The Neglected Mpox Virus: From Historical Review to Future Perspectives

Yan Wang[1], Yan-Xia Zhang[1], Xiao-Yi Liang[1], Ya-Fang Liu[1], Wei Gao[1], Hang Yuan[1], Yu-Qing Jin[1], Zhiguang Ren[1], Xin-Ying Ji[1], and Dongdong Wu[1]

[1]Henan University School of Basic Medical Sciences

April 5, 2023

Abstract

Mpox (MPX), a zoonotic infection reported as early as 1970, is a double-stranded DNA virus, Mpox virus (MPXV), belonging to the genus Orthopoxvirus. MPX, a virus closely related to smallpox, was once considered a geographically restricted infection because it was predominantly endemic in West and Central Africa, except for the Democratic Republic of the Congo (DRC). However, in May 2022, a rare case of MPX was diagnosed in the UK. As of February 25, 2023, 86,127 confirmed cases and 97 deaths have been reported globally. It spreads through close contact with an infected person, infected animal, or an object which an infected person has touched. Although most people infected with MPXV may present with mild symptoms and will recover fully within a few weeks, people can have serious diseases and complications and may need to be hospitalized with it. Although smallpox vaccines and antiviral drugs are also effective against MPX, there is still no specific vaccine or drug for MPXV infection. Therefore, we need to take the right attitude and measures to stop the MPXV outbreak. In this review, we summarize the characteristics, mechanisms, immunology, and transmission of MPXV, as well as current vaccines, diagnostics, and treatments used for MPX, and provide clues for controlling MPX outbreaks and preventing such diseases.

The Neglected Mpox Virus: From Historical Review to Future Perspectives

Yan Wang[1,2], Yan-Xia Zhang[1,2], Xiao-Yi Liang [1,2], Ya-Fang Liu[1,2], Wei Gao [1,2], Hang Yuan[1,2], Yu-Qing Jin[1,2], Zhi-Guang Ren[1,2,*], Xin-Ying Ji[1,2,3,4,6,7,*], Dong-Dong Wu [1,2,5,*]

1 School of Basic Medical Sciences, Henan University, Kaifeng, Henan 475004, China

2 Henan International Joint Laboratory of Nuclear Protein Regulation, Henan University college of Medicine, Kaifeng, Henan 475004, China

3 Institute of Nursing and Health, School of Nursing and Health, Henan University, Kaifeng, Henan 475004, China

4 Kaifeng Key Laboratory of Infectious Diseases and Biosafety, Kaifeng, Henan 475004, China

5 School of Stomatology, Henan University, Kaifeng, Henan 475004, China

6 School of Clinical Medicine, Henan University, Kaifeng, Henan 475004, China

7 Faculty of Basic Medical Subjects, Shu-Qing Medical College of Zhengzhou, Mazhai, Erqi District, Zhengzhou Henan 450064, China

* Corresponding authors.

E-mail addresses: renzhiguang66@126.com (Z.-G. R.), 10190096@vip.henu.edu.cn (X.-Y. J.), ddwu-biomed2010@163.com (D.-D. W.).

Abstract

Mpox (MPX), a zoonotic infection reported as early as 1970, is a double-stranded DNA virus, Mpox virus (MPXV), belonging to the genus Orthopoxvirus. MPX, a virus closely related to smallpox, was once considered a geographically restricted infection because it was predominantly endemic in West and Central Africa, except for the Democratic Republic of the Congo (DRC). However, in May 2022, a rare case of MPX was diagnosed in the UK. As of February 25, 2023, 86,127 confirmed cases and 97 deaths have been reported globally. It spreads through close contact with an infected person, infected animal, or an object which an infected person has touched. Although most people infected with MPXV may present with mild symptoms and will recover fully within a few weeks, people can have serious diseases and complications and may need to be hospitalized with it. Although smallpox vaccines and antiviral drugs are also effective against MPX, there is still no specific vaccine or drug for MPXV infection. Therefore, we need to take the right attitude and measures to stop the MPXV outbreak. In this review, we summarize the characteristics, mechanisms, immunology, and transmission of MPXV, as well as current vaccines, diagnostics, and treatments used for MPX, and provide clues for controlling MPX outbreaks and preventing such diseases.

Keywords: Mpox; Epidemic; Smallpox; Outbreak; Poxvirus.

Introduction

Mpox (MPX), formerly known as Monkeypox, is a zoonosis caused by the Mpox virus (MPXV), which belongs to a genus of viruses called Orthopoxvirus, family Poxviridae [1,2]. MPXV has probably been infecting humans for a long time, but it was first identified in laboratory monkeys imported from Singapore to Denmark in 1958 (hence the name) and the first human case of MPX was reported in a 9-month-old infant from the Democratic Republic of the Congo in 1970 [3,4]. Since then, most cases have been reported from rural rainforest regions of the Congo Basin, particularly in the Democratic Republic of the Congo [5]. MPX was considered a rare sporadic disease with a limited ability to spread between humans [6]. However, the 2022 outbreak of the MPXV pandemic took the world by storm. From May 6, 2022, the number of infections and deaths in non-endemic countries was increasing dramatically [7]. On July 23, 2022, the World Health Organization (WHO) declared MPX a Public Health Emergency of International Concern [8]. As of February 25, 2023, a total of 110 countries have reported cases of MPX, with 86,127 laboratory-confirmed cases and 1,084 probable cases, including 97 deaths [9] (Fig. 1).

