International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 6 Nov-Dec 2022, pp: 792-799 www.ijprajournal.com ISSN: 2456-4494

Review On Monkeypox Virus: A Tale Of Two Clades

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Submitted: 15-11-2022 Accepted: 26-11-2022

ABSTRACT
Monkeypox is a viral disease which is transmitted to humans through close contact with infected animals (viral zoonosis) or humans. It is caused by monkeypox virus, a member of the orthopoxvirus genus in family Poxviridae. Monkeypox is a disease of global public health importance as it not only affects countries in west and central Africa, but the rest of the world. The clinical symptoms involve fever rashes and swollen lymph nodes and may lead to a range of medical complications. Clinical representation of monkeypox resembles that of smallpox, a related orthopoxvirus infection which was declared eradicated worldwide in 1980. Vaccines used during the smallpox eradication programme also provided protection against monkeypox. PCR is the preferred laboratory test while serology and antigen detection methods are not recommended as they do not provide monkeypox-specific confirmation.

Keywords: Monkeypox, Orthopoxvirus, Zoonotic, Poxviridae

I. INTRODUCTION

Monkeypox is a viral zoonosis with symptoms similar to those seen in the past in smallpox patients. Monkeypox is a rare disease caused by the monkeypox virus which was discovered in 1958,when two outbreaks of a pox like disease occurred in groups of monkeys being used for research.It spreads mainly through human contact with infected rodents,but can sometime be spread through skin-to-skin contact with a person who is infected.

Comparatively monkeypox and chickenpox are symptomatically similar as they both cause skin rashes but the viruses responsible for their cause are different. Monkeypox is an orthopox virus while chickenpox is an herpes virus. People with monkeypox are more prone to have swollen lymph nodes compared to people with chickenpox. Chickenpox rashes appear in waves however monkeypox sores develop at the same time. Similarly both viruses can be spread through skin-to-skin or prolonged face-to-face contact but chickenpox is very contagious and spreads more easily than monkeypox. Smallpox which was eradicated by 1980 and monkeypox are both part of the orthopoxvirus family, so they are caused by similar but distinct viruses. Smallpox was very contagious and spread more easily than monkeypox. Monkeypox symptoms are similar to smallpox, but milder.

Monkeypox was first identified in humans in 1970 in the democratic republic of the Congo in a 9 month old boy. For decades, monkeypox was mostly seen in Africa. However, it's occasionally found in other countries including the United States. In the spring of 2003, the first outbreak of monkeypox outside of a Africa occurred in the U.S. A shipment of infected animals from Ghana was imported into Texas. The infected rodents spread the virus to pet prairie dogs, which then infected 47 people in the Midwest. Since 2017, Nigeria has experienced a large outbreak, with over 500 suspected cases and over 200 confirmed cases and case fatality ratio of approximately 3%. Monkeypox has also been reported in travelers from Nigeria to Israel in September 2018, United Kingdom in September 2018 , December 2019, may 2021 and may 2022 to Singapore and to the United States of America in July and November 2021. In May 2022, multiple cases of monkeypox were identified.

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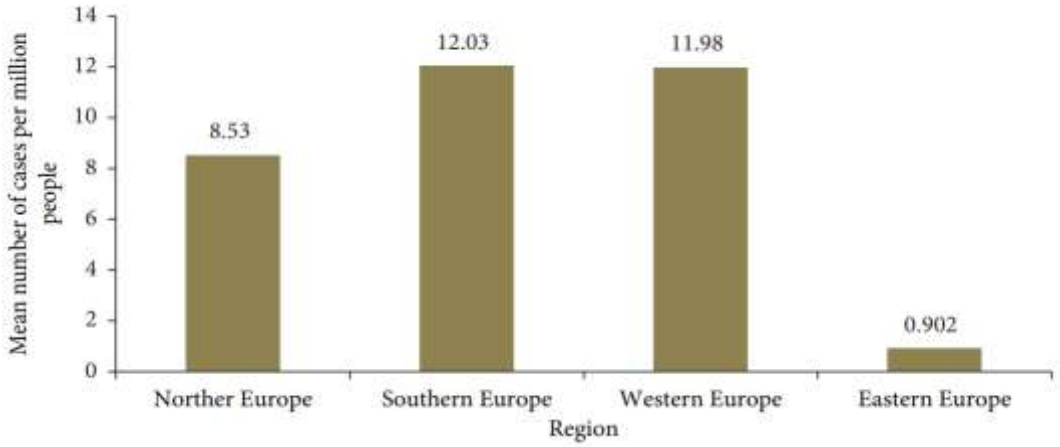

Figure 1: Monkeypox means cases per one million people in the different regions of Europe (cases presented from May 7, 2022, to July 7, 2022).

