Elahi A, Maddox PA, Khuram H, Lewis J, Hirani R. A Brief Review of the Monkeypox Outbreak: Transmission, Presentation, and Developments in Treatment and Vaccines. J Immunological Sci. (2023); 7(1): 35-39

Journal of Immunological Sciences

Journal of Immunological Sciences

Mini Review Article Open Access

A Brief Review of the Monkeypox Outbreak: Transmission, Presentation, and Developments in Treatment and Vaccines

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Article Info

Article Notes
Received: February 07, 2023
Accepted: March 07, 2023

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Keywords
Monkeypox
Vaccines
Anti-viral
Public health risk
Transmission and presentation

ABSTRACT

The medical response to monkeypox(mpox) is a key demonstration of how COVID-19 remodeled the global response to viruses in the medical field. As a result of the 2019 pandemic, the 2022 mpox outbreak was met with mass production of vaccines, widely available PCR testing, and increased public health and research efforts. Easy access to vaccines such as the ACAM2000 and the JYNNEOS vaccines bolstered prevention while antivirals alleviated symptoms and shortened viral duration in at-risk patients. Various methods of detection have been developed for mpox over a short period with PCR currently being used in an attempt to isolate specific strains of the virus. In this brief review, we discuss its classical presentation, and detection and treatment strategies adapted to mitigate this public health risk.

Introduction

The Mpox virus belongs to the orthopoxvirus genus, which also includes the Variola virus responsible for smallpox and the Vaccinia virus used in the smallpox vaccine[1,2]. It was originally isolated from research monkeys shipped from Singapore hence its original name. However, it is more likely to be found in rodents and small mammals such as Rope squirrels, tree squirrels, Gambian pouched rats, and door mice[3,4]. In 1958, the first mpox virus was isolated in Copenhagen and in 1970 the first human case of mpox was reported in a 9-month-old boy in the Democratic Republic of Congo. Although there have been more cases of mpox since then, it was not until recent years that the incidence of mpox became prominent[3]. Previous outbreaks have occurred, but on a much smaller scale. In 2003, it was a clade I mpox outbreak in the Republic of Congo where serial human-to-human transmission was seen[5]. Also occurring in 2003, 37 people in the U.S. were infected with clade II mpox from prairie dogs with no human-to-human transmission and a milder disease course[6]. The most recent outbreak began in May 2022 among men who have sex with men (MSM) across multiple countries, particularly in Spain where 595 confirmed cases were found[7]. Up until this point, cases of mpox outside of Africa were rare[7,8].

As of January 25,2023, the mpox outbreak consisted of 30,093 total cases and 26 deaths in the US, according to the Centers for Disease Control and Prevention (CDC)[9]. Globally, as of February 2023, the most recent number of cases is 85,469[10]. However, compared to other orthopoxviruses such as smallpox, it has a much lower case fatality rate ranging from 0-1% for clade II infections[1].

In addition, cases were not as infectious as other viruses such as COVID-19 and were mostly confined to MSM, thus minimizing the spread of the disease[9,11]. As a result, on Jan 31, 2023, the U.S. Department of Health and Human Services (HHS) ended the U.S. mpox public health emergency[9]. However, it is important to study this past outbreak of mpox to enhance future outcomes and prevent future outbreaks of similar diseases. The purpose of this review is to create a comprehensive understanding of the recent information and developments related to the mpox virus with the aim of improving future outcomes. Here, we present a complete overview of the recent mpox outbreak with an emphasis on transmission and presentation along with developments on immunotherapy and vaccines.

Transmission and Presentation

Transmission can occur through body fluids such as respiratory droplets. It can also be spread via fomites through direct contact with the lesions of the individual or in towels and bedding[3,12]. However, recent studies have shown that the viral load for mpox is higher in bodily fluids such as semen, urine, feces as well those found in rectal and nasopharyngeal swabs. Thus, although the virus can be transmitted through respiratory droplets and fomites, the primary driver of transmission is sexual, particularly in MSM[13]. This mechanism of transmission prevents it from being a highly transmitted disease compared to COVID-19, that is easily transmitted through respiratory droplets.

Following exposure, mpox has historically had an incubation period of 5-14 days[14]. However, the most recent strain observed in 2022 has had a shorter incubation period with an average of 8-9 days varying depending on transmission route[9]. This incubation period is typically defined by a viral prodrome including fever, malaise, myalgias, headache and lymphadenopathy. This lymphadenopathy is most common in the submandibular, neck, and groin lymph nodes and occurs in up to 90% of patients[15]. However, it is important to note that the symptoms and timeline of these systemic symptoms have varied more with the 2022 strain[9,14]. The systemic symptoms that present with the highest frequency include fever followed by malaise, myalgias, headache, and sore throat (62% vs. 41% vs. 31% vs. 21%)[15]. Some studies have reported systemic symptoms manifesting after rash development or even an absence of these symptoms altogether[14].

