Conflict of interest

The authors declare that they have no conflict of interest.

9.3. Funding information

None.

9.4. Authors Contribution

Reza Mahmoud Robati and Hamideh Moravvej contributed to the study's conception and design. Data collection was performed by Zohreh Tehranchinia and Hamideh Moravvej. The first draft of the manuscript was written by Mojtaba Memariani, Zohreh Tehranchinia, and Hamed Memariani and revised by Reza Mahmoud Robati. All authors read and approved the final manuscript.

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