The Pathogen

Monkeypox virus is an enveloped double-stranded DNA virus that belongs to the Orthopoxvirus genus of the Poxviridae family. There are two distinct genetic clades of the monkeypox virus: the central African (Congo Basin) clade and the west African clade. The Congo Basin clade has historically caused more severe disease and was thought to be more transmissible. Various animal species have been identified as susceptible to monkeypox virus. This includes rope squirrels, tree squirrels, Gambian pouched rats, dormice, non-human primates and other species.

Transmission

Animal-to-human (zoonotic) transmission can occur from direct contact with the blood, bodily fluids, or cutaneous or mucosal lesions of infected animals. In Africa, evidence of monkeypox virus infection has been found in many animals including rope squirrels, tree squirrels, Gambian pouched rats, dormice, different species of monkeys and others. The natural reservoir of monkeypox has not yet been identified, though rodents are the most likely. Eating inadequately cooked meat and other animal products of infected animals is a possible risk factor. People living in or near forested areas may have indirect or low-level exposure to infected animals.

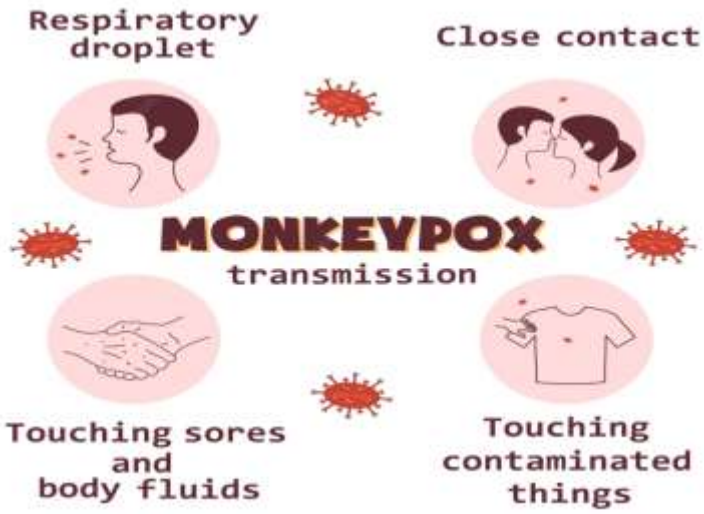

Figure 2 : Transmission

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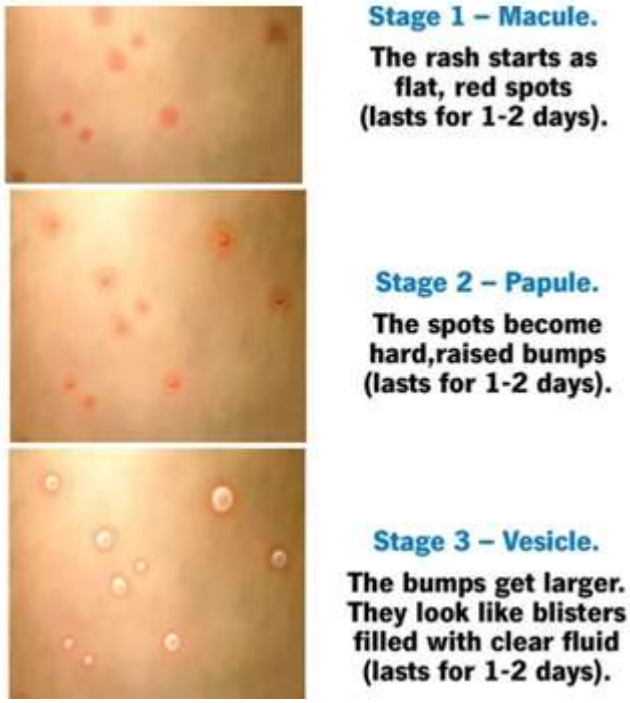
Human-to-human transmission can result from close contact with respiratory secretions, skin lesions of an infected person or recently contaminated objects. Transmission via droplet respiratory particles usually requires prolonged face-to-face contact, which puts health workers, household members and other close contacts of active cases at greater risk. However, the longest documented chain of transmission in a community has risen in recent years from 6 to 9 successive person-to-person infections. This may reflect declining immunity in all communities due to cessation of smallpox vaccination. Transmission can also occur via the placenta from mother to fetus (which can lead to congenital monkeypox) or during close contact during and after birth. While close physical contact is a well-known risk factor for transmission, it is unclear at this time if monkeypox can be transmitted specifically through sexual transmission routes. Studies are needed to better understand this risk.

Signs and symptoms

After exposure, it may be several days to a few weeks before you develop symptoms. Early signs of monkeypox include flu-like symptoms, including:

- Fever.
- Chills.
- Headache.
- Muscle aches.
- Fatigue.
- Swollen lymph nodes.



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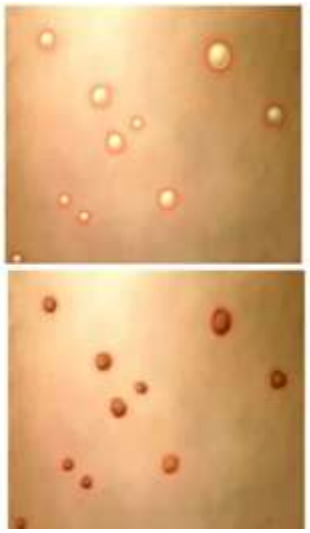

After a few days, a rash often develops. The rash starts as flat, red bumps, which can be painful. Those bumps turn into blisters, which fill with pus. Eventually, the blisters crust over and fall off — the whole process can last two weeks to four weeks. You can also get sores in your mouth, vagina or anus.

Not everyone with monkeypox develops all the symptoms. In fact, in the current (2022) outbreak, many cases aren't following the usual pattern of symptoms. This atypical presentation includes only a few lesions, no swollen lymph nodes, less fever and other signs of illness. You can have it and not know it. Even if you don't show many signs of infection, you can still spread it to others through prolonged close contact.

Diagnosis

The clinical differential diagnosis that must be considered includes other rash illnesses, such as chickenpox, measles, bacterial skin infections, scabies, syphilis, and medication-associated allergies. Lymphadenopathy during the prodromal stage of illness can be a clinical feature to distinguish monkeypox from chickenpox or smallpox.

Polymerase chain reaction (PCR) is the preferred laboratory test given its accuracy and sensitivity. For this, optimal diagnostic samples for monkeypox are from skin lesions – the roof or fluid from vesicles and pustules, and dry crusts. Where feasible, biopsy is an option. Lesion samples must be stored in a dry, sterile tube (no viral transport media) and kept cold.

As orthopoxviruses are serologically cross-reactive, antigen and antibody detection methods do not provide monkeypox-specific confirmation. Serology and antigen detection methods are therefore not recommended for diagnosis or case investigation where resources are limited. The Orthopox BioThreat Alert® (Tetracore, Rockville, MD) is a point-of-care diagnostic test that can directly detect pox virus antigens from the material taken from skin lesions. It is, therefore, useful in the field settings, but is less sensitive than PCR and cannot distinguish MPX from other pox viruses.

Treatment

Treatment should be considered for use in people who have the following clinical manifestations:

- Severe disease — consider severe disease when a patient has conditions such as hemorrhagic disease; a large number of lesions such that they are confluent; necrotic lesions; severe lymphadenopathy that can be necrotizing or obstructing (such as in airways); involvement of multiple organ systems and associated comorbidities (for example, pulmonary involvement with nodular lesions; sepsis; encephalitis; myocarditis; ocular or periorbital infections); or other conditions requiring hospitalization
- Involvement of anatomic areas which might result in serious sequelae that include scarring or strictures — these include lesions directly involving the pharynx causing dysphagia, inability to control secretions, or need for parenteral feeding; penile foreskin, vulva, vagina, urethra, or anorectum with the potential for causing strictures or requiring catheterization; anorectal lesions interfering

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with bowel movements (for example, severe pain); and severe infections (including secondary bacterial skin infections), especially those that require surgical intervention such as debridement.

Treatment should also be considered for use in people who are at high risk for severe disease:

- People currently experiencing severe immunocompromised due to conditions such as advanced or poorly controlled human immunodeficiency virus (HIV), leukemia, lymphoma, generalized malignancy, solid organ transplantation, therapy with alkylating agents, antimetabolites, radiation, tumor necrosis factor inhibitors, high-dose corticosteroids, being a recipient of a hematopoietic stem cell transplant <24 months post-transplant or ≥24 months but with graft-versus-host disease or disease relapse, or having autoimmune disease with immunodeficiency as a clinical component1
- Pediatric populations, particularly patients younger than 8 years of age2
- Pregnant or breastfeeding people
- People with a condition affecting skin integrity — conditions such as atopic dermatitis, eczema, burns, impetigo, varicella zoster virus infection, herpes simplex virus infection, severe acne, severe diaper dermatitis with extensive areas of denuded skin, psoriasis, or Darier disease (keratosis follicularis)

For patients at high risk for progression to severe disease, treatment should be administered early in the course of illness along with supportive care and pain control.

Tecovirimat (TPOXX, ST-246)

Tecovirimat is an antiviral medication that is approved by FDA for the treatment of smallpox in adults and children. studies using a variety of animal species have shown that tecovirimat is effective in treating disease caused by orthopoxviruses. A clinical trial focused on safety in healthy people without monkeypox virus showed the drug had an acceptable safety profile.

Tecovirimat can be considered for prophylactic use in an exposed person with severe immunodeficiency in T-cell function for which smallpox or monkeypox vaccination following exposure to monkeypox virus is contraindicated.

Brincidofovir (CMX001 or Tembexa)

Brincidofovir is a prodrug of cidofovir that is approved by the FDA for the treatment of human smallpox disease in adult and pediatric patients, including neonates. Brincidofovir should not be used simultaneously with cidofovir.

Vaccinia Immune Globulin Intravenous (VIGIV)

VIGIV is licensed by FDA for the treatment of complications due to vaccinia vaccination. However, it is not approved for treatment of monkeypox. Therefore, CDC holds an expanded access IND protocol that allows the use of stockpiled VIGIV for the treatment of orthopoxviruses (including monkeypox) in an outbreak.

VIGIV can be considered for prophylactic use in an exposed person with severe immunodeficiency in T-cell function for which smallpox or monkeypox vaccination following exposure to monkeypox virus is contraindicated.

Cidofovir (Vistide)

Cidofovir is an antiviral medication that is approved by the FDA for the treatment of cytomegalovirus (CMV) retinitis in patients with Acquired Immunodeficiency Syndrome (AIDS), and is commercially available as an injection.Data are not available on the effectiveness of cidofovir in treatment of monkeypox virus infection in people. However, it has shown to be effective against orthopoxviruses in in vitro and animal studies. It is unknown whether a person with severe monkeypox infection will benefit from treatment with cidofovir.

Brincidofovir (a prodrug of cidofovir) may have an improved safety profile over cidofovir.

Vaccination

Vaccination against smallpox was demonstrated through several observational studies to be about 85% effective in preventing monkeypox. Thus, prior smallpox vaccination may result in milder illness. A newer vaccine based on a modified attenuated vaccinia virus (Ankara strain) was approved for the prevention of monkeypox in 2019. This is a two-dose vaccine for which availability remains limited.

Types of **smallpox** vaccines :

- ACAM2000 - live vaccinia virus
- Modified vaccinia Ankara (MVA) (Jynneos, Imvanex, Imvamune)
- LC16m8 (modified vaccinia virus) - licensed in Japan

The current study demonstrated an early expansion of activated effector CD4+ and CD8+ T

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cells as a result of monkeypox virus infection which persists over time. All participants also developed a strong cytokine response irrespective of HIV infection. Thus, the MVA vaccine can be used as an anti-monkeypox vaccine for the high-risk population.

Prevention

Raising awareness of risk factors and educating people about the measures they can take to reduce exposure to the virus is the main prevention strategy for monkeypox.

Prevention depends on decreasing human contact with infected animals and limiting person-to-person spread. The best way to help prevent the spread of monkeypox virus is to:

- Avoid contact with infected animals (especially sick or dead animals).
- Avoid contact with bedding and other materials contaminated with the virus.
- Thoroughly cook all foods that contain animal meat or parts.
- Wash your hands frequently with soap and water.
- Avoid contact with people who may be infected with the virus.
- Practice safe sex, including the use of condoms and dental dams.
- Wear a mask that covers your mouth and nose when around others.
- Clean and disinfect frequently touched surfaces.
- Use personal protective equipment (PPE) when caring for people infected with the virus.

II. CONCLUSION

Monkeypox has been declared a global emergency and the disease burden will increase. The human monkeypox cases rapidly spread in all the four European subregions, involving 30 European countries, infecting 6077 people from early May 2022 to July 7, 2022. Monkeypox is usually a self-limited disease with symptoms lasting from two weeks to four weeks. Most people with monkeypox get better on their own without treatment. Following diagnosis, your healthcare provider will monitor your condition and try to relieve your symptoms, prevent dehydration and give you antibiotics to treat secondary bacterial infections if they develop.There's currently not an approved antiviral treatment for monkeypox. Antiviral drugs may help, but they haven't been studied as a treatment for monkeypox. Several investigational antivirals with activity against monkeypox are available, but only as part of a research study.

III. ACKNOWLEDGEMENT

It gives us great pleasure in presenting the review report on 'A tale of two clades : Monkeypox virus' . We would like to take this opportunity to thank our Principal prof.Rajesh oswal for providing us with this wonderful opportunity to work and also our internal guide Ms.Mugdha Nandedkar for giving us all the help and guidance we needed. We are really grateful for her kind support. Their valuable suggestions were very helpful. The completion of the project would not have been possible without their help and insights.

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