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Human monkeypox virus: A review on the globally emerging virus

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Abstract

Monkeypox is a contagious complaint that affects both mortal and beast health and has lately come under the attention of all worlds. A genomic to developments in DNA sequencing, the genomic chart of the contagion has been known, which offers perceptivity into its elaboration and possible modes of transmission across different species. Understanding the complex mechanisms and studying the transmission of monkeypox is pivotal for disseminating the complaint's spread from beast sources to mortal populations. Global frequency patterns demonstrate the complex connections between source hosts, vectors, and susceptible populations, and the deficit of exploration in Pakistan permits further disquisition into the possible public health counteraccusations. It's matter of great significance to completely explore the inheritable and antigenic parcels of this contagion, with its strong correlation with the etiology of monkeypox. PCR has proven to be a tool for accurate identification in the ongoing fight against this contagious disease. The variety of clinical signs and symptoms, which can vary from mild fever to severe lymphadenopathy, highlights the critical need for effective opinion and treatment strategies. Also, the maturity of available treatment options presently corresponds of probative care and antiviral specifics. Further exploration and cooperative sweats are necessary to increase our understanding and develop feasible therapeutics. This discussion highlights the need for a comprehensive plan to lessen the mischievous goods of monkeypox on the health of people and creatures. Beforehand discovery, visionary surveillance, and substantiation-grounded operation strategies must be put into practice.

Introduction

In the ultramodern world, contagions pose a lesser trouble to global public health than they did a century ago which leads to multitudinous contagious conditions in humans and creatures [1]. After smallpox was canceled encyclopedically in 1980, the most important OPXV for public health was monkeypox [2]." Monkeypox" was named because when monkeypox first appeared, it was discovered among monkeys covered for exploration in 1958 [3]. In the Democratic Republic of the Congo (DRC), the mortal monkeypox (HPXV) contagion was first discovered in a case in 1971 [4]. The United States recorded the discovery of the first circumstance outside of Africa in 2003 [5].

The monkeypox virus, one of the four orthopoxvirus species, has been split into the West African and Central African genetic clades [6]. These two clades differ geographically, and this is accompanied by diverse epidemiological and clinical characteristics. Contrary to the Central African clade, also known as the Congo Basin clade, which has a CMR of roughly 11% and a recorded human-to-human transmission, the West African clade has a case mortality rate (CMR) of less than 1% and no evidence of human-to-human transmission [6-8]. The most common MPX and smallpox symptoms included rash, fever, lymphadenopathy, tiredness, and headache, however, the presence of swollen lymph nodes at the outset of fever helps to distinguish MPX from smallpox, but both diseases can also be asymptomatic [9, 10].

The majority of recent MPXV-related cases are spread specifically through sexual contact, especially for guys who have intercourse with other men [11, 12], Monkeypox virus (MPXV) may spread through close, direct, and frequent contact with one's skin. This involves coming into contact with a patient's rash, scabs, or bodily fluids; handling items, or materials (such as clothing, bedding, or towels) who has the monkeypox, or contact with respiratory secretions. Through the placenta, a pregnant individual can transmit the virus to their developing baby. Additionally, by being bitten, scratched, cooking or consuming meat from an infected animal, or by utilizing its products, people can catch monkeypox from ill animals [5, 12-20]. Infected skin sores and huge aerosol droplets of saliva or blood can also spread the disease. The virus exhibits clinical indications of fever, headache, myalgia, lymphadenopathy, and fatigue after an incubation period of 5–41 days, which is comparable to the smallpox infection [21]. The lab will conduct a polymerase chain reaction (PCR) test to see if the sample contains any viruses. The apparent rise in human monkeypox in recent years concern for this newly discovered zoonosis has increased due to incidences in a large geographic area and the possibility of further spread[13]. Historical evidence supports the smallpox immunization (Imvanex), which is 85% effective against monkeypox. Monkeypox can be treated with antivirals like Tecovirimat, Cidofovir, and Vaccinia Immune Globulin Intravenous (VIGIV), which are approved to treat smallpox [22]. The Summary of Scientist's Contribution for the Monkeypox Discovery is shown in **Table 1**.