One to four days following the viral prodrome, single or multiple painful skin rashes manifest in various areas of the patient. Historically, this rash would arise on the face or on the palms of the hands and soles of the feet and spread outward, but the 2022 strain has seen these rashes localize to the genital, anorectal, or perioral areas of the body[15,16]. These rashes are described as centrifugally-distributed, well-circumscribed, vesicular rashes and develop in up to 95% of patients[14,15]. The rash can present with lesions in synchronized stages of development or varied stages. This vesicular appearance, staging, and location of the rash can make it difficult to discern mpox from other pathologies like varicella, herpes simplex virus, and smallpox[14,15]. The evolution of the rash goes from macules to papules and then vesicles within the first two days. This is followed by pustule formation on the fifth to seventh days that eventually crust over and scab for up to a total of two weeks[15]. The rash itself is painful when it first manifests, but as they crust over by the 7th day, they become increasingly pruritic until the scabs heal[14]. The total duration of mpox is about 2-4 weeks and the majority of cases resolve without fatality[1].

Detection & Treatment

Mpox is primarily identified through viral DNA swabs taken from crusts of vesicles and ulcers. RT-qPCR test is a highly sensitive test that allows for the disease to be detected in its early stages. PCR has been a mainstay of testing since the beginning of the current outbreak[17]. However, developments are being made to detect the different strains of the virus, not just the generic, to improve the reach of the test[18]. Other diagnostic tests include electron microscopy, immunohistochemistry, rash cultures, and serologic testing. A significant setback in the serologic testing is the significant possibility for false positives as it can detect antibodies from other orthopoxviruses and vaccines[19,20].

Currently there are two vaccines available for pre-exposure protection against orthopoxviruses, including Mpox[21]. Smallpox vaccines have been shown to be protective against monkeypox, with one study finding 85% cross protection[22]. These are the ACAM2000, a second-generation live Vaccinia virus vaccine, and JYNNEOS, an attenuated third-generation vaccine based on modified vaccinia Ankara (MVA). The ACAM2000 was initially developed to replace the Dryvax vaccine for mpox since the former utilized more current standards of quality control for vaccine production[23]. As a result, most of the US Strategic National Stockpile consists of the ACAM2000 vaccine[24]. The JYNNEOS vaccine was developed after the ACAM2000 vaccine to address the latter vaccine's weaknesses[21]. The difference between the ACAM2000 and the JYNNEOS vaccine is that the former is replication competent while the latter is replication deficient[3]. As a result, the ACAM2000 vaccine is associated with side effects not typically found in JYNNEOS such as a large cutaneous reaction at inoculation site, progressive vaccinatum in immunocompromised individuals, and eczema vaccinatum in those with atopic dermatitis[25]. There is also a risk of myopericarditis in 5.7 per 1000 people. Furthermore, since ACAM2000 is replication competent,

there is a risk of inadvertent inoculation to a close contact, especially those who are immunocompromised[3]. This is problematic as up to 50% of individuals diagnosed with mpox also had a positive HIV status[26]. Therefore, unlike ACAM2000, JYNNEOS can be used for patients that are immunosuppressed including HIV, a disease that disproportionately affects the MSM community[10,27]. As a result, the CDC currently recommends JYNNEOS, a 2-dose vaccine, given 4 weeks apart[16]. The vaccine is recommended for high-risk patients such as those who were exposed to someone with mpox, those in the MSM community with multiple partners or a new diagnosis of STI, those diagnosed with HIV or immunosuppression, or anyone who works at an orthopoxvirus laboratory[10]. Additionally, the use of these vaccines as post-exposure prophylaxis has been offered from the start of this outbreak, although early on only 50.5% of European institutions surveyed had potential access to vaccines[17]. However, due to possible limitations on access to the JYNNEOS, the FDA has still given the ACAM2000 an Expanded Access Investigational New Drug application (EA-IND) for prevention of mpox to limit the spread of disease[28].

The efficacy of ACAM2000 against mpox in humans is uncertain, but one study suggests that its predecessor, the first-generation smallpox vaccine Dryvax, provided protection against mpox in vaccinated individuals during an outbreak in the Democratic Republic of the Congo[29,30]. In addition, ACAM2000 has been shown to be efficacious in preventing mpox in nonhuman primate studies[31].The evidence for its immunogenicity is moderate, but there is no established minimum threshold of antibodies required for protection and no data on its clinical efficacy against Monkeypox[32].

