

Review Article

Monkeypox: A Global Public Health Emergency of 2022- Are We Ready?

*Afroze T¹, Salam MU², Rahman N³, Ahmad MM⁴, Alam FM⁵, Joysoual MR⁶

Abstract:

Monkeypox is a zoonotic viral disease endemic to the tropical rainforest regions of Central and West Africa. The 1st virus isolation was done from a group of research monkeys in 1958 and the 1st human case was detected in the Democratic Republic of Congo (DRC) in 1970. Outbreaks outside Africa by 2021 were always small-scale and associated with travel to endemic regions or the importation of infected animals. But in 2022, more than 2000 cases were reported from 1st January to 3rd August from more than 80 countries worldwide, and the majority of them had no travel or contact history. Neighboring country India has also detected four monkeypox cases for the first time with one death which is a concern for Bangladesh. This review article gives a brief overview of the monkeypox virus, the disease, and most importantly, the preventive measures in the context of the current global outbreak.

Key words: Monkeypox, zoonotic virus, Monkeypox virus, poxvirus

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Introduction:

Monkeypox is a rare zoonotic viral disease that is endemic in remote, poor, and underprivileged populations near the tropical rainforest regions of Central and West Africa.¹ The virus responsible for Monkeypox is different from other types of poxviruses that cause diseases in animals and rarely in humans.² It is found in a total of 11 African countries since the first attack on a 9-year-old boy in the DRC (Democratic Republic of Congo) in 1970. In Congo and Nigeria 6000 and 3000 cases per year are diagnosed per year.

The first virus isolation was done from a group of research monkeys brought from Africa to Denmark in 1958, hence it was named monkeypox.^{2,3} But its actual animal reservoir is attributed to African rodents and non-human primates.⁴

All of the small and large outbreaks that occurred outside of Africa by 2021, involved travel to the endemic regions or the importation of infected animals.⁴ For example, in 2003, 53 people were infected in the United Kingdom (UK), the source being imported infected Gambian rats from Ghana. One was affected in Israel in October 2018 and one in Singapore in May 2019. They both had a travel history to Nigeria. In 2021, three members of the same family were sequentially affected in the UK, the first having a similar, recent history of travel. In the same year, a case in Texas in July and, a case in Maryland in November were detected after returning back from Nigeria.⁵

However, Monkeypox emerged in a new shape in 2022 with the usual small and unusual large outbreaks even in several non-endemic countries outside of endemic areas of Africa that had no suggestive links to international travel or animal contact. Up to August 3 of this year, 88 countries reported a total of 28,053 confirmed cases with 11 deaths. The highest number of cases were reported from the European regions,

1. Dr. Tamanna Afroze, Assistant Professor, Dept. of Microbiology, Udayan Dental College, Rajshahi.
2. Dr. Mahjuba Umme Salam, Professor and Head, Dept. of Medicine, Sylhet Women's Medical College.
3. Dr. Nahreen Rahman, Assistant Professor, Dept. of Microbiology, Rajshahi Medical College.
4. Dr. Md. Masuq Ahmad, Assistant Registrar, Dept. of Medicine, SWMCH.
5. Dr. Fatema Mohammad Alam, MD, Microbiology.
6. Dr. Mita Rani Joysoual, Lecturer, Dept. of Pharmacology, Rajshahi Medical College

Corresponding author: Tamanna Afroze

Assistant Professor, Department of Microbiology
Udayan Dental College, Rajshahi.
Email: drtamanna86@gmail.com

which was eventually declared as the disease epicenter. And 99% of the cases were males in the 31-43 years age group and, a significant portion of them being homosexual and bisexual.^{6,7,8}

Monkeypox is closely related to smallpox. According to WHO (World Health Organization), the smallpox vaccine is 85% cross-protective against monkeypox.⁹ But as the smallpox vaccination has perished since the 1980s, the immunity against monkeypox has declined over time. Simultaneously, owing to socio-political and ecological changes in the endemic regions, human exposure to reservoir animals has increased. The incidence rose by 20-fold from 2005 to 2007.¹⁰ The median age presentation was 4 years in 1970 but it became 21 years in 2010-2019.¹¹ Cases with human-to-human transmission has also increased. Monkeypox can be transmitted up to six sequential human chains and the secondary attack rate is approximately 10%.¹² Wildlife trade and international travels caused increased outbreaks outside the endemic region. In particular, the 2022 unusual outbreak of monkeypox has imposed an ever-increasing threat to human health security.^{13,14}

