ScientificScholar®
Knowledge is power
Publisher of Scientific Journals

www.surgicalneurologyint.com

Surgical Neurology International

Editor-in-Chief: Nancy E. Epstein, MD, Clinical Professor of Neurological Surgery, School of Medicine, State U. of NY at Stony Brook.

SNI: Infection

Editor
Ali Akhaddar, MD, IFAANS
Avicenne Military Hospital, Marrakech, Morocco

SNI
Open Access

*Review Article*

# A brief review of the monkeypox virus and emerging concerns for neuroinvasiveness

Atul Anand[1#], Anand Kumar Das[2#], Sona Bhardwaj[3], Saraj Kumar Singh[2]

Departments of [1]General Surgery, and [2]Neurosurgery, All India Institute of Medical Sciences, [3]Department of Microbiology, ESIC Hospital, Patna, Bihar, India.

E mail: Atul Anand - atulanand@aiimspatna.org; Anand Kumar Das - dranand0822@gmail.com; Sona Bhardwaj - dr.sonarajx1@gmail.com;
*Saraj Kumar Singh - dr.sarajkumarsingh@gmail.com
#These authors have equally contributed to this work.

***Corresponding author:**
Saraj Kumar Singh,
Department of Neurosurgery,
All India Institute of Medical Sciences, Patna, Bihar, India.

dr.sarajkumarsingh@gmail.com

Received : 30 December 2022
Accepted : 17 February 2023
Published : 03 March 2023

**DOI**
10.25259/SNI_1176_2022

**Quick Response Code:**

## ABSTRACT

**Background:** Amidst the ongoing COVID-19 pandemic, monkeypox virus (MPXV) disease has been recognized as another disease of pandemic nature by the World Health Organization. Nearly four decades after the eradication of smallpox, as half of the world population is naïve to ortho-pox viruses (supposedly due to lack of immunity by vaccination), MPXV remains the most pathogenic species of the family of poxviruses.

**Methods:** The articles on MPXV were searched on PubMed/Medline and data were retrieved and analyzed.

**Results:** Although reported as a disease of milder exanthem and lower mortality as compared to smallpox, the MPXV disease tends to be neuroinvasive. This article highlights the neurological signs and symptoms of MPXV disease and discusses, in brief, the management strategies.

**Conclusion:** Neuroinvasive properties of the virus as demonstrated in *in vitro* studies, and further verified by neurological illnesses in patients, present a special threat to mankind. Clinicians must be prepared to recognize and treat these neurological complications and start treatment to limit long-lasting brain injury as seen in patients with COVID-19.

**Keywords:** Central nervous system, Monkeypox virus, Neurological, Pathogenesis

## INTRODUCTION

Viruses are important contributors to the World Health Organization's (WHOs) current list of priority diseases. Crimean-Congo hemorrhagic fever, Marburg virus disease, Middle East respiratory syndrome coronavirus, severe acute respiratory syndrome, Ebola virus disease, Lassa fever, Nipah virus diseases, Zika virus disease, Rift Valley fever, and the novel coronavirus (COVID-19) are currently included in the list.[16,53] Many of these illnesses have some manifestations in the central nervous system (CNS) (meningitis, encephalitis, intracranial hemorrhage, seizures, etc.). This is reinforced by the ongoing COVID-19 pandemic, which has drawn attention to it in particular and serves as a reminder that the nervous system may be impacted by infections with the capacity to spread quickly and extensively despite intensive efforts.[15,41] The WHO has recently recognized the monkeypox virus (MPXV) illness as a "Public Health Emergency of International Concern (PHEIC)."[64] As the MPXV infection spreads across the globe, reports of its neurological symptoms are emerging. These symptoms might be linked

to the virus's neuroinvasive characteristics. While there is a paucity of literature commenting on these neurological manifestations, it is essential to have a thorough review of the neurological symptoms of the MPXV to begin treatment as soon as a diagnosis is made and prevent long-lasting brain damage like that seen in the COVID-19 pandemic.[41]

## TAXONOMY AND EPIDEMIOLOGY

MPXV is a double-stranded enveloped DNA virus of the family *Poxviridae*, subfamily *Chordopoxvirinae*, and genus *Orthopoxvirus*.[32,60] There are two separate strains of MPXV, one from Central Africa's Congo Basin and the other from West Africa, of which the former is more virulent in terms of morbidity, mortality, and human-to-human transmission.[11,37] The exact reservoir of this zoonotic disease is unknown; it was first identified in captive monkeys at the State serum institute of Copenhagen, Denmark in 1958.[38] Other possible reservoirs are squirrels of the genera *Funisciurus* and *Heliosciurus*, elephant shrew, and Gambian giant rats (*Cricetomys* spp.).[8,34] The first case of human infection was documented in 1970 in a 9-month-old child from Zaire (now the Democratic Republic of Congo).[36] The increase in MPXV cases was steady till 2017 when outbreaks were reported in the Democratic Republic of Congo, Central African Republic, Cameroon, Liberia, and Nigeria.[17,42] The situation updates of the WHO published on 27 June 2022 have reported the outbreak of MPXV disease in non-endemic countries, for example, the European nations, predominantly in the United Kingdom (UK), Germany, Spain, and Portugal.[44] Monkeypox viral disease was deemed a 'PHEIC by the WHO on July 23, 2022.[64] As per the WHO data, a total of 67,556 cases across 106 countries have been confirmed with a death toll of 27 (till September 29, 2022). A total of 12 confirmed cases have been reported in India to date.[1]