The threat of a new epidemic is concerning because countries are still coping with the COVID-19 pandemic. The truth is that scientists already have a lot of knowledge on monkeypox, like COVID-19 in early 2020[23]. On May 23, 2022, a pair of cases of the human monkeypox virus were found in Pakistan's Lahore Jinnah Hospital. The National Institutes of Health (NIH) urgently recommended the country's healthcare establishments to treat the condition with care following the detection [24]. On April 26, 2023, a 25-year-old man who had recently returned from Saudi Arabia was diagnosed with monkeypox according to the National Institutes of Health (NIH) in Pakistan. Even if the likelihood of widespread transmission is now seen as minimal, it is crucial to comprehend any potential effects on Pakistan's healthcare system [25]. In addition to raising awareness of potential preventive measures and outlining potential future drug discovery and development targets, this review seeks to highlight the state of knowledge regarding monkeypox, including genetics, prevention and prevalence, immunization, and treatment options.

Cell entry and Genome expression

Monkeypox virus (MPXV) infiltrates host cells through a precisely coordinated process involving viral envelope proteins [26]. Hemagglutinin (HA) and fusion proteins (F), key players in this mechanism, allow the virus to bind to specific receptors on the surface of the host cell, facilitating infection and evading the immune system [27]. Glycosylation and conformational changes of HA increase virus affinity for receptors in the epidermis, respiratory tract and lymphoid tissue [28]. MPXV exhibits selective interaction with cellular receptors, including

Table: 1: Summary of scientists' contribution to monkeypox discovery.

Authors	Key Points
Ligon (2004) [3]	Monkeypox is named after the discovery of monkeys.
Woolhouse & Gowtage-Sequeria (2005) [4]	Viruses spread rapidly, causing global complications and mortality.
Saijo et al. (2008) [22]	MPX spreads through contact with skin, fluids, items, and animals; also transmitted by bites.
Howard and Fletcher (2012) [1]	Viruses contribute to infectious diseases, more threatening than a century ago.
McCollum and Damon (2014) [23]	MPX transmission via bites, scratches, and infected animal products; possible aerosol transmission.
Nolen et al. (2016) [11]	Human monkeypox (HPXV) was first found in DRC.
Sklenovská and Van Ranst (2018) [15]	MPX and smallpox share symptoms; MPX may show swollen lymph nodes.
Petersen et al. (2019) [13]	Monkeypox virus has West African and Central African genetic clades.
Ihekweazu et al. (2020) [9]	Post-smallpox eradication, monkeypox is vital for public health.
Adler et al. (2022) [12]	First monkeypox occurrence outside Africa in the US.
Antinori et al. (2022) [18]	Recent MPX cases spread through sexual contact, especially in men who have sex with men.
Du et al. (2022) [23]	MPX clinical signs resemble smallpox; incubation period of 5-41 days.
Upadhayay et al. (2022) [29]	Scientific knowledge on monkeypox similar to COVID-19 in early 2020.
Xiang and White (2022) [5]	Monkeypox (MPX) is caused by orthopoxvirus, related to smallpox.
Najeeb and Huda (2022) [28]	Smallpox immunization (Imvanex) is 85% effective against monkeypox.
Zeeshan et al. (2022) [2]	MPX shows variations in epidemiology, clinical presentation, and genetic clades.
Farahat et al. (2022) [19]	Increasing monkeypox incidence sparks concern due to potential spread.
Patrocinio-Jesus and Peruzzu (2022) [25]	Genomic analysis reveals evolutionary patterns and transmission routes of MPX.
Ferdous et al. (2023) [6]	The Poxviridae family includes double-stranded DNA viruses like Orthopoxviruses.
Abdullah et al. (2023) [30]	Human monkeypox cases detected in Pakistan; awareness and healthcare impact considered.

glycosaminoglycans, integrins, and chemokine receptors [29]. Heparan sulfate, which is widely distributed in the extracellular matrix, promotes reversible attachment, thus setting the stage for viral invasion [8]. Integrins and chemokine receptors, particularly CCR5 and CXCR4, play a crucial role in virus entry, fusion and initiation of infection. After binding, MPXV undergoes fusion with host cell membranes and releases its genetic material [30, 31]. The fusion protein (F) undergoes receptor-mediated endocytosis triggered by acidification in endocytic vesicles, releasing the virus core into the host cell [32, 33]. Removal of the coating is essential for the transport of viral DNA to the host cell nucleus and ensures replication and protein synthesis [34].