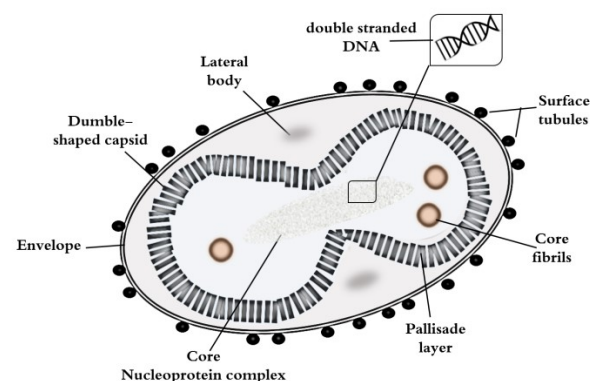
The global alarm is on and, Bangladesh though is still safe, needs to be alert in advance right away. Proper understanding of the virus, its transmission, disease progression, diagnostic procedures, treatment options, and especially, the preventive measures are to be disseminated fast. This review briefly discussed these issues to propagate knowledge and awareness among medical personnel and common people.

The virus

Monkeypox virus (MPV) is a virus of the *orthopox* genus of the *poxviridae* family and shares the same genus as the smallpox virus. Under an electron microscope, the virion is a 200 to 250 nm brick-shaped or ovoid-shaped enveloped particle with characteristic surface tubules outside and a dumbbell-shaped capsid inside. The capsid contains the linear double-stranded DNA genome and enzymes required for viral un-coating and replication (Figure 1).^{5,16} The virus replicates in the local tissues but,

unlike most other DNA viruses, it replicates entirely in the cytoplasm rather than the nucleus. It exists in two genetically distinct clades. A Congo Basin clade is more virulent with a 1-10% mortality rate. The other is the West African clade which is less virulent with a mortality rate of less than 3%.^{1,17} In the preliminary genome sequencing, it was seen that the outbreak in 2022 (Figure 2) occurred by the West African clade.¹⁸

Figure 1: Different parts of monkeypox virion (courtesy-Mahjuba Umme Salam)



Epidemiology

Since its first report in the DRC in 1970, monkeypox had been considered endemic in 10 countries of Africa. The USA was the first non-endemic country to have a case of this zoonotic disease in 2003, presumed to have contracted it from Nigeria. Afterwards, small outbreaks have been reported from other non-endemic areas of the world from time to time (Figure 2).^{7,8} The disease then was prevalent among people not immunized against smallpox.¹⁶ The recent outbreak began with the detection of a case in the UK on 6th May 2022 and then the subsequent cases in other parts of Europe were reported. Along with more case detection in the UK, other European countries-Belgium, France, Germany, Italy, Netherlands, Portugal, Spain and, Sweden have been affected. It even spread to Australia, Canada and the USA (Figure 3). Among the Arab countries, the United Arab Emirates (UAE) has been the first to get the disease. Long after the eradication of smallpox from the world, this new outbreak with monkeypox has raised serious concerns and

WHO has labelled the current outbreak as PHEIC (Public Health Emergency of International Concern).^{18,19} Besides this, the mode of transmission, clinical features, complications and death rates of the current pandemic are way different from the previous outbreaks (Table 1).^{12,20,21} The disease now is exhibiting predominant human-to-human transmission, prevalence among males with homosexual behavior. Immuno-deficient status has emerged as a risk factor of note and, nearly half of the victims are HIV positive. India reported its first 4 cases, one from Delhi and the rest three from Kerala the index case confirmed its diagnosis on the 15th July 2022.^{20,22,23} And thus, the subcontinent is on alert. Though the disease was of low virulence in the past, experts presume that it might turn to fatal quarters soon if necessary steps are not taken.