Characteristics of MPXV

MPXV has the typical rectangular shape and size of other poxviruses such as Smallpox, with a size of approximately 200 × 250 nm [10]. It has a dumbbell-shaped core with lateral bodies and the surface membranes show surface tubules or filaments [11] (Fig. 2). MPXV is an enveloped double-stranded DNA virus with approximately 197kb of genomic DNA encoding up to 280 genes and contains about 190 nonoverlapping open reading frames (ORFs, >180 nucleotides) [12,13]. As shown in Fig. 3, the genome of MPXV consists of a large conserved central genomic region with variable regions containing inverted terminal repeats (ITRs) at both ends [14]. Except for four ORFs located in the ITRs, all ORFs are present in the central region of the genome[15]. The non-conserved genes of MPXV, located in the variable regions at both ends, are most host range and virulence genes, which are mainly involved in MPXV immune escape [16,17]. In contrast, the genes in the central genomic region of MPXV are relatively conserved and encode structural proteins and essential enzymes [12]. The genome-wide analysis confirmed that there are two clades of MPXV: the Central African (Congo Basin) clade and the West African clade [18]. However, to avoid discriminatory geographical identification, the WHO announced the renaming of the MPXV clades on August 12, 2022, with new names consisting of Roman numerals and lowercase English letters. The experts convened by WHO referred to the previous Central African clade as Clade I and the previous West African clade as Clade II. Clade II includes two subclades, IIa and IIb, with IIb being the main group of virus variants transmitted in the 2022 Mpox outbreak. [19,20]. Clade I and Clade II are genetically different and have different toxicity and case fatality rate, 10.6% and 3.6%, respectively [18,21–23]. The genomic comparison revealed that the nucleotide divergence between the two clades was 0.55-0.56%. The Clade I had 173 unique functional genes, while the

Clade II had 171. Of the 56 virulence genes, 53 viral genes were shared by the two clades. The most striking differences between these two clades are in the gene orthogonal of BR-203, BR-209, and COP-C3L [21].

Pathogenesis of MPXV

MPXV may enter the host via the oropharynx, nasopharynx, or intradermal pathways. In the respiratory tract, the MPXV can infect airway epithelial cells, while in the skin, the virus infects keratinocytes, fibroblasts, and endothelial cells, establishing productive and cytopathic infections. In addition, antigen-presenting cells such as dendritic cells, Langerhans cells, and macrophages in the skin are infected by abortion, allowing them to survive long enough to carry the antigen to draining lymph nodes [24]. After a period of initial viremia, the virus spreads to other body organs. MPXV is a DNA virus, but its life cycle occurs in the cytoplasm and involves six stages, namely virus entry, uncoating, DNA replication, assembly, morphogenesis, and release (Fig. 4). There are two different infectious virus particles in MPXV: intracellular mature virus (IMV) and extracellular enveloped virus (EEV) [25]. IMVs with an outer lipoprotein envelope are responsible for transmission between hosts, and they enter the host cell by microcellular action or fusion and are released only during host cell lysis. In contrast, EEVs with an antigenically distinct outer triple envelope are responsible for transmission within the host, and they enter the host by fusion and are released by exocytosis [26]. MPXV replication is initiated by multi-subunit DNA-dependent RNA polymerases encoded by MPXV, which then translates early, intermediate, and late proteins on the host ribosome [27]. Late proteins are assembled to form the infectious virus IMVs, which are then encapsulated by a double membrane from the Golgi apparatus to form the intracellular enveloped virus (IEVs). IEVs lose their outer membrane wrapping by triggering actin polymerization and subsequently fuse with the cell membrane to form cell-associated enveloped viruses and eventually release to form EEVs [28]. Notably, cellular proteins such as COG4, COG7, vesicle protein sorting proteins VPS52 and VPS54 and some toxicity-related genomic regions such as ORF17-31, 181-192 are essential for MPXV infection, but how these proteins or genes collaborate to regulate MPXV-induced host pathogenesis is still unclear [29–31].

Immunology of MPXV

MPXV infection elicits both intrinsic and adaptive immune responses in the host. Pathogen-associated molecular patterns (PAMPs) from poxviruses and their envelope or core proteins can be sensed by pattern recognition receptors (PRRs) to initiate a faster but less specific innate immune response [32]. Intrinsic immunity is the host's first line of defense against poxvirus infection and includes the role of antiviral proteins such as IFN-I, pro-inflammatory cytokines, chemokines, and intrinsic immune cells such as NK cells [24,33–35]. These effector molecules and cells mediate direct antiviral effects or coordinate adaptive immune responses to contain different stages of poxvirus infection. Among them, IFN-I is the hallmark effector of the antiviral response, which interferes with viral replication by mediating viral mRNA degradation and inhibiting translation [36]. NK cells are important players in the host's innate defense against viral infection and contribute to cell-mediated immunity through cytokine secretion [37]. In addition, in a study of VARV-infected cynomolgus macaques, levels of IFN-γ, IL-8, IL-6, CCL2, and CCL4 were significantly increased during the first four days after infection [38]. In MPXV-infected rhesus monkeys, the number of NK cells in peripheral blood and lymph nodes was significantly increased [39]. The importance of B cells and immunoglobulins against poxvirus can be demonstrated by the successful global vaccination campaign using a live VACV vaccine [40,41]. Cross-reactive VACV-induced immunoglobulins from human vaccines have now been shown to recognize 14 MPXV proteins that have the potential to become antigen-based serodiagnostic tools [42]. In particular, three proteins, A26, D8, and H3, can be targets by neutralizing MPXV antibodies, while proteins A33, A44, and C19 are the major antigens of IgM isolated from macaques in the acute phase of MPXV infection [42]. T cells not only support antibody development but also exert a direct anti-orthopoxvirus effect. Helper T lymphocytes ($CD4^+$ T cells) play a role in promoting the recall and differentiation of memory B cells into antibody-secreting cells [43]. In a mouse model of VACV infection, $CD8^+$ T cells have been shown to eradicate virus-infected monocytes and minimize virus transmission [44]. In addition, IFN-γ secreted by $CD8^+$ T cells has been shown to protect against lethality [45].

Like many viruses, MPXV excels at blocking, evading, and tricking the body's immune protection in a variety

of ways. Here, we briefly discuss some of these mechanisms. MPXV can interfere with the recognition of viral molecules by intrinsic immune cells. Intrinsic immune cells are activated by binding PAMPs through their PRRs. Common PRRs include Toll-like receptor (TLR), NOD-like receptor, RIG-1-like receptor, C-type lectin-like receptor, and cytoplasmic protein kinase receptor [46,47]. Once the PRR binds to a viral molecular ligand, it initiates signaling cascade responses that activate inflammation-related transcription factors such as NF-ϰB, IRFs, and AP-1 [48]. MyD88, TRIF, and TRAM are intracellular adapter proteins involved in TLR signaling and are essential for triggering intracellular immune responses [49]. MPXV contains genes encoding a variety of proteins, such as protein A47R, which can interact with and impair the function of adaptor proteins, thereby inhibiting the activation of the inflammation-related transcription factors NF-ϰB and IRF3, resulting in the inability of the intrinsic immune system to recognize the virus [50]. In addition, MPXV inhibits the ability of cells to undergo apoptosis. For example, MPXV may block the activity of caspase-1, caspase-8, and caspase-9, which are essential for apoptosis [50,51]. MPXV also has genes encoding Bcl-2 protein mimetic activity, which play a key role in the regulation of apoptosis [50,52]. MPXV has been shown to evade intrinsic host immunity against viruses by encoding an F3 protein that inhibits multiple steps of IFN signaling [53,54]. MPXV encodes a complement control protein that prevents the initiation of the complement activation pathway [55]. In addition to the above mechanisms, MPXV has several genes encoding proteins that may interfere with cytokine and chemokine production and ubiquitin-proteasome activity, thereby disrupting various stages of the host inflammatory cascade response [50].

