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Beyond smallpox: The emergence of monkeypox as a threat to human health - symptoms and treatment

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Abstract. A double-stranded DNA pox virus known as monkeypox is a member of the *Poxviridae* family, which is divided into the West African and Congo Basin clades. Spreading originally from countries in Africa. Monkeypox has since spread to numerous other countries and was proclaimed a worldwide health emergency. There are no current treatments designed for monkeypox, therefore it is important to discuss the therapeutic options and prevention methods. For the symptomatic management of monkeypox, antiviral medications are utilized. Numerous studies conducted in animal models proved the safety and efficiency of antiviral drugs designed for monkeypox, despite the risk factors. The monkeypox virus can also be prevented by using previous smallpox vaccines. Here, we focus on the epidemiology, the transmission and the pathology of monkeypox. Further, we review the current therapies and vaccines for monkeypox to help to limit the spread and influence of monkeypox, and further, to bring insight in further studies involving antiviral drugs and vaccines to treat monkeypox.

Keywords: Monkeypox, Orthopoxvirus, Antiviral Drugs, Vaccine.

1. Introduction

Since the emergence and eradication of smallpox, a new and closely related zoonotic disease, the monkeypox virus, has appeared as a rare but impactful global outbreak. While monkeypox is a milder variation of smallpox, it has identical clinical manifestations and transmission mechanisms. Usually, infecting rodents or nonhuman primates and rarely spreading to people, monkeypox is a rare condition brought on by the pox virus from the *Poxviridae* family [1, 2]. Despite their inability for mRNA translation, their distinctive structure and DNA enable replication and transcription assembly with their own genomes. It is believed that primates such as squirrels, rats, monkeys, and primates are the main carriers of monkeypox in the African regions [1]. Although the Democratic Republic of the Congo saw the first human instance of monkeypox in 1970, it has since been linked to numerous additional human cases in Africa as well [1]. With the initial spread of monkeypox to other countries, many countries faced a shortage of vaccines and antiviral drugs. Since then, vaccines and antiviral drugs for monkeypox are now available for providers and patients. There are currently cases of monkeypox in numerous nations, including the United States, largely supported by a lack of prior smallpox vaccinations [1]. Particularly in the DRC and Central and West Africa, the monkeypox virus remains a severe hazard to human life. Human interactions with one another through respiratory droplets or close

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exposures to an infected person or their fluids is the main cause of the current outbreak. Due to the similarities between monkeypox and smallpox, clinical differentiation between the two is also challenging unless with specific tests [1]. With the ongoing outbreak of monkeypox, there are increasing concerns of monkeypox becoming a more severe human pathogen, bringing in more waves of the outbreak. Currently tests of antiviral drugs and vaccines are now being conducted for their effectiveness against monkeypox. This review will discuss the definition and pathology of monkeypox and the current possible treatment options for monkeypox. It will also discuss the current trials and studies done with antiviral drugs and the two vaccines specified for monkeypox.

2. Epidemiology of monkeypox

2.1. Epidemiology

In Copenhagen at the end of 1958, the monkeypox virus was first identified. It was given the name "monkeypox" both for its resemblance to other poxviruses and the cynomolgus monkeys that it afflicted [1]. The first instance of monkeypox in a human was discovered in Africa in 1970 [1]. From 1970 to 1971, six cases of human monkeypox were detected, most of which were young children without the injection of smallpox virus [1]. Thereafter, the monkeypox virus causes many outbreaks in African nations between 1970 and 1986, with most cases occurring in central Africa, especially in the DRC, and a small number of cases in western Africa [3]. During these years, several Congo Basin countries include Cameroon, Central Africa Republic, and DRC report 394 cases of monkeypox in total [3]. Monkeypox outbreaks have been predominant outside of Africa since 2003, alongside the very initial case being detected in central Western America [2]. The following crucial outbreak of monkeypox swept through Nigeria in the period between 2017 and 2018 with a mortality rate of 6% [4]. Reported cases are 122, in which contains seven death cases, indicating a mortality rate of 6% [4]. 10 cases are reported that they have direct contact with animals [4]. After this outbreak, it is thought that the virus is transmitting through a new way, as it appears in city environment and the patients sometimes have genital lesions, which confirms that sexual contact may be a means of virus transmission [4]. At the year of 2022, there is another monkeypox outbreak in European countries and in North America. Portugal, Spain and Canada each reports cases of 14, 7, and 13 [4]. In 2022 May 20th, Netherland, Germany and France also report their first case. Another 11 instances were reported on the same day by the UK's health secretary, raising the total number of cases in excess of 70 [4]. Notably in this outbreak, most incidents occur between men and men with a sexual relationship. These cases are increasing rapidly mostly through sexual contact, with a chance that the virus might also spread through the air.

