Monkeypox: An Emerging Global Threat

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Zaman Javed[1], Muhammad Akram Khan[1], Munibullah[2], Usama Bin Matloob Abbasi[1], Tayyaba Rehmat[2], Sulaiman Khan[2] and Muhammad Arif Zafar[2*]

ABSTRACT

An increase in illegal wildlife trade and deforestation in the past few decades increased the interaction between humans and wild animals, leading to the emergence and spread of several zoonotic diseases, such as “Monkeypox” infection. Monkeypox is a life-threatening disease caused by the Monkeypox virus that belongs to the genus Orthomyxovirus of the Poxviridae family. Monkeypox virus has been isolated from a variety of animal species, including rodents, monkeys, humans, and dogs. Transmission of the infection mostly occurs by direct contact with the infected lesions, body fluid, respiratory droplets, sexual contact, consuming products of the infected animal, or biting by the infected animals. After gaining entry through micropinocytosis, the virus completes its lifecycle within the cytoplasm of the host's cell. The virus starts infection from nasopharynx or oropharynx, leading to viremia and then spread to other organs. The clinical manifestation of the disease exists in the eruptive (characterized by fever, chill, and lymphadenopathy and the pre-eruptive stage (characterized by weakness, fatigue, and headache). After these stages, rashes appear at the mouth and then proceed to the whole face, palms, and soles. The important risk factors of the disease include sexual contact with an infected person, profession, hunting, vaccination against smallpox, etc. For an effective management of the disease, early diagnosis is essential, which can be possible with ELISA, PCR, Immunochemistry, viral culture, and IgG and IgM. There is no specific treatment available for this disease, however, supportive care and some antiviral drugs can be effective.

Keywords: Monkeypox, Year-2022 outbreak, Zoonosis, Viral diseases, Animals.

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[1]Department of Pathology
[2]Department of Clinical Studies, Pir Mehr Ali Shah-Arid Agriculture University, 46300, Rawalpindi
***Corresponding author:** dr.mazafar@uaar.edu.pk

1. INTRODUCTION

Due to urbanization, forests are being cut down, increasing the interaction of wildlife and humans. Similarly, the illegal trade of wildlife between countries is increasing day by day, especially in developing countries due to poor legislation. This is resulting in the emergence of new and spread of existing zoonotic diseases such as human monkeypox infection which appeared in 1970, when the world's main focus was eradicating smallpox. A 9-month-old boy was reported with fever, headache, fatigue, lymphadenopathy, and rash on the arms and legs in the Democratic Republic of the Congo (Gessain et al. 2022). These signs were similar to smallpox except for lymphadenopathy, which was not characteristic of the smallpox virus. On investigation, monkeypox was isolated from skin lesions. Later, six new cases were reported in West African countries and most patients were not vaccinated against smallpox (McCollum and Damon 2014). Monkeypox gained more attention in 2003 when the virus was isolated from 71 patients (Center for Disease Control and Prevention 2003). In May 2022, almost 17,300 suspected and confirmed monkeypox cases were identified. Due to the global outbreak, WHO declared a Public Health Emergency of International Concern (PHEIC) in July 2022 (Nuzzo et al. 2022).
Monkeypox infection was first described as the disease of the primate in 1958 when the virus was isolated in the infected cynomolgus monkeys shipped from Singapore to Denmark (Mitjà et al. 2023). Despite the name, the reservoir hosts appear to be rodents especially squirrels, Gambian pouched rats, and dormice (Guarner et al. 2022). In humans, the monkeypox virus starts with a flu-like prodrome and the presence of smallpox-like rashes on the skin (Elsayed et al. 2022). Human-to-human transmission is possible by direct contact with sores, body fluids, bedding, etc., of the infected human or animal (Rizk et al. 2022).

2. ETIOLOGY

Monkeypox virus is a double-stranded DNA virus that belongs to the genus Orthomyxovirus of the Poxviridae family with a genome size of 197kb with 190 genes. Human monkeypox virus is almost 200 to 250 nm large, brick-shaped, and enveloped virus that utilizes glycosaminoglycans to gain entry into the host's cells (Lansiaux et al. 2022). The Monkeypox virus has two important clades: a more virulent Central African/Congo Basin (CA) and a less virulent West African (WA) clade. The CA clade of the monkeypox virus is responsible for 10% mortality in non-vaccinated humans, whereas WA causes a very mild infection (Lansiaux et al. 2022). Due to its larger size, the monkeypox virus finds it more difficult to breach the junction gap to enter the host's cells and replicate rapidly. Their larger size also helps the host's immune response to recognize the virus at early stages of infection. But orthopoxviruses, including the Monkeypox virus, use specific proteins to evade the host's immune response. These proteins include:

- Intracellular Modulatory Proteins.
- Extracellular modulatory proteins (Okyay et al. 2022).

