Review

Monkeypox virus: a re-emergent threat to humans

Qizan Gong a, Changle Wang b, Xia Chuaib,*, Sandra Chiu a, *

a Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, 230026, China
b Department of Pathogenic Biology, Hebei Medical University, Shijiazhuang, Hebei, 050017, China

ARTICLE INFO

Keywords:
Monkeypox virus (MPXV)
Orthopoxvirus
Smallpox vaccine
Antiviral drugs

ABSTRACT

Human monkeypox (MPX) is a rare zoonotic infection characterized by smallpox-like signs and symptoms. It is caused by monkeypox virus (MPXV), a double stranded DNA virus belonging to the genus Orthopoxvirus. MPXV was first identified in 1970 and mostly prevailed in the rural rainforests of Central and West Africa in the past. Outside Africa, MPXV was reported in the United Kingdom, the USA, Israel, and Singapore. In 2022, the resurgence of MPXV in Europe and elsewhere posed a potential threat to humans. MPXV was transmitted by the animals-human or human-human pathway, and the symptoms of MPXV infection are similar to that of smallpox, but in a milder form and with lower mortality (1%–10%). Although the smallpox vaccination has been shown to provide 85% protection against MPXV infection, and two anti-smallpox virus drugs have been approved to treat MPXV, there are still no specific vaccines and drugs against MPXV infection. Therefore it is urgent to take active measures including the adoption of novel anti-MPX strategies to control the spread of MPXV and prevent MPX epidemic. In this review, we summarize the biological features, epidemiology, pathogenicity, laboratory diagnosis, and prevention and treatment strategies on MPXV. This review provides the basic knowledge for prevention and control of future outbreaks of this emerging infection.

1. Introduction

Monkeypox (MPX) is a rare zoonotic infectious disease caused by the monkeypox virus (MPXV). The earlier outbreaks happened mostly in Central and West Africa, commonly known as “monkey smallpox”. Its symptoms are similar to that of smallpox, but the disease is milder, mainly manifested as high fever, headache, lymphadenopathy, and systemic blisters and pustules, with a case fatality rate of about 1%–10% (Doshi et al., 2019; Ogoina et al., 2019). Recently, MPXV has occurred in Europe and North America. Since MPX cases were first reported in Europe in early May 2022, more than 400 confirmed or suspected cases have emerged in at least 20 non-African nations (Kozlov, 2022b). The UK’s first case of MPV in 2022 had traveled to Nigeria before its diagnosis, but many of the new confirmed cases had no history of travel to Nigeria or Africa, suggesting that MPXV had begun community transmission (Mahase, 2022). The continuous emergence of the MPX epidemic has attracted widespread attention around the world and has been suspected to be a potential threat to wider populations. Although smallpox vaccine has been reported to provide 85% protection against MPXV (Fine et al., 1988), the smallpox virus vaccination has been discontinued since 1980 (Jezeck et al., 1987), when the WHO announced the eradication of smallpox. And there is a lack of specific drugs and vaccines to MPXV. Therefore, to curb the spread of MPX epidemics, it is necessary to have an in-depth understanding of the biological characteristics and pathogenicity of MPXV. Here, we reviewed the current research progress of MPXV and provided clues for prevention and control of MPX outbreak.

2. Biological features of MPXV

MPXV belongs to the genus Orthopoxvirus, family Poxviridae. The virus particles are oval or brick-shaped and approximately 200 × 250 nm in size (Cho and Wenner, 1979). Poxvirus produces two infectious viral particles during replication: intracellular mature virus (MV) and extracellular enveloped virus (EV). The outer layer of MV has a lipoprotein envelope that encloses the viral core and lateral body containing some proteins. MV is released upon cell lysis and it is relatively stable in the external environment. It is mainly used for transmission between animals. EV is released by exocytosis and formed by a lipid membrane wrapped around MVs. It is derived from the transport Golgi apparatus or endosomes (Pickup, 2015). The MPXV genome is a linear, double-stranded DNA, approximately 197 kb (Kugelman et al., 2014), with inverted terminal repeats (ITRs) at its ends, and more than 190
ORFs were encoded by some MPXV strains (e.g. Congo,2003_358). The non-conserved genes of the virus are generally located in ITRs at both ends, which are poxvirus species and host-specific. They are mostly associated with the immune escape of the poxvirus, such as inhibiting apoptosis, interfering with antigen presentation and recognition, and overcoming interferon (IFN) influence and disturbing with other signal paths (Esposito and Knight, 1985), etc. Like all orthopoxviruses, genes encoding viral replication enzymes and structural proteins are relatively conservative, mostly located in the central region of the genome. They encode all the proteins needed for viral DNA replication, transcription, assembly, and release (Kugelman et al., 2014).