2.2. Monkeypox clades

The Western Africa Clade and the Central Africa, or Congo Basin, Clade are two distinct subgroups of monkeypox. Studies suggest that the sequence similarity between two clades of monkeypox is around 95% or over 99% [5]. The Congo Basin Clade is more harmful and deadly, and with an average percentage of deaths of 10.6%, the clade can transmit more easily from one individual to another. [5]. The Central Africa Clade is detected in the cases found in DRC and South Sudan [5]. It is thought that the Central African Clade is associated with milder symptoms, even though the human-to-human transmission is not readily obvious, and it has a much lower mortality rate of 3.6% [5]. It is believed that cases in Nigeria from 2010 to 2019 are infected by the Western Africa Clade [5]. The clade is also responsible for all cases that happened outside of Africa, including the current monkeypox outbreak [5]. Unexpectedly, it is discovered that there are 40 mutations in all among the isolates of the present monkeypox outbreak, most likely as a result of its capacity for human-to-human transmission [6].

2.3. Transmission and symptoms of monkeypox

The animal host of monkeypox virus remains unclear, but the major animal infection sources are identified as rodent animals, especially infected prairie dogs, which are responsible for the 2003

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outbreak of monkeypox in US [1]. Transmission from patient to patient typically occurs when contaminated skin, body fluids, or respiratory droplets come into connection with each other [4]. Monkeypox virus could also have Mother-to-child transmission (MTCT) through placenta and lead to congenital monkeypox infection [6]. The virus enters the body, multiplies swiftly where it was introduced, and then quickly spreads to surrounding lymph nodes, which will cause lymphadenopathy which is a specific symptom observed on monkeypox patients [6]. According to clinical diagnosis, monkeypox virus takes up to 21 days for developing an explicit symptom, usually accompanied by some prodromal illness including headache, fever, and lymphadenopathy [6]. Within up to 10 days of the virus developing, the exanthema stage, which follows the prodromal stage, is accompanied by vesiculopustular rashes that first appear on the face and then spread throughout the body [6]. The virus is self-limiting and after 2 weeks of exposure, an antigen could be detected in the serum [6]. Many patients in the most recent monkeypox outbreak in 2022 displayed vaginal and peri-anal infections, swelling of the lymph nodes, fever, and difficulty swallowing, whereas some of the patients merely displayed symptoms in the form of a few sores [7]. Meanwhile, though not very clear, the route of infection might also influence the clinical symptoms [8]. Patients with respiratory or mucosal infection experienced a more typical monkeypox illness progression, including a 2–3-day febrile prodrome, less overall systemic symptoms, and no accompanied gastrointestinal involvement [8].

3. Pathogenesis of monkeypox

Monkeypox is a kind of *Orthopoxvirus*. These viruses have a genomic size of 130 to 360 kbp and are large, linear, double-stranded DNA viruses [1]. Genes important in crucial processes like transcription and virus assembly are found in the genome's center, whereas those near the termini are engaged in interactions between viruses and their hosts, such as host range restriction and immune evasion [1]. Due to the large sizes of poxviruses, they are much harder to breakthrough the immune defense of the host [2]. Thus, as a response to evade from the host's immune system, the virulence genes of orthopoxviruses produce a series of chemicals that will serve as modulators by targeting elements of the host's immune system [1]. There are mainly two groups of modulator proteins as shown in the graph (Figure 1). In the case of intracellular modulatory proteins, virotransducer proteins will function through interfering cells' response ability to extracellular virus invasions, including the oxidative burst and apoptosis mechanism [2]. Virostealth proteins function inside the cell as well. To reduce the chance that the host's immune system would detect the virus, they work by downregulating immune recognition markers, such as MHC I and $CD4^+$ [1, 2]. Extracellular modulatory proteins also play an important role in poxvirus infection. The viroreceptors, a type of glycoprotein, competitively bind the cytokines and chemokines of the host, preventing them from fulfilling their intended function [2]. The viromimic proteins will modulate immune system response. Virolokines are created to limit host responses that are harmful to viral life, boosting responses that are crucial for viral reproduction and dissemination.

