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An Update of Monkeypox Virus and mpox Characteristics

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ABSTRACT

Monkeypox virus (MPXV) is the etiological agent of monkeypox (mpox), a zoonotic disease. MPXV is endemic in the forested regions of West and Central Africa, but the virus has recently spread globally, causing outbreaks in multiple non-endemic countries.

We review the characteristics of the virus, including its ecology, genomics, infection biology, and evolution. We study the interactions that modulate the virus infection biology, signal transduction, pathogenesis, and host immune responses. And the pathophysiology and epidemiology of MPXV and summarize recent advances in the prevention and treatment of mpox. Probably, the future research directions will be addressing the knowledge gaps, and get a one and only Health approach as an effective strategy to prevent future epidemics of mpox. We're a team!!! And in these difficult situations, physicians need the most the nurses to get the goal.

Keywords

Monkeypox, Genomics, Evolution, Antivirals, Epidemiology, Infection biology, Biosafety, Team.

Introduction

Monkeypox virus (MPXV) is the etiological agent of a zoonotic disease called monkeypox (mpox). For five decades, MPXV was endemic in West and Central Africa [1], and exportation of the virus to non-endemic regions was rare [2]. However, the incidence (since 2017) of mpox outside endemic regions has increased, and the epidemiological profile of the disease within endemic regions has changed. This may have led to the MPXV emergence and re-emergence in endemic countries in 2022 [2].

In this paper, I´m trying to update the current state of knowledge on the characteristics of MPXV and mpox, the infection biology, molecular pathogenesis, and evolution of MPXV as well as the clinical features, diagnosis, epidemiology, and therapeutic options against mpox. Before 1970, there was no documented report of human MPXV infection, although the virus had previously caused infections in monkeys and apes [3]. Infections in monkeys were reported in laboratory/captive animals and were first identified in captive monkeys in Denmark in 1958. The first human mpox case emerged in a 9-month-old boy in the Democratic Republic of the Congo (DRC) in August 1970. Six additional mpox cases were identified between September 1970 and April 1971 in Liberia, Sierra Leone and Nigeria. Since then, MPXV has been reported in different countries and is endemic in Benin, Cameroon, the Central African Republic, the DRC, Gabon, Ivory Coast, Liberia, Nigeria, the Republic of Congo, Sierra Leone, and South Sudan [4,5]. Between1970 and 2021, the cases have been sporadic and geographically limited within endemic regions [6].

The DRC is the only country that still reports yearly cases of mpox with tropical rainforest regions accounting for 98.7% of all cases pre-2022 [6,7]. At the end of 2017, Nigeria recorded 88 cases, and during this outbreak, travel-related cases in non-endemic countries were reported in the United Kingdom (UK), the United States of America (USA), Israel, and Singapore, between 2018 and 2021 [8]. The first mpox outbreak in a non-endemic country was reported in 2003 in the USA linked to importation of rodents from Ghana [9-11].

There were no other travel-related cases reported until 2018. Between 2018 to 2021, 11 travel-related mpox cases were recorded in the UK, Singapore, Israel, and the USA, four of them were in

secondary cases: one healthcare worker in the UK was infected by contaminated bedding, a dad and his child from the UK had travelled to Nigeria, and one traveller to Israel who had visited Nigeria in 2018. Between 2019 and 2021, a total of seven mpox outbreaks occurred outside Africa in Singapore, the UK and the USA. All travel related cases originated in Nigeria, with high-throughput sequencing confirming it as Clade II [12-14]. Between 2017 and October 30, 2022, a total of 830 cases were recorded in 33 out of 36 states in Nigeria.

The current global mpox outbreak started in May 2022 [8,15] and was declared a public health emergency of international concern on July 23, 2022. Until August 02, 2023, there´re 88,600 laboratory-confirmed cases and 152 deaths (case-fatality rate, 0.17%) across 113 countries including 106 countries which have not historically reported mpox [5].

Epidemiology

Between 1970-2015 showed that 71%-83% of the disease occurred in children (<10 years of age) and 51%-67% in males [16].

In contrast, the median age for the 2017-2018 outbreak in Nigeria was 29 years, with males accounting for 64% of the cases. In 2022 males have risen until 96.8% of the cases, and the median age was 34 years (Interquartile range: 29 – 41) [5]. In the African region, children (0-9 years old) accounted for 23.08% of mpox cases compared to <1% in Europe and the Americas [5].