Intracellular proteins include virotransducer proteins and virostealth proteins. Virotransducer proteins lower the ability of the immune cells to respond to infection. Similarly, virostealth proteins help the virus to escape from the host's immune system. Extracellular proteins include viromimic proteins, interfere with the action of cytokines, and help viruses to replicate and spread rapidly (Kaler et al. 2022). Fig. 1 highlights the difference in size between monkeypox virus and other related viruses.

3. EPIDEMIOLOGY

3.1. HOSTS

As already discussed in the previous section, the reservoir hosts of the monkeypox virus include several small mammalian species such as squirrels and dormice, but still more study is needed to recognize other

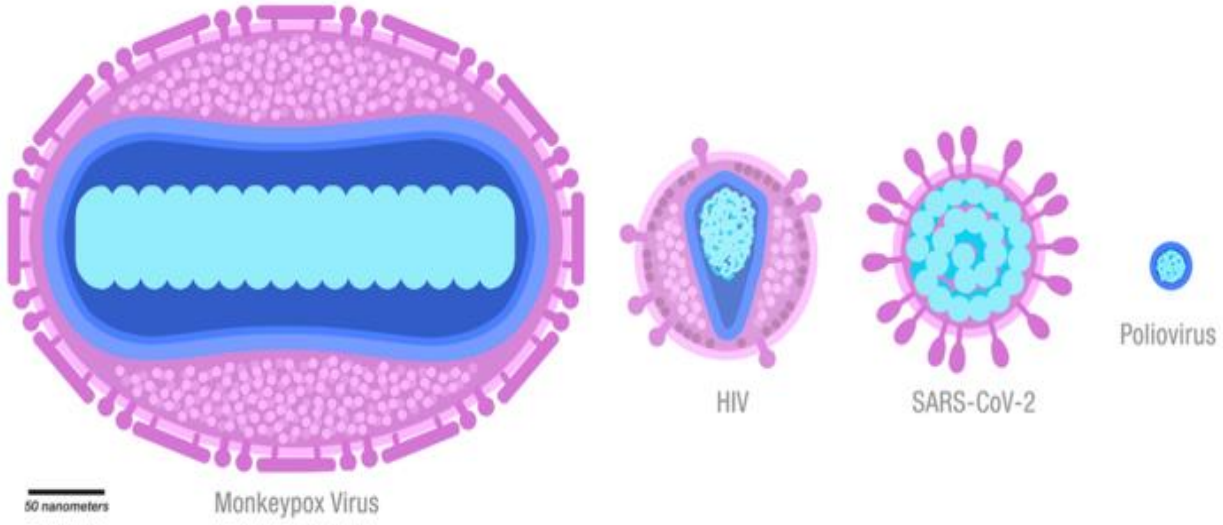

Fig. 1: Monkeypox virus size in comparison with other important viruses

reservoir hosts of the virus. Based on field investigation, viruses have also been identified in a variety of rodents, including rabbits, mice, jerboas, and hamsters (Ullah et al. 2023).

Although the exact reservoir host of the monkeypox virus is still unknown. However, many investigations and research have proved that monkeys are also incidental intermediate hosts of the virus. Dogs, like humans, can also be the fixed or intermediate host of the monkeypox infection. In 2003, a pet prairie dog was found infected with monkeypox infection. Upon further investigation, it was revealed that the dog had contact with other animals which were imported from US to Ghana (Kaler et al. 2022). Another case was reported in dogs in 2022 when a 4-year-old Italian greyhound sick dog was presented with clinical signs of monkeypox infection. On further investigation, it was found that the dog shared the bed with an infected person (Choudhary et al. 2022).

3.2. TRANSMISSION

The transmission of the monkeypox infection can be through direct contact with the lesions, body fluid, respiratory droplets, consuming products of the infected animal, or biting by the infected animals. The virus can gain entry through the respiratory tract or mucus membrane of the skin, eyes, and mouth (Kumar et al. 2022). Human-to-human transmission is a common feature of the monkeypox virus. Mostly, this type of transmission occurs through close contact with the infected patient and contact with the bedding of the infected patient (Huang et al. 2022).