MPXV completes its replication process in the cytoplasm. The invasion of host cells by poxvirus is mainly completed by three steps: adsorption, membrane fusion and core invasion. Specific cell receptors for poxvirus have not been identified, but for vaccinia virus (VACV), which is most in likely MPXV, four viral proteins (D8, A27, A26 and H3) were found to mediate viral adsorption on the cell surface. D8 binds to chondroitin (Matho et al., 2018), A27 and H3 bind to heparan (Singh et al., 2016), and A26 binds to laminin (Chiu et al., 2007). Knockout of genes encoding A27 and H3 significantly reduces the infectivity of VACV. MPXV E8, A29, A28 and H3 proteins are the VACV D8, A27, A26 and H3 orthologs respectively, which share the same functions as those in VACV (Hughes et al., 2014). For VACV, membrane fusion and core invasion of MV are mediated by 11 viral proteins, including A16, A21, A28, F9, G3, G9, H2, J5, L1, L5, and O3, which together form an entry fusion complex (EFC) mediating the invasion of MV and EV after viral adsorption (Schin et al., 2021; Senkevich et al., 2005). Except for the O3 protein, the remaining 10 proteins are necessary for poxvirus replication, but the deletion of the gene encoding O3 protein can also seriously affect VACV replication. EFC is known to have three subcomponents, A28-H2, A16-G9, and G3-L5. A16-G9 sub-complex interacts with the viral A56-K2 complex to inhibit cell fusion under repeated infections and neutral pH conditions, and can also interact with A26 proteins on the surface of MV to prevent fusion under neutral pH conditions after adsorption (Chang et al., 2012). L1 and A28 are VACV envelope proteins which are essential for cellular entry (Foo et al., 2009). A28 binds to the H2 protein and its immunogenicity is enhanced (Kaever et al., 2014). After the membrane of MV is fused with cytomembrane or the membrane of endosome, the viral core enters the cytoplasm and is de-hulled under the action of several viral proteins, such as A16L, A21L, A28L, F9L, G3L, G9R, H2R, J5L, and L5R, initiating the process of viral biosynthesis (Brown et al., 2006; Senkevich et al., 2005). Due to the high homology between the genome of MPXV and VACV, they may share the same features in virus entry-fusion step (Senkevich et al., 2005).

Poxviruses encode host range factor (Hrf) that regulates certain cell-specific antiviral responses to ensure the virus can replicate in some cells. The gene encoding Hrf is generally located in a reverse repeat sequence at both ends of the poxvirus genome, called host range gene (Hrg). MPXV encodes a variety of host range proteins, such as the virulence protein BR-203, which exerts antiviral-affected apoptosis effects, and BR-209 protein is an IL-1β-binding protein that inhibits IL-1β and IL-1 receptor binding. These two proteins are not present in smallpox virus (Weaver and Isaacs, 2008). In addition, MPXV F3 protein encoded by host genes F3L, a homologue of the VACV E3 protein, was shown to inhibit the cellular antiviral immune response (Arndt et al., 2015). MPXV A29L, M1R and B6R, the orthologous to A27L, L1R and B5R VACV antigens respectively, were selected as MPXV vaccine candidates and were shown to be able to elicit a protective immune response against lethal MPXV challenge (Franceschi et al., 2015). MPXV has a wide range of tissue tropism. Osorio et al. found that in severe combined immunodeficiency (SCID) mice infected with MPXV, MPXV antigens were detected in multiple tissues such as ovarian, brain, heart, kidney, liver, pancreas, and lung; and the viral titer in ovarian tissue was higher than other tissues, suggesting that ovarian was highly sensitive to MPXV (Osorio et al., 2009). Histopathological studies by Zsauca et al. on Macca fasciulasis have shown that lymphoid tissue is the principal target for MPXV, and viral antigens have been detected in salivary epithelium, follicles, lip sebaceous tissue, and many other tissues (Zsauca et al., 2001).

MPXV can be cultured in a variety of cells such asvero (Realegeno et al., 2017), A549 (Realegeno et al., 2017), HAP1 cells (Lopera et al., 2015), HeLa (Arndt et al., 2016), RK-13 (Arndt et al., 2015), and typical inclusion bodies are visible in the cytoplasm of infected cells. Several small animals such as rabbits, rats, squirrels, prairie dogs (Hutson and Damon, 2010), mice (Earl et al., 2015; Sergeev et al., 2016) and non-human primates (NHPs) are all susceptible to MPXV. Rabbits challenged with MPXV by intravenous route will develop acute illness and generalized rash (Hutson and Damon, 2010). The prairie dog model is remarkably similar to human MPXV incubation/presentation, so it is widely utilized in the characterization of MPX disease and evaluation of medical countermeasures (MCMs) against MPXV (Hutson et al., 2011, 2015, 2021). NHPs aerosol challenged with MPXV can produce expected disease progression and 67%-100% lethality (Nalca et al., 2015; Zsauca et al., 2001). Infected-NHPs such as rhesus and cynomolgus macaques with MPXV can serve as models to study MPXV pathogenesis and to test vaccines and antiviral drug candidates (Barnewall et al., 2012; Hatch et al., 2015; Russo et al., 2020).