Figure 2: Outbreaks in non-endemic areas of the world before 2022

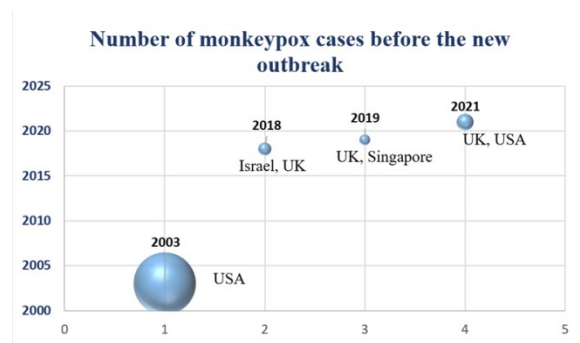


Figure 3: Global spread of monkeypox up to 3rd August 2022⁶

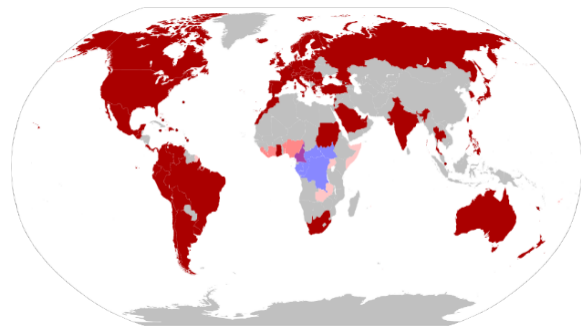


Table 1: Difference between previous and the 2022 outbreak of monkeypox

Outbreak criteria	Before 2022	In 2022
Geographic location	Mainly endemic regions of central and west Africa. Rarely outside Africa.	Simultaneously in non-endemic and endemic countries in widely different geographic regions.
Outbreaks outside Africa	Linked to travel to endemic region or contact with infected animal	No such links were found
Community transmission	rare	Exclusive
Transmission through sexual contact	Rare or absent	Exclusive
Main victims	Those who came in contact with an infected animal or an infected person	Mainly men who have sex with men
Symptoms	Always classical	In many patients, the symptoms took a non-classical form
Death outside Africa	No	Yes

Transmission:

The route of viral entry is broken skin, respiratory tract, or mucous membranes of the eye, mouth, and nose.²⁴ The source may be the infected lesions, blood, body fluids, or respiratory droplets of an infected animal or human.^{4,11,24} Animal-to-human transmission is historically dominant and occurs through bites, scratches, or direct handling of infected animals.² According to previous documents, human-to-human transmission may occur in 10-30% of cases¹⁵ and, it increased over time and became almost exclusive in the 2022 outbreak.^{14,2} This transmission can be through direct contact with infected lesions or contact

with contaminated clothing, bedding, and utensils.^{15,25} People can also acquire the virus through inhalation of large respiratory droplets during direct and prolonged face-to-face contact (within a 6-foot radius for >3 hours).^{16,17} Trans placental transmission from mother to fetus can also occur.^{9,25,26} Transmission through semen or vaginal fluid is still questionable. One study reported the presence of viral DNA in the semen of infected persons¹⁸, but according to WHO, it is not enough to call monkeypox a sexually transmitted disease. Rather, the 2022 outbreak affecting predominantly the MSM (men who have sex with men) group is due to direct and prolonged contact with local genital/anal lesions, not due to sexual fluid.^{19,20}

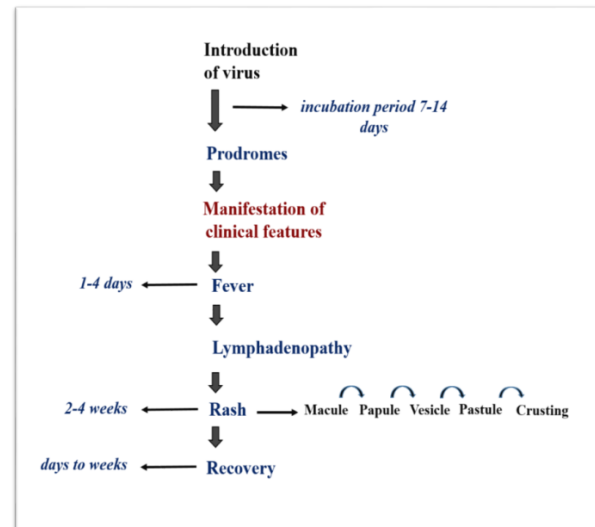
Pathogenesis:

The pathogenesis of monkeypox is almost the same as that of smallpox, although its clinical course and features are mild and self-limiting.⁴ After entering the human host via the appropriate route, the virus first replicates in local tissues, then travels through the lymphatic vessels to the local lymph nodes. After replicating in the mononuclear phagocytic cells, the virus enters the bloodstream, develops primary viraemia, and then gets seeded in different organs. This phase correlates with the incubation period.^{24,26} Then, it develops secondary viraemia that corresponds to the appearance of prodromal symptoms. Eventually, the virus localizes into the skin.⁵ Virus replication in the skin cells and the subsequent immunological reaction and damage are probably responsible for the skin lesions.^{21,27}

Clinical features:

Entry of the virus into the body sets a sequential cascade of clinical features (Figure 4). Classically, after an incubation period of 7 to 14 days (can range from 5 to 21 days), the prodromal symptoms appear with the fever, headache, muscle aches, backache, chills, and exhaustion.^{23,27} Lymphadenopathy (generalized or localized to several areas; especially submental, submandibular, cervical, and inguinal) is a prominent feature that clinically helps to differentiate monkeypox from smallpox.^{25,27,28}

Figure 4: Evolution of clinical features of monkeypox



One to three days after the onset of fever, the patient develops a rash, centrifugal in distribution, a few to several thousand in number, starts as a macule, then simultaneously evolves into papules, vesicles, pustules, and eventually dries out in the form of crust (Figure 5 and Figure 6).^{9,25} These lesions are 0.5 in diameter but can be bigger. The patient remains infectious to others from the appearance of symptoms to the shedding out of crusts.²⁴ This classical clinical course was not apparent in all cases in the 2022 outbreak. Non-classical features include localized lesions in the genitalia, asynchronous stages of lesions, lesions appearing before fever, etc.^{14,28} Symptoms usually resolve in two to four weeks but depend on the patient's health and economical status, hospital facilities, type of virus, and the amount of virus exposure.^{9,23} The overall case fatality rate is 3-6% in the current outbreak.²⁸ The risk group includes children, adults under 50 years, pregnant women, and immuno-deficient persons.⁹ Complications include secondary bacterial infections, permanent skin scarring, hypo or hyper skin pigmentation, vision loss, pneumonia, dehydration, sepsis, encephalitis, etc.²⁶

Figure 5: Evolution of skin rash from macule to crust formation ²⁵



Figure 6: Classic Presentation of Monkeypox (DRC, 1997) ²⁵



Diagnosis:

So far, PCR (polymerase chain reaction) is the preferred laboratory test for the diagnosis of monkeypox due to its accuracy and sensitivity. The preferred sample is skin lesions (roof or fluid from vesicles and pustules; dry crusts) as the quantity of virus is highest in skin lesions. Positive samples are sent to the CDC (Centers for Disease Control and Prevention) for viral clade detection.²⁸ Although serological and antigen detection tests are available, they are not recommended as routine diagnostic tests for the possibility of false positive result in previously orthopox virus infected persons and persons vaccinated with vaccinia based vaccine because orthopox viruses are serologically cross-reactive.²⁹ If proper facilities are available, in the presence of trained and skilled personnel, the monkeypox virus can be detected from a sample under the electron microscope and virus isolation can be done in cell culture. But these are also not recommended as routine diagnostic tests.^{9,26,30}

Differential diagnoses:

Febrile illnesses with maculo-papulo-vesicular eruptions, like smallpox, chickenpox, bacterial skin infections, scabies, and drug reactions, are the commonly considered differentials of monkeypox. Smallpox, though eradicated from the world should always be considered for re-emergence, when one is dealing with a suspected case of monkeypox.^{27,28} These two diseases have similarities and dissimilarities, which a healthcare professional should have a clear knowledge of. All these conditions present with skin rash but should be distinguished by other features (Table 2 and Table 3).