Several studies prove the vertical transmission of the monkeypox virus. A study conducted at the General Hospital of Kole found that two out of four monkeypox-infected women experienced a miscarriage at the early stages of the pregnancy, and another woman experienced miscarriage at 18 weeks of gestation. On further investigation, monkeypox virus DNA was found in the placenta, fetal tissue, and umbilical cord (Fahrni and Choudhary, 2022). The presence of the virus in the seminal fluid of the 29 people indicates that the virus can be transmitted through semen as well (Thornhill et al. 2022). There is more need for the study to check whether the monkeypox virus can be transmitted through breastfeeding or not.

In 2022, most of the monkeypox cases were reported in homosexuals. The presence of rashes on the anogenital and perineal areas suggests that virus can be transmitted through close sexual contact (Martínez et al. 2022). The high occurrence of the infection in homosexuals doesn't describe monkeypox

infection as a sexually transmitted disease, but the disease entered in the homosexual community accidentally and was transmitted due to "close contact" during sexual activities (Thornhill et al. 2022). Fig. 2 and 3 shows the transmission of the monkeypox virus from animal to human and from human to human.

4. PATHOGENESIS

The pathogenicity of the monkeypox virus starts soon after its transmission from an infected animal to a human or from an infected human to an animal (reverse zoonosis as in the case of the Prairie dog). Monkeypox virus (DNA virus) completes its lifecycle in the cytoplasm, which is usually characteristic of RNA virus. For replication, transcription, and packaging, monkeypox utilizes a number of proteins. A virus enters the host's cell by binding through fusion and micropinocytosis. The nasopharynx or oropharynx is the most important host's site from where the virus starts infection and replication before spreading to lymph nodes. Monkeypox virus, just like other orthopoxviruses, needs to cause viremia to spread to other organs and lymph nodes. The incubation period of the monkeypox virus is 7 to 14 days. Some studies suggest the incubation period can be longer up to 21 days (Saied et al. 2022; Anwar et al. 2023).

During pathogenesis, the monkeypox virus, like other members of poxviridae, exhibits two forms: Extracellular Enveloped Viruses and Intracellular Mature viruses. Most of the viruses remain within the cells and lack an envelope (IMV). However, some viruses are transported through microtubes and become enveloped by two Endoplasmic reticulum membranes. These cells sometimes leave the cell cytoplasm and become Extracellular Enveloped Virion (EEV) (Smith et al. 2004).

An increase in the level of cytokines is one of the most common features involved in the pathophysiology of monkeypox infection. Studies found that the level of IL4-, IL-5, and IL-6 increases in monkeypox infection. Similarly, some specific types of tumor necrosis factor (such as TNF-alpha), Interferon-gamma, and levels of IL-2 decrease during the monkeypox infection (Ježek et al. 2015).

During monkeypox infection, the host's epithelial cells show intracytoplasmic eosinophilic inclusions, which is a unique characteristic of the poxviridae family. Similarly, the epithelial cells show hyperplasia, ballooning degeneration, and necrosis of the keratinocytes. The presence of neutrophils, eosinophils, and giant cells can also be seen (Thakur et al. 2023).

5. GEOGRAPHICAL DISTRIBUTION OF INFECTION

The first human monkeypox infection was reported in 1970 in Congo. Since 1970, it was thought that monkeypox is endemic to Central and West Africa. Almost 400 monkeypox cases were reported in the period between 1970 to 1990. Most of these cases were reported in the Democratic Republic of Congo (DRC) (Fig. 4). However, in 1996, a sudden increase in monkeypox cases was seen in DRC with 71 confirmed cases in just six months. Later on, the cases were increasing continuously (Huang et al. 2022). Between 1996 to 1996, the infection rate was 22 cases out of 1000 population (Pal et al. 2017).

5.1. OUTBREAK IN 2003 AND 2017

Monkeypox infection gained the attention of the scientific community in 2003 when an outbreak occurred in the US, with more than 47 confirmed and 10 suspected cases. Investigation suggested that the infection was transmitted from the non-African species, cohoused with the prairie dogs (Reynolds et al. 2006). Most of the infected people had direct and indirect contact with the dog. Some were involved in the handling of the dog, some were bitten by the dog, and few shared rooms with the sick dog. In 2017, Nigeria experienced an outbreak of monkeypox infection with almost 122 confirmed cases in more than 17 states. The mortality rate was 6% during this outbreak (Yinka-Ogunleye et al. 2019).

