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Review Article

Narrative review on recent outbreaks of monkeypox: a global public health emergency

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ABSTRACT

Several cases of monkeypox have been reported since July 2022 and was hence declared a global public health emergency (GPHE). Recent reports from WHO indicate a rise in mpox cases over 2 years, even when vaccination is considered a protective measure. In this review, we discussed the recent spread of cases worldwide from 1st January 2024 to 1st October 2024, providing updated evidence on clinical features of different strains, epidemiology, diagnosis, treatment, and preventive measures. Ever since the 2022 outbreak, monkeypox virus has been undergoing novel mutations, leading to different strains at an alarming rate. According to the Ministry of Health, India has reported a total of 30 cases to date with the most recent case reported in September 2024. Recent outbreaks from Clade Ib were reported among young males with a median age of 34 years and sexual contact being a common mode of transport. Mpox commences with prodromal flu-like symptoms and a maculopapular rash with centrifugal distribution followed by fever. Diagnosis is confirmed by PCR testing of the lesions. Prompt vaccination after exposure might reduce the risk of disease progression. However, antiviral treatments and symptomatic care should be considered for severe patient populations. This review gives an insight into the current mpox scenario by educating people on emerging global endemics and their preventive strategies. Unlike other neglected diseases, we now have treatment and prevention options for mpox, but access to treatment is limited in most parts of the world. Identification and spread of new cases can be tracked more efficiently with the help of improved surveillance methods.

Keywords: Monkeypox, PCR testing, Global public health emergency, World Health Organization, Maculopapular rash, Centrifugal distribution

INTRODUCTION

After the outbreak of monkeypox in July 2022 in central and western Africa, it was declared as a global public health emergency by WHO. Monkeypox virus is a double-stranded DNA virus belonging to the genus orthopoxviridea of the family poxviridea. In 1958, the virus was first isolated from the cynomolgus breed of monkeys at a laboratory in Denmark.[1] The first case of mpox virus was reported in an infant from the Democratic Republic of Congo in 1970.[2] Only about 10 cases of monkeypox had been reported from 1978 to 2017 in West Africa. In 2017, a major outbreak was seen in West Africa with 188 cases after the re-emergence of clade II.[3] Many cases were reported in the UK in May 2022 after which a rapid rise was seen in Asia, Europe, North America, and South America.

This propelled WHO to declare monkeypox as a global health emergency in July 2022. There were two genetic variants of mpox detected from Central Africa (clade I) and West Africa (clade II), the most severe form that caused the global outbreak was clade I with a higher mortality rate according to CDC.[4] The case fatality rate for clade I was 10.6% and for clade II was 3.6%. The true burden of the disease is yet to be discovered.

EPIDEMIOLOGY AND GENETICS

Monkeypox was discovered in 1958 from a breed of monkeys transported from Singapore to Denmark for research purposes. Since 2022, WHO reported a total of 99,176 cases, and 208 deaths due to Monkeypox from 116 countries globally.[5] All the sequence outbreaks till recently were associated with clade II. But on Aug 14, 2024, WHO declared a new strain of virus clade Ib which was believed to be fatal to young adults.

Up-to-date total 30 mpox cases have been detected in India (15-Kerala & 15-Delhi) according to the Ministry of Health, India.[6] As mentioned, there are two clades (subtypes) of the virus- Clade Ia, Ib and Clade IIa, IIb. The route of transmission of clade Ia was through contact with infected wild animals, households, skin contact with lesions and needlestick injuries during patient care.[7]

Clade Ib was responsible for the recent outbreaks of mpox since January 2024 and spread through sexual contact affecting young males aged 15-35 years. According to WHO statistics the no. of mpox clade Ib cases detected was 6911 worldwide, with 53 deaths documented from 1st January 2024 to 1st October 2024 as shown in the Table 1.

MOLECULAR PATHOGENESIS

Mpox is a brick-shaped, pleomorphic double-stranded DNA virus. The genome comprises two identical telomeres with oppositely oriented nucleotide sequences called inverted terminal repeats (ITR) which are responsible for genetic mutations and variations.[8] The genome consists of several essential viral proteins- which assist the virus in attaching to the glycoprotein receptors of the host cells via macropinocytosis, to proliferate intracellularly and to serve as immunomodulators for host cell defenses.[9]

The size of the Mpox virus alerts the host immune system so immunomodulating proteins facilitate its survival in the host system. Three categories of Iproteins are- virotransducer proteins, virostealth proteins, and viromimic proteins. The virotransducer proteins inhibit innate signaling pathways that involve oxidative burst and apoptosis. The virostealth proteins impede viral deduction by inhibiting APCs such as Major Histocompatibility Complex (MHC-1) and CD4+ thus reducing cell-mediated immunity.