Intermediate gene expression: regulation and functions

MPXV harbors an extensive double-stranded DNA genome with unique terminal inverted repeat (TIR) structures that facilitate replication and transcription. Three classes of genes (early, middle and late) regulate different functionalities during the viral life cycle [35, 36]. Early genes control virus replication, with essential enzymes (DNA polymerase, thymidine kinase, DNA helicase) catalyzing DNA synthesis and unwinding [37]. Concatemeric DNA synthesis in virus factories sets the stage for subsequent replication [38]. Intermediate genes, including viral interferon resistance proteins (VIPs) and host immune evasion proteins, manipulate the host immune response. The mechanism of action of monkeypox is shown in **Fig. 1**. VIPs inhibit interferon signaling, thereby supporting MPXV replication [39, 40]. Late genes control virus assembly and maturation and encode structural proteins (A27L, A17L, A9L) that are crucial for the stability, infectivity and morphology of virions [41, 42]. Viral factories in the cytoplasm of the host cell facilitate the development of virions, thereby ensuring successful replication and multiplication [43].

Interaction between monkeypox virus and host: Immune response

In the context of monkeypox virus infection, host cells utilize specialized receptors such as Toll-like receptors (TLRs) and RIG-I-like receptors (RLRs) to recognize and respond to viral components [44]. Activation of these pattern recognition receptors

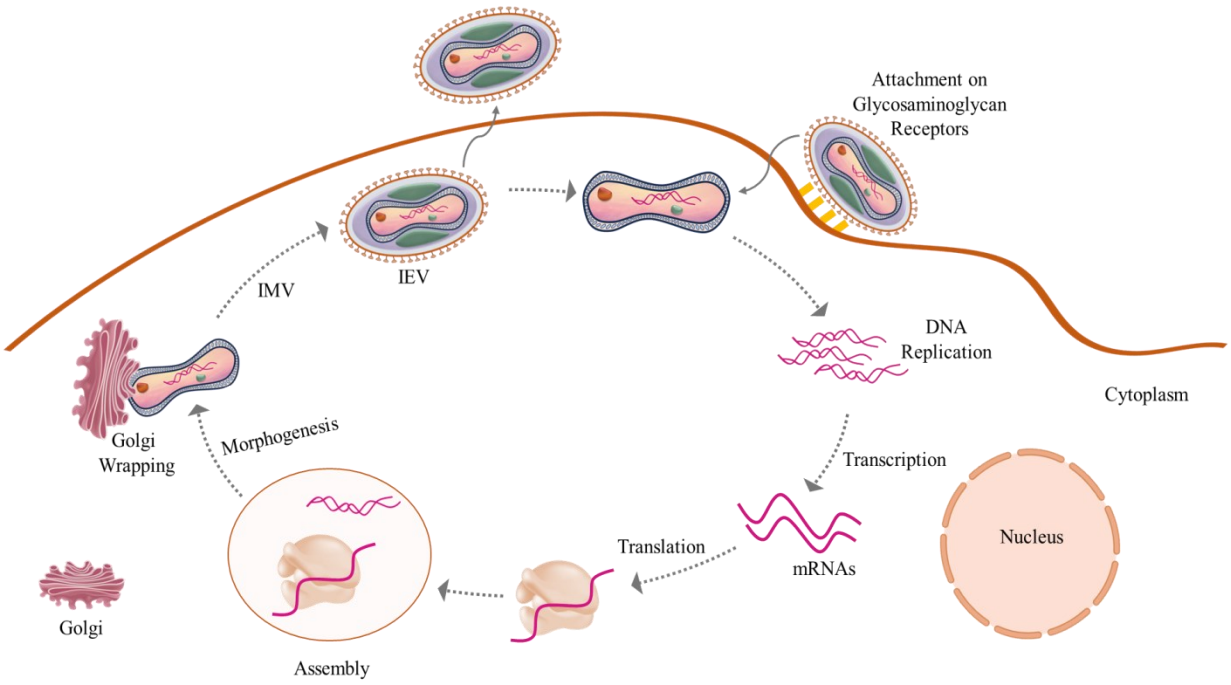

Fig. 1: Life cycle of monkeypox virus.

(PRRs) triggers a cascade of molecular events leading to the synthesis and release of interferons (IFNs) and pro-inflammatory cytokines, which are crucial for the innate immune response [45]. Type I interferons (IFN-alpha and IFN-beta) play a fundamental role in combating viral infections and induce an antiviral state [46].