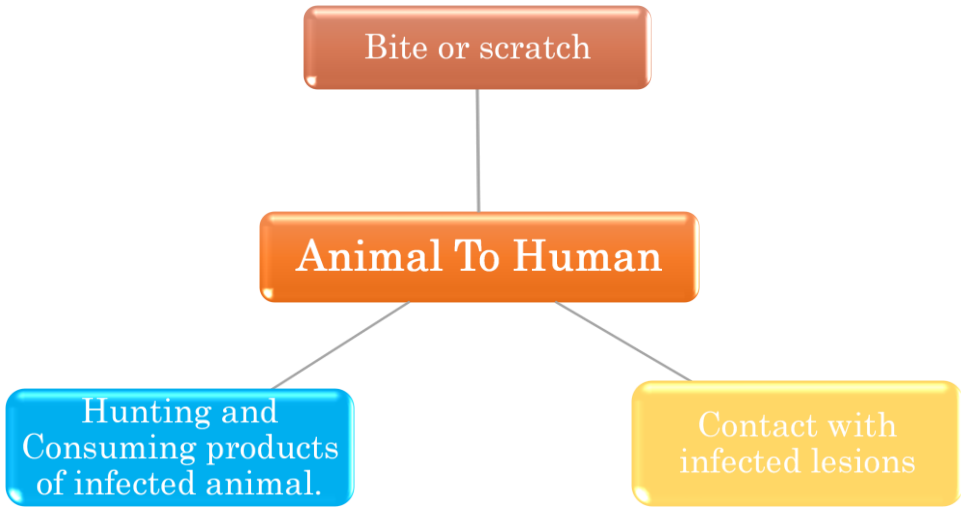

Fig. 2: The sources transmission of MPXV from animal to human.

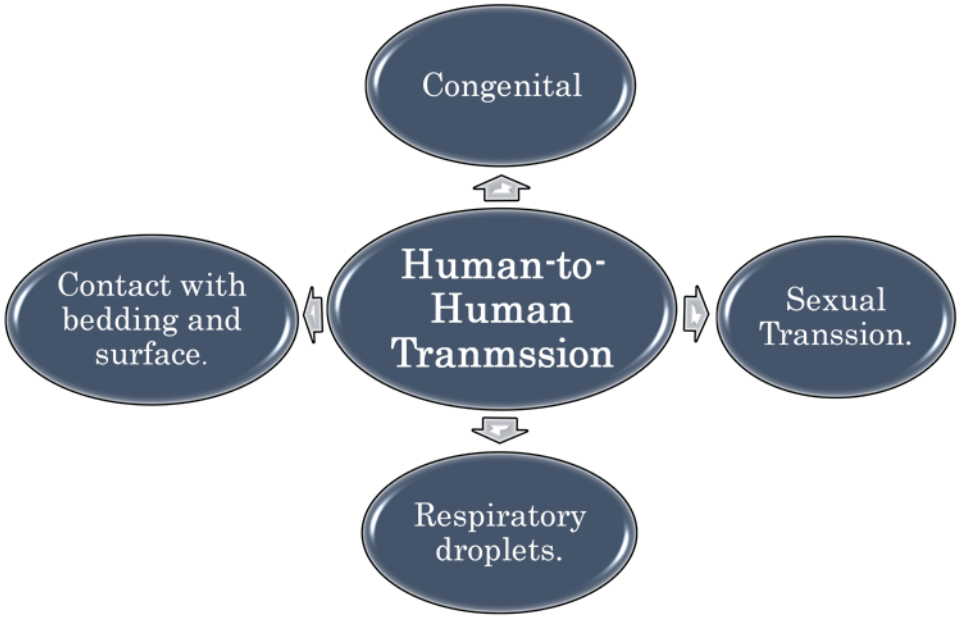

Fig. 3: The sources of transmission of MPXV from Human to human.