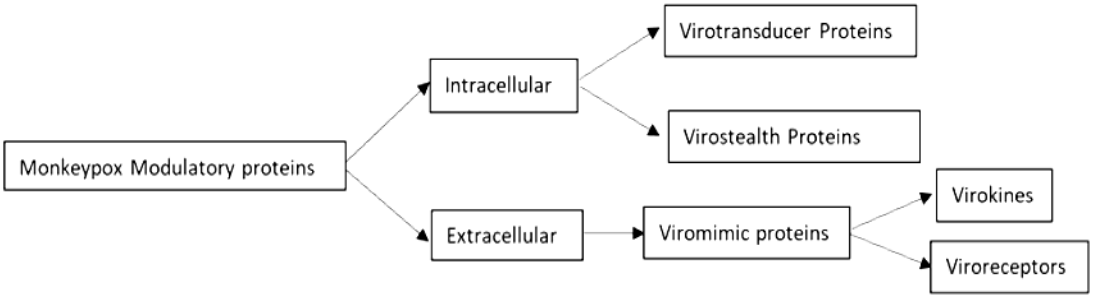

Figure 2. Types of monkeypox modulatory proteins.

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In the case of monkeypox, DNA replication happens in cytoplasmic structures which are referred to as factories [9]. Factories are DNA structures that are compressed in the early stages of infection and are enclosed with membranes that appear to come from the cell's rough endoplasmic reticulum [9]. Every factory is the product of a single contagious particle [2]. These factories will keep enlarging with the continuous formation of DNA. A more erratic shape will also eventually take shape when cavities containing viral mRNA and host translation factors form [1, 9]. When the replication cycle is about to finish, the endoplasmic reticulum membranes that surround the cell break down and produce crescent-like structures that serve as the building blocks for the immature virions (IV). A collection of viral membrane building proteins as well as a complex of late gene products will be generated [1]. Then, from the IV, the most prominent infectious species, MV, are produced [9]. Following their incorporation with the cytoplasmic membrane, these MV will leave the cell [2].

4. Clinical therapy of monkeypox

Presently, no identified treatments are available for monkeypox. Despite this, antiviral drugs such as cidofovir, brincidofovir, and tecovirimat, based on previous smallpox experiences, may be helpful in the treatment of monkeypox [10]. By preventing viral DNA polymerase from functioning, these antiviral medications primarily stop the spread of both smallpox and monkeypox. Several of these antiretroviral studies have been carried out in humans, but there is still little proof of their effectiveness [4]. The antiviral drug, cidofovir, could potentially work, however, it has not been recognized by the FDA for treating monkeypox and should only be utilized in extreme situations under proper authority. The specific advantages of cidofovir are still unknown and can have negative effects, despite research in vitro and on animals showing beneficial results [7]. The nucleotide analog of cidofovir, brincidofovir, is a lipid conjugate of cidofovir. In comparison with cidofovir, brincidofovir has faster enzyme conversion to its active form, has better cellular uptake, and is also orally bioavailable, being able to be created into tablets for drug delivery. As a result, the use of brincidofovir may be safer than cidofovir. Additionally, brincidofovir has demonstrated encouraging outcomes in numerous *Orthopoxvirus* animal models, particularly in a prairie dog model where it increases the survival rates against monkeypox [10]. However, regarding the use of brincidofovir for monkeypox, it was briefly discontinued due to the possibility of hepatic dysfunction [7]. Currently, not enough data is present to prove the efficacy of brincidofovir in humans but based on the studies conducted in animal models, brincidofovir could be used to reduce symptoms of monkeypox while carrying minimal risks. Another antiviral medication, tecovirimat, or TPOXX, ST-246, has demonstrated effective results in treating diagnosed instances of monkeypox. Being first approved for smallpox treatment, tecovirimat can stop the spread of monkeypox by blocking the VP37 protein on the virus' envelope [10]. The use of tecovirimat for diseases brought on by orthopoxviruses, such as monkeypox, has been authorized by the CDC [7, 10]. Results from clinical trials have proven the safety of using tecovirimat on humans and show improved survivability rates against lethal monkeypox strains. The results showed that when injected with a dose of tecovirimat for up to 5 days before the challenge of monkeypox, the antiviral drug can reduce the amount of virus in the body, suppressing many of the symptoms, and reduces the spread of monkeypox [10]. Having undergone testing in both human and animal models, with positive outcomes, the FDA has approved tecovirimat for clinical applications [7]. It can be taken orally as an oral capsule or injected intravenously. However, tecovirimat is difficult to obtain for less severe cases of monkeypox because of its limited supply. Although promising results have surfaced from each of the antiviral therapeutic drugs, currently, more insight is necessary to accurately evaluate the safeness and direct causes of each antiviral medicine.