Over the past five decades, the secondary attack rate for mpox has been stable and ranges from 0% to 10.2% [17,18]. Higher estimates were reported in the 2013 outbreak in the DRC (50% among 16 households) and Nigeria (71% in the 2017- 2018 outbreak from a single household) [14,19].

Transmission

Transmission of MPXV can occur from animal-to-human (zoonotic) and from human-to-human (interhuman). Zoonotic transmission usually happens through contact with an infected animal's bodily fluid or through a bite or scratch. Exposure to animal reservoirs, especially in regions with deforestation enhancing animal-human contact, and uncooked meat products are major risk factors for zoonotic transmission.

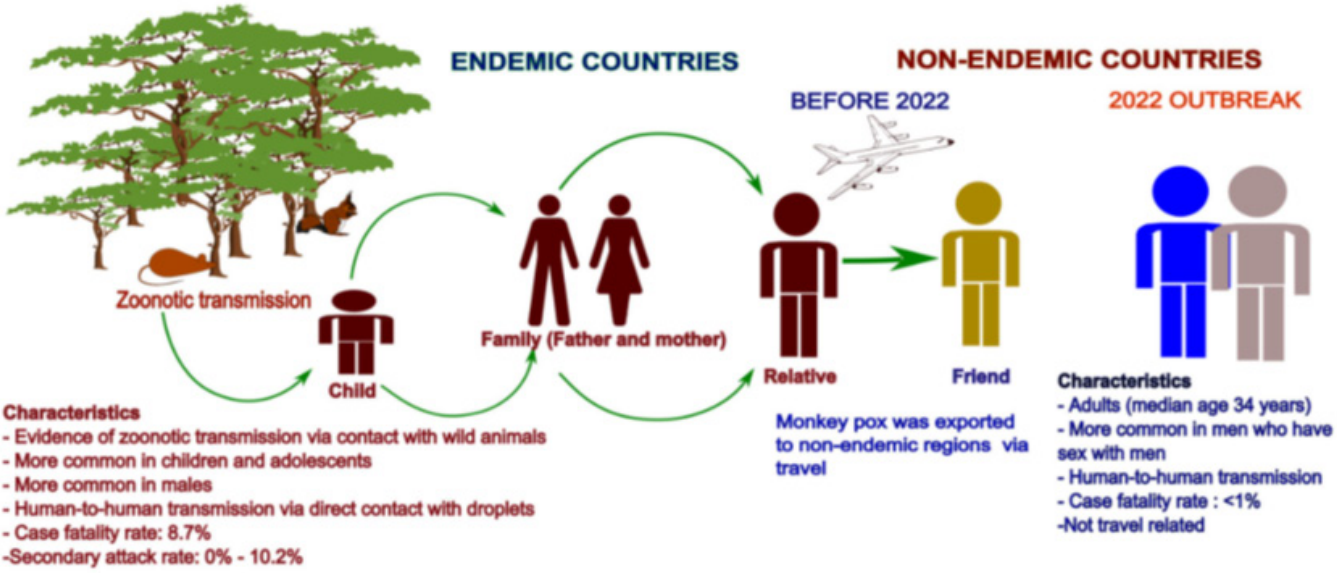
During the 2003 USA outbreak, exposure was classified as "non-invasive" (touching an infected animal) or "complex" (invasive bite from an ill animal any exposure that did not break the skin). Patients with complex exposures were more likely to develop systemic illness compared to those with non-invasive exposure [20]. Large respiratory droplets, bodily fluids, contaminated fomites, and viral shedding through hikes are also considered risk factors for viral transmission.

Airborne transmission of MPXV between animals in experimental settings has also been reported and MPXV was detected in upper respiratory samples, suggesting that interhuman transmission of MPXV via the airborne route may be possible. However, epidemiological observations do not support airborne transmission as the primary way of transmission. The virus can also cross the placenta, suggesting vertical transmission [21]. At least 12 pregnant women have been infected during the 2022 outbreak, but vertical transmission was not observed in any case [22].

MPXV has also been detected in human semen [23] and in archival testes tissue of crab-eating macaque, suggesting potential sexual transmission of the virus. Recent outbreak suggests that MSM subpopulation may also be at an increased risk.

Low immunity against smallpox has been considered another potential risk factor for the disease. Evidence from early outbreaks in the 1980s showed that previous smallpox vaccination provided 85% protection against mpox. Most cases reported were among those born after vaccination ceased in 1980, and herd immunity has significantly decreased.

