Monkeypox Virus: A comprehensive narrative review

Hassan S, Paudyal N, Emaan A, Ibrahim S

Nobel Medical College Teaching Hospital

Kanchanbari, Morang, Biratnagar.

Corresponding Author

Seema Hassan,

Nobel Medical College Teaching Hospital,

Kanchanbari, Morang, Biratnagar.

E-mail: seema22hassan@gmail.com

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ABSTRACT

Monkeypox virus, now known as Mpox virus is a large, enveloped, double stranded deoxyribonucleic acid (DNA) virus belonging to the Orthopox viridae genus of the Poxviridae family. Though, Mpox, have earlier been endemic to only African countries, the 2022 outbreak has shown its rapid spread throughout the world. The May 2022 outbreak have shown primarily human to human transmission in contrast to animal to human transmission that had been seen previously. Recent data also suggest a possibility of a pre symptomatic spread. After an incubation period of 9 days, patients with Mpox can present with a prodrome of symptoms followed by a rash. If untreated, severe complications develop in the high-risk groups especially children and pregnant woman. Such groups of people will benefit from antiviral treatments. The current approach to prevent against it is pre-exposure and post exposure prophylaxis with vaccines. The vaccines that have been approved by Food and Drug Administration to date is ACAM2000 and JYNNEOS. Several diagnostic methods exist, among which polymerase chain reaction has proven to be the most specific and sensitive. In this review, we will discuss its epidemiology, the clinical manifestations, diagnostic modalities, complications, treatment approaches and preventive measures.

KEY WORDS

Monkeypox, Outbreak, Pandemic, Prophylaxis, Transmission

INTRODUCTION

Monkeypox virus (MPXV), formerly named Monkeypox virus is a large, enveloped, double stranded deoxyribonucleic acid (DNA) virus belonging to the Orthopox viridae genus of the Poxviridae family.[1,2] Poxviridae family is subclassified into Entomopoxvirinae and Chorodopoxvirinae subfamily based on whether the virus infects vertebra or insects.[2] Mpox (MPX) belongs to this Chorodopoxvirinae subfamily. The major host of MPXV are rodents, rabbits, and non-human primates and occasionally humans.[3]

Since the first incidence of human infection was discovered, and up until 2003, human cases of MPXV have primarily been reported in Central and West Africa. However, cases have started to emerge from other corners of the world. As Monkeypox is comparable to smallpox and has the potential to create epidemics, it is considered a public health concern. Surveillance and monitoring are important in detecting and controlling outbreaks of disease.

METHODS

The authors searched PubMed, Google Scholar using the key words such as monkeypox. We included case reports, case series, retrospective studies, systemic reviews, clinical guidelines, narrative reviews and online resources. The literature search was restricted to studies and resources published in English. A total of 47 resources were selected for inclusion in this review.

HISTORY AND EPIDEMIOLOGY

MPX was initially found in Danish laboratory in 1958 during an outbreak amongst cynomolgus monkeys.[4-6] However, this virus was recognized as a human virus 12 years later when a nine-month-old infant became infected in Democratic Republic of Congo (DRC).[6,7] Ever since then, DRC continues to report outbreaks of MPX.

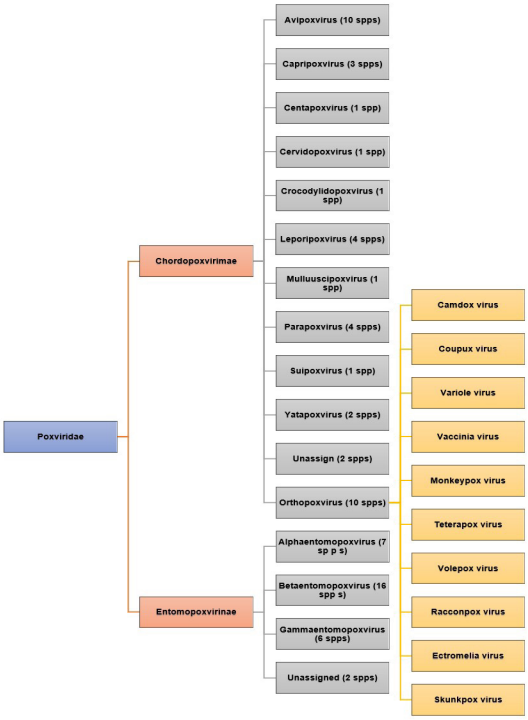

Figure 1. Taxonomy of poxviruses.