Monkeypox virus infection induces the secretion of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, which are crucial for initiating and amplifying the inflammatory response [47]. Chemokines direct immune cells to specific foci of infection and thus contribute significantly to the overall immune response against the monkeypox virus. The T cell response is triggered upon recognition of viral antigens and triggers a personalized immune response. Effector CD8+ T lymphocytes combat virus-infected cells, while CD4+ T lymphocytes support B cells and CD8+ T lymphocytes [48]. The B cell response involves the generation of virus-specific antibodies through a complex process that ensures targeted and robust defense against viral pathogens [49].

Interaction with host mobile machines

When invading, the monkeypox virus attacks certain cellular receptors, triggering a cascade for successful invasion. Modulation of these receptors is essential for the success of an infection [50]. MPXV utilizes the host actin cytoskeletal network for efficient intracellular transport, ensuring a highly efficient egress process. The virus disrupts cell signaling pathways and impairs the host immune response by downregulating pro-inflammatory cytokines and disrupting interferon signaling [51, 52].

Zoonotic potential and interspecies transmission of monkeypox virus

Monkeypox virus persists in natural reservoir hosts such as rodents, potentially impacting intermediate hosts and amplifying the virus for transmission [53]. Monkeypox is prone to zoonotic outbreaks transmitted from animals to humans, with significant human-animal convergence [54]. In humans, symptoms range from elevated body temperature to life-threatening conditions [55]. Factors affecting interspecies transmission include genetic heterogeneity of the virus, host susceptibility, and human-animal encounters. Changes in land use patterns impact the likelihood of zoonotic transmission [56]. Surveillance and prevention strategies are crucial for surveillance and timely identification, providing data for specific prevention measures, including vaccination campaigns and improved biosecurity protocols [57].

Virus spread and pathogenesis of the monkeypox virus

MPXV utilizes cell-to-cell multiplication and cell-free spread for efficient dissemination [58]. During cell-to-cell spread, viral particles are transmitted through direct contact, thereby avoiding extracellular immune responses [59]. In cell-free dissemination, virions are released independently by infiltrating distant cells and contributing to systemic dissemination [60]. Actin-based motility is crucial for the intracellular transport of MPXV [61]. MPXV-encoded proteins such as A36R interact with actin and promote the assembly of actin tails for efficient virus movement [62].

Immune evasion strategies

The monkeypox contagion (MPXV) uses different and sophisticated strategies to shirk the host's vulnerable defenses. It manipulates vulnerable system signaling pathways by snooping with important motes like interferons and cytokines, thereby injuring the host's vulnerable response [63]. MPXV also prevents vulnerable surveillance by dwindling pro-inflammatory cytokines [64]. In particular, the contagion targets dendritic cells and macrophages, injuring antigen donation and suppressing T cell activation. In addition, MPXV regulates major histocompatibility complex (MHC) motes, thereby hindering the recognition of cytotoxic T cells [65]. MPXV neutralizes the host ingrain vulnerable response by producing viral interferon resistance proteins (VIPs), thereby dismembering interferon product and function [66]. VIPs impede interferon regulatory factors (IRFs) and inhibit molecular signals from interferon receptors, allowing the virus to evade antiviral responses and increase replication [67]. MPXV utilizes antigenic variations to modulate surface proteins to evade immunological detection [68]. It negatively regulates ligands recognized by NK cells, thereby hindering cytotoxic reactions. The virus also expresses decoy ligands that block NK cells and T cells and induce apoptosis in T cells, thereby impairing immune recognition [69, 70].

Prevalence of Monkey Pox in Pakistan and the world

A viral disease called monkeypox typically affects monkeys and rodents, but it can also infect people. The monkeypox virus brings it on, a member of the same family of viruses as smallpox and the Orthopoxvirus genus [71]. In Democratic Republic of the Congo (formerly Zaire), monkeypox was originally discovered in primates in 1958. Human infections were then discovered there in 1970 during a nationwide epidemic. Through direct contact with infected animals, i.e., bites or scratches, or contact with their bodily fluids or lesions, monkeypox can be transmitted from monkeys to humans. Human-to-human transmission is also possibile, most frequently when skin lesions or respiratory droplets come into contact [72]. In isolated forested areas of Central and West Africa, monkeypox is an endemic disease [73].