MPXV is not heat-resistant, and can be inactivated after 30 min of treatment at 56 °C. The virus is easily inactivated by organic solvents such as formaldehyde, methanol, sodium dodecyl sulfonate (SDS), phenol, and chloroform. MPXV is resistant to drying and low temperature, and it can maintain vitality for a long time at 4 °C (Cho and Wenner, 1973).

### 3. Epidemiological characteristics of MPXV

MPXV currently has evolved into two distinct clades: West African and Congo Basin (Likos et al., 2005). The epidemiological and clinical features of the disease caused by the two MPXV clades are different. Congo Basin has a case fatality rate of up to 10% (Doshi et al., 2019), while West African has a case fatality rate of about only 1%, with a higher mortality rate in patients with HIV co-infection (Ogoina et al., 2019). MPXV was first identified in 1958, and the first human MPX case was found in Democratic Republic of the Congo (DRC) in 1970 (Bremen et al., 1980). Since then, MPXV has become endemic to DRC and has spread to other African countries, mainly in Central and West Africa. From 1970 to 1979, there were 47 human MPX cases reported in five Central and West African countries, of which 38 cases were reported from DRC, all occurring in tropical rain forest areas and associated with animal contact (Bremen et al., 1980). After the extinction of smallpox, a total of 338 cases of human MPX were found in DRC from 1981 to 1986. The mortality rate is as high as 9.8% in people who had not been vaccinated against smallpox. Seventy two percent of the cases are zoonotic transmission and most of the cases occur in children, with an average age of 4.4 years (Damon, 2011). Since the end of the WHO monitoring project in 1986, reports of persistent occurrence of MPX in human have decreased. From 1986 to 1992, only 13 cases were reported, and no cases were reported from 1993 to 1995 (Heymann et al., 1998). However, in 1996, there was a sudden increase in the number of human MPXV infected cases reported in DRC, and by 1997, a total of 88 people had been confirmed to have MPX infection (Heymann et al., 1998; Hutin et al., 2001). In 2003, MPX broke out in the United States. This is the first reported MPX outbreak outside Africa and has been related to the carriage of MPXV by marmots imported from Africa in the United States, resulting in a total of 47 people being diagnosed in five states (Reed et al., 2004; Saie et al., 2006). In 2005, an outbreak of MPX in Sudan reported a total of 10 confirmed cases and 9 suspected cases of MPXV from September to December 2005 (Formenty et al., 2010). Between 2006 and 2007, Human MPX infection was found again in DRC. MPX transmission had increased 20-fold since the 1980s, and smallpox-vaccinated people have a 21-fold lower risk of infection than unvaccinated people (Rimoin et al., 2010). Zoonotic transmission occurred in most cases. Since September 2017, MPX have broken out in Nigeria, with a total of 183 confirmed
cases reported in 18 states as of November 2019. The outbreak was also the largest epidemic on record in West African (Alakunle et al., 2020; Nguyen et al., 2021; Yinka-Ogunleye et al., 2018). Subsequently, imported cases of MPX were reported in Israel (Erez et al., 2019), the United Kingdom (Vaughan et al., 2018), Singapore (Ng et al., 2019) and other countries. Up to May 2022, MPX outbreaks have occurred in several countries around the world, which has aroused the strong vigilance of scientists in many countries (Kozlov, 2022a).

4. Pathogenicity

4.1. Transmission of MPXV to humans

The host reservoir of MPXV is not fully defined, and to date, MPXV has only been isolated from *Funisciurus anerythrus* (Kholodkevich et al., 1986) and *Cercocerusatys* (Radonic et al., 2014). A variety of rodents such as squirrels, Gambian rats, and other primates are considered to be the natural hosts for MPXV (Durski et al., 2018). MPXV is usually transmitted from animals to humans. Human infection with MPXV is mainly caused by bites from infected animals or direct contact through blood, body fluids, and MPX lesions of infected animals, and eating infected animals improperly cooked can also lead to the spread of the virus to human (Ellis et al., 2012; Ikekwetelu et al., 2020). After the eradication of smallpox, the population’s immunity to orthopoxvirus is gradually reduced, and occasional human-to-human transmission of MPXV can occur, usually in direct, long-term face-to-face contact, or through a large number of respiratory droplets containing the virus. It can also be transmitted through direct contact with the infected person’s body fluids or virus-contaminated items, such as clothing and bedding (Hutson et al., 2011), and transmitted from mother to fetus through the placenta. In addition, there is a possibility of sexual transmission of MPXV (Alakunle et al., 2020; Ogoina et al., 2019). In the recent outbreak, most cases were among young men who have sex with man (MSM) with genital lesions.

Workers slaughtering wild game, pet lovers, staff at animal breeding facilities, and the direct contacts of MPX patients may be at high risk (Fig. 1).