Clinical features

The clinical symptoms of MPXV infection are similar to those of other orthopoxviruses, but lymphadenopathy is a unique hallmark of MPXV infection [56]. There are three periods of human MPXV infection: incubation, onset, and rash periods. The incubation period is about 6 to 13 days and may be up to 21 days. The onset period lasts about 5 days and has atypical symptoms, including fever, chills, sweating, headache, sore throat, muscle pain, back pain, fatigue, and lymphadenopathy. The rash period usually begins after 1 to 3 days of fever and lymphadenopathy. The rash may initially start in the mouth, then on the face, and then appear elsewhere in the body. The rash goes through several stages of change, evolving in turn from maculae to papules, vesicles, and pustules, which may appear simultaneously in different stages, eventually crusting and healing [57]. However, in the 2022 MPX pandemic, many patients presented with atypical disease manifestations such as anal pain and bleeding, and these lesions were usually located in the genital, perineal, or perianal regions [2]. MPX is a self-limiting disease, the duration of its symptoms usually lasts 5 to 21 days, and most MPXV-infected patients will heal on their own within 2 to 4 weeks [58]. However, in some cases, it can make the condition worse and may even lead to life-threatening complications. For example, those patients with untreated HIV infection who are co-infected with MPXV have a longer duration of disease, more severe lesions, and a higher incidence of secondary bacterial skin infections and genital ulcers [59]. The overall mortality rate of MPXV infection varies depending on the age of the patient, the branch of the virus, and the region of the outbreak.

Transmission

MPX is a zoonotic disease. The natural reservoir for MPX has not yet been identified, but it is thought that rodents could be the most likely reservoir for this particular virus. Transmission of MPXV from animals to humans can occur in contact with the body fluids of infected animals or when scratched by infected animals, and transmission through urine and feces may be an additional source of infection (Fig. 5). Interpersonal transmission can occur through continuous face-to-face contact with large respiratory droplets, or through direct contact with viral lesions, body fluids, and through virally infected materials such as bedding and clothing, etc [60]. According to the Centers for Disease Control and Prevention (CDC), MXPV transmission is more likely to come from intimate person-to-person contact, including kissing, hugging, sex, or touching body parts with MPX sores [61]. Mother-to-child transmission can also occur through the placenta during and after birth through close contact [61]. The first major outbreak of MPX in 2022 in a non-endemic country mainly affected men (homosexual or bisexual) [62,63]. Unlike other viral diseases such as SARS-CoV-2 infection, MPXV-infected individuals seem to spread only after the first symptoms appear [64]. It is

not clear whether MPXV can be transmitted through semen and vaginal fluids.

Diagnosis

The diagnostic analysis is essential to confirm MPXV infection and to rule out other infectious diseases. Samples of skin lesions are the best clinical samples for laboratory analysis, such as swabs of vesicular lesions, exudates, or crusts kept in cool, dry sterile tubes [57]. Viral cultures should be obtained by oropharyngeal or nasopharyngeal swabs [57]. Medical history, clinical symptoms, and laboratory studies help to diagnose MPXV infection. Laboratory studies include PCR, ELISA, Western Blot, and immunohistochemistry, and according to WHO, RT-PCR is the test of choice to identify MPXV during severe infection [2].

Vaccination

Due to genetic similarity, Smallpox vaccination cross-protects against MPX (Tab. 1). The U.S. Food and Drug Administration (FDA) has approved the Smallpox vaccine JYNNEOS (Bavarian Nordic) for high-risk populations to prevent MPX, and the ACAM2000 vaccine can be used off-label for the same purpose [65]. According to the CDC, MPXV infection is expected to be prevented if the vaccine is administered within four days of exposure to MPXV due to the long incubation period of the virus [61]. In the United States and Canada, MVA, a third-generation Smallpox vaccine, has been licensed for use against MPX [66]. WHO classifies the current MPXV vaccine into replicating vaccine (ACAM2000), minimal replicating vaccine (LC16m8), and non-replicating vaccine (MVA-BN), the latter being the currently used vaccine [2] (Tab. 2).

	Mpox	Smallpox
Virus	Mpox virus	Variola virus
Strains and Genotypes	2 clades	4 types of variola major smallpox
Reservoirs	Monkeys, rodents, etc.	Humans
Incubation period	6 13 days, may be up to 21 days	7˜19 days
symptoms	Fever, rash in the mouth or on the face primarily	Fever, small red spots on the tongue, rash on t
Fever	1˜5 days	2 4 days
Lymphadenopathy	Yes	No
How long illness lasts	2 4 weeks	Up to 5 weeks
Mortality	1˜10% of cases	Up to 30% of cases
Vaccine	Smallpox vaccine	Smallpox vaccine

Tab.1 Mpox and Smallpox compared

Vaccine	ACAM2000	LC16m8	MVA-BN
Country	USA	Japan	USA
Vaccine type	Live replicating vaccinia virus	Live, replicating attenuated vaccine	non-replicating
Dose	1 dose, scarification, booster every 3 years	Single dose, scarification	2 doses, s.c., primary se
Date approved	2007.08	1975	2019.09
Generation	Second-generation	Third-generation	Third-generation