## PATHOGENESIS WITH NEUROINVASIVE POTENTIAL

Monkeypox is a vesicopustular illness with a secondary attack rate of around 10% in those who have not received the smallpox vaccine.[30] The two modes of transmission are zoonotic transmission and human-to-human transmission [Figure 1]. Zoonotic transmission occurs during the hunting and handling of these animals.[51] Human-to-human transmission, the main mechanism responsible for recent outbreaks, occurs by direct inoculation through contact with body fluids, such as blood, saliva, respiratory droplets, and exudates from lesions.[30] On entry, the virus multiplies at the site of inoculation. It then either spreads to draining lymph nodes or blood (primary viremia). A secondary viremia occurs after its spread from lymphatic organs to blood. Finally, the virus lodges in the skin and other mucosal sites such as the nose, pharynx, eyes, and anogenital areas.[63] At the cellular level, viral entry into host cells is facilitated by the interaction of viral proteins with host glycosaminoglycans and subsequent endocytosis.[3] The mechanisms of neuroinvasion of the virus into the CNS in humans are unknown at present, due to a lack of studies in humans. Animal investigations have provided us with some insights regarding the MPXV's neuroinvasiveness. The works of Tesh *et al.*,[62] Kulesh *et al.*,[35] Xiao *et al.*,[65] Hutson *et al.*,[27-29] Falendysz *et al.*,[21-23] Earl *et al.*,[18,19] and Sergeev *et al.*[58,59] deserve mention. In a series of tests, they inoculated animals such as squirrels, dogs, mice, and rats through different routes (primarily intraperitoneal and intranasal). The viral load was assessed by nucleic acid amplification tests, bioluminescence, and plaque assays in the blood, liver,

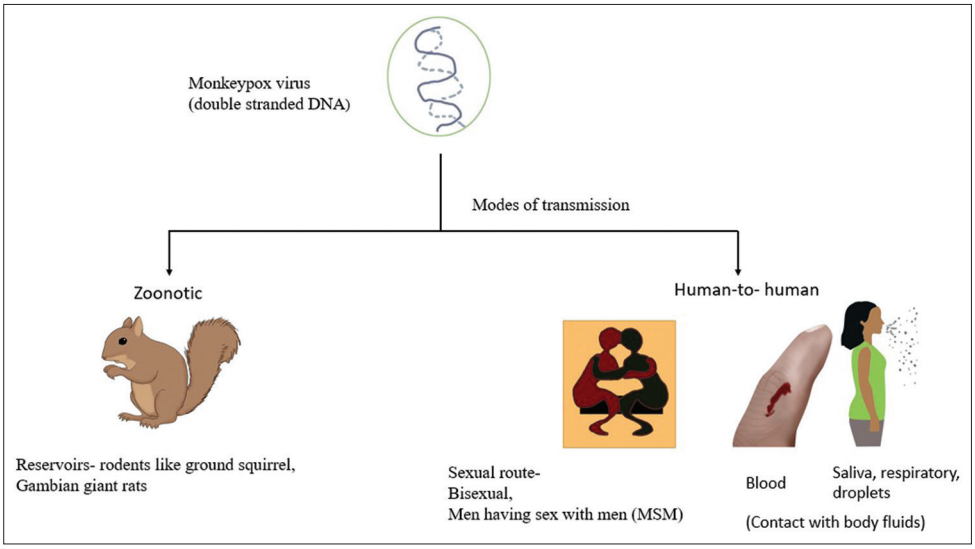
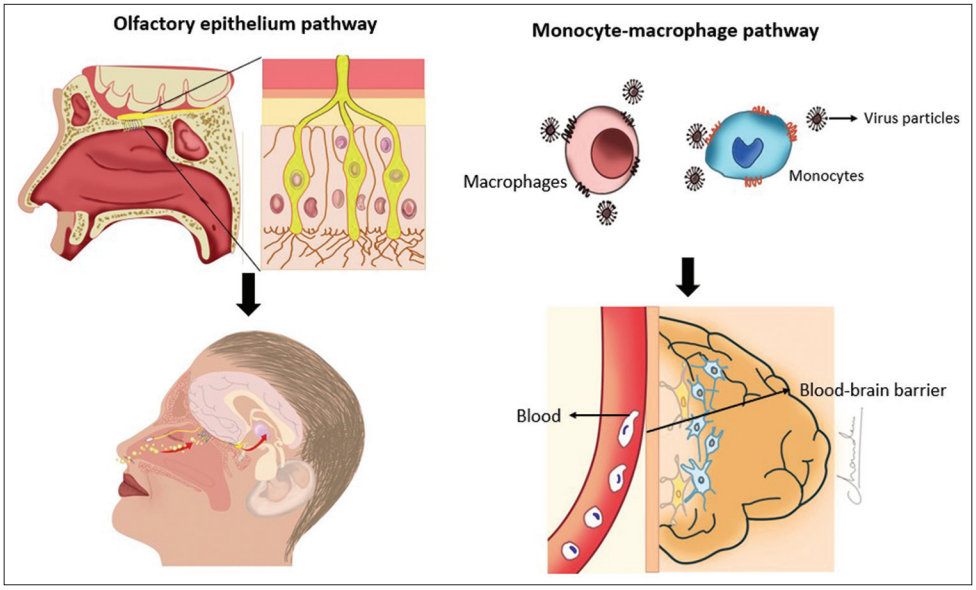



