Monkeypox virus in 2022 outbreak: what do we need to know?

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Abstract

Monkeypox disease is a zoonotic disease that is caused by the monkeypox virus (MPXV). The MPXV belongs to the Poxviridae family as same as variola virus which cause smallpox disease. MPXV caused multiple outbreaks in endemic and non-endemic countries since the first human case discovered in 1970 in Democratic Republic of Congo. Although there have been multiple outbreaks, the largest outbreak occurred in 2022 which gained MPXV a lot of attention from the world. This review aims to provide the currently founding evidence of clinical symptoms, treatment, and prevention of monkeypox disease. This review highlights the genetic changed of MPXV in 2022 outbreak. In previous endemic, MPXV had been classified into 2 clade, clade I and clade II. However, MPXV found in 2022 outbreak had been reported to be new strain named clade III which many mutations related to human-to-human transmission potential. Most of the cases from the 2022 outbreak were among young men particularly men who has sex with men different from previous endemic which most cases were children. There is currently no treatment specifically made for MPXV, however, because MPXV is genetically similar to smallpox, the treatments used for smallpox can be used to treat monkeypox disease.

Keywords: Monkeypox disease; Orthopoxvirus; infectious disease; outbreak; vaccination

1. History of Monkeypox

In 1958, the first reported case of Monkeypox virus (MPXV) was discovered in monkeys that were housed in a research institute at Copenhagen, Denmark [1]. However, the first human case of Monkeypox was

not found until September of 1970 in the Democratic Republic of Congo. Before the first MPXV outbreak was discovered in 2003, the following known cases were prevalent throughout central and west Africa. Also known as the 2003 Midwest monkeypox outbreak, most human cases were believed to be caused by contact with infected prairie dogs that were transported alongside African rodents from Ghana [2]. In the years before the 2022 outbreak, there has been clusters of monkeypox cases in the UK, Singapore, Israel and the US which all linked back to Nigeria. For the first and second outbreak (1970 and 1996-1997 relatively), Monkeypox virus was circulating in endemic countries such as the Democratic Republic of Congo, Cameroon, and Nigeria. However, after third outbreak in 2003, monkeypox cases began to be reported in non-endemic countries such as the US.

1.1. First Case of Monkeypox virus outside Africa

Although MPXV was discovered in 1958 in laboratory monkeys, blood tests were done on African animals which revealed a number of African rodents infected with a Monkeypox infection. The first human case of monkeypox was found in a 9-month-old boy living in the Democratic Republic of the Congo in 1970 [3]. The symptoms of the 9-month-old boy were fevers and a rash which later progressed into haemorrhagic lesions. Ultimately, this led to the first MPXV outbreak in 1970, which caused monkeypox to become endemic in the Democratic Republic of the Congo and other Central and West African nations including: Liberia, Sierra Leone, Nigeria, and the Ivory Coast.

1.2. Difference between the 2022 outbreak and past outbreaks

There has been a total of five outbreaks of monkeypox in recorded history: in 1970, 1996–1997, 2003, 2018, and the most recent outbreak, which had over 26,000 cases and spread to more than 50 non-endemic nations on multiple continents, happened in 2022 [4]. The three nations with the greatest number of cases in the 2022 outbreak are Spain, Germany, and England. In the past outbreaks, travelling to a country where the disease is endemic or when there was previous exposure to infected people were not linked to the monkeypox cases. This led to several hypotheses to be proposed. One of the possibilities is the discontinuation of the widespread smallpox vaccination program in the 1980s, which provided up to 85% cross protection against monkeypox causing an increased human susceptibility to the virus. Given the increased number of cases reported across different locations, it is possible that some of these genetic modifications may favour more effective methods

of transmission and dispersion. This suggests that sexual transmission may be involved, however, this is simply speculation and requires further study [5].

Furthermore, there is more information in preventing the spread of monkeypox and controlling the spread of the outbreak by applying the lessons learnt from COVID-19 to the monkeypox outbreak in 2022. For instance, more frequent hand washing can limit the MPXV virus from spreading. Additionally, the use of social media (such as TikTok and Twitter) has been used to provide information to people around the world, increasing public awareness. As a result, due to enhanced selective pressure, MPXV has developed immune evasion mechanisms that have boosted its transmissibility.