Tab.2 Available Mpox vaccines

Treatment

MPXV usually causes mild symptoms and most patients recover without treatment. However, in severe cases of MPX, supportive care, symptom management, and treatment of secondary bacterial infections remain the main recommendations [57]. No effective antiviral therapy has been identified yet, however, some antiviral drugs for Smallpox can also be used for MPX [7]. Tecovirimat (ST-246) was first proposed as an antiviral

candidate for the treatment of orthopoxvirus infections in 2005 [67]. Studies have proven that treatment with Tecovirimat is effective in animal models and human cases, with a significant reduction in mortality [68,69]. Tecovirimat has been approved by the FDA for use in the treatment of MPX during outbreaks [70]. F13/VP37, the viral structural protein of MPXV, plays an essential role in the formation of cell-associated enveloped viruses prior to viral release. Tecovirimat inhibits the spread of the virus within the infected host by inhibiting F13/VP37 [71]. Some studies have now demonstrated the potential of drugs targeting inhibition of the MPXV-F13 protein for the successful treatment of MPXV, although additional in vitro and in vivo experiments are still necessary [72,73]. Cidofovir is a broad-spectrum antiviral drug effective against almost all DNA viruses, and its anti-MPXV activity in vivo has been demonstrated in different monkey infection models [74]. However, cidofovir is only effective in preventing death if given before the onset of the rash [75]. Because cidofovir causes significant nephrotoxicity and has limited efficacy data in human MPX, the use of this drug is likely to remain limited to the treatment of severe cases [27]. CMX001 and Brincindofovir, as cidofovir derivatives, block orthopoxvirus DNA polymerase-mediated viral DNA synthesis. These drugs have a better renal safety profile compared to cidofovir. A UK report found that seven patients recovered completely from MPX infection after treatment with Brincindofovir, although three of them developed elevated alanine transaminases [58]. Vaccinia Immune Globulin Intravenous can be used to treat MPX during outbreaks and complications due to vaccinia vaccination [7].

Conclusion and outlook

Unlike the SARS-CoV-2, which is emerging in 2019, MPXV is a re-emerging old virus. Few cases of MPX were once reported in countries outside of Central and West Africa. However, the MPXV pandemic that broke out in the summer of 2022 has spread to nearly 110 different countries including the United States, Canada, Australia, and some European countries. The exact cause of the pandemic is not yet known, but it may be related to the phasing out of Smallpox vaccination in various countries starting in 1980 [76]. Although the threat of MPXV to global mass epidemics is much less severe than SARS-CoV-2 and the number of MPX cases has been declining, there is still a need to focus on completely containing the outbreak. Due to globalization and advances in transportation, humans and animals are exposed to many new diseases for which natural immunity is lacking, thus accelerating the emergence of the unprecedented spread of infectious diseases such as MPX. We cannot predict the next infection to emerge, but this outbreak of MPX in a non-endemic area is a wake-up call. Outbreaks in low-resource areas have long lacked the attention and resources needed for an effective response, such as the vast disparities in access to vaccine resources around the world. To ensure that all MPX-affected countries end this nightmare once and for all and that humanity does not repeat it in the future, countries must not ignore infectious agents that are considered to be geographically limited. Whether it is health education, behavior change, or vaccination and treatment utilization, public health organizations and countries need to take a proactive and equitable approach.

Conflicts of interest

The authors declare that they have no competing interests.

Authors' contributions

DDW, ZGR and XYJ conceived the study. YW, YXZ, XYL, YFL, WG, HY, and YQJ drafted the manuscript and prepared the figures. All authors read and approved the final manuscript.

Acknowledgments

This work was supported by grants from the National Natural Science Foundation of China (Nos. 31902287, 81670088), the Training Program for Young Backbone Teachers of Institutions of Higher Learning in Henan Province, China (No. 2020GGJS038), and the Foundation of Science & Technology Department of Henan Province, China (Nos. 222102310490, 222102310495).

REFERENCE

[1] Anon WHO recommends new name for monkeypox disease

[2] WHO 2022 Monkeypox

[3] Magnus P von, Andersen E K, Petersen K B and Birch-Andersen A 2009 A POX-LIKE DISEASE IN CYNOMOLGUS MONKEYS Acta Pathologica Microbiologica Scandinavica 46 156–76

[4] Ladnyj I D, Ziegler P and Kima E 1972 A human infection caused by monkeypox virus in Basankusu Territory, Democratic Republic of the Congo Bull World Health Organ 46 593–7

[5] Nolen L D, Osadebe L, Katomba J, Likofata J, Mukadi D, Monroe B, Doty J, Hughes C M, Kabamba J, Malekani J, Bomponda P L, Lokota J I, Balilo M P, Likafi T, Lushima R S, Ilunga B K, Nkawa F, Pukuta E, Karhemere S, Tamfum J-J M, Nguete B, Wemakoy E O, McCollum A M and Reynolds M G 2016 Extended Human-to-Human Transmission during a Monkeypox Outbreak in the Democratic Republic of the Congo Emerg Infect Dis 22 1014–21

[6] Anon 1984 The current status of human monkeypox: Memorandum from a WHO Meeting Bull World Health Organ 62 703–13

[7] Kumar N, Acharya A, Gendelman H E and Byrareddy S N 2022 The 2022 outbreak and the pathobiology of the monkeypox virus J Autoimmun 131 102855

[8] WHO 2022 WHO Director-General's statement at the press conference following IHR Emergency Committee regarding the multi-country outbreak of monkeypox - 23 July 2022

[9] Anon 2022-23 Mpox (Monkeypox) Outbreak: Global Trends

[10] Cho C T and Wenner H A 1973 Monkeypox virus. Bacteriol Rev 37 1–18

[11] Anon 130s.pdf

[12] Kugelman J R, Johnston S C, Mulembakani P M, Kisalu N, Lee M S, Koroleva G, McCarthy S E, Gestole M C, Wolfe N D, Fair J N, Schneider B S, Wright L L, Huggins J, Whitehouse C A, Wemakoy E O, Muyembe-Tamfum J J, Hensley L E, Palacios G F and Rimoin A W 2014 Genomic Variability of Monkeypox Virus among Humans, Democratic Republic of the Congo Emerg Infect Dis 20 232–9

[13] Smith G L and Law M 2004 The exit of vaccinia virus from infected cells Virus Res 106 189–97

[14] Moss B 2001 Poxviridae: the viruses and their replication, vol. 2 Knipe, DMl

[15] Berthet N, Descorps-Declère S, Besombes C, Curaudeau M, Nkili Meyong A A, Selekon B, Labouba I, Gonofio E C, Ouilibona R S, Simo Tchetgna H D, Feher M, Fontanet A, Kazanji M, Manuguerra J-C, Hassanin A, Gessain A and Nakoune E 2021 Genomic history of human monkey pox infections in the Central African Republic between 2001 and 2018 Sci Rep 11 13085