Finally, viromimic proteins imitate the reservoir's cytokines and chemokines, dysregulating their physiological operations. All these factors work synergistically to elude the host immune response and facilitate viral replication.[10]From the site of entry, the virus extends to the regional lymph nodes and then to the bloodstream, this covers the incubation period of 7-17 days. The primary viremia disseminates to the other organs via circulation which usually lasts for 1-4 days along with the prodromal phase.

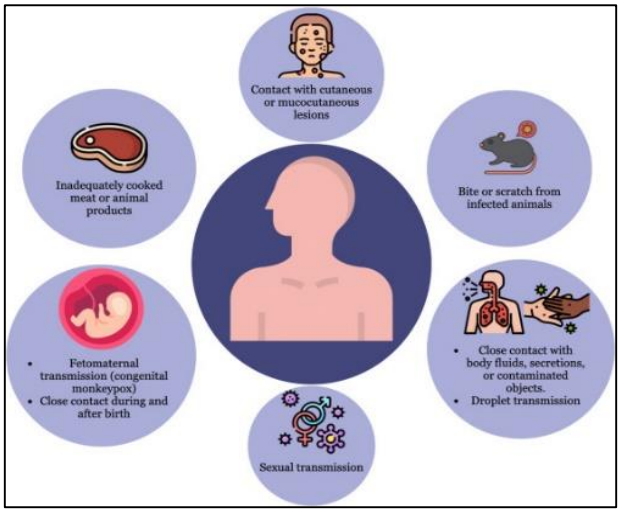

Figure 1: Route of transmission of mpox virus.

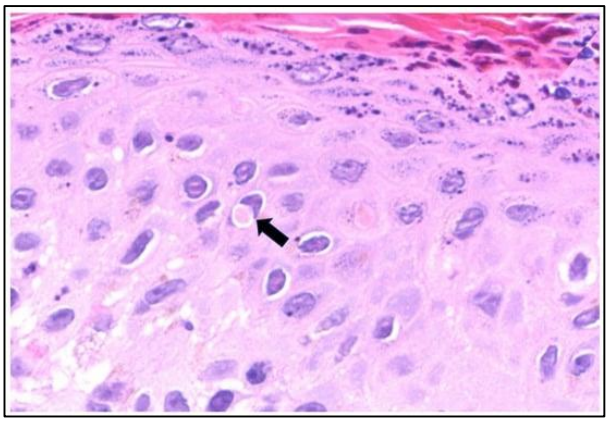

Figure 2: Ballooned, viable keratinocytes, with a cytoplasmic eosinophilic inclusion (arrow), also called a Guarnieri body.

CLINICAL PRESENTATION

Mpox is usually a self-limiting disease with symptoms lasting from 2-4 weeks. It is generally characterized by an incubation period, a prodrome, and a rash. The average age of presentation is between 4-21 years. The pathognomonic finding is the presence of vesicula-papular rash preceded by prodromal symptoms such as fever, chills, myalgia, and lymphadenopathy- it occurs 1-2 days before the onset of rash which is a distinguishing feature of mpox, differentiating it from smallpox and chickenpox. The incubation period of the virus is 5-21 days.[11]

A maculopapular rash with centrifugal distribution appears 3-4 days after the prodromal phase. Mpox is usually transmitted through rodents, mammals such as squirrels, African pouched rats and non-human primates (NHP). The transmission is through infected mammals or household contacts, sexual transmission, contact with bodily fluids, or needlestick injuries for healthcare professionals as shown in Figure 1. Progression of Mpox cases in sexual workers including homosexual, bisexual and men who

have sex with other men has become predominant in most parts of the world. Rectal discomfort and penile edema are the most commonly seen clinical manifestations in sexually infected individuals.[12] The rash may begin as peri-anal or peri-genital and subsequently extend to the trunk, extremities, and face. 95% of instances, the rash occurs on the face, 75% on the palms and soles, 70% on the mucous membranes, 30% on the genitals, and 20% on the cornea and conjunctiva.[13] The infected lesions are firm, rubbery, well-defined, with a central depression, buried in deeper skin layers, and can be painful or itchy. The lesions progress through four stages- macular, papular, vesicular, and pustular—before scabbing over and desquamation. The infectious stage continues until the desiccation of skin lesions and complete healing may take up to 4 weeks.[14] In the current outbreak, studies suggest that inguinal lymphadenopathy is the distinguishing feature, whereas the previous outbreaks documented more submandibular, cervical and axillary lymphadenopathy. This suggests that viral replication has multiplied over the years. The severity of the illness depends on the health status and transmission route. HIV patients with lower CD4 counts have a high mortality risk when compared to the general population. Secondary bacterial complications such as bronchopneumonia, keratitis, encephalitis and sepsis are seen in unvaccinated people with underlying medical conditions.[15]

Table 1: No. of Mpox CLADE I cases and deaths as of 1st October 2024 according to who statistics.