**Figure 1:** Modes of transmission of the monkeypox virus.




**Figures 2:** (a and b) Potential pathways of "neurotropism" of the virus.

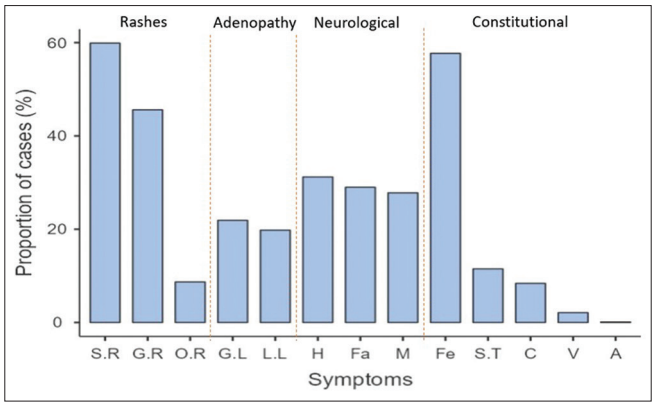



**Figure 3:** Bar diagram showing proportion of symptoms in monkeypox illness (see Table 1 for details). Adapted from: 2022 Monkeypox Outbreak: Global Trends [Internet]. [Cited 2022 Dec 19]; Available from: https://worldhealthorg.shinyapps.io/mpx_global/. (S.R: Systemic rashes, G.R: Genital rashes, O.R: Oral rashes, G.L: General lymphadenopathy, L.L: Local lymphadenopathy, H: Headache, Fa: Fatigue, M: Myalgia, Fe: Fever, S.T: Sore throat, C: Chills, V: Vomiting, A: Asymptomatic).

**Table 1:** Symptoms of monkeypox illness.

| Symptoms | Proportion of cases (%) |
|---|---|
| Rashes | |
| Systemic (S.R) | 59.9 |
| Genital (G.R) | 45.6 |
| Oral (O.R) | 8.7 |
| Lymphadenopathy | |
| General (G.L) | 21.9 |
| Local (L.L) | 19.8 |
| Neurological | |
| Headache (H) | 31.2 |
| Fatigue (Fa) | 29.0 |
| Myalgia (M) | 27.8 |
| Others-Photophobia, Encephalitis, Meningitis, Seizures, Paralysis | |
| Constitutional symptoms | |
| Fever (Fe) | 57.7 |
| Sore throat (S.T) | 11.5 |
| Chills (C) | 8.4 |
| Vomiting (V) | 2.1 |
| Asymptomatic (A) | 0.1 |

spleen, brain, lymph nodes, and other organs (mainly on necropsy specimens). All of these experiments consistently showed the presence of the MPXV in brain tissues. Although these experiments highlight the neurotropism of the MPXV, identifying the MPXV transmission paths to the CNS is also crucial. Although the precise MPXV transmission channels are currently unknown, recent research on animal subjects has identified two plausible routes that may be responsible for neuroinvasiveness are: the olfactory epithelium pathway and the monocyte-macrophage pathway [Figure 2].[57] For example, after intranasal injection of ground squirrels with the Congo Basin strain, the virus dramatically increased in the nasal septum and brain tissue.[59] In addition, intranasal inoculation of the MPXV revealed that the virus replicated more intranasally and in the animal brain according to bioluminescence imaging.[18] Although again, there is a paucity of studies in humans, these results indicated that MPXV transmission into the brain parenchyma may occur primarily through the nasal cavity and olfactory epithelium. Another way for the MPXV to enter the CNS, which may be responsible for CNS spread in humans as well, is through infecting circulating leukocytes, such as macrophages and monocytes, which is evident from the detection of MPXV-

**Table 2a:** Neurological symptoms of monkeypox illness in studies from African countries.

| Country | Authors | Year | Study design | Number of cases | Age group | Animal reservoir | Neurological symptoms (number of cases) | Outcome |
|---|---|---|---|---|---|---|---|---|
| DRC | Jezek *et al.*[31] | 1980–85 | Cohort | 282 | 1 mo–69 yr | N/R | Encephalitis (1), Coma (1) | 1 death |
| Sudan | Formenty *et al.*[24] | 2005 | Retrospective review | 10 | 8 mo–32 yr | N/R | Myalgia (8), Headache (6) | No death |
| DRC | Pittman *et al.*[52] | 2007–11 | Cohort | 216 | 0–6 yr | Squirrel, monkey | Malaise (184), Headache (51), Myalgia (15), Meningitis (9), Visual changes (5), Dizziness (3) | 3 deaths |
| DRC | Hughes *et al.*[25] | 2009–14 | Cross-sectional | 134 | 6 mo–79 yr | N/R | Headache (99), Myalgia (90) | N/R |
| CAR | Kalthan *et al.*[33] | 2016 | Cohort | 26 | 1–58 yr | N/R | Myalgia (7), Headache (7) | 2 deaths |
| Nigeria | Yinka-Ogunleye *et al.*[68] | 2017 | Cohort | 1 | 11 yr | N/R | Headache (1), Malaise (1) | N/R |
| Nigeria | Ogoina *et al.*[47] | 2017 | Cross-sectional | 18 | 6–45 yr | N/R | Headache (12), Myalgia (5), Photophobia (3) | 2 deaths |
| Nigeria | Yinka-Ogunleye *et al.*[67] | 2017–18 | Cohort | 118 | 2 d–50 yr | N/R | Headache (89), Myalgia (74), Photophobia (24) | 7 deaths |
| Nigeria | Ogoina *et al.*[46] | 2017–18 | Cross-sectional | 40 | 28 d–54 yr | N/R | Headache (19), Myalgia (25), Photophobia (9), Seizure (1) | 5 deaths |