5.2. OUTBREAK IN 2022

As already discussed, before the 2022 outbreak, it was thought that monkeypox virus infection was only limited to Central and West Africa because there were few cases reported in other countries. However, in 2022, soon after the emergence of the first case in the United Kingdom, the infection started to increase dramatically and took the shape of endemic in several countries. Upon further investigation, most of the cases have travel history to the UK, Spain, and other countries in which cases were continuously reported (Kraemer et al. 2022). Six cases were reported in the UK between 13 to 16 May 2022 with no travel history to an African country and contact with important animals. However, most of the patients were homosexual. Later on, in September 2022, 24,017 cases were reported in almost 44 European republics (Ullah et al. 2023). Keeping the situation in view, WHO declared monkeypox a "Public Health Emergency of International Concern." Similarly, monkeypox prevention and treatment guidelines have been issued in several countries around the world (Webb et al. 2022). Until September 2022, the total number of

Fig. 4: First outbreaks of Monkey Pox virus.

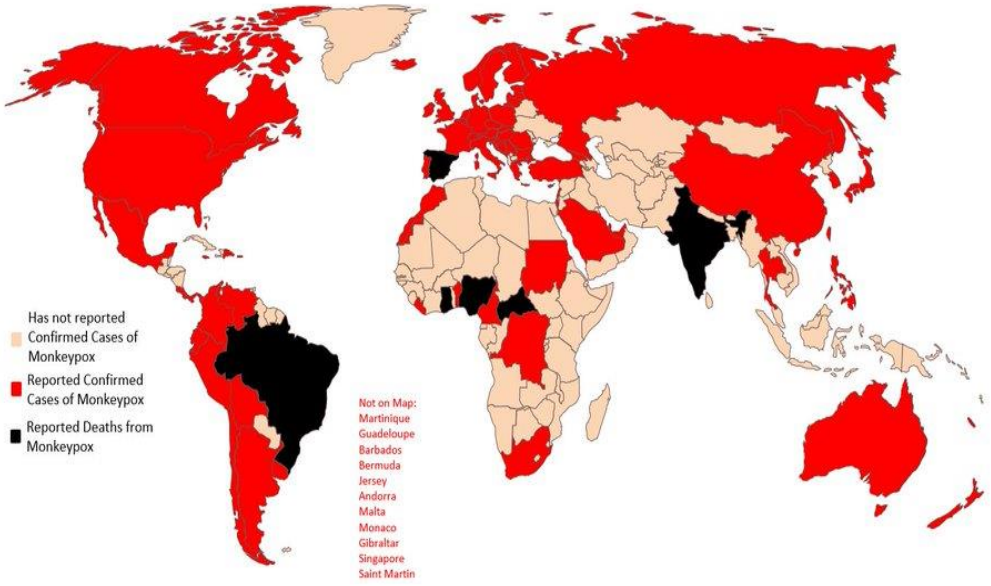

Fig. 5: Map showing spread of the MPX infection in different regions until 06 August 2022

monkeypox cases was 57,995 in more than 100 countries, with 18 mortalities. During the outbreak, youngsters were more affected by the monkeypox infection because of the termination of smallpox immunization after the eradication of smallpox (Ullah et al. 2023). Several factors are responsible for the rise in monkeypox infection during the recent era, including deforestation, illegal trade, climate change, and rapid demographic expansion of the monkeypox endemic regions (Quarleri et al. 2022). Fig. 5 shows the map indicating the spread of MPX in different regions.

6. CLINICAL MANIFESTATION

Resistance against smallpox infection plays a critical role in the onset of monkeypox infection. Several studies proved that monkeypox infection is more common in people younger than 15 years old (Damon 2011). The incidence and the severity of the monkeypox infection depends on a variety of factors including age, sex, and vaccination status of an individual against smallpox. But pre-eruptive and eruptive are the two most important clinical features of the monkeypox illness that are seen in every case (Thakur et al. 2023).

6.1. PRE-ERUPTIVE STAGE

The infection begins with some prodromal symptoms including, fever, chill, and lymphadenopathy (which were not characteristics of smallpox infection). Fever during the pre-eruptive stage of the infection ranges from 38.5 to 40.5℃. Other signs of the pre-eruptive stage include weakness, fatigue, and headache. After these symptoms, rashes appear on different body sites but initially start at the mouth and then proceed to the whole face, palms, and soles (Thakur et al. 2023). Problems associated with the upper respiratory tract and gastrointestinal tract can also be found in monkeypox infection (Reynolds et al. 2006).