Who regions	No. of cases	No. of deaths
Democratic republic of Congo (DRC)	5399	25
Nigeria	55	0
Burundi	564	0
USA	113	9
India	10	1
Australia	245	0
Spain	136	0
Japan	16	1
Mexico	76	1
Peru	80	3
Thailand	148	9
Portugal	44	1
South Africa	25	3
Total	6911	53

Table 2: Progression of mpox lesions through four different stages.

Stage	Duration	Characteristics
Enanthem		Lesions first form on the tongue then in the mouth
Macules	1-2 days	Macular lesions appear
Papules	1-2 days	Lesions progress from macular(flat) to popular(raised)
Vesicles	1-2 days	Turn into vesicular (raised, filled with clear fluid)
Pustules	5-7 days	Become pustularm (filled with opaque fluid)- sharply raised, usually round and firm to touch(deep-seated). Finally, lesions develop a depression in the center (umbilication). The pustules will remain for 5-7days before they crust
Scabs	7-14 days	By the end of the second week, pustules crust and scab off. Scabs remain for about a week before they begin to fall off

DIAGNOSTIC WORKUP

The typical rash of mpox appears to have a different distribution and density in current outbreaks. For both the clades (I, II) of mpox infection, lesions often occur in genital, anorectal and oral areas confined to only a few lesions or a single lesion. Anogenital lesions are most manifested in the current outbreak with clade Ib.[16] Smallpox has similar symptomology with mpox but only differs in the stage of a lesion, where the latter presents with different stages of lesions.[17] The gold standard for diagnosis is the PCR testing of the skin lesion. Histopathologic findings show eosinophilic inclusion bodies called "Guarnieri bodies" or "B-type inclusions" findings (Figure 2) like orthopoxvirus.[18] CDC guidelines recommend collecting multiple samples by vigorously swabbing or brushing the lesion for clade-specific testing. Serology has limited diagnostic value since it cannot distinguish amongst orthopoxviruses due to cross-immunological reactivity. However, antibody titers can be assessed for vaccine responses. All the suspected individuals should be monitored for relevant signs and

symptoms for 21 days from the day of exposure.[19] According, to Nagata et al, a rise in TLC count is generally seen in bacterial sepsis, but in fulminant mpox infections- a decrease in neutrophil count or neutropenia is observed signifying higher morbidity and mortality.[20]

TREATMENT & PREVENTION

Mpox is treated with supportive care for symptoms such as pain and fever, with close attention to nutrition, hydration, skin care, prevention of secondary infections and treatment of co-infections, including HIV. According to Evans et al, vaccination against smallpox provides immunological protection and is 85% effective against monkeypox a live attenuated vaccinia virus vaccine has been modified and developed under brand names "JYNNEOS" in USA, "IMVANEX" in Europe, and "IMVAMUNE" in Canada.[21,22] A vaccinia virus vaccine approved by FDA in 2007 is ACAM2000TM which is a replication-competent vaccine recommended for post-exposure.[23] The safety of this vaccine is still under debate as it causes cardiac complications and uncomfortable cutaneous reactions.[24] Hence it is no longer licensed. In the year 2019, FDA (Food and Drug Administration) approved JYNNEOS for prophylaxis of smallpox and monkeypox in high-risk groups with a recommended dose of two subcutaneous doses of 0.5 ml with an interval of four weeks for first smallpox vaccination, but if previously vaccinated then the recommended dose is only one. JYNNEOS is a brand name for Modified Vaccinia virus Ankara Bavarian Nordic (MVA-BN) vaccine.[25] JYNNEOS is safer than ACAM2000TM with proven efficacy according to Sah et.al.[26] However, both vaccines are recommended for high-risk patients.

CDC recommends both pre-exposure and post-exposure prophylaxis for high-risk groups such as immunocompromised or healthcare personnel frequently exposed to mpox virus stains.[27] The post-exposure prophylaxis given within 4-14 days of exposure helps reduce the infection risk. There are currently no active medications for mpox. However, FDA has approved using certain antiviral drugs such as brincidofovir, cidofovir, tecovirimat and vaccinia immune globulin intravenous so far.[28] Among these, tecovirimat is most effective and 100% effective in decreasing disease severity.[29] It targets the F13L gene encoding VP37 membrane protein and prevents the dissemination of viral particles in the host body.[30] Certain preventive strategies can stop the spread of the virus – avoiding close contact with affected individuals and animals, proper hygiene, safe sex practices and isolation of infected people.

CONCLUSION

Unlike any other virus, monkeypox is also a self-limiting illness with prevention as the main measure. Global cessation of the smallpox vaccine is believed to be the reason for recurrent mpox cases. The 2022 outbreak hit multiple countries in the world with two different strains identified so far. Prevention and treatment of mpox cases should be widely disseminated. An awareness campaign for all healthcare professionals, emphasizing the signs and symptoms of the disease and the importance of timely reporting of cases has to be implemented. Human-to-human spread of Mpox can be controlled by public health measures including enhanced surveillance, early case finding, diagnosis and care, isolation and contact tracing. A globally focused health strategy for disease control and prevention is needed to manage future outbreaks.

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