[16] Shchelkunov S N, Totmenin A V, Safronov P F, Mikheev M V, Gutorov V V, Ryazankina O I, Petrov N A, Babkin I V, Uvarova E A, Sandakhchiev L S, Sisler J R, Esposito J J, Damon I K, Jahrling P B and Moss B 2002 Analysis of the Monkeypox Virus Genome Virology 297 172–94

[17] Esposito J J and Knight J C 1985 Orthopoxvirus DNA: a comparison of restriction profiles and maps Virology 143 230–51

[18] Likos A M, Sammons S A, Olson V A, Frace A M, Li Y, Olsen-Rasmussen M, Davidson W, Galloway R, Khristova M L, Reynolds M G, Zhao H, Carroll D S, Curns A, Formenty P, Esposito J J, Regnery R L and Damon I K Y 2005 A tale of two clades: monkeypox viruses Journal of General Virology 86 2661–72

[19] Happi C, Adetifa I, Mbala P, Njouom R, Nakoune E, Happi A, Ndodo N, Ayansola O, Mboowa G, Bedford T, Neher R A, Roemer C, Hodcroft E, Tegally H, O'Toole Á, Rambaut A, Pybus O, Kraemer M U G, Wilkinson E, Isidro J, Borges V, Pinto M, Gomes J P, Freitas L, Resende P C, Lee R T C, Maurer-Stroh S, Baxter C, Lessells R, Ogwell A E, Kebede Y, Tessema S K and de Oliveira T 2022 Urgent need for a non-discriminatory and non-stigmatizing nomenclature for monkeypox virus PLoS Biol 20 e3001769

[20] Anon 2022 Monkeypox: experts give virus variants new names

[21] Chen N, Li G, Liszewski M K, Atkinson J P, Jahrling P B, Feng Z, Schriewer J, Buck C, Wang C, Lefkowitz E J, Esposito J J, Harms T, Damon I K, Roper R L, Upton C and Buller R M L 2005 Virulence differences between monkeypox virus isolates from West Africa and the Congo basin Virology 340 46–63

[22] Parker S and Buller R M 2013 A review of experimental and natural infections of animals with monkeypox virus between 1958 and 2012 Future Virol 8 129–57

[23] Bunge E M, Hoet B, Chen L, Lienert F, Weidenthaler H, Baer L R and Steffen R 2022 The changing epidemiology of human monkeypox—A potential threat? A systematic review PLoS Negl Trop Dis 16 e0010141

[24] Lum F-M, Torres-Ruesta A, Tay M Z, Lin R T P, Lye D C, Rénia L and Ng L F P 2022 Monkeypox: disease epidemiology, host immunity and clinical interventions Nat Rev Immunol 22 597–613

[25] Swiss Institute of Bioinformatics (SIB) 2022 Orthopoxvirus ˜ ViralZone

[26] Pickup D J 2015 Extracellular Virions: The Advance Guard of Poxvirus Infections PLoS Pathog 11 e1004904

[27] Kmiec D and Kirchhoff F 2022 Monkeypox: A New Threat? Int J Mol Sci 23 7866

[28] Smith G L, Vanderplasschen A and Law M 2002 The formation and function of extracellular enveloped vaccinia virus J Gen Virol 83 2915–31

[29] Realegeno S, Priyamvada L, Kumar A, Blackburn J B, Hartloge C, Puschnik A S, Sambhara S, Olson V A, Carette J E, Lupashin V and Satheshkumar P S 2020 Conserved Oligomeric Golgi (COG) Complex Proteins Facilitate Orthopoxvirus Entry, Fusion and Spread Viruses 12 707

[30] Realegeno S, Puschnik A S, Kumar A, Goldsmith C, Burgado J, Sambhara S, Olson V A, Carroll D, Damon I, Hirata T, Kinoshita T, Carette J E and Satheshkumar P S 2017 Monkeypox Virus Host Factor Screen Using Haploid Cells Identifies Essential Role of GARP Complex in Extracellular Virus Formation J Virol 91 e00011-17

[31] Lopera J G, Falendysz E A, Rocke T E and Osorio J E 2015 Attenuation of monkeypox virus by deletion of genomic regions Virology 475 129–38

[32] Yu H, Bruneau R C, Brennan G and Rothenburg S 2021 Battle Royale: Innate Recognition of Poxviruses and Viral Immune Evasion Biomedicines 9 765

[33] Bartlett N W, Dumoutier L, Renauld J-C, Kotenko S V, McVey C E, Lee H-J and Smith G L 2004 A new member of the interleukin 10-related cytokine family encoded by a poxvirus J Gen Virol 85 1401–12

[34] Wong P-S, Sutejo R, Chen H, Ng S-H, Sugrue R J and Tan B-H 2018 A System Based-Approach to Examine Cytokine Response in Poxvirus-Infected Macrophages Viruses 10 692

[35] Lalani A S and McFadden G 1997 Secreted poxvirus chemokine binding proteins J Leukoc Biol 62 570–6

[36] Meng X, Schoggins J, Rose L, Cao J, Ploss A, Rice C M and Xiang Y 2012 C7L Family of Poxvirus Host Range Genes Inhibits Antiviral Activities Induced by Type I Interferons and Interferon Regulatory Factor 1 J Virol 86 4538–47

[37] Paust S, Senman B and von Andrian U H 2010 Adaptive immune responses mediated by natural killer cells Immunol Rev 235 286–96

[38] Jahrling P B, Hensley L E, Martinez M J, LeDuc J W, Rubins K H, Relman D A and Huggins J W 2004 Exploring the potential of variola virus infection of cynomolgus macaques as a model for human smallpox Proc Natl Acad Sci U S A 101 15196–200

[39] Song H, Josleyn N, Janosko K, Skinner J, Reeves R K, Cohen M, Jett C, Johnson R, Blaney J E, Bollinger L, Jennings G and Jahrling P B 2013 Monkeypox virus infection of rhesus macaques induces massive expansion of natural killer cells but suppresses natural killer cell functions PLoS One 8 e77804

[40] Strassburg M A 1982 The global eradication of smallpox American Journal of Infection Control 10 53–9