Non-human infection with monkeypox virus

In 1958, two shipments of cynomolgus (Macaca cynomolgus) monkeys that had been imported from Singapore and landed in Copenhagen were noticed by Von Magnus to have two outbreaks of a non-fatal sickness similar to pox [74]. Between 51 and 62 days after the animals arrived in Copenhagen, a skin outbreak that resembled pox started to manifest. About 20 to 30 percent of the animals had clinical illness. In 1959, monkeypox broke out in Merck, Sharp, and Dohme's animal housing. Dohme lives in Philadelphia. It was determined that at least 10% of the 2,000 companion monkeys in the colony were ill. Of them, 56% were Macaca mulatta, 41% were *Macaca philippinensis*, and 3% were Cercopithecus aethiops var. subareas. Less than 0.5% of people affected by the event died [75]. *Macaca philippinensis* made up the majority of the sick macaques, though Macaca mulatta also displayed symptoms of the disease. Compared to 25 (93%) of the 27 cynomolgus exposed to the virus, only 5 (11%) of the 45 cynomolgus monkeys whose exposure to MPV had gone unnoticed acquired specific antibodies. In 1964, Peters described an outbreak of monkeypox in Rotterdam's Zoological Garden. Three squirrel monkeys, one gibbon, six of the nine orangutans, and one marmoset were among the eleven creatures that perished out of the 23 that were injured. One anteater, seven orangutans, three gorillas, and several different kinds of monkeys were found to have MPV. Between 1965 and 1967, there were four further cases of monkeypox-like illness in the United States, but none of the illnesses were virologically proven [75].

Human infection with monkeypox virus

The primary cause of human monkeypox (6 human infections) was discovered in a toddler in the Democratic Republic of the Congo in 1970. It was endemic in West and Central African nations until

May 6, 2022, and sporadic outside of Africa [76]. Despite the World Health Organization's (WHO) 1980 proclamation that Smallpox had been eliminated, MPX still appears infrequently in the region of West and Central Africa [77]. In 2003, a pet retailer imported mice from Ghana, sparking an outbreak in the country [77]. The recent MPX pandemic in Nigeria from October 2017 to February 2018 had a catastrophic impact on the healthcare sector. An individual from the UK who entered Nigeria on April 20, 2022, traveled to Lagos and Delta State, left Lagos on May 3, 2022, and landed in the UK on May 4, 2022, was involved in the current MPX incident. Numerous authorities, including specialists, were unable to determine the epidemic's root cause at first [78]. The summary of the prevalence of monkeypox is shown in **Table 2**. Following the MPX outbreak in Nigeria in September 2017, the nation routinely reported solitary viral cases from all 22 states, a total of 558 cases and eight fatalities. Between September 2017 and April 30, 2022, there were 46 suspects and 15 confirmed cases from seven states, however, there have been no deaths reported [79]. MPXV is a possible biological warfare weapon similar to SARS-CoV-2 due to its virulence, which is comparable to that of the Variola virus, the cause of smallpox, with a 10% mortality rate. Between September 2018 and November 2021, seven instances of human monkeypox associated with travel were reported outside of Africa: one each in Israel, Singapore and the US. Teenagers are particularly impacted [80]. The unexpected spread of monkeypox in areas with no known epidemiological connections raises questions about the virus's evolution, which allows for long-term undetected transmission. As of May 25, 2022, 219 confirmed cases have been reported from countries where the virus is not regarded as prevalent. Australia (2), Argentina (1 suspected case), Canada (15), the UK (71), Israel (1), Switzerland (2), the United States (9), the United Arab Emirates (1 with a history of travel to West Africa), and Morocco (3 suspected cases) are among the countries reporting cases outside the EU/EEA. [81]. As of 3 July 2023, there had been a total of 11.86 confirmed cases of monkeypox across 115 different nations during the ongoing outbreak. During the current outbreak, there were 14.71 confirmed cases of monkeypox worldwide and 0.14 cases in Pakistan.

Endemic regions in Africa

After widespread immunizations were stopped in the 1980s, the virus that causes monkeypox became more contagious in humans. Infrequent reports of it in people have been made in a number of African nations, including Cameroon, Nigeria, the Democratic Republic of Congo, and others. The importation of infected animals has led to a few sporadic outbreaks in the United States, the United Kingdom, and Israel, but overall, instances outside of Africa have remained infrequent [84]. Monkeypox outbreaks have repeatedly occurred in these nations, frequently in isolated and forested areas where there are higher opportunities for human-wildlife encounters. Due to the existence of natural reservoirs and intermediate hosts as well as cultural behaviors that put people in close contact with infected animals, these endemic locations have a high prevalence of monkeypox [85].

Sporadic outbreaks outside Africa

Although outbreaks of monkeypox have occasionally occurred outside of Africa, it is primarily found there. These epidemics are frequently linked to imported cases or close contact with diseased animals [86]. In these cases, rodents carried the sickness. In these nations, limiting persistent transmission has required quick diagnosis, isolation, and public health interventions [87].