DRC: Democratic Republic of Congo, CAR: Central African Republic, d: Days, mo: Months, yr: Years, and N/R: Not reported

Zaire 79 antigens in monocytes of macaques after intravenous injection.[61]

## CLINICAL FEATURES WITH NEUROLOGICAL MANIFESTATIONS

On inoculation, a febrile prodromal phase follows with an incubation period of 7–17 days. This phase manifests as fever, headache, malaise, myalgia, and lymphadenopathy, and lasts for about 1–4 days. The febrile phase is followed by a rash period lasting about 14–28 days, characterized by centrifugally distributed painful and pruritic rashes, which evolve from maculopapular to vesicopustular.[20,40] Notably, these rashes are all of similar sizes, at the same stage of evolution, and are often umbilicated.[40] Adenopathy is more marked as compared to smallpox.[14,20] In addition to mostly cutaneous involvement of facial, truncal, and skin of extremities in the previous outbreaks, the recent outbreaks are characterized by involvement of mucosal sites of the oral cavity, genitourinary tract, and anal canal–manifesting as severe proctitis, urethritis, balanitis, and pharyngitis, highlighting the importance of the sexual route of transmission as seen in bisexual, and men having sex with men (MSM) groups.[50] As the lesions become pustular and secondary bacterial infections occur, a second febrile phase follows.[20]

Mortality is uncommon-the case fatality rate varies from 1% to 11%.[7,14] Infants, young children <10 years of age, pregnant women, patients with HIV, and other immunodeficiency states constitute the vulnerable groups. Smallpox vaccination offers some protection, as severe complications are more common in the unvaccinated group (74%) than in vaccinated ones (40%).[40] Typical complications include bronchopneumonia, encephalitis, blindness due to corneal scarring, and septicemia.[20,40]

Neurological manifestations range from non-specific symptoms such as headache, myalgia, fatigue, and photophobia to severe complications such as seizures and encephalitis. The WHO data report headache as one of the symptoms in about 30% of patients [Table 1 and Figure 3].[1] In keeping with this, other studies have also reported headache as the most prevalent neurologic symptom among MPXV disease cases that have been documented in the literature (50%), with seizures, disorientation, or encephalitis being less common (2%).[5] Existing human MPXV illness case series occasionally mentioned patients with neurologic issues, although there were rarely many specifics given. On a careful review of studies of cases in the African continent [Table 2a][24,25,31,33,46,47,52,67,68] and the non-African nations [Table 2b][2,4,10,13,26,45,48,54,55,56,66], there was a dearth of information on radiological findings of CNS infestations, and cerebrospinal fluid (CSF) analysis in patients infected with the monkey-pox virus. None of the studies from African nations[24,25,31,33,46,47,52,67,68] reported on radiological findings and CSF changes, while only few cases[48,56] in non-African nations had these findings reported [Tables 2a and b]. In an analysis of 282 instances in the Congo Basin during the 1980s, a case of a 3-year-old girl who developed encephalitis and succumbed after being in a coma, the 2nd day after hospitalization has been mentioned.[31] In an examination of 40 hospitalized cases of monkeypox sickness from Nigeria, a 28-day-old neonate and, a 43-year-old man with HIV had probable encephalitis and seizures.[46] Acute disseminated

**Table 2b:** Neurological symptoms of monkeypox illness in studies from countries outside Africa.

| Country | Authors | Year | Study design | Number of cases | Age group | Animal reservoir | Neurological symptoms (number of cases) | Radiology | CSF picture | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|
| USA | Anderson *et al.*[4] | 2003 | Case report | 1 | 1–18 yr | Prairie dogs | Headache (1), myalgia (1) | N/R | N/R | Cured |
| USA | Reed *et al.*[54] | 2003 | Cohort | 11 | 3–43 yr | Prairie dogs | Headache (11), myalgia (1) | N/R | N/R | All cured |
| USA | Sejvar *et al.*[56] | 2003 | Case series | 3 | 6, 30, 33 yr | Prairie dogs | Headache (2), Encephalitis (1), Seizure (1) | MRI-brain edema, meningeal enhancement | IgM+ | All cured |
| USA | Huhn *et al.*[26] | 2003 | Cohort | 34 | 6–47 yr | Domestic pets | Headache (23), Myalgia (19), Meningitis (5), Confusion (2), Seizure (1), Encephalitis (1) | N/R | N/R | All cured |
| USA | Croft *et al.*[13] | 2003 | Cohort | 19 | 3–48 yr | Prairie dogs | Headache (13) | N/R | N/R | N/R |
| USA | Reynolds *et al.*[55] | 2003 | Case series | 37 | 15–50 yr | Prairie dogs | Myalgia (36), Headache (32) | N/R | N/R | N/R |
| Singapore | Ng *et al.*[45] | 2019 | Case report | 1 | 38 yr | N/R | Myalgia (1) | N/R | N/R | N/R |
| UK | Adler *et al.*[2] | 2018-21 | Cohort | 7 | 2–50 yr | N/R | Low mood (3), Emotional lability (1) | N/R | N/R | All cured |
| USA | Charniga *et al.*[10] | 2022 | Cohort | 21 | 28–61 yr | N/R | Headache (15) | N/R | N/R | N/R |
| USA | Pastula *et al.*[48] | 2022 | Case series | 2 | 30 yr | Absent | Flaccid paralysis (2), Bowel- bladder incontinence (1) | Demyelinating changes in frontal lobe, enhancing lesions in cervical and thoracic segments | Lymphocytic pleocytosis, raised protein, normal glucose | Cured with plasma exchange |
| India (travelers from UAE) | Yadav *et al.*[66] | 2022 | Case series | 2 | 31, 35 yr | N/R | Headache (1), Myalgia (2), Backache (1) | N/R | N/R | N/R |