Those patients who are immunocompromised due to HIV and other underlying conditions are at increased risk of severe mpox disease



[24]. A high proportion of patients with mpox in the 2022 outbreak had concurrent HIV infection and sexually transmitted infections (STI) [25,26]. Mpox patients with HIV infection were more likely to be hospitalized than those without HIV infection [27]. But, the reason for hospitalization is limited, and it is unknown if it reflects a more severe mpox illness [27].

Indeed, co-infection with other conditions with rashes, such as a varicella-zoster virus (VZV), can occur. This herpesvirus causes chickenpox is frequently misdiagnosed as mpox in regions where both diseases are endemic. Chickenpox is exclusive to humans and more common in younger age population, and co-infection with mpox has been reported more commonly among children.

Diagnosis

The Center for Disease Control and Prevention [28], mpox cases should be confirmed by real-time polymerase chain reaction (qPCR) or Next-Generation sequencing and isolation of MPXV in culture from a clinical specimen. The F3L, E9L, B6R and J2R genes are all target of qPCR in MPXV diagnosis [15,29,30]. The suspected mpox cases are characterized by fulfilling one of the epidemiological criteria (within 21 days of illness onset), as outlined by CDC [28].

One of the most important ways of controlling the spread of mpox is contact tracing. Individuals exposed to MPXV should be monitored for 21 days checking mpox symptoms, and those with suspected or confirmed mpox cases should be isolated to avoid infecting others. Velavan et al. predicted the mpox outbreak would not last provided that cases are well isolated through the contact tracing. Human-human contact tracing, animal-animal and animal human contact tracing especially due to non-specificity of reservoir hosts for MPXV. Cannot be undermined in curtailing mpox as surveillance would provide more insight into the epidemiology of the disease. In Nigeria, the Outbreak Response Management and Analysis System(SORMAS) for mpox surveillance across portions of 8 states was implemented in November 2017 for the mpox outbreak. The use of the system increased the quantity of epidemiological data collected and the communication of aggregate case data.

Prevention

There is no specific vaccine for MPXV, the smallpox vaccines have been reported to give 85% cross-immunity against MPXV due to shared antigenic features [15].

ACAM2000™ is a replication-competent vaccinia virus vaccine licensed by Food and Drug Administration (FDA) in August 2007 for smallpox prevention, and it is derived from a single clonal viral isolate from Dryvax, which is a first-generation smallpox vaccine. As a second-generation attenuated vaccinia virus vaccine [31], ACAM2000™ has been recommended as MPXV post-exposure prophylaxis [32]. Although high level of protection against mpox in animal models has been recorded, the safety of ACAM2000™ in humans is a of great challenge as cardiac complications, and extremely painful and uncomfortable cutaneous reaction at the injection site have been associated with the vaccine [33]. Therefore, the vaccine is no longer licensed by European Union. JYNNEOS (Imvamune or Imvanex) was approved by FDA in September 2019 for prevention of smallpox and mpox in adults aged >18 years [15]. JYNNEOS is the brand name of Modified Vaccinia virus Ankara Bavarian Nordic (MVA-BN) vaccine, a non-replicating third generation attenuated vaccine. JYNNEOS is considered safer (with proven efficacy in animals and humans) than ACAM2000™. The Advisory Committee on Immunization Practices has recommended JYNNEOS as an alternative to ACAM2000™. Both vaccines (JYNNEOS and ACAM2000™) have been recommended for MPXV high-risk groups.

LC16m8 is another potential vaccine for MPXV which is obtained by subjecting VACV lister to 36 serial passages at low temperature (30°C) in primary rabbit kidney cells. It's a third-generation attenuated vaccine [31], LC16m8 has been shown to be protective against MPXV in animal models with lower neurotoxicity. The frameshift mutation in LC16m8's major extracellular enveloped virion antigen (B5R) contributes to the vaccine replication competence and low virulence. Presently, LC16m8 is only licensed in Japan.

Treatment

There are no specific antivirals for mpox, but some antivirals (tecovirimat, brincidofovir, cidofovir) have been studied.