4.2. Clinical features of monkeypox

The symptoms of MPX are very similar to those of smallpox patients, but not as severe. The incubation period for MPX is usually 7–14 days, with a maximum of 21 days. Sufferers often have a history of exposure to animals or people infected with MPXV, initially showing symptoms similar to “influenza”, followed by herpes on the skin, experiencing pustules, and scarring after scabs. The process of MPXV infection is mainly divided into two phases: the prodromal phase (lasting about 0–2 days): fever, fatigue, severe headache, lymphadenopathy, muscle aches, and the rash phase (lasting 7–21 days). The rash usually begins to appear within 1–5 days after fever, and the patient is contagious when the rash appears. The rash is concentrated on the face and extremities, affecting the face (95%), palms and soles of the feet (75%), oral mucosa (70%), genitals (30%) and conjunctiva (20%). The rash lasts about 2–4 weeks and evolves from plaque to papules, blisters, pustules, scabs and then shedding. Lesions can occur in locations ranging from a few to several thousands (Petersen et al., 2019c). In severe cases, the areas of lesions can merge and cause large patches of skin to fall off. Patients often present with characteristic lymphadenopathy, most commonly in the groin, and may also be accompanied by a range of complications such as secondary bacterial infection, respiratory distress, bronchopneumonia, encephalitis, corneal infection with vision loss, and dehydration due to vomiting and diarrhea (Brown and Leggat, 2016; Petersen et al., 2019c). MPX is a self-limiting disease, and the severity of the disease is related to the degree of exposure to the virus, the patient’s health conditions and the nature of its complications. Severe cases occur more commonly in children, and also lead to death, with a case fatality rate of 1%–10% (Doshi et al., 2019; Ogoina et al., 2019) (Fig. 1).

5. Laboratory diagnosis

Rapid diagnosis plays an essential role in controlling the outbreak and epidemic of MPX. The clinical manifestations of MPXV infection are difficult to distinguish from the other poxvirus caused diseases. Hence, laboratory tests are critical for diagnosing MPXV infection (Di Giulio and Eckburg, 2004; Macneil et al., 2009).

5.1. Nucleic acid testing

Currently, a variety of methods have been developed for MPXV nucleic acid detection, among which real-time PCR (RT-PCR) is the preferred method for routine diagnosis. Generally, the conserved regions of extracellular envelope protein gene (*E6L* (Li et al., 2010), *Yinka-Ogunleye et al., 2019*), DNA polymerase gene (*E9L* (Li et al., 2006), *E6L*, *E9L*, and *N3R* (Kolesh et al., 2004)), *DNA polymerase subunit 18* (*RPO18*) gene (Orba et al., 2015), and complement binding protein (*C3L* (Li et al., 2010), *F3L* and *N3R* (Kolesh et al., 2004)) genes are usually selected as targets for PCR amplification. The whole genome sequencing is the gold standard for distinguishing MPXV from other orthopoxvirus (Cohen-Gibson et al., 2020; Farlow et al., 2010). At present, the genome sequencing of the current MPXV that caused the global outbreak has been carried out. Phylogenetic analyses from the first genome sequence of the current MPXV outbreak suggest the virus from this outbreak belongs to the mild West African clade and is closely related to the MPX virus isolated from the 2018–2019 UK, Singapore, and Israel
sequencing technology is limited in some areas. In addition, recombinase
mation (Isidro et al., 2022). However, due to the high cost, the
gene, an average of 50 single-nucleotide diversity locus (SNPs) mu-
the specific disease (Isidro et al., 2022).

5.2. Serological testing

Enzyme-linked immunosorbent assay (ELISA) can be used to detect
the specific IgM and IgG antibodies in the serum of MPX patients after 5-
and 8-days infection, respectively. A 4-fold increase in serum antibodies
at both acute and convalescent stages can be used in the diagnosis of
MPXV infection. Due to the antigenic cross reaction between MPXV and
other poxviruses, the specificity is insufficient. Therefore, this method
cannot accurately identify MPXV and is often used in epidemiological
investigation (Alakunle et al., 2020).

5.3. Electron microscope observation

Electron microscopy could be used to assist diagnosis according to the
morphological characteristics of MPXV. Since, MPXV and other poxvi-
ruses are not distinguishable in morphology, this method can’t confirm
the diagnosis, and can only provide clues that the virus belongs to
poxvirus family. Moreover, the sensitivity of electron microscope is not
high, and the preparation electronic sample is complicated and the
period is long. Meanwhile, the electron microscopy is expensive and the
operation is extremely complex, which limit its application in the prac-
tical detection.

5.4. Other tests

Immunochemistry analysis and multiplexed immunoﬂuorescence
imaging could be used for MPXV antigen detection (Doellinger et al.,
2015). Viral isolation and culture that live virus is grown and charac-
terized from a patient specimen are also required to establish a deﬁni-
tive diagnosis (Petersen et al., 2019c).