2. Monkeypox virus

Monkeypox virus is a double stranded DNA virus, a member of the genus Orthopoxvirus, family Poxviridae [6]. The closest relatives of Monkeypox include the smallpox disease, vaccinia virus and cowpox virus. Monkeypox virus have the size ranging from 200nm to 250 nm ovoid or brick-shaped particles similar to other orthopoxviruses morphology. The biconcave core, a membrane bound linear double stranded DNA virus, enzymes for uncoating and replication and transcription, and lateral body are protected by the outer membrane. Monkeypox virus genome is a linear, double stranded DNA encoded by approximately 190 genes. The genome is one of the largest viral genomes of 197kbp. The monkeypox genome could be assigned to three parts, a core region, a left arm, and right arm. The core region is the gene encoded protein for viral replication and assembly. The left and right arm region had been reported to be involved in the host range and pathogenicity. These regions contain an inverted terminal repeat (ITR), an identical but opposite sequence, made up for hairpin loop. Monkeypox virus complete its replication in host cells' cytoplasm. During replication two viral particles are produced, intracellular mature virus (MV) and extracellular enveloped virus (EV). MV is released on cell lysis, while EV is released by exocytosis and formed by a lipid membrane wrapped around MVs. In principle, monkeypox viruses have a low mutation rate based on the stability of the double stranded DNA genome. However, the genetic instability had been reported in the Monkeypox virus. Currently Monkeypox virus has evolved into three distinct clades [7]: clade 1 (Central African or Congo Basin Clade), clade 2 (West African clade) and clade 3 (2017-2022 outbreak). The loss or gain of genetic material had been reported in monkeypox virus. The clade 1 and clade 2 showed 900 bp genome length difference. The clade 1 had higher pathogenicity, severity outcome and fatality rates than clade [8]. The 2022 outbreak monkeypox virus belongs to clade 3 which had the same origin with clade 2. The B1 lineage (2022 outbreak strain) had a series of mutations in a short period of time. Therefore, it became the most attention clade. The 46 single-nucleotide polymorphisms (SNPs)

have been observed in the lineage when compared to the Monkeypox reference sequence. These mutations led to rapid evaluation to host immune and high human to human transmission.

3. Monkeypox Disease

3.1. Symptoms

The incubation period for Monkeypox virus is between 5 to 21 days. The first symptom to appear is often fever that is accompanied by headaches or fatigues. A blister-like rash will then appear 1 to 5 days after the first symptom [9]. The rash will start at the face and will spread to other parts of the body including the mouth, hands, genitals, and anus. The rash will go through many stages and the first being flat spots turning into blisters. The blisters will then fill with pus, scab over and fall off, a new layer of skin will then form. This would take around 2 to 4 weeks. Other symptoms include swollen lymph nodes, muscle ache, exhaustion, and respiratory symptoms. Additionally, it is important to be aware that MPXV can spread from the time the symptoms appear until the rash heals.

3.2. Diagnosis

There are four different methods of diagnosis: genetic, phenotypic, immunological and electron microscopy [1]. The primary testing option is the genetic method, which necessitates the use of real-time polymerase chain reaction (RT-PCR) and whole genome sequencing using next-generation sequencing (NGS) technology. Although this is the industry standard for testing, the technology is costly, and the energy-intensive downstream processing of sequencing data makes this method unsuitable for low-income nations. The immunological method uses ELISA (enzyme-linked immunosorbent assay) to detect IgM and IgG antibodies to check for specific antigen markers. Another immunological method is immunochemistry analysis. Although this method is less sensitive than the ELISA method, immunochemistry analysis can be used to differentiate between the different poxviruses and the location of the proteins in a tissue section. The Electronic Microscopy method is a technique to obtain high resolutions images of the monkeypox. Monkeypox will appear as brick shaped with a central core that measures around 200 to 300 nanometres. Considering that the OPV species cannot be recognized morphologically, this is insufficient to diagnose monkeypox but this method allows scientists to know which family the virus belongs to. The Phenotypic method is the observable features of an individual infected with monkeypox. For instance, the patient may have lymph node enlargement, rashes starting from the face and spreading round the body or drenching sweats. One of the symptoms that allows them to differentiate between smallpox and monkeypox is the swelling of the lymph nodes. This method may not be accurate as there are symptoms that are similar to those of smallpox.