yr: Years, N/R: Not reported, DRC: Democratic Republic of Congo, CAR: Central African Republic, USA: United States of America, UAE: United Arab Emirates

encephalomyelitis and Guillain-Barre syndrome are caused by secondary immune-mediated neurological insults and the neurotropism of the MPXV.[12] CSF, electroencephalogram (EEG), and magnetic resonance findings of the brain have been described as a case report in a 6-year-old girl from the Mid-West United States outbreak of 2003.[56] The CSF analysis picture initially showed increased pleocytosis with polymorphonuclear predominance with was later replaced by lymphocytic predominance as pleocytosis decreased by day 5–7 of the illness.[56] IgM antibodies to the virus have been identified by enzyme-linked immunosorbent assay (ELISA) in the CSF.[56] EEG shows diffuse slowing. Magnetic resonance imaging demonstrates diffuse brain edema, meningeal enhancement, and signal abnormalities in the parietal cortex and thalamus.[56] Neurological symptoms, though reported as case reports, can be further limited by starting treatment as early as the diagnosis of monkeypox illness is made.

## LABORATORY DIAGNOSIS

As evident in the UK Health Security Agency case definition of probable monkeypox infection,[43] the diagnosis of monkeypox is clinical, which includes a proper history (focusing on occupation, contact with possible reservoirs, and history of travel to endemic regions, especially Africa), and typical distribution of rashes. Specific viral DNA detection may be carried out by polymerase chain reaction tests in a specimen from skin or mucosal lesions, CSF, and serum.[40] Electron microscopy may identify the virions in tissue specimens.[6,40] ELISA for detection of IgM antibodies in CSF and serum may show cross-reactivity with other ortho-pox viruses, is not able to distinguish a recent infection from vaccination, and may be negative in immunodeficient individuals who are not able to mount an immune response against the virus.[40] All laboratory tests must be carried out in a biosafety level three cabinet.[32]

## MANAGEMENT

In the absence of a clinically approved anti-viral agent, prevention remains the key. Behavioral risk-reduction strategies include avoidance of close contact with anyone suspected to have Monkeypox infection. This may be accomplished by home-based or hospital-based isolation. Airborne and contact precautions, including hand-hygiene practices as learned from the COVID-19 pandemic, are encouraged among healthcare workers. Considering the recent outbreaks, MSM should be cautious.

Symptomatic cases usually have a mild self-limiting illness, and the treatment is supportive focusing on analgesia, hydration, and nutrition. Acetaminophen, non-steroidal anti-inflammatory agents, and topical antihistamines are used when required.[49] Antibiotics are used only when rashes become pustular and secondary bacterial superinfections are suspected.

Chemotherapeutic agents at various stages of trial against the MPXV include NIOCH-14, Cidofovir, and CMX-001.[39,40] Centers for Disease Control and Prevention in association with the US Food and Drug Administration (US-FDA) has given Tecovirimat (TPOXX) the expanded access investigational new drug (EA-IND) status for use against monkeypox.[9] It acts by inhibiting the VP37 envelope-wrapping protein of ortho-poxviruses, thus preventing the release of virions from the intracellular compartment.[40] As part of the US Strategic National Stockpile, the medication is currently kept on hand for use against smallpox in the event of a bioterrorist attack.[9,40] Vaccinia virus immunoglobulin can also be used against monkeypox infection, due to serological cross-reaction amongst ortho-poxviruses. JYNNEOS vaccine is US-FDA approved for protection against both smallpox and MPXVs. It is administered with two subcutaneous injections spaced 28 days apart.[9] The FDA-approved ACAM2000 vaccine for monkeypox protection falls under the EA-IND classification. It is given as a single dose.[9,40]

## CONCLUSION

The recent outbreaks of the MPXV may be attributed to the encroachment of human civilization into areas with zoonotic reservoirs in the setting of waning immunity against the smallpox virus. MPXV disease is a systemic illness with its effect on most organ systems unknown. Neuroinvasive properties of the virus as demonstrated in *in vitro* studies, and further verified by neurological illnesses in patients, present a special threat to mankind. Clinicians must be prepared to recognize and treat these neurological complications and start treatment to limit long-lasting brain injury as seen in patients with COVID-19. Lessons learned from the COVID-19 pandemic, especially the isolation and hand-hygiene practices hold true for protection against the MPXV and other potential pandemics given the emerging list of pathogens that cause human disease.

### Author contributions

Saraj Kumar Singh contributed to the study conception. Material preparation and data collection were performed by Atul Anand, Anand Kumar Das and Sona Bhardwaj. The first draft of the manuscript was written by Atul Anand and Anand Kumar Das and all authors commented on previous versions of the manuscript. The first two authors have contributed equally in the preparation of the manuscript. All authors read and approved the final manuscript.

**Acknowledgments**

We acknowledge our digital artist Chandan Kumar for preparing the schematic representation.

**Declaration of patient consent**

Patient's consent not required as there are no patients in this study.

**Financial support and sponsorship**

Publication of this article was made possible by the James I. and Carolyn R. Ausman Educational Foundation.