6. Prevention and treatment

6.1. Vaccines

At present, there is no speciﬁc vaccine against MPXV infection. Smallpox vaccination has been reported to provide 85% protection
against MPXV (Brown and Leggat, 2016; Nasir et al., 2018). Epidemi-
ological investigations indicated that approximately 90% of conﬁrmed
MPXV cases had not been infected with other poxviruses, and most cases
were born after the end of the smallpox virus eradication program, very
likely having not been vaccinated with smallpox vaccine (Brown and
Leggat, 2016). There are currently two approved vaccines for preventing
smallpox virus and MPXV: the second-generation vaccine ACAM 2000
and the third-generation vaccine IMVAMUNE. During the MPXV
epidemic in the United States in 2003, ACAM 2000 was demonstrated to
reduce the symptoms of MPX (Brown and Leggat, 2016), but side effects
may occur in patients with atopic dermatitis and immunocompromised
persons. This vaccine is not available to the public and is not used in
MPXV endemic areas. IMVAMUNE is a replication-deﬁcient, attenuated,
third-generation modiﬁed vaccinia Ankara (MVA) vaccine that has also
been approved by the Food and Drug Administration (FDA) and the
European Medicine Agency (EMA) for the prevention of smallpox virus
and MPXV in adults aged 18 years or older of high-risk population. Un-
like ACAM 2000, IMVAMUNE can be used in patients with atopic
dermatitis and immunodeﬁciency persons (Petersen et al., 2019a). So far,
neither ACAM2000 nor IMVAMUNE is approved for use in the general
population. Therefore, whether these approved smallpox vaccines could
be effective in preventing MPXV diseases in the MPXV endemic areas re-
mains to be determined (Brown and Leggat, 2016; McCollum and
Damon, 2014; Petersen et al., 2019b) (Table 1).

### Table 1

| Categories          | Names              | Features                     | Anti-poxvirus                      | Reference                        |
|---------------------|--------------------|------------------------------|-----------------------------------|----------------------------------|
| **Vaccines**        |                    |                              |                                   |                                  |
| ACAM 2000           |                    | Second-generation vaccine    | Smallpox virus, MPXV              | Brown and Leggat (2016)          |
| IMVAMUNE            |                    |                              | Smallpox virus, MPXV              | Petersen et al. (2019a)          |
| **Antiviral drugs** | Tecovirimat (ST-246)| Third-generation vaccine     | Smallpox virus, MPXV              |                                  |
| Cidofovir           | Brincidofovir (CMX001)| Small molecule virus inhibitor | Smallpox virus, MPXV, and cowpox virus. | Yang et al. (2005), Thakur et al. (2022) |
| Nioch-14            |                    | Viral DNA polymerase inhibitors | MPXV                               | Magee et al. (2005)            |
| Ribavirin, Tiazofurin|                    | Nucleoside analogues inhibitor | MPXV and vaccinia virus           | Delaune and Iseni (2020)        |
| C-CA3-ADO, C3-NPC A | HPMA, Adenosine N1 oxide (ANO)| Inosine monophosphate dehydrogenase inhibitors | All of poxviruses                 | Baker et al. (2003)            |

Until now, there are no speciﬁc antiviral drugs for the treatment of
MPX, and most of the treatments are symptomatic and supportive ther-
apies. Anti-smallpox virus drugs can play a role in anti-MPXV.

Tecovirimat (ST-246) is a small molecule virus inhibitor, which has a
strong activity against orthopoxvirus, such as smallpox virus, MPXV,
and cowpox virus. It can prevent virus spread by inhibiting the function of the
major envelope protein (F13L), thereby preventing the virus from leaving
an infected cell (Yang et al., 2005). It was approved in Europe in 2022 for
the treatment of MPX (Thakur et al., 2022). Cidofovir and Brincidofovir
derivative (CMX001) are both viral DNA polymerase inhibitors. Cidofo-
vir is an acyclic nucleoside phosphate. When the CMX001 is ingested by
the host cells, the lipid wrap of the drug can be cleaved to release free
Cidofovir, which will be phosphorylated into Cidofovir-diphosphate
(CDV-PP). CDV-PP inhibits the synthesis of viral DNA polymerase in
the form of a substrate matrix, and eventually blocks viral DNA synthesis
at the DNA polymerase level (Magee et al., 2005, 2008). Both Cidofovir
and Brincidofovir have demonstrated that they can inhibit MPXV repli-
cation in vitro and in vivo (Delaune and Iseni, 2020). The nucleoside an-
alogues inhibitor, Nioch-14, has strong antiviral activity against many
orthopoxviruses, and its anti-MPXV and VACV effects are comparable to
those of Tecovirimat. Nioch-14 is considered as a potential anti-MPXV
drug since it can be easily produced (Delaune and Iseni, 2020). Ribava-
virin and Tiazofurin are inosine monophosphate dehydrogenase (IMP)
inhibitors, that can reduce the replication of all poxviruses, and variola virus (VARV) and MPXV are more sensitive to them. 