3.3. Transmission

Monkeypox can be transmitted through skin-to-skin contact including contact with bodily fluids and touching an item contaminated by someone infected with monkeypox. Transmission via respiratory droplets is less common as the respiratory droplets can only travel a few feet, requiring prolonged face to face contact for transmission to occur [10]. Zoonotic transmission can also occur which is the transmission from animals to humans. Any direct contact with blood or consumption of the viral hosts can lead to a monkeypox infection. The last known route of transmission is from mother to child (MTCT) where this will occur via the placenta or close contact during and after birth. The 2022 outbreak led to many suspecting monkeypox can be transmitted through sexual contact as many of the cases were between men who has sex with men (MSM)[11]. However, there is not enough research data to support the claim that monkeypox can be transmitted through sexual contact.

4. Prevention

Since Monkeypox virus is a member of orthopoxvirus, immunization with an orthopoxvirus vaccine lends immunologic cross-protection against other viruses in the genus. Therefore, immunization with smallpox vaccine would provide cross-protection against monkeypox. There are currently three licensed smallpox vaccine ACAM2000, JYNNEOS (MVA-BN) and LC16 [12]. ACAM2000, a replication-competent vaccinia virus was licensed in 2007 by the US Food and Drug Administration (FDA). It's recommended to use in 2003 during USA Monkeypox endemic. This vaccination proved to reduce the symptoms and did not prevent disease. However, ACAM2000 vaccination produced a cutaneous reaction at site of inoculation. Because of ACAM2000 is a replication-competent vaccinia virus, these is serious adverse events such as progressive vaccinia, eczema vaccinatum and myopericarditis. JYNNEOS, a replication-deficient vaccinia virus has been licensed by Food and Drug Administration (FDA) and the European Medicine Agency (EMA) for the prevention of smallpox and monkeypox for adults (18 years or older). Unlike ACAM2000, JYNNEOS vaccination did not cause cutaneous reaction at site of inoculation and lower side effects. The replication deficient poxvirus strains pose a substantially lower risk of adverse events compared with replication-competent strains. LC16m8, a live replicating attenuated smallpox vaccine is a 3rd generation vaccine derived from the Lister (Elstree) strain of vaccinia. This vaccine had an improved safety profile and can be administered to immunocompromised individuals. In 19 August 2022, WHO recommended these vaccines for primary preventive (pre-exposure) vaccination (PPV) for prevention of monkeypox in individuals at high risk of exposure, health workers at risk of exposure.

5. Treatment

Despite the lack of a specialized treatment for monkeypox, smallpox and monkeypox have genetic similarities, making it possible to treat and prevent monkeypox using the same antiviral medications and immunizations used for smallpox disease. There are three FDA approved antiviral drugs that can be used to treat Monkeypox disease[13]. Brincidofovir is the oral antiviral drugs use for smallpox disease. it works by inhibiting the viral DNA polymerase which prevents viral replication. Research on this drug that shown that Brincidofovir has a high cellular toxicity. The Centers for Disease Control and Prevention (CDC) plans to use Brincidofovir as a treatment strategy and is working on an Expanded Access Investigational New Drug (EA-IND). Cidofovir, a nucleotide analogues inhibit viral DNA polymerase and use to treat cytomegalovirus. The CDC recommend using Cidofovir as a treatment for severely ill monkeypox patients, but there has not enough clinical data to know the final outcome. The other antiviral drug is Tecovirimat [14]. Tecovirimat is a small molecule that inhibits the synthesis virus envelope protein, VP37. The Tecovirimat works by preventing the virus from producing an outer membrane with the Golgi apparatus and by inhibiting the release of the extracellular virus. This limit spread of the virus in the body. Tecovirimat is safe to be given, however, there is not enough data on human trials to be considered effective against MPXV.

6. Conclusion

Monkeypox virus is a highly contagious Orthopoxvirus and was currently causing a global outbreak. More factual information should be given to the public so that the public will be more alert and cautious. Additionally, the development of treatments and vaccines for MPXV is important to control the spread of the disease.

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