**Conflicts of interest**

There are no conflicts of interest.

## REFERENCES

1. 2022 Monkeypox Outbreak: Global Trends. Available from: https://www.worldhealthorg.shinyapps.io/mpx_global [Last accessed on 2022 Sep 30].
2. Adler H, Gould S, Hine P, Snell LB, Wong W, Houlihan CF, *et al*. Clinical features and management of human monkeypox: A retrospective observational study in the UK. Lancet Infect Dis 2022;22:e177.
3. Alakunle E, Moens U, Nchinda G, Okeke MI. Monkeypox virus in Nigeria: Infection biology, epidemiology, and evolution. Viruses 2020;12:1257.
4. Anderson MG, Frenkel LD, Homann S, Guffey J. A case of severe monkeypox virus disease in an American child: Emerging infections and changing professional values. Pediatr Infect Dis J 2003;22:1093-8.
5. Badenoch JB, Conti I, Rengasamy ER, Watson CJ, Butler M, Hussain Z, *et al*. Neurological and psychiatric presentations associated with human monkeypox virus infection: A systematic review and meta-analysis. EClinicalMedicine 2022;52:101644.
6. Bayer-Garner IB. Monkeypox virus: Histologic, immunohistochemical and electron-microscopic findings. J Cutan Pathol 2005;32:28-34.
7. Beer EM, Rao VB. A systematic review of the epidemiology of human monkeypox outbreaks and implications for outbreak strategy. PLoS Negl Trop Dis 2019;13:e0007791.
8. Bengis RG, Leighton FA, Fischer JR, Artois M, Mörner T, Tate CM. The role of wildlife in emerging and re-emerging zoonoses. Rev Sci Tech 2004;23:497-511.
9. CDC. Monkeypox in the U.S. Centers for Disease Control and Prevention; 2022. Available from: https://www.cdc.gov/poxvirus/monkeypox/index.html [Last accessed on 2022 Sep 25].
10. Charniga K, Masters NB, Slayton RB, Gosdin L, Minhaj FS, Philpott D, *et al*. Estimating the Incubation Period of Monkeypox Virus During the 2022 Multi-National Outbreak. Public and Global Health; 2022. Available from: https://www.medrxiv.org/lookup/doi/10.1101/2022.06.22.22276713 [Last accessed on 2022 Sep 25].
11. Chen N, Li G, Liszewski MK, Atkinson JP, Jahrling PB, Feng Z, *et al*. Virulence differences between monkeypox virus isolates from West Africa and the Congo basin. Virology 2005;340:46-63.
12. Chowdhury SR, Datta PK, Maitra S. Monkeypox and its pandemic potential: What the anaesthetist should know. Br J Anaesth 2022;129:e49-52.
13. Croft DR, Sotir MJ, Williams CJ, Kazmierczak JJ, Wegner MV, Rausch D, *et al*. Occupational risks during a monkeypox outbreak, Wisconsin, 2003. Emerg Infect Dis 2007;13:1150-7.
14. Damon IK. Status of human monkeypox: Clinical disease, epidemiology and research. Vaccine 2011;29:D54-9.
15. Das AK, Mani SK, Singh SK. COVID-19-induced atypical pneumonia in an unseparated adult conjoined twin in a remote setup of developing country: Management by telemedicine. Illustrative case. J Neurosurg Case Lessons 2022;4:CASE22181.
16. Das AK, Mani SK, Singh SK. Surgical management of post-COVID invasive rhino-orbito-cerebral mucormycosis and its outcomes: Role of neurosurgeons in a tertiary care center. Surg Neurol Int 2022;13:335.
17. Durski KN, McCollum AM, Nakazawa Y, Petersen BW, Reynolds MG, Briand S, *et al*. Emergence of monkeypox-West and central Africa, 1970-2017. MMWR Morb Mortal Wkly Rep 2018;67:306-10.
18. Earl PL, Americo JL, Cotter CA, Moss B. Comparative live bioluminescence imaging of monkeypox virus dissemination in a wild-derived inbred mouse (*Mus musculus* castaneus) and outbred African dormouse (*Graphiurus kelleni*). Virology 2015;475:150-8.
19. Earl PL, Americo JL, Moss B. Lethal monkeypox virus infection of CAST/EiJ mice is associated with a deficient gamma interferon response. J Virol 2012;86:9105-12.
20. Falcinelli SD, Chertow DS, Kindrachuk J. Integration of global analyses of host molecular responses with clinical data to evaluate pathogenesis and advance therapies for emerging and re-emerging viral infections. ACS Infect Dis 2016;2:787-99.
21. Falendysz EA, Londoño-Navas AM, Meteyer CU, Pussini N, Lopera JG, Osorio JE, *et al*. Evaluation of monkeypox virus infection of black-tailed prairie dogs (*Cynomys ludovicianus*) using *in vivo* bioluminescent imaging. J Wildl Dis 2014;50:524-36.
22. Falendysz EA, Lopera JG, Doty JB, Nakazawa Y, Crill C, Lorenzsonn F, *et al*. Characterization of monkeypox virus infection in African rope squirrels (*Funisciurus* sp.). PLoS Negl Trop Dis 2017;11:e0005809.
23. Falendysz EA, Lopera JG, Lorenzsonn F, Salzer JS, Hutson CL, Doty J, *et al*. Further assessment of monkeypox virus infection in Gambian pouched rats (*Cricetomys gambianus*) using *in vivo* bioluminescent imaging. PLoS Negl Trop Dis 2015;9:e0004130.
24. Formenty P, Muntasir MO, Damon I, Chowdhary V, Opoka ML, Monimart C, *et al*. Human monkeypox outbreak caused by novel virus belonging to Congo Basin clade, Sudan, 2005. Emerg Infect Dis 2010;16:1539-45.
25. Hughes CM, Liu L, Davidson WB, Radford KW, Wilkins K, Monroe B, *et al*. A tale of two viruses: Coinfections of monkeypox and varicella zoster virus in the democratic republic of Congo. Am J Trop Med Hyg 2020;104:604-11