7. Conclusions
The outbreak of MPX has become endemic in more than 20 countries since May 2022. The infectivity of MPXV is relative low and MPX may not become a pandemic as stated by WHO officer (Cenof and Adalja, 2022).

Conflict of interest
The authors declare no conflict of interest.

Acknowledgments
This work was partially funded by grants from the Natural Science Foundation of Hebei Province, China (no. H2020206352), the National Natural Science Foundation of China (no. 81902026), Science and Technology Project of Hebei Education Department (no. BJ2020018), Project for the Introduction of overseas students of Hebei Provincial Department of Human Resources and Social Security (no. C20200344).

References
Alakunle, E., Moens, U., Nchinda, G., Okeke, M.I., 2020. Monkeypox virus in Nigeria: infection biology, epidemiology, and evolution. Virol. J. 12, 1257.

Brown, K., Leggat, P.A., 2016. Human monkeypox: current state of knowledge and implications for the future. Trav. Med. Infect. Dis. 4, 55–65.

Centor, R., Adalja, A., 2022. Annals on call - monkeypox: should we worry about another pandemic? Ann. Intern. Med. 175, OC1.

Chang, S.J., Shih, A.C., Tang, Y.L., Chang, W., 2012. Vaccinia mature virus fusion regulator A26 protein binds to A16 and G9 proteins of the viral entry fusion complex and dissociates from mature viruses at low pH. J. Virol. 86, 3809–3818.

Chu, W.L., Lin, C.L., Yang, M.H., Tsou, D.L., Chang, W., 2007. Vaccinia virus F9 virion membrane protein is required for entry but not virus assembly, in contrast to the related L1 protein. J. Virol. 80, 9455–9464.

Damon, I.K., 2011. Status of human monkeypox: clinical disease, epidemiology and vaccination. Virol. J. 8, 278.

Damon, I.K., 2015. Comparison of monkeypox virus clade kinetics and pathology across Africa. J. Wildl. Dis. 51, 335–347.

Damon, I.K., Mandai, K., Malejani, K., Cohen, G.H., 2009. Vaccinia virus L1 binds to cell surfaces and blocks virus entry independently of glycosaminoglycans. Virology 385, 368–382.

Davies, S.A., Doshi, R.H., Gaglani, S.A.J., Doty, J.B., Babuex, A.D., Matheny, B., Burgada, J., Townsend, M.B., Morgan, C.N., Sathishkumar, P.S., Ndalaka, N., Kanjingankolo, T., Konte, Z., Malekani, K., Cooney, B., Faye, O., Njai, Y., Melamed, S., McCallum, A.M., Reynolds, M.G., Mombouli, J.V., Nakazawa, Y., Petersen, B.W., 2020. Epidemiologic and ecological investigations of monkeypox, likouala department, republic of the Congo, 2017. Emerg. Infect. Dis. 25, 281–289.

Davies, S.A., Doshi, R.H., Gaglani, S.A.J., Doty, J.B., Babuex, A.D., Matheny, B., Burgada, J., Townsend, M.B., Morgan, C.N., Sathishkumar, P.S., Ndalaka, N., Kanjingankolo, T., Konte, Z., Malekani, K., Cooney, B., Faye, O., Njai, Y., Melamed, S., McCallum, A.M., Reynolds, M.G., Mombouli, J.V., Nakazawa, Y., Petersen, B.W., 2020. Epidemiologic and ecological investigations of monkeypox, likouala department, republic of the Congo, 2017. Emerg. Infect. Dis. 25, 281–289.

Djibali, D.B., Eckburg, P.B., 2004. Human monkeypox: an emerging zoonosis. Lancet. Infect. Dis. 4, 15–25.

Donaire, J., Schaade, L., Nitsche, A., 2015. Comparison of the cowpox virus and vaccinia virus mature virion proteome: analysis of the species- and strain-specific protein. PLoS One 10, e0141507.

Doshi, R.H., Gaglani, S.A.J., Doty, J.B., Babuex, A.D., Matheny, B., Burgada, J., Townsend, M.B., Morgan, C.N., Sathishkumar, P.S., Ndalaka, N., Kanjingankolo, T., Konte, Z., Malekani, K., Cooney, B., Faye, O., Njai, Y., Melamed, S., McCallum, A.M., Reynolds, M.G., Mombouli, J.V., Nakazawa, Y., Petersen, B.W., 2020. Epidemiologic and ecological investigations of monkeypox, likouala department, republic of the Congo, 2017. Emerg. Infect. Dis. 25, 281–289.

Dungan, C., Okeke, M.I., Malejani, K., Cohen, G.H., 2009. Vaccinia virus L1 binds to cell surfaces and blocks virus entry independently of glycosaminoglycans. Virology 385, 368–382.