From 1970-1979, 47 human MPX cases were reported in 5 central and west African countries of which 38 were reported in DRC.[8] This all occurred in tropical rainforest areas and associated with animal contact. From 1981-1986, 338 cases were reported in DRC, most cases occurring in children with an average age of 4.4 years.[9,10] From 1986 onwards, number of MPX cases started declining. Only 13 cases were reported between 1986-1992, according to the WHO monitoring project. And no cases were reported between 1993-1995. However, by 1997, numbers increased to 88 confirmed cases.[11]

A total of 40 human MPX samples collected between 1970 and 2010 were classified into two distinct clades.[12] Isolates from the DRC, ROC, Gabon and Cameroon form the Congo Basin (CB) clade, and isolates from Nigeria, Cote d'Ivoire, Sierra Leone, Liberia and the USA (Ghana) form the West African (WA) clade. As MPX has emerged outside West Africa, discussion about the possibility of name change and the definitions of three clades are underway. The 3rd clade originated from the West African clade.[7]

The first reported incident of MPX outside Africa was in 2003 in USA after 800 mammals were shipped from Ghana to Texas.[13,14] After that it continued to spread to five other states. The 2nd epidemic outside the west African region was in 2005 which occurred in Sudan.[15]

In 2017, Monkeypox was rediscovered in Nigeria. This was after a 40 years gap between the last confirmed case of MPX from Nigeria. Between 2017 and 2021, 226 laboratory-confirmed cases and eight deaths (3.5% case fatality rate) due to MPX were reported in Nigeria. A number of cases were exported by international travel from Nigeria to USA and Europe between 2018 and 2021.[16]

Current outbreak

On May 6, 2022, the British resident traveling back from Nigeria to UK became the 1st index case of MPX in UK. On May 14, 2022, two additional cases of human MPXV were identified in London in two unrelated cohabitants of the previous case and new cases have been confirmed in the United Kingdom, in and outside of London.

A total of 86,516 laboratory confirmed cases and 1265 suspected cases, including 111 fatalities, have been reported to WHO as of March 14, 2023. A significant majority of these cases since May 13th, 2022, have come from nations where there is no history of MPX transmission. Cases and sustained chains of transmission have never before been documented in nations without immediate or direct epidemiological connections to regions of West or Central Africa.

In the months following August, the number of cases recorded weekly has dropped significantly from a worldwide peak of 7576 cases seen in the week of August 8, 2022.[17]

CLINICAL FEATURES

Routes of Transmission

- **Animal to human transmission**

Initially rodents and primates including monkeys were believed to be the hosts to the virus. In 2003, it was seen in the United States that the Prairie dogs that were kept together with infected Gambian rats and hamsters were associated with spread of MPX. This accounted to more than 70 cases of human infection.[18] MPXV can be transmitted to humans through bites from animals and contact with infected animals either living or dead or with their bodily fluids.[4]

- **Human to human transmission**

Broken skin is considered a primary source of infection including microscopic wounds. Infected fluids may also cause infection via eyes, nose or mouth. Individuals such as healthcare workers and veterinarians in contact with animal care takers are therefore at a higher risk of transmission.[18]

The virus can be transmitted via respiratory droplets; however, this requires face-to-face contact for an extended duration.[4] MPXV has been documented to be transmitted sexually in rare cases and it appears that the recent outbreak is mostly among men who have sex with men (MSM), gay and bisexual groups.[7]

There is limited evidence for congenital transmission of the disease. In one incidence at Congo, two out of four pregnant women who had prior Monkey Pox infection, had early fetal loss at 18 weeks period of gestation. The still born fetus had a skin rash and traces of MPXV DNA were isolated

from fetal and placental DNA. Another report from the USA in July 2002 however showed that a pregnant woman infected with MPX gave birth to a healthy baby. Therefore, these reports show that the vertical transmission is not always assured. Currently there is no evidence for risk of transmission via breast milk and breastfeeding.[18]

Clinical Manifestations

a. Incubation period and prodromal phase

Clinical manifestations occur after an incubation period of 3 to 34 days with a mean incubation period of 13 days.[7] The initial phase of illness also known as the invasion phase or prodromal phase is characterized by systemic illness.[19] This consists of fever, malaise, sweat, lymphadenopathy, arthralgia, myalgia, and headache.[19,20] According to findings from an ECDC-WHO analysis of data from 660 patients having at least one prodromal symptom, 49.0% had a localized lymphadenopathy.[7] The affected lymph nodes approximately 1-4 cm size, firm, painful and tender, involving the submandibular, cervical, axillary or inguinal regions occurring singly or in combination.[19] Lymphadenopathy in the early phase of the disease is helpful in differentiating it from chicken pox and smallpox.[7]

b. Eruptive phase

The second phase characterized by skin eruption occurs 2-4 days following the prodromal phase. The eruptive phase last for 14-28 days and during this time skin lesions appear in a centrifugal distribution. These lesions start as macules progressing through several stages of papules, vesicles, and pustules, which subsequently crust over and then desquamate.