26. Huhn GD, Bauer AM, Yorita K, Graham MB, Sejvar J, Likos A, *et al*. Clinical characteristics of human monkeypox, and risk factors for severe disease. Clin Infect Dis 2005;41:1742-51.
27. Hutson CL, Carroll DS, Gallardo-Romero N, Weiss S, Clemmons C, Hughes CM, *et al*. Monkeypox disease transmission in an experimental setting: Prairie dog animal model. PLoS One 2011;6:e28295.
28. Hutson CL, Gallardo-Romero N, Carroll DS, Salzer JS, Ayers JD, Doty JB, *et al*. Analgesia during monkeypox virus experimental challenge studies in prairie dogs (*Cynomys ludovicianus*). J Am Assoc Lab Anim Sci 2019;58:485-500.
29. Hutson CL, Lee KN, Abel J, Carroll DS, Montgomery JM, Olson VA, *et al*. Monkeypox zoonotic associations: Insights from laboratory evaluation of animals associated with the multi-state US outbreak. Am J Trop Med Hyg 2007;76:757-68.
30. Jezek Z, Grab B, Szczeniowski MV, Paluku KM, Mutombo M. Human monkeypox: Secondary attack rates. Bull World Health Organ 1988;66:465-70.
31. Jezek Z, Szczeniowski M, Paluku KM, Mutombo M. Human monkeypox: Clinical features of 282 patients. J Infect Dis 1987;156:293-8.
32. Kabuga AI, El Zowalaty ME. A review of the monkeypox virus and a recent outbreak of skin rash disease in Nigeria. J Med Virol 2019;91:533-40.
33. Kalthan E, Tenguere J, Ndjapou SG, Koyazengbe TA, Mbomba J, Marada RM, *et al*. Investigation of an outbreak of monkeypox in an area occupied by armed groups, Central African Republic. Med Mal Infect 2018;48:263-8.
34. Khodakevich L, Jezek Z, Messinger D. Monkeypox virus: Ecology and public health significance. Bull World Health Organ 1988;66:747-52.
35. Kulesh DA, Loveless BM, Norwood D, Garrison J, Whitehouse CA, Hartmann C, *et al*. Monkeypox virus detection in rodents using real-time 3'-minor groove binder TaqMan assays on the Roche LightCycler. Lab Investig 2004;84:1200-8.
36. Ladnyj ID, Ziegler P, Kima E. A human infection caused by monkeypox virus in Basankusu territory, Democratic republic of the Congo. Bull World Health Organ 1972;46:593-7.
37. Likos AM, Sammons SA, Olson VA, Frace AM, Li Y, Olsen-Rasmussen M, *et al*. A tale of two clades: Monkeypox viruses. J Gen Virol 2005;86:2661-72.
38. Magnus P, Andersen EK, Petersen KB, Birch-Andersen A. A pox-like disease in cynomolgus monkeys. Acta Pathol Microbiol Scand 1959;46:156-76.
39. Mazurkov OY, Kabanov AS, Shishkina LN, Sergeev AA, Skarnovich MO, Bormotov NI, *et al*. New effective chemically synthesized anti-smallpox compound NIOCH-14. J Gen Virol 2016;97:1229-39.
40. McCollum AM, Damon IK. Human monkeypox. Clin Infect Dis 2014;58:260-7.
41. McEntire CR, Song KW, McInnis RP, Rhee JY, Young M, Williams E, *et al*. Neurologic manifestations of the world health organization's list of pandemic and epidemic diseases. Front Neurol 2021;12:634827.
42. Monkeypox Outbreak in Nigeria: Situation Report 9 Nigeria ReliefWeb. Available from: https://www.reliefweb.int/report/nigeria/monkeypox-outbreak-nigeria-situation-report-9-23-november-2017 [Last accessed on 2022 Sep 25].
43. Monkeypox: Case Definitions. GOV.UK. Available from: https://www.gov.uk/guidance/monkeypox-case-definitions [Last accessed on 2022 Sep 25].
44. Multi-Country Monkeypox Outbreak: Situation Update. Available from: https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON396 [Last accessed on 2022 Sep 25].
45. Ng OT, Lee V, Marimuthu K, Vasoo S, Chan G, Lin RT, *et al*. A case of imported monkeypox in Singapore. Lancet Infect Dis 2019;19:1166.
46. Ogoina D, Iroezindu M, James HI, Oladokun R, Yinka-Ogunleye A, Wakama P, *et al*. Clinical course and outcome of human monkeypox in Nigeria. Clin Infect Dis 2020;71:e210-4.
47. Ogoina D, Izibewule JH, Ogunleye A, Ederiane E, Anebonam U, Neni A, *et al*. The 2017 human monkeypox outbreak in Nigeria-Report of outbreak experience and response in the Niger Delta University Teaching Hospital, Bayelsa State, Nigeria. PLoS One 2019;14:e0214229.
48. Pastula DM, Copeland MJ, Hannan MC, Rapaka S, Kitani T, Kleiner E, *et al*. Two cases of monkeypox-associated encephalomyelitis-Colorado and the District of Columbia, July-August 2022. MMWR Morb Mortal Wkly Rep 2022;71:1212-5.
49. Pastula DM, Tyler KL. An overview of monkeypox virus and its neuroinvasive potential. Ann Neurol 2022;92:527-31.
50. Patel A, Bilinska J, Tam JC, Da Silva Fontoura D, Mason CY, Daunt A, *et al*. Clinical features and novel presentations of human monkeypox in a central London centre during the 2022 outbreak: Descriptive case series. BMJ 2022;378:e072410.
51. Pattyn SR. Monkeypoxvirus infections. Rev Sci Tech 2000;19:92-7.
52. Pittman PR, Martin JW, Kingebeni PM, Tamfum JJM, Wan Q, Reynolds MG, *et al*. Clinical Characterization of Human Monkeypox Infections in the Democratic Republic of the Congo; 2022. Available from: https://www.medrxiv.org/content/10.1101/2022.05.26.22273379v1 [Last accessed on 2023 Feb 17].
53. Prioritizing Diseases for Research and Development in Emergency Contexts. Available from: https://www.who.int/activities/prioritizing-diseases-for-research-and-development-in-emergency-contexts [Last accessed on 2022 Sep 29]
54. Reed KD, Melski JW, Graham MB, Regnery RL, Sotir MJ, Wegner MV, *et al*. The detection of monkeypox in humans in the Western Hemisphere. N Engl J Med 2004;350:342-50.
55. Reynolds MG, Yorita KL, Kuehnert MJ, Davidson WB, Huhn GD, Holman RC, *et al*. Clinical manifestations of human monkeypox influenced by route of infection. J Infect Dis 2006;194:773-80.
56. Sejvar JJ, Chowdary Y, Schomogyi M, Stevens J, Patel J, Karem K, *et al*. Human monkeypox infection: A family cluster in the midwestern United States. J Infect Dis 2004;190:1833-40.
57. Sepehrinezhad A, Ahmadabad RA, Sahab-Negah S. Monkeypox virus from neurological complications to neuroinvasive properties: Current status and future perspectives. J Neurol 2022;270:101-8.
58. Sergeev AA, Kabanov AS, Bulychev LE, Sergeev AA, Pyankov OV, Bodnev SA, *et al*. The possibility of using the