[41] Cherry J D, McIntosh K, Connor J D, Benenson A S, Alling D W, Rolfe U T, Todd W A, Schanberger J E and Mattheis M J 1977 Primary Percutaneous Vaccination The Journal of Infectious Diseases 135 145–54

[42] Keasey S, Pugh C, Tikhonov A, Chen G, Schweitzer B, Nalca A and Ulrich R G 2010 Proteomic Basis of the Antibody Response to Monkeypox Virus Infection Examined in Cynomolgus Macaques and a Comparison to Human Smallpox Vaccination PLOS ONE 5 e15547

[43] MacLeod M K L, Clambey E T, Kappler J W and Marrack P 2009 CD4 memory T cells: what are they and what can they do? Semin Immunol 21 53–61

[44] Hickman H D, Reynoso G V, Ngudiankama B F, Rubin E J, Magadán J G, Cush S S, Gibbs J, Molon B, Bronte V, Bennink J R and Yewdell J W 2013 Anatomically restricted synergistic antiviral activities of innate and adaptive immune cells in the skin Cell Host Microbe 13 155–68

[45] Goulding J, Abboud G, Tahiliani V, Desai P, Hutchinson T and Salek-Ardakani S 2014 CD8 T cells utilize IFN-γ to protect against the lethal effects of a respiratory poxvirus infection J Immunol 192 5415–25

[46] Iwasaki A and Medzhitov R 2010 Regulation of adaptive immunity by the innate immune system Science 327 291–5

[47] Kawai T and Akira S 2006 Innate immune recognition of viral infection Nat Immunol 7 131–7

[48] Rathinam V A K and Fitzgerald K A 2011 Innate Immune sensing of DNA viruses Virology 411 153–62

[49] O'Neill L A J and Bowie A G 2007 The family of five: TIR-domain-containing adaptors in Toll-like receptor signalling Nat Rev Immunol 7 353–64

[50] Shchelkunov S N 2012 Orthopoxvirus Genes That Mediate Disease Virulence and Host Tropism Adv Virol 2012 524743

[51] Shi Y 2004 Caspase activation, inhibition, and reactivation: A mechanistic view Protein Sci 13 1979–87

[52] Youle R J and Strasser A 2008 The BCL-2 protein family: opposing activities that mediate cell death Nat Rev Mol Cell Biol 9 47–59

[53] Arndt W D, White S D, Johnson B P, Huynh T, Liao J, Harrington H, Cotsmire S, Kibler K V, Langland J and Jacobs B L 2016 Monkeypox virus induces the synthesis of less dsRNA than vaccinia virus, and is more resistant to the anti-poxvirus drug, IBT, than vaccinia virus Virology 497 125–35

[54] Arndt W D, Cotsmire S, Trainor K, Harrington H, Hauns K, Kibler K V, Huynh T P and Jacobs B L 2015 Evasion of the Innate Immune Type I Interferon System by Monkeypox Virus J Virol 89 10489–99

[55] Hudson P N, Self J, Weiss S, Braden Z, Xiao Y, Girgis N M, Emerson G, Hughes C, Sammons S A, Isaacs S N, Damon I K and Olson V A 2012 Elucidating the Role of the Complement Control Protein in Monkeypox Pathogenicity PLoS One 7 e35086

[56] Jezek Z, Szczeniowski M, Paluku K M and Mutombo M 1987 Human monkeypox: clinical features of 282 patients J Infect Dis 156 293–8

[57] Petersen E, Kantele A, Koopmans M, Asogun D, Yinka-Ogunleye A, Ihekweazu C and Zumla A 2019 Human Monkeypox Infect Dis Clin North Am 33 1027–43

[58] Adler H, Gould S, Hine P, Snell L B, Wong W, Houlihan C F, Osborne J C, Rampling T, Beadsworth M B, Duncan C J, Dunning J, Fletcher T E, Hunter E R, Jacobs M, Khoo S H, Newsholme W, Porter D, Porter R J, Ratcliffe L, Schmid M L, Semple M G, Tunbridge A J, Wingfield T, Price N M, and NHS

England High Consequence Infectious Diseases (Airborne) Network 2022 Clinical features and management of human monkeypox: a retrospective observational study in the UK Lancet Infect Dis 22 1153–62

[59] Ogoina D, Iroezindu M, James H I, Oladokun R, Yinka-Ogunleye A, Wakama P, Otike-Odibi B, Usman L M, Obazee E, Aruna O and Ihekweazu C 2020 Clinical Course and Outcome of Human Monkeypox in Nigeria Clin Infect Dis 71 e210–4

[60] Hutson C L, Carroll D S, Gallardo-Romero N, Weiss S, Clemmons C, Hughes C M, Salzer J S, Olson V A, Abel J, Karem K L and Damon I K 2011 Monkeypox disease transmission in an experimental setting: prairie dog animal model PLoS One 6 e28295

[61] CDC 2022 Monkeypox in the U.S. Centers for Disease Control and Prevention

[62] Vivancos R, Anderson C, Blomquist P, Balasegaram S, Bell A, Bishop L, Brown C S, Chow Y, Edeghere O, Florence I, Logan S, Manley P, Crowe W, McAuley A, Shankar A G, Mora-Peris B, Paranthaman K, Prochazka M, Ryan C, Simons D, Vipond R, Byers C, Watkins N A, Welfare W, Whittaker E, Dewsnap C, Wilson A, Young Y, Chand M, Riley S, Hopkins S, Charlett A, Finnie T, McAuslane H, Weeple B, Fifer H, Sinka K, Edwards D, Lopez-Bernal J, Rampling T, Lee A, Mellon D, Kliner M, Young N, Makki S, Coles S, Shepherd W, Latham V, Tabor R, Graham A, Yuan J, MacDonald N, Vusirikala A, Ma T, Cooper K and Saavedra-Campos M 2022 Community transmission of monkeypox in the United Kingdom, April to May 2022 Euro Surveill 27 2200422