Formenty, P., Muntair, M.O., Damon, I., Chowdhary, V., Opoka, M.L., Monimart, C., Muris, E.M., Manougoguerra, J.C., Davidson, W.B., Kareem, K.L., Cabeza, J., Wang, S., Malik, M.R., Durand, T., Khalid, A., Rioton, T., Kuong-Ruay, A., Babiker, A.A., Karasi, M.E., Abdalla, M.S., 2010. Human monkeypox outbreak caused by novel virus belonging to Congo Basin clade, Sudan, 2005. Emerg. Infect. Dis. 11, 1539–1545.

Frairicheschi, V., Parker, S., Jucova, S., Crump, R.W., Doronin, K., Hembrador, E., Pompilio, D., Tehabi, G., Teste, R.D., Wong, S.W., Buller, M.R., Donofrio, G., 2018. BolV-4-Based vector single heterologous antigen delivery protects STAT1(-/-) mice from monkeypoxvirus lethal challenge. PLoS Neglected Trop. Dis. 9, e0003850.

Hutson, C.L., Damon, I.K., 2010. Monkeypox virus infections in small animal models for vaccine testing. J. Virol. 84, 1170–1592.

Hutson, C.L., Kondas, A.V., Mauldin, M.R., Doty, J.B., Grossi, I.M., Morgan, C.N., 2010. Monkeypox virus infections in small animal models for vaccine testing. J. Virol. 84, 1170–1592.

Heymann, D.L., Szczeniowski, M., Esteves, K., 1998. Re-emergence of monkeypox in Africa: a review of the past six years. Br. Med. Bull. 54, 693–702.

Hughes, L.J., Goldstein, J., Pohl, J., Hooper, J.W., Lee Pitts, R., Townsend, M.B., Morgan, C.N., Satheshkumar, P.S., Ndakala, N., Kanjingankolo, T., Konte, Z., Malekani, K., Cooney, B., Faye, O., Njai, Y., Melamed, S., McCallum, A.M., Reynolds, M.G., Mombouli, J.V., Nakazawa, Y., Petersen, B.W., 2020. Epidemiologic and ecological investigations of monkeypox, likouala department, republic of the Congo, 2017. Emerg. Infect. Dis. 25, 281–289.

Hutson, C.L., Damon, I.K., 2015. Comparison of monkeypox virus clade kinetics and pathology across Africa. J. Wildl. Dis. 51, 335–347.

Hutson, C.L., Damon, I.K., 2020. Monkeypox virus infections in small animal models for evaluation of anti-poxvirus agents. Viruses 2, 2763–2776.

Hutson, C.L., Kondas, A.V., Mauldin, M.R., Doty, J.B., Grossi, L.M., Morgan, C.N., Ostergaard, S.D., Hughes, C.M., Nakazawa, Y., Kling, C. Martin, B.E., Ellison, J.A., Carroll, D.S., Gallagher-Romero, N., Olson, V.A., 2021. Pharmacokinetics and efficacy of a potential smallpox therapeutic, Brincidofovir, in a lethal monkeypox virus animal model. mSphere 6, e00927–20.

Heymann, D.L., Szczeniowski, M., Esteves, K., 1998. Re-emergence of monkeypox in Africa: a review of the past six years. Br. Med. Bull. 54, 693–702.

Hughes, L.J., Goldberg, E., Poh, J., Hooper, J.W., Lee Pitts, R., Townsend, M.B., Morgan, C.N., Satheshkumar, P.S., Ndakala, N., Kanjingankolo, T., Konte, Z., Malekani, K., Cooney, B., Faye, O., Njai, Y., Melamed, S., McCallum, A.M., Reynolds, M.G., Mombouli, J.V., Nakazawa, Y., Petersen, B.W., 2020. Epidemiologic and ecological investigations of monkeypox, likouala department, republic of the Congo, 2017. Emerg. Infect. Dis. 25, 281–289.

Hutson, C.L., Damon, I.K., 2015. Comparison of monkeypox virus clade kinetics and pathology across Africa. J. Wildl. Dis. 51, 335–347.

Hutson, C.L., Damon, I.K., 2010. Monkeypox virus infections in small animal models for evaluation of anti-poxvirus agents. Viruses 2, 2763–2776.

Hutson, C.L., Kondas, A.V., Mauldin, M.R., Doty, J.B., Grossi, L.M., Morgan, C.N., Ostergaard, S.D., Hughes, C.M., Nakazawa, Y., Kling, C. Martin, B.E., Ellison, J.A., Carroll, D.S., Gallagher-Romero, N., Olson, V.A., 2021. Pharmacokinetics and efficacy of a potential smallpox therapeutic, Brincidofovir, in a lethal monkeypox virus animal model. mSphere 6, e00927–20.
lizuka, I., Sajo, M., Shiotu, T., Ami, Y., Suzuki, Y., Nagata, N., Hasegawa, H., Sakai, K., Fukuishi, S., Mizunari, T., Ogata, M., Nakasui, M., Kurane, I., Mizuguchi, M., Matsuoka, S., 2016. Isolated inoculated accelerated amplification-based diagnostic assay for monkeypox virus infections. J. Med. Virol. 88, 1102–1108.