6.2. ERUPTIVE STAGE

During this stage of the infection, the lesions start to increase (number varies from 10 to 150) and remain for 4 weeks and then ultimately scab over and fall off (Adler et al. 2022). Lesions turn from macules to papules to vesicles and pustules. Similarly, necrosis, ulceration, and pruritis are other important features of smallpox lesions. Pain can also occur due to secondary bacterial infection. In children, lesions can be 1 to 5 mm in diameter and can be similar to arthropod bite reactions (Pal et al. 2017).
In case of severe infection, the monkeypox virus triggers a robust immune response and ultimately leads to sepsis, an abscess of the deeper tissues, and severe respiratory disease. In monkeypox-mediated immune injury, damage to the other vital organs also occurs and causes tonsillitis, thymitis, myeloid hyperplasia, and splenic injury. Many studies have shown that immunopathogenesis in severe monkeypox infection occurs due to impaired Natural-Killer (NK cells), increased granulocytes and monocytes, immune evasion, and inhibition of the host complement system. Monkeypox-mediated immune injury increases the chances of mortality (Li et al. 2023).

7. RISK FACTORS

Understanding the risk factors associated with the occurrence of any disease in the community is very important. It allows the scientific community to describe the steps that help them to avoid the further spread of the disease. Below are a few important points that can act as risk factors for the transmission of monkeypox infection:

7.1. INDIVIDUAL CHARACTERISTICS

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(21- to 40-year-old) (Antinori et al. 2022).

Table 1: Tests for the detection of the monkeypox infection. (Cheema et al. 2022)

Test	Description.	Sample.
PCR	It is an ideal approach to identifying the monkeypox virus DNA; real-time PCR is perfect.	Fluid from lesions.
Electron microscopy	Help in morphological identification of the virus.	Biopsy specimen, scab material, vesicular fluid
Immunohistochemistry	Confirm the presence of *Orthopoxvirus*-specific antigens	Biopsy specimen.
Viral culture.	The virus can be isolated from the patients and grown in a specific medium.	Fluid from the lesions.
IgG and IgM	Help in the recent exposure to the virus or early detection.	Blood.

7.2. PROFESSION

Occupation of the individual also acts as a risk factor for the transmission of the monkeypox infection. Usually, the infection is most commonly seen in people involved in hunting activities or those who have direct contact with non-human primates. Similarly, farmers are also at higher risk of infection due to their contact with rodents (Quiner et al. 2017).

Monkeypox infection is considered the most important nosocomial infection and is most commonly seen in healthcare workers. The hospital-born occurrence of monkeypox infection is very severe and long-term and demands solid steps to avoid the spread among healthcare workers, who are life saviors for mankind. The most common example of the nosocomial spread was seen in the UK, where a medical employee who was involved in the collection of the dressing and blankets of the monkeypox-infected patients, got monkeypox infection (Vivancos et al. 2022).

7.3. DIRECT CONTACT WITH INFECTED PERSON OR ANIMAL

Direct contact with the lesions, blood, or fluid of the infected person or the animal can also increase the risk of infection. Consuming the uncooked meat of rodents or other reservoir hosts can cause the rapid spread of the disease within the human community. Similarly, people living near the forest have more contact with the animals and their waste and are at higher risks compared to those living in the cities or urban areas. Human-to-human transmission can occur through direct contact with respiratory discharges, skin lesions, or body fluid. However, transmission through aerosol needs a specific distance between the infected and healthy individuals (Petersen et al. 2019; Ullah et al. 2023).

7.4. SEXUAL ACTIVITIES

In 2022, the monkeypox outbreak affected the people who were involved in homosexual activities. The reason behind this is still unknown but it indicates that the LGBTQ community is at higher risk compared to others (Singla et al. 2022).

The common risk factors associated with the monkeypox infection are described in Fig. 6.

8. DIAGNOSIS

The clinical signs of the monkeypox infection have a very close resemblance with chickenpox and smallpox infection. Thus, a definitive diagnosis is essential to prevent the disease from spreading. Although many bovine and caprine diseases, including bovine stomatitis and Orf, cause skin lesions similar to monkeypox, these diseases can be easily distinguished from orthopoxviruses via electron microscopy (Weinstein et al. 2005).