[63] Philpott D, Hughes C M, Alroy K A, Kerins J L, Pavlick J, Asbel L, Crawley A, Newman A P, Spencer H, Feldpausch A, Cogswell K, Davis K R, Chen J, Henderson T, Murphy K, Barnes M, Hopkins B, Fill M-M A, Mangla A T, Perella D, Barnes A, Hughes S, Griffith J, Berns A L, Milroy L, Blake H, Sievers M M, Marzan-Rodriguez M, Tori M, Black S R, Kopping E, Ruberto I, Maxted A, Sharma A, Tarter K, Jones S A, White B, Chatelain R, Russo M, Gillani S, Bornstein E, White S L, Johnson S A, Ortega E, Saathoff-Huber L, Syed A, Wills A, Anderson B J, Oster A M, Christie A, McQuiston J, McCollum A M, Rao A K, Negrón M E, Griffin I, Khan M, Ogale Y, Sims E, Lash R R, Rainey J J, Charniga K, Waltenburg M A, Dawson P, Quilter L A S, Rushmore J, Stenger M R, Kachur R E, Whitehill F, Jackson K A, Collins J, Signs K, Richardson G, Hand J, Spence-Davizon E, Steidley B, Osborne M, Soliva S, Cook S, Ayuk-Takor L, Willut C, Snively A, Lehnertz N, Quilliam D N, Durham M, Cardona-Gerena I R, Bell L J, Control E, Kuljanin M, Gibbons-Burgener S, Westergaard R, Sosa L E, Beddo M, Donahue M, Koirala S, Dewart C, Murray-Thompson J, Peake L, Holshue M L, et al 2022 Epidemiologic and Clinical Characteristics of Monkeypox Cases — United States, May 17–July 22, 2022 MMWR Morb Mortal Wkly Rep 71 1018–22

[64] Daskalakis D, McClung R P, Mena L, Mermin J, and Centers for Disease Control and Prevention's Monkeypox Response Team 2022 Monkeypox: Avoiding the Mistakes of Past Infectious Disease Epidemics Ann Intern Med 175 1177–8

[65] Commissioner O of the 2020 FDA approves first live, non-replicating vaccine to prevent smallpox and monkeypox FDA

[66] Volz A and Sutter G 2017 Modified Vaccinia Virus Ankara Adv Virus Res 97 187–243

[67] Yang G, Pevear D C, Davies M H, Collett M S, Bailey T, Rippen S, Barone L, Burns C, Rhodes G, Tohan S, Huggins J W, Baker R O, Buller R L M, Touchette E, Waller K, Schriewer J, Neyts J, DeClercq E, Jones K, Hruby D and Jordan R 2005 An orally bioavailable antipoxvirus compound (ST-246) inhibits extracellular virus formation and protects mice from lethal orthopoxvirus Challenge J Virol 79 13139–49

[68] Russo A T, Berhanu A, Bigger C B, Prigge J, Silvera P M, Grosenbach D W and Hruby D 2020 Co-administration of tecovirimat and ACAM2000TM in non-human primates: Effect of tecovirimat treatment on ACAM2000 immunogenicity and efficacy versus lethal monkeypox virus challenge Vaccine 38 644–54

[69] Anon Monkeypox Virus Infection in Humans across 16 Countries — April–June 2022 | NEJM

[70] Anon FDA Mpox Response | FDA

[71] Russo A T, Grosenbach D W, Chinsangaram J, Honeychurch K M, Long P G, Lovejoy C, Maiti B, Meara I and Hruby D E 2021 An overview of tecovirimat for smallpox treatment and expanded anti-orthopoxvirus applications Expert Review of Anti-infective Therapy 19 331–44

[72] Ali Y, Imtiaz H, Tahir M M, Gul F, Saddozai U A K, ur Rehman A, Ren Z-G, Khattak S and Ji X-Y 2023 Fragment-Based Approaches Identified Tecovirimat-Competitive Novel Drug Candidate for Targeting the F13 Protein of the Monkeypox Virus Viruses 15 570

[73] Chen Z-R, Lv Q-L, Peng H-W, Liu X-Y, Hu W-L and Hu J-F 2022 Drug screening against F13 protein, the target of tecovirimat, as potential therapies for monkeypox virus J Infect

[74] Andrei G and Snoeck R 2010 Cidofovir Activity against Poxvirus Infections Viruses 2 2803–30

[75] Meyer H, Ehmann R and Smith G L 2020 Smallpox in the Post-Eradication Era Viruses 12 138

[76] Jezek Z, Marennikova S S, Mutumbo M, Nakano J H, Paluku K M and Szczeniowski M 1986 Human monkeypox: a study of 2,510 contacts of 214 patients J Infect Dis 154 551–5

Figure Legends

Figure 1. (A) Timeline of development related to the Mpox (MPX) outbreaks. hMPX: human Mpox, the DRC: the Democratic Republic of the Congo, the USA: the United States of America, the UK: the United Kingdom, WHO: the World Health Organization, PHEIC: Public Health Emergency of International Concern. **(B)** World distribution map of laboratory-confirmed cases of MPX. **(C)** Daily confirmed cases of MPX. (Data from WHO from January 1, 2022, to February 25, 2023)

Figure 2. Structure of Mpox virus (MPXV). MPXV has two morphological structures, the mature virus (MV) and the extracellular enveloped virus (EV). the outside of the MV is a lipid membrane and the MV wrapped by another lipid membrane is the EV morphological structure. Inside the membrane are a lateral body and a dumbbell-shaped internal core containing MPXV double-stranded DNA and some other proteins.

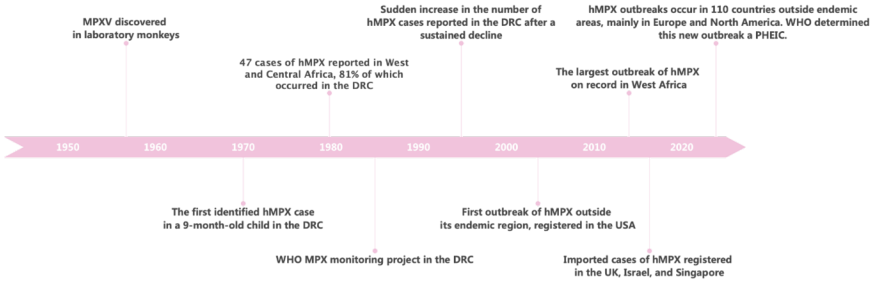
Figure 3. Genomic structure of Mpox virus (MPXV). The genome of MPXV is approximately 197 kb and consists of two variable regions and a large conserved central genomic region. The central genomic region (from C10L to A25R) consists of 101,476 bp. The terminal inverted repeat (ITR) located in the two variable regions is 6,379 bp, and the region consists of some ORFs, an 80 bp hairpin loop, 45 bp short tandem repeats, NR1 (85 bp) and NR2 (322 bp) regions, and the coding region.