Lesions predominantly affected the face (95% of infected people), palms and soles (75%), mucous membranes (70%), and, less commonly, genitals. Cornea and conjunctiva can be affected too.[20,21]

The rash is similar to the pleomorphic picture seen in chicken pox however, unlike the rash in chickenpox which appears at different stages at a given time, lesions of monkey pox are at the same stage of development.[7]

DISEASE COURSE AND PROGNOSIS

The disease is generally self-limiting with symptoms lasting from 2 to 4 weeks. Severity of the disease varies among patients vaccinated and unvaccinated against smallpox. A publication covering 282 patients of MPX in Congo region during 1980-1985 reported no deaths among patients vaccinated against smallpox while the mortality rate for unvaccinated patients was 11% with a large percentage of them being young children (15%).[5,19] Prognosis is also usually worse in patients with immunocompromised states, prolonged exposure to viral particles, and the presence of severe complications such as bronchopneumonia, encephalitis, and visual loss due to ocular infection.[6]

Comparison with current outbreaks

As of February 2023, new data showed the possibility of a pre-symptomatic spread of a monkey pox in the current global outbreak. Some people might infect others 1-4 days before they develop symptoms. Mpox have also been detected in people without any symptoms.[22]

Transmission is mainly sexual, especially among defined gay, bisexual or MSM groups. According to UK health security agency analysis, mean incubation period is 9.22 days.[7] Some patients present with rash without a prodromal period. The rash also progress at different rates in contrast to simultaneous progression. The distribution also differs, the newer pattern being more centripetal (presenting more on genital, anal and perianal regions) than centrifugal.

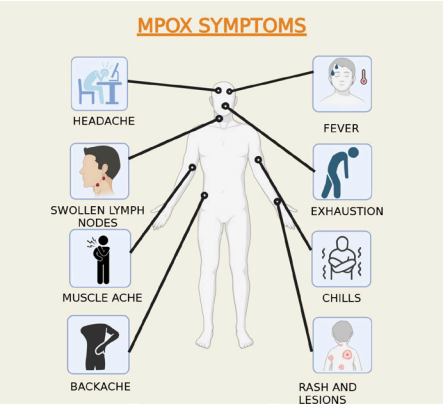

Figure 2. Clinical features of Mpox.

DIAGNOSIS

Those with the aforementioned clinical symptoms, travel history to endemic areas, and history of contact with symptomatic patients may have monkey pox. When a patient exhibits a sexually transmitted infection (STI)-related rash or when examining genital-ulcer illnesses, it should also be included in the differential diagnosis. Laboratory testing are used to confirm the diagnosis because the clinical signs are comparable to those of other pox virus diseases. Several techniques can be used on samples collected from the lesions.

Sample collection

Surface lesions and/or skin materials such as exudates, swabs, and crusts make suitable samples.[23] The diagnosis is aided by samples collected from multiple sites. Also, in order to get a good sample, the swabs need to be forcefully pushed against the lesion. Clinicians are advised by the CDC to collect two samples from each patient to ensure an accurate diagnosis. Specimens should be frozen (20°C or lower) or chilled (2-8°C) within an hour of collection.[23]

Diagnostic methods

Several diagnostic methods are being used in detection of MPXV infection.