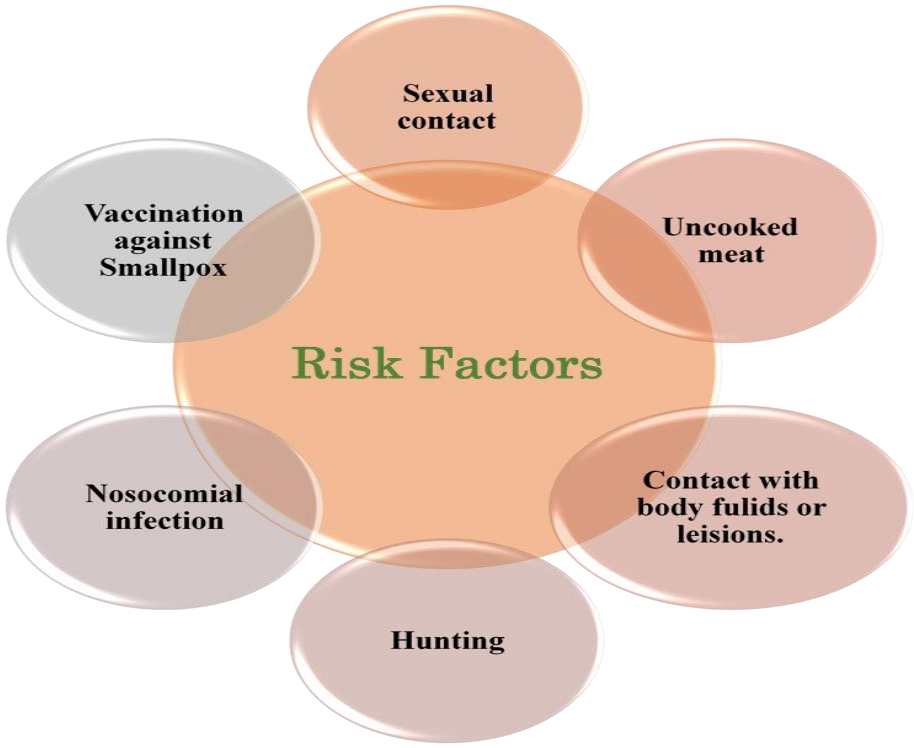

Fig. 6: Common Risk Factors associated with Monkey Pox Virus

Monkeypox infection results in several structural changes in the tissues that can be observed microscopically. Histologically, the lesions seen in the monkeypox infection show similar characteristics as seen in other viral exanthems, such as cowpox infection and herpes simplex infection. Usually, the histology of the monkeypox infection bulla varies from the stage of infection (Schmidle et al. 2023).
Clinical characteristics of the disease can help to differentiate skin lesions from other infections, but laboratory confirmation is essential (Ullah et al. 2023). Table 1 explains the essential laboratory tests along with the samples:

9. TREATMENT

Most monkeypox-infected people show mild symptoms and recover without professional attention or treatment. However, in hospitalized patients, the symptoms of the infection, such as nausea, vomiting, pain etc., can be cured with specific supportive therapy. However, antiviral therapy should be considered in patients with severe illness (Goyal et al. 2022).

9.1. SUPPORTIVE CARE

Patients with gastrointestinal symptoms should be treated with appropriate drugs according to the signs. Multivitamins should be administered to support the body's immune system. Similarly, to avoid secondary infection, antibiotics can also be used (Rizk et al. 2022).

9.2. ANTIVIRAL DRUGS

Antiviral drugs can be used to treat monkeypox infection. Most of these drugs are approved for managing small animals, and many studies have also proved their efficacy against monkeypox infection (Adler et al.

2022). The following are a few of the most important antiviral medicines that can be used against monkeypox infection in severe illness;

9.2.1. TECOVIRIMAT

Tecovirimat is an essential antiviral drug that was first described for the treatment of smallpox. Tecovirimat has activity against the envelope protein p37 and prevents viral release from the infected cells. Although the efficacy of this drug against the monkeypox virus has still not been studied, many researchers have proved that tecovirimat can improve the survival of monkeypox-infected patients. The drug also has an effect against rabbitpox in rabbits (Carvalho 2022).

9.2.2. CIDOFOVIR

Cidofovir is an important antiviral drug that has shown its effect against monkeypox infection during the 2022 outbreak. After administering the drug to monkeypox-infected patients, a significant decrease in the lesions has been reported, along with improved clinical signs, including fever and lymphadenopathy (Raccagni et al. 2023).