The effectiveness of JYNNEOS against medically attended mpox disease is 69%[21]. There is a dramatic reduction in efficacy with partial vaccination (1 dose) at 37%[21]. Maximum immunity is anticipated to occur 14 days after receiving the second dose of the JYNNEOS vaccine. The longevity of immunity after one or two doses is still undetermined[21,33]. It is thought that the JYNNEOS vaccine allows for efficient expression of virtually all viral proteins and elicits a strong immune response, similar to a replication-competent vaccine such as ACAM2000. This is because the cell entry, gene expression, and genome replication steps are intact. However, unlike replication-competent vaccines, the final step of virion morphogenesis is blocked by the deletion of the viral genes C12L and C16L/B22R[34].

Currently, there is very little information available regarding the development of a new mpox vaccine. Given the success of the COVID-19 mRNA vaccine, a nucleic acid vaccine against mpox may provide a cost effective and safe vaccination option[35]. A 2011 study by Hirao et al. demonstrated preliminary success in creating a multivalent DNA vaccine that offered protection against a lethal monkeypox challenge in macaques[36]. In this study, 8 vaccinia genes encoding for both mature and enveloped virion targets were used in a novel DNA vaccine that was able to confer protection against mpox. Additionally, this vaccine produced neutralizing antibody titers comparable to Dryvax in similar animal models. Using conserved DNA sequences, it may be possible to create a multipotent nucleic acid vaccine that confers immunity against mpox, Vaccinia, and Variola[35]. Additionally, mpox encodes several proteins for multiple envelope glycoproteins. Perhaps these glycoproteins could be used as immunogens in developing prophylactic vaccines.

The prognosis of monkeypox is favorable with the majority of patients able to recover without medical treatment. From the onset of the 2022 outbreak, most cases have been managed symptomatically only[17]. Providers should ensure that they are provided with adequate oral/IV rehydration if they have vomiting and diarrhea[37]. However, further steps can be taken for patients that are symptomatic. For pain management, patients can be treated with acetaminophen or NSAIDS[38]. Topical steroids can be added to genital lesions for pain and swelling[39]. Stool softeners have been found to mitigate pain with bowel movements in patients that have proctitis as well as warm sitz baths for acute pain. If the patient has oropharyngeal lesions, then management can include clean saltwater four times a day and, for severe cases, viscous lidocaine or a variety of analgesic mouth washes[38].

If necessary, antivirals can be used for patients who are at risk for severe disease, immunocompromised (CD4 count <200), or have infection in the eyes, mouth, or anogenital area[3,28]. Tecovirimat is an antiviral that functions by inhibiting the viral envelope of VP37, preventing viral maturation and spread. However, the efficacy of tecovirimat may be contingent on the onset of symptoms. Additionally, availability of tecovirimat and other antivirals was very limited early into the outbreak[17]. A study by Russo et. al shows that the effectiveness of Tecovirimat is reduced if given after 5 days since onset[40]. In a study with 369 monkeypox patients treated with Tecovirimat, adverse events were reported in only 3.5% of patients. Although there is limited experience using this agent, tecovirimat appears to be well tolerated and may shorten the duration of illness and viral shedding[41]. Current efficacy is being tested in the STOMP Trial with the primary outcome measuring time to clinical resolution. The study has an estimated enrollment of 530 participants and may provide more information regarding the efficacy of this drug[42,43].

In a study by Desai et al., a complete resolution of lesions was reported in 40% of patients after 7 days of Tecovirimat therapy and 93% of both lesions and pain after

21 days. Brincidofovir and its IV analogue Cidofovir, target the DNA polymerase of the virus preventing replication. For individuals with severe disease, Tecovirimat can be combined with Brincidofovir[44].

Conclusion

There is undoubtedly a significant effect on the coronavirus epidemic on how we approach and treat mpox. COVID-19 has provided the global community with experience in the mass production of vaccines, highly available testing, and public health measures. Although mpox is not as transmissible as COVID-19, health-care professionals have learned the benefits of measures such as early identification via PCR[45,46]. Thus, the COVID-19 pandemic had propelled the medical and pharmaceutical communities to rapidly provide highly available treatment, vaccination, and testing while working in conjunction with governmental health authorities. This shift will be crucial for future pandemics and outbreaks. The recent mpox outbreak has demonstrated the value of continuous monitoring and preventative measures for emerging viruses. Although mpox has a lower mortality rate and transmissibility than COVID-19 and other orthopoxviruses, it is still important to study this virus to prevent future outbreaks. The primary approach for mpox prevention is through vaccines, particularly the smallpox vaccine.

Although there are efficacious vaccines and treatments for mpox, outcomes are highly contingent on the availability of these treatments and public health policies. This can vary between communities and thus future efforts should focus on accessibility and cost effectiveness. In this increasingly interconnected global community that we live in, the importance of preventing future outbreaks of emerging diseases is incredibly important. The insight and knowledge gained from studying mpox will take us one step further towards preparing us for the next challenges we face in the realm of infectious diseases.

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