1. Nucleic acid detection

The most sensitive and specific approach for nucleic acid detection currently available is PCR.[3,43] The extracellular envelope protein gene (B6R), the 16 DNA polymerase gene (E9L), the DNA dependent RNA polymerase subunit 18 (RPO18) gene, and the complement binding proteins C3L, F3L, and N3R are some of the targets that have been chosen for PCR amplification.[8] When combined, the genes E9L and B6R demonstrated 100% specificity for monkeypox in RT-PCR experiments.[24] Following a positive test, contact tracing, testing, and immunization of those exposed are recommended. Further tests listed below can be performed if RT PCR is negative.[6]

The gold standard for differentiating MPXV from other orthopoxviruses is whole genome sequencing,[8,25] although its application is limited, particularly in underdeveloped nations.[24] The current outbreak's MPXV's genomic sequencing reveals that it originates from the West African Clade.[26,27] An average of 50 single-nucleotide diversity locus (SNPs) mutations have surfaced compared to the viral genome during 2018–2019.[8]

2. Serological testing

IgM antibodies can be found using enzyme-linked immunosorbent assay, 5 days after infection, while IgG antibodies can be found using ELISA 8 days after infection.[8] However, since MPXV and other orthopox viruses exhibit antigenic cross reactivity, the specificity is insufficient.[28,29] But in both the acute and convalescent stages, there is a 4-fold rise in antibodies that help with diagnosis.[8]

3. Electron microscopy

MPXV and the other orthopox viruses share the similar morphology. Hence, the MPXV diagnosis cannot be supported by electron microscopy. Also, due to the complicated sample preparation requirements, time commitment, and expensive cost, it is not really beneficial in epidemics.[8]

4. Viral isolation and culture

The diagnosis can be confirmed by this method. It is grown as a live virus that is then utilized to classify different species. The drawback is that it can be disturbed by bacterial invasion and takes several days to produce results. The frequency of monkeypox culture-based testing in diagnostic or clinical laboratories should be limited.

5. Other methods

For the detection of MPXV antigen, immunochemistry analysis and multiplexed immunofluorescence imaging could also be employed. Antigens unique to the orthopox viral infection are found using immunohistochemistry.[30]

COMPLICATIONS OF MPOX

Children typically experience more severe infections and

Table 1. Diagnostic methods in Mpox

Test	Characteristics
PCR	High sensitivity and specificity Detects viral genes
Serology	Detects antibodies against mpox viral genes Insufficient specificity due to antigenic cross reaction
Viral culture	Live virus can be grown Can confirm the diagnosis
Electron microscopy	Expensive Limited role in developing countries
Immunochemistry	Detects orthopoxvirus-specific antigens

is correlated with the extent of viral exposure, patient's overall health status, and the nature of sequelae. Patients can experience a variety of health issues affecting various organ systems. It is crucial to consider these potential implications while screening and treating infected individuals.

1. Ocular complications of MPXV

Ocular signs are often overlooked when discussing systemic viral infection. Yet, it is a plausible route of transmission in MPXV, as well as something that might cause significant morbidity and mortality. About 4-5% of MPXV cases have ocular complications with 1% of cases exhibiting an ocular rash.[31,32] Virus make their way into the body through the conjunctiva, which is the outermost mucosal surface. It can then evolve to blepharitis, keratitis, and uveitis, ultimately leading to corneal scarring and visual loss.[33,34] Nevertheless, whether the eye is harmed as a result of a primary viral infection or subsequent bacterial problems is debatable.

2. Gastrointestinal system complication of MPXV

As a result of the vomiting and diarrhea that occur during the second week, severe dehydration may ensue.[35] Furthermore, the existence of oral and throat ulcers impairs the individual's ability to consume adequate nourishment due to swallowing difficulties, which might exacerbate the risk of dehydration.

3. Neurological complications of MPXV

MPVX can produce a wide range of neurological consequences, from minor symptoms including headache, agitation, weariness, and myalgia to more serious complications like seizure, encephalitis, and coma.[33] Studies have shown that several psychological features such as mood disturbances, anxiety, depression and neuropathic pain are common, although it is unclear whether these conditions are caused by the neurological tropism of monkeypox virus or due to stigma and isolation.[43,44] Several neural complicated cases have also been reported. For example, a severe case reported in USA have shown headache and myalgia and in addition seven other MPXV confirmed cases in western hemisphere of USA also have reported headache, fatigue and myalgia as frequent neurological complications.[42] Furthermore, in a cross-sectional study

conducted in Bayelsa state of Nigeria reported variety of neurological complications such as headache, myalgia, pain and photophobia in MPXV confirmed cases.[42] In the course of current outbreak of MPXV three cases of encephalitis have been reported in two male Spanish patients and one young male Indian patient. All three cases resulted in mortality.[43] Research conducted on animals indicates that MPXV enters the brain parenchyma via the olfactory epithelium and via infected monocytes/macrophages.[33] From there, the virus can spread to other areas of the brain and cause inflammation and damage to brain tissue. However further studies are needed to fully understand the mechanisms of MPXV neuroinvasive and neurotropism and its effects on the human brain.