9.2.3. VACCINIA IMMUNE GLOBULIN (VIG)

It is an intramuscular preparation of the hyperimmune globulin, prepared from the blood of the individual vaccinated against the smallpox infection. VIG is very effective against infections caused by the vaccinia viruses (Huang et al. 2022). The efficacy of the VIG against monkeypox infection is still being studied, but many researchers have proved that VIG is very effective against vaccination side effects, including eczema vaccinatum and aberrant infections caused by the vaccinia virus. However, VIG is contraindicated in individuals with severe T-cell function immunodeficiency (Chakraborty et al. 2022).
Immunotherapies, including immune-modulating agents, monoclonal antibodies, and NK-based cell therapy, are a few important options that can be considered to treat the monkeypox infection. Human IFN-β inhibits monkeypox infection and can be a safe and novel treatment against human monkeypox infection. Before this, human IFN-β was also effective against other infections, including SARS-CoV-2 and hepatitis viruses (Johnston et al. 2012). NK cells-mediated antibody-dependent cellular cytotoxicity is effective against a variety of infected cells, such as HIV, orthopoxviruses, and SARS-CoV-2 (Fang et al. 2008).

10. FUTURE INTERVENTIONS

The rapid spread of the monkeypox infection soon after COVID-19 made it more dangerous, not only for public health but also for the world's economy. In just three months, almost 10,000 cases were reported in non-endemic countries (May to July 2022) (Kmiec and Kirchhoff 2022). Monkeypox infection can be catastrophic for developing countries. The scientific community needs to generate awareness among the public about the possible consequences of monkeypox infection. The struggling healthcare system of developing countries, including Pakistan, will be on the verge of collapse if monkeypox starts to spread.
To tackle the spread of the infection, awareness among physicians about the general signs, symptoms, and precautions of the monkeypox infection is essential to ensure timely quarantine and nosocomial transmission. Similarly, proper disease surveillance is essential to control and monitor cases effectively. (Mansoor et al. 2022). There is a very close relationship between monkeypox and HIV infection. A study conducted on 528 human monkeypox-infected patients revealed that 41% had a human

immunodeficiency virus infection (Thornhill et al. 2022). Thus, physicians should also focus on HIV diagnosis when monkeypox is suspected or confirmed in an individual. Patients with both HIV and human monkeypox infection have more compromised immune systems; thus, to reduce the severe illness in infected patients, physicians should focus on proper treatment. Tecovirimat is a first-line medication that can be effective against HIV and human monkeypox infection when used in combination with antiviral therapy (O'Laughlin et al. 2022).

Equal access to the vaccine is essential for effective control of the disease globally. Currently, Jynneos (a vaccine against monkeypox infection) is just limited to the US, UK, and other developed countries (Freeman et al. 2022). However, this approach for high-income countries can benefit them in the short term. Many studies have proved that the self-prioritization strategy of the high-income country is an immoral act that has led to the emergence of new variants of concern. Although a mutation within the viruses can occur by chance, the large density population of developing countries can exacerbate the transmission and increase the chances of mutation (Yamin 2022). Thus, high-income countries should support developing countries for equal vaccination access. A survey conducted in 7 developed countries suggests that 70% population of high-income countries supports the donation for equal access to vaccines in developing countries (Clarke et al. 2021).

As already discussed, monkeypox infection is mainly reported in homosexuals. It highly indicates that the virus can be transmitted from one person to another through close contact during sexual activities. Thus, proper physical distance should be maintained during the outbreak. The rodent's meat should be properly cooked, and always avoid direct contact with the animal's lesions and fluid.

Illegal trade is another major factor in the zoonotic transmission of monkeypox and other zoonotic diseases. Unfortunately, regulation and enforcement are still insufficient to control the illegal wildlife trade and demand some extra steps from the government bodies and the general public to avoid the emergence of new zoonotic diseases and the spread of existing diseases, including monkeypox infection. There is more need to empower local communities to value wildlife and support international regulations (Rosen and Smith 2010).

11. CONCLUSION

To sum up, monkeypox poses a growing threat to the world and has to be addressed right now with a coordinated, multinational response. The recent global increase in monkeypox cases have brought attention to the virus's ability to start epidemics, travel across borders, and pose a threat to public health systems. Considering monkeypox as a global health concern requires a multifaceted strategy. International cooperation is crucial beyond everything else. Cooperation among nations is necessary to exchange knowledge, assets, and skills in order to effectively identify, manage, and eradicate monkeypox epidemics. This entails enhancing diagnostic skills, fortifying surveillance systems, and creating potent immunizations and therapies Through collaborative efforts, prioritizing research, and increasing public awareness, we can effectively tackle this dilemma and mitigate its effects on worldwide health.

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