4.1. Vaccines

Besides taking antiviral drugs as a treatment, vaccines are also repurposed for monkeypox. The characteristic of the vaccine allows the body to stimulate its protective immune responses without the virus infecting the body or spreading. According to data, several smallpox vaccines have demonstrated similar effects against the monkeypox virus and can be used as a preventative against the disease [10].

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Today, JYNNEOS and ACAM2000, are the two main vaccines used for the prevention of monkeypox, exhibiting comparable protection against smallpox and monkeypox [10]. The JYNNEOS vaccine is produced by altering the attenuated, non-replicating Ankara-Bavarian Nordic variant from the *Orthopoxvirus*. The FDA authorized and cleared JYNNEOS for use in adults as a smallpox and monkeypox disease preventative [10]. In studies conducted in non-human primates, the effectiveness of JYNNEOS provided complete protection against a lethal monkeypox threat. In clinical studies regarding the use of JYNNEOS in animal models, vaccinated animal models expressed less mortality rate when compared to unvaccinated animal models [11]. These research and data have made JYNNEOS the preferred vaccination for monkeypox due to its effectiveness in protecting against smallpox and monkeypox without major adverse effects. However, JYNNEOS is only available to adults who have been found to have a hazard risk of developing fatal symptoms. In addition, the FDA has also authorized the ACAM2000 vaccine to treat monkeypox during an outbreak. Similar to JYNNEOS, the ACAM2000 vaccine contains the live vaccinia virus. Unlike JYNNEOS, the vaccinia virus in ACAM2000 is capable of replication, infecting cells, and producing infectious particles. As a result, using ACAM2000 carries a danger of inadvertent inoculation and autoinoculation, however, using

Table 1. Comparison between ACAM2000 and JYNNEOS.

Characteristics	**Name**	
	ACAM2000	**JYNNEOS**
Vaccine type	Self-Replicating	Unable to replicate itself
Recommended to take vaccine	Yes	Yes
Possible adverse events	Yes	No major risks proven with tests
Risk of cardiac events	5.7 cases per 1,000 people	Not enough clinical tests to accurately determine risks
Effectiveness	Insufficient clinical result to determine efficacy against monkeypox	Can reduce risk and transmission of monkeypox
Administration	Single dose	Consists of 2 doses, about 4 weeks separate

JYNNEOS carries no such risk (Table 1) [10]. Studies employing ACAM2000 on animal models showed that the survival rate was higher than that of unvaccinated animal models [11]. Nevertheless, statistics indicated that JYNNEOS provided a greater survival rate when compared to ACAM2000. Receiving JYNNEOS is recommended for adults with high risk of experiencing serious side events from ACAM2000 and those who have severe monkeypox disease. Studies employing ACAM2000 on animal models showed that the survival rate was higher than that of unvaccinated animal models [11]. Additionally, it should be highlighted that immunizations are exclusively to prevent monkeypox. Other than the use of antiviral medications to lessen some of the symptoms, there are no specific treatments after the initial infection of monkeypox.

5. Conclusion

The spread of monkeypox among people around the world has raised concerns and put many families' lives in danger. Since its first discovery in the continent of Africa, monkeypox has spread across the world, creating a multi-country outbreak. Initial outbreaks of monkeypox caused shortages of treatments across the world. Over the years, with research and development in technology, recent studies figured out the transmission and pathology of monkeypox. Using pre-existing therapeutic drugs and vaccines of smallpox, which shows the similar feature as monkeypox, people with monkeypox were treated from their complications. Using non-human primate and animal models, those antiviral drugs and vaccines were tested for their effectiveness. Despite lacking clinical trials and

a defined treatment for monkeypox, emerging studies of antiviral drugs and smallpox vaccines have shown effective results to combat cases of monkeypox. The safety and accessibility of the present antiviral medications and vaccines would increase with further clinical trials and testing. With continued development of antiviral drugs and vaccines, the therapy of monkeypox could be more effectively. However, despite ongoing outbreaks across the world, awareness and knowledge of monkeypox remains uncommon among the population. In addition, hesitancy towards vaccination is also common among the population. Future efforts to combat monkeypox and other illnesses may be more coordinated if there is greater understanding of monkeypox and vaccine acceptance. Although it may not be possible to eradicate monkeypox in the foreseeable future, with developing treatments and therapeutics, severe symptoms of monkeypox can become less lethal over time.

Authors contribution

All the authors contributed equally and their names were listed in alphabetical order.

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