Table 2: Difference between features of monkeypox and smallpox

Differentiating point	monkeypox	smallpox
Disease severity	milder form	severe form
Lymphadenopathy	present	absent
Mortality	Low 1-10%	High 50%
Global prevalence	Emerged since 1970	Eradicated since 1977

Table 3: Difference between features of monkeypox, chickenpox and measles

Differentiating point	monkeypox	chickenpox	measles
Incubation period	7-14 days	14-21 days	10-12 days
Fever prior rash	1-5 days	1-2 days	3-5 days
Rash	Appearance	All lesions at the same stage	Lesions at different stage
	Development	Slow	Rapid
	Type	Macule, papule, vesicle, pustule	Vesicles on erythematous base
	Distribution	Most dense on face, present in the palm and sole	Most dense in the trunk, absent in the palm and sole
Lymphadenopathy	Present	Absent	Absent
Mortality	1-10%	Rare	Variable

Treatment:

Since the symptoms of monkeypox are mild and self-limiting, some supportive management like fluid correction and analgesics to reduce fever and pain are sufficient in the majority of patients. Some indicated patients (for eg. immunocompromised patients, pediatric patients under 8 years of age, patients with atopic dermatitis or other active exfoliative skin conditions, pregnant and breastfeeding women, and patients with complications) can use USFDA (United States Food and Drug Administration) approved antiviral drugs tecovirimat, cidofovir, and brincidofovir under the supervision of health care professionals.³¹ There are no specific data on the effectiveness of any of the three mentioned drugs against monkeypox. But CDC has allowed their compassionate use (also called expanded access) in case of monkeypox outbreaks, depending on their effectiveness on orthopox viruses in invitro and animal studies. CDC has also allowed the compassionate use of VIGIV (vaccinia immunoglobulin intravenous) in severe cases although there is no available data on its effectiveness.^{27,29}

Prevention:

Due to the unusual mode of transmission and rapid worldwide spread, on 23rd July 2022, WHO declared monkeypox a global health emergency.⁷ The main strategy of prevention is to avoid contact with a patient. The patient should be kept in complete isolation until the last lesion crusts off and direct skin-to-skin contact with the patient should be avoided. Also, the patient's bedding, items of clothing, and utensils should be kept in separation and if handling is required gloves must be worn. Caregivers and clinicians should use gloves, goggles, and filtered n95 masks for their protection. Hands should be washed frequently with soap and water and regularly used surfaces should be cleaned frequently with disinfectant.³²

In case of suspected exposure, the person should be monitored for developing symptoms for up to 21 days. There are currently two USFDA-approved vaccines for monkeypox prevention: JYNNEOS and ACAM2000. According to CDC, for post-exposure prophylaxis,

vaccinating the exposed persons within four days of exposure

will prevent disease. However, if vaccinated within four to 14 days, the disease will not be prevented but the severity of symptoms will be reduced.^{29,32}

Some indicated persons, for example, health workers at high risk of exposure, laboratory personnel working with orthopoxviruses, clinical laboratory personnel performing laboratory testing for monkeypox, outbreak response team members, and other individuals who may be at high risk like persons with multiple sex partners can take vaccine for pre-exposure prophylaxis.^{8,33}

Historically, since monkeypox is a zoonotic disease, not only during outbreaks but also during normal periods, avoiding contact with risky animals and careful handling and cooking for the consumption of meat is especially important. In the case of imported rodents and nonhuman primates, suspected infected animals and other animals that have come in their contact should be handled with standard precautions, quarantined for 30 days, and observed for monkeypox symptoms.^{9,30}

Conclusion:

World Health Organization has urged upon a strategic approach to prevent monkeypox and thus, combat this public health emergency of international concern. Widespread awareness and, education about preventive measures can minimize loss. Rapid case detection, contact tracing, and medical care are to be ensured and enhanced. Lastly, a coordinated approach of government, public health officials, clinicians, and community workers is implied.

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