1) Tecovirimat (ST-246 or TPOXX®) 4- F trifluoromethylphenol derivative, was approved (for smallpox) by FDA in 2018 and approved by European Medicines Agency in January 2022 for treatment of smallpox and cowpox. Tecovirimat inhibits VP37 (p37) protein of VACV by targeting the viral F13L gene [34] and the CPXV homolog V016 gene. VP37, a highly conserved protein in OPXV genus, is required for viral maturation and release from the infected cell. Inhibition of VP37 prevents viral spread within an infected animal model. It´s recommended to be administered as first line of mpox treatment in pregnant and breastfeeding patients [35]. A tecovirimat analogue (synthesized by the State Research Center of Virology and Biotechnology, Russia) has been highlighted as ampromising antivirals against OPXV infections.

2) Cidofovir (CDV or Vistide®) prodrug is an acyclic nucleoside phosphate [15] that was approved by FDA in 1996 for the treatment of retinitis (caused by cytomegalovirus) in AIDS patients. The efficacy of CDV has been identified during the *in vitro* studies in MPXV-infected animals, but the clinical data of CDV efficacy against mpox in human are not available.

3) Brin cidofovir (CMX001 or hexadecyloxypropylcidofovir), a CDV derivative, was approved for smallpox treatment in 2021 by FDA, and it has lesser toxic effects than CDV. Evaluation of CMX001 efficacyand safety in human mpox through the clinical trials is needed.

Recombination with vaccinia virus and other OPXV

Due to inadequate genome surveillance data particularly in

endemic regions, little information about MPXV recombination is available, but there are some evidence of recombination between coinfecting or superinfecting OPXVs both in a laboratory setting and in nature [36-41]. MPXV circulating in non-endemic regions where other OPXVs are endemic, for instance, CPXV in Europe and VACV-like in south America, and vaccination against mpox with JYNNEOUS or ACAM 2000 are scenarios for coinfection and superinfection between different species of OPXV. An also, there remains a potential risk of recombination between MPXV and other OPXVs that may result in MPXVs with mosaic genomes and altered biological characteristics.

Bioterrorism

Although there is insufficient evidence of MPXV being used for bioterrorism at the moment, scientists have expressed concerns over its potential use for bioterrorism because there is a report that there was an attempt by the former Soviet Union to use MPXV as a bioweapon [42].

The chance of MPXV as a potential bioweapon due to its global re-emergence and its clinical similarities with VARV has placed the virus on the global public health agenda [43]. For instance, the USA has made preparation for the possibility of smallpox virus as a potential bioterror biological by storing smallpox vaccines and antivirals after the 9/11 attack [44]. Smallpox virus is in category A of the CDC list of bioterrorism agents.

The risk of bioterrorism has been greater knowing that MPXV genomes can be synthesized from publicly available sequence data and life viruses (with or without further genetic modification) canbe re-constituted. This has already been demonstrated with horsepox virus (HPXV), which shares the same genus as MPXV. Hence, a strict dual-use policy must be agreed upon and implemented in all laboratories across the globe.

Sexual orientation (especially LGBQTI+ community) and racial are two stigmas associated with MPXV. The narrative of the media alongside many scientists linking the mpox 2022 outbreak to Africa/West Africa/Nigeria is alarming. Despite the mpox 2022 outbreak, which occurred outside Africa, the nomenclature and the geographical labels of MPXV strains still reference West African, even though the origin of this outbreak is still unresolved and high mpox cases were reported among MSM.

The hypothesis is that these men contracting MPXV because they engaged in sexual intercourse with fellow men, meanwhile the spread of the virus can occur regardless the sex. Vaccine inequality affects lower- and middle-income countries (LMICs). An unknown number of mpox cases in LMICs are not captured due to a shortage of resources like limited testing and surveillance capacity. As highlighted by Malta et al., the MPXV vaccines are presently accessible only in high-income countries (Canada, the USA, and the UK).

Conclusion

MPXV has emerged and re-emerged for over five decades and we do not much about the virological profile and the characteristics of the disease it causes. The reservoir host of MPXV remains unknown, the viral, host and environmental factors that modulate the virus maintenance in the wild, animal-to-animal transmission, zoonotic transmission and reverse spillover are still a mystery.

Current and future studies should help us on understanding the molecular basis of MPXV infection to develop effective drugs and vaccines against mpox as well as functional mutational studies that will shed insight into the dynamics of MPXV transmission across hosts. The laboratories particularly in resource-poor countries should be equipped with genome-based surveillance capacity and capability. Lastly, MPXV and mpox affect human, animal, and ecosystem health. Thus, a One Health strategy is indispensable to the prevention and treatment of current and future outbreaks.

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