4. Respiratory system complications of MPXV

Respiratory complications appear late in the course of the illness, suggesting that the lung is affected as a secondary infection. A few infected patients have had pulmonary discomfort or bronchopneumonia. Bronchopneumonia, on the other hand, is more common in people who are also infected with the influenza virus.[36,37] These complications can restrict air intake and reduce a patient's willingness or ability to consume food and drinks.

PREVENTION

Individuals who have received the smallpox vaccine demonstrated protection against MPXV. Smallpox vaccine is currently recommended for post-exposure prophylaxis, typically within 4 days of exposure, however it can be administered up to 2 weeks after exposure. Additionally, individuals at high risk, such as health care workers, may receive pre-exposure prophylaxis.[38]

People should not be in close, skin-to-skin contact with those who have monkey pox rash. The CDC recommends general hygiene practices such as handwashing or using an alcohol-based hand sanitizer before touching your face, eating, or going to the restroom to prevent MPXV infection. Affected patients should be kept in isolation rooms, and if they are carried out for medical attention, they should wear masks and gowns to conceal any skin lesions. It is critical to safeguard the eye since, in severe circumstances, it might result in visual loss.[47] Isolation measures should be followed until all lesions have crusted, separated, and a fresh layer of healthy skin has grown beneath. Health care providers who work with such patients should use full protective gear. Individuals suffering from minor illness can be isolated at home.[39]

TREATMENT

Since there are no specific treatments for viral infections, MPXV care is primarily supportive. Except in children, pregnant women, and those with impaired immune system, MPXV is a mild, self-limiting condition. Antipyretics for fever, analgesics for pain, and antibiotics for any subsequent bacterial infections can all be administered throughout the duration of illness. In addition to these treatments, MPXV is being treated with several pharmacological substances. Below are a few of the therapeutic medications for treating the virus that are readily available on the market.

1. Tecovirimat

The European Medicines Agency (EMA) authorized Tecovirimat (ST-246), a SIGA technologies drug, in January 2022 for the management of MPXV.[8] A drug that have been previously used for treatment of smallpox. However, this antiviral medication has a narrow therapeutic window and works mainly against orthopox viruses.[40] The mechanism in which the drug works is by targeting on the lipid envelope protein P37, which is necessary for the lipid envelop to develop around MPXV which allows the virus to create a way out from the cell and disseminate to neighboring cells. Though ST-246 alone does not prevent replication of the MPXV, it is believed that combination of this drug with DNA replications inhibitors might provide synergistic effects. Furthermore, combining immunity boosters such as zinc, vitamin C, thymoquinone may increase efficacy in immunocompromised patients.[41]

Among all the various medications used for treatment of MPXV, this is the first-line therapy. In addition, it has been demonstrated in studies to shorten the duration of illness.[40,34] Another case series showed that by using FDA-approved dose for smallpox, 25 people suffering from MPXV showed complete recovery.[40] Patients receiving this drug should be informed about the clinical trial for tecovirimat ((Study of Tecovirimat for Human Monkeypox Virus) (STOMP) clinical trial)

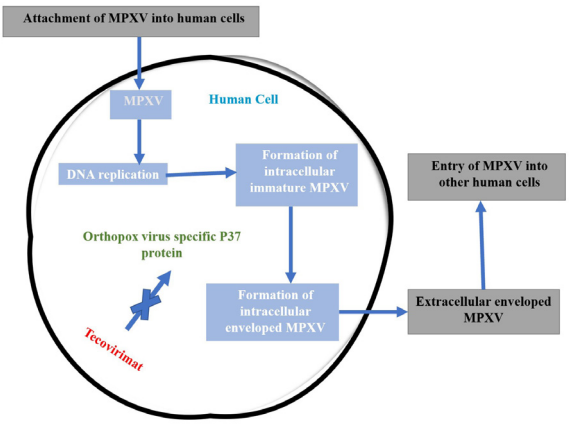

Figure 3. Mechanism of action of Tecovirimat

2. Cidofovir

This drug belongs to DNA polymerase inhibitor that has the potential to prevent viral replication.[40] Unlike Tecovirimat it is a broad-spectrum antiviral agent and is effective against a variety of different orthopox viruses. It was licensed by the FDA in 1996 for the treatment of cytomegalovirus (CMV) retinitis and acquired immuno deficiency syndrome