Figure 4. Replication cycle of Mpox virus (MPXV) and mechanism of action of some anti-poxvirus drugs. Tecovirimat prevents the formation of cell-associated enveloped virus (CEV) and extracellular enveloped virus (EEV), while cidofovir and brincidofovir inhibit viral DNA polymerase

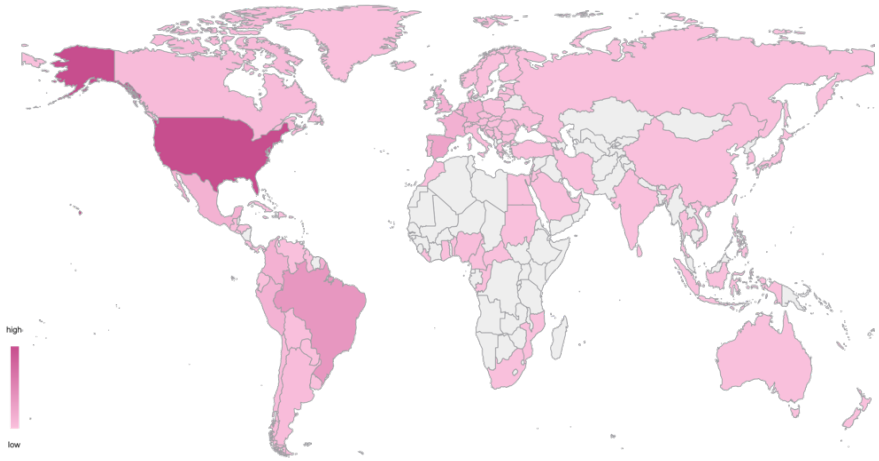
Figure 5. Mpox (MPV) transmission. MPV can be transmitted in many ways. Animal-to-human transmission can occur through direct contact with the body fluids of animals infected with the MPXV (e.g., monkeys, squirrels, etc.) or lesions of infected animals, scratching or biting of animals, and consumption of meat from infected animals, while human-to-human transmission can occur through sexual contact and contact with contaminated objects, respiratory secretions of these infected individuals, skin lesions, and their bedding and clothing.

Figure 1

(**A**)



(B)



(C)

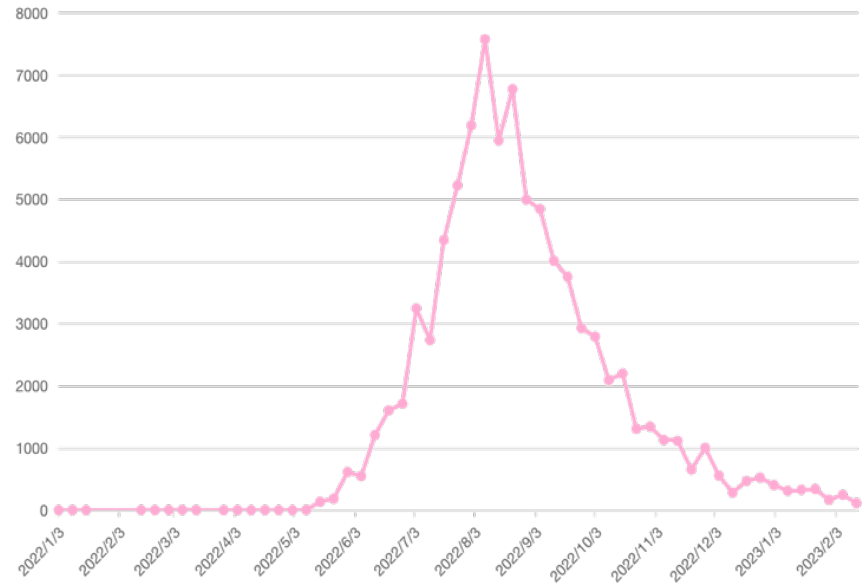


Figure 2

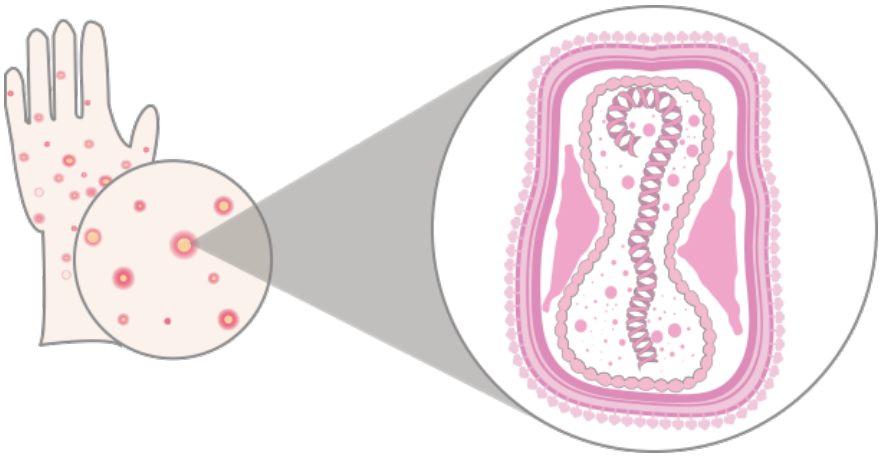


Figure 3

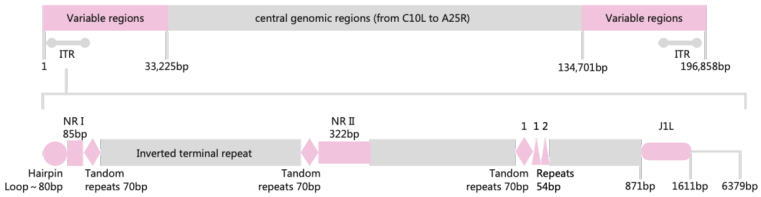


Figure 4

Hosted file

`image6.emf` available at https://authorea.com/users/603537/articles/633824-the-neglected-mpox-virus-from-historical-review-to-future-perspectives

Figure 5

Hosted file

`image7.emf` available at https://authorea.com/users/603537/articles/633824-the-neglected-mpox-virus-from-historical-review-to-future-perspectives