Isidro, J., Borges, V., Pinto, M., Sobral, D., Santos, J.D., Nunes, A., Mixão, V., Ferreira, R., Santos, D., Duarte, S., Vieira, L., Borrego, M.J., Nascimento, S., de Carvalho, L.L., Pereira, A., Cordon, L., 2022. Phylogenetic characterization and signs of microevolution in the 2022 multi-country outbreak of monkeypox virus. Nat. Med. https://doi.org/10.1038/s41591-022-01907-y.

Jeeck, Z., Khodakevich, L.N., Wickett, J.F., 1987. Smallpox and its post-eradication surveillance. Bull. World Health Organ. 65, 425–434.

Kaefer, T., Meng, X., Matho, M.H., Schlossman, A., Li, S., Ofran, Y., Buller, M., Crump, R.W., Parker, S., Frazier, A., Crotty, S., Zajonc, D.M., Peters, B., Xiang, Y., 2014. Potent neutralization of vaccinia virus by divergent murine antibodies targeting a common site of vulnerability in Li protein. J. Virol. 88, 11339–11335.

Kodavedeh, L., Jeeck, Z., Kinzanika, K., 1986. Isolation of monkeypox virus from wild squirrel infected in nature. Lancet 1, 98–99.

Kool, M. 2022a. Monkeypox goes global: why scientists are alert. Nature 606, 15–16.

Kool, M. 2022b. Monkeypox outbreaks: 4 key questions researchers have. Nature 606, 258–259.

Kugelman, J.R., Johnston, S.C., Mulembakani, P.M., Kishu, L., Lee, M.S., Koelewa, G., McCarthy, S.E., Gestode, M.C., Wolfe, N.D., Fair, J.N., Schneider, B.S., Wright, L.L., Huggins, J., Whitehouse, C.A., Wemakoy, E.O., Muyembe, J.J., Hung's, C., Thomas, Y., Ogawa, H., Hang’ombe, B.M., 2019a. Monkeypox in humans: knowledge gained and lessons learned. Emerg. Infect. Dis. 27, 1007–1014.

Kool, M. 2022b. Monkeypox outbreaks: 4 key questions researchers have. Nature 606, 258–259.

Lopera, J.G., Falendysz, E.A., Rocke, T.E., Osorio, J.E., 2015. Attenuation of monkeypox virus in rhesus monkeys (Macaca fascicularis). Lab. Invest. 81, 1581–1592.

Magee, W.C., Aldern, K.A., Hostetler, K.Y., Evans, D.H., 2008. Mechanism of inhibition of vaccinia virus DNA polymerase by Cidofovir Diphosphate 49, effective inhibitors of vaccinia virus DNA polymerase when incorporated into the clades: monkeypox viruses. J. Gen. Virol. 86, 2661–2670.

M الأكثر موثوقية في البحث عن سلالة فيروس المونكي بوكس

McCollum, A.M., Damon, D., 2014. Human monkeypox. Clin. Infect. Dis. 58, 260–267.

Nakahata, T., Livingstone, V.A., Garza, N.L., Zumbrun, E.E., Frick, O.M., Chapman, J.L., Hartings, J.M., 2010. Experimental infection of cynomolgus macaques (Macaca fascicularis) with aerosolized monkeypox virus. PloS One 5, e12880.

Nair, I.A., Dangan, A., Ojiremien, I., Emeribe, A.U., 2018. Reminiscing the recent occurrence of monkeypox in Nigeria: its ecologic-epidemiology and literature review. P. T. Med. 41, 1–9.

Ng, O.T., Lee, V., Marimuthu, K., Vasoo, S., Chan, G., Lin, R.T.P., Leo, Y.S., 2019. A case of monkeypox With real-time PCR assays. J. Clin. Virol. 36, 194–203.

Ng, O.T., Lee, V., Marimuthu, K., Vasoo, S., Chan, G., Lin, R.T.P., Leo, Y.S., 2019. A case of monkeypox With real-time PCR assays. J. Clin. Virol. 36, 194–203.

Ng, O.T., Lee, V., Marimuthu, K., Vasoo, S., Chan, G., Lin, R.T.P., Leo, Y.S., 2019. A case of monkeypox With real-time PCR assays. J. Clin. Virol. 36, 194–203.

Ng, O.T., Lee, V., Marimuthu, K., Vasoo, S., Chan, G., Lin, R.T.P., Leo, Y.S., 2019. A case of monkeypox With real-time PCR assays. J. Clin. Virol. 36, 194–203.