ICR mouse as an animal model to assess antimonkeypox drug efficacy. Transbound Emerg Dis 2016;63:e419-30.
59. Sergeev AA, Kabanov AS, Bulychev LE, Sergeev AA, Pyankov OV, Bodnev SA, *et al*. Using the ground squirrel (*Marmota bobak*) as an animal model to assess monkeypox drug efficacy. Transbound Emerg Dis 2017;64:226-36.
60. Shchelkunov SN, Totmenin AV, Babkin IV, Safronov PF, Ryazankina OI, Petrov NA, *et al*. Human monkeypox and smallpox viruses: Genomic comparison. FEBS Lett 2001;509:66-70.
61. Song H, Janosko K, Johnson RF, Qin J, Josleyn N, Jett C, *et al*. Poxvirus antigen staining of immune cells as a biomarker to predict disease outcome in monkeypox and cowpox virus infection in non-human primates. PLoS One 2013;8:e60533.
62. Tesh RB, Watts DM, Sbrana E, Siirin M, Popov VL, Xiao SY. Experimental infection of ground squirrels (*Spermophilus tridecemlineatus*) with monkeypox virus. Emerg Infect Dis 2004;10:1563-7.
63. Thornhill JP, Barkati S, Walmsley S, Rockstroh J, Antinori A, Harrison LB, *et al*. Monkeypox virus infection in humans across 16 countries-April-June 2022. N Engl J Med 2022;387:679-91.
64. WHO Director-General's Statement at the Press Conference Following IHR Emergency Committee Regarding the Multi-country Outbreak of Monkeypox-23 July 2022. Available from: https://www.who.int/director-general/speeches/detail/who-director-general-s-statement-on-the-press-conference-following-IHR-emergency-committee-regarding-the-multi--country-outbreak-of-monkeypox--23-july-2022 [Last accessed on 2022 Sep 29].
65. Xiao SY, Sbrana E, Watts DM, Siirin M, da Rosa PA, Tesh RB. Experimental infection of prairie dogs with monkeypox virus. Emerg Infect Dis 2005;11:539-45.
66. Yadav PD, Reghukumar A, Sahay RR, Sudeep K, Shete AM, Raman A, *et al*. First two cases of monkeypox virus infection in travellers returned from UAE to India, July 2022. J Infect 2022;85:e145-8.
67. Yinka-Ogunleye A, Aruna O, Dalhat M, Ogoina D, McCollum A, Disu Y, *et al*. Outbreak of human monkeypox in Nigeria in 2017-18: A clinical and epidemiological report. Lancet Infect Dis 2019;19:872-9.
68. Yinka-Ogunleye A, Aruna O, Ogoina D, Aworabhi N, Eteng W, Badaru S, *et al*. Reemergence of human monkeypox in Nigeria, 2017. Emerg Infect Dis 2018;24:1149-51.

**How to cite this article:** Anand A, Das AK, Bhardwaj S, Singh SK. A brief review of the monkeypox virus and emerging concerns for neuroinvasiveness. Surg Neurol Int 2023;14:78.