Table 2. Comparison between ACAM200 and JYNNEOS vaccine

Vaccine	Vaccine type	Route of administration	Injection volume	Timing	Main complications
ACAM2000	2nd generation, live replicating	Percutaneous	0.0025 ml droplet of reconstituted vaccine	Single dose	Cardiac complications like myocarditis, pericarditis
JYNNEOS	3rd generation, live attenuated, non replicating	Subcutaneous	0.5 ml 0.1 ml	4 weeks apart	Injection site reactions

(AIDS) patients. It has shown effectiveness in several animal studies, however evidence in human subjects is limited. As a result, a dosage of 5 mg/kg is used for MPXV treatment.[40] Furthermore, due to shortage of clinical data, it is unclear whether patients will benefit from Cidofovir therapy. The primary disadvantage of this drug is that it has significant kidney toxic effects. As a result, it is contraindicated in people with creatinine levels more than 1.5 mg/dl. To counteract renal toxicity, Brincidofovir was invented.

3. Brincidofovir

This is a lipid prodrug of Cidofovir, also known ad CMX001/ Tembexa. After it is taken into the cell this prodrug gets converted to Cidofovir, which is subsequently phosphorylated to form cidofovir diphosphate (CDV-PP), which inhibits viral replication at the DNA polymerase level.[8] In comparison to cidofovir, brincidofovir has higher cellular absorption and more effective conversion to active form by intracellular enzymes. There is no data on its effectives in treating MPXV in humans. However, it has proven efficacy in treating orthopoxvirus in vitro and in animal studies. The most serious adverse effects include gastrointestinal and hepatotoxicity.[40]

4. Immunoglobulins

Vaccinia immune Globulin Intravenous (VIGIV) was initially used to treat complications associated after smallpox immunization. Presently, it used off label, which means that the CDC has an enhanced access protocol that allows use of VIGIV in treating orthopoxviral infection such as MPXV in an epidemic. Though the data are lacking regarding its effectiveness, a recent case report have shown that when combined with tecovirimat, VIGIV is effective against MPXV.[40]

VACCINES

Currently there are no specific vaccines against MPXV. However, vaccines that has been approved for smallpox is being used to control the epidemic as it has shown 85% efficacy.

There are 2 vaccines licensed for use against MPXV in USA.

1. ACAM2000

This is a second-generation, replication competent vaccine which is derived from Dryvax, a first-generation smallpox vaccine.[38] It's licensed for use against smallpox, however it has off label use for MPXV prevention. Mpox vaccines can be given in two situations: Pre-exposure to prevent infection and disease among those at high risk or post exposure to improve infection and disease outcomes. Currently ACAM2000 is indicated for pre-exposure prophylaxis of MPXV infection in the group of people considered as high risk for disease transmission, such as, clinical and research laboratory workers and healthcare and public health emergency response teams appointed by public health authorities.[40] It can also be given for post exposure prophylaxis. It is best given within 4 days of exposure. It can prevent the disease if given within 4 days of exposure but can only limit symptoms if given between 4-14 days.[38] Even though studies have shown the effectiveness of this vaccine, due to ACAM2000's infectious profile, it can cause serious side effects like progressive vaccinia, encephalitis and eczema vaccinatum. Therefore, an alternative like JYNNEOS vaccine should be used. A comparison between these two vaccines is given in table 2.

2. JYNNEOS

Known by brand names such as IMVAMUNE and IMVANEX, JENNOS is a third-generation vaccine which is licensed in USA for both smallpox and MPXV. It is manufactured by Bavarian Nodic A/S. The non-replicating modified vaccinia virus Ankara (MVA) strain with 10% of its genome deleted is used for the production of this vaccine. JYNNEOS is the primary vaccine which is being used in the current outbreak. The vaccine was well tolerated with no clinically relevant differences between the populations studied. Unlike the first- and second-generation smallpox vaccines, IMVAMUNE had no reported complications linked with the first-generation vaccines. Since this vaccine has an attenuated phenotype, it has an improved safety profile. Therefore, it can be administered to immunocompromised individuals.

CONCLUSION

The current epidemic is evidence that infections from previous epidemics can re-emerge in ways that are more dangerous and in a more easily transmissible form. Genomic sequence shows that the mpox virus has undergone genetic mutation compared to previous epidemics meaning that in the future it may show further changes. Even though breakthroughs have come in the forms of antivirals and vaccines targeted against mpox, extensive further research is needed into developing safer drugs against mpox and early case detection in order to prevent complications. Furthermore, the role of public education regarding prevention of infectious diseases cannot be emphasized enough.

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