Imported cases and risks of international spread

Monkeypox outbreaks brought into the country run the risk of spreading abroad. The possibility of the virus crossing international borders has increased due to the globalization of trade and travel. Monkeypox carriers may travel to areas where the virus is not endemic, which could result in isolated outbreaks. Monkeypox can spread to new locations by the importation of exotic animals like rodents or primates. To stop future transmission and confine imported cases and reduce the likelihood of persistent spread, vigilant surveillance, early discovery, and quick action are crucial [88].

Historical perspective of Monkeypox in Pakistan

Early Reports and Recognition

In Pakistan, monkeypox was first identified in the 1970s. The earliest cases that have been reported date from that time, and other reports have intermittently surfaced over the years. The earliest instances were primarily linked to close contact with animals that

Table: 2: Summary of the prevalence of monkeypox.

Year	Pendamic places	No. of Cases	Reference
1958	When two outbreaks of the disease were noticed in monkeys maintained for research, Von Megnus made the initial discovery of Monkeypox (MPXV).	20%-30% of animals had clinical illness.	[74].
1959	Monkeypox broke out in Merck, Sharp, and Dohme's animal housing.	Less than 0.5% of people affected. It was determined that at least 10% of the 2,000 companion monkeys in the colony were ill. Of them, 56% were Macaca mulatta, 41% were Macaca philippinensis, and 3% were Cercopithecus aethiops var. subaeus.	[75]
1962	At the Walter Reed Army Institute of Research in Washington, monkeypox has been discovered in the primate colony.	Compared to 25 (93%) of the 27 cynomolgus exposed to the virus, only 5 (11%) of the 45 cynomolgus monkeys whose exposure to MPV had gone unnoticed acquired specific antibodies. Additionally seropositive were 52 of 67 rhesus and 6 of 14 African green monkeys.	[82]
1964	In the Rotterdam Zoological Garden, Peters described a monkeypox outbreak.	Among the eleven creatures that perished out of the 23 that were injured. One anteater, seven orangutans, three gorillas, and several different kinds of monkeys were found to have MPV	[75].
1965 – 1967	In the United States	Four further viral cases of monkeypox-like illness but none of the illnesses were virologically proved.	[75].
1970	In the Democratic Republic of the Congo, a youngster was found to have the first instance of human Monkeypox (MPXV). In 11 African nations, there were documented instances of mumps.	6 human infections.	[76]
1980	Still appears frequently in the region of West & Central Africa.		[77]
2003	Monkeypox (MPXV) is introduced to the U.S. All infected individuals have closed intact with prairie dogs.	47 people were infected in 6 states.	[77].
2000-2009	DRC & Nigeria countries most effected	Reported 10,000 Monkeypox (MPXV) cases.	
2000-2019	DRC & Nigeria experience a rise in Monkeypox (MPXV) cases.	18,000 confirmed or suspected cases reported	[78].
2017	In Nigeria	558 viral cases from 22 states & 8 fatalities.	[78].
2018-2021	Monkeypox (MPXV) cases were reported from Nigeria to Israel, US and Singapore.	one each in Israel, Singapore and the US.	[80]
July 15, 2021	U.S. resident tests positive after travelling to Nigeria.	Potential exposure to 200 people, but no additional cases were reported.	
1Jan.–30 April (2022)	In Nigeria	46 cases reported	[78].
25 May 2022	Countries where the virus is not regarded as prevalent.	219 confirmed cases were reported.	[83].
30 June 2022	In U.S. & U.K.	396 in the U.S. & nearly 1200 confirmed cases in U.K.	[83].

could act as reservoirs for the virus, like rodents and monkeys. However, Pakistan has experienced varying levels of monkeypox prevalence and incidence, and the country is not thought to be an endemic monkeypox hotspot [89].

Geographical distribution and endemicity

Monkeypox is not considered endemic in Pakistan, with isolated cases reported in various parts of the country due to factors such as human-animal interactions and travel patterns. Cases occurred in urban and rural areas [90]. To identify and monitor infectious diseases, Pakistan uses the Field Epidemiology and Laboratory Training Program (FELTP) and the Integrated Disease Surveillance and Response System (IDSR) [91].

Symptoms of the Monkeypox virus

The uncommon viral disease known as "monkeypox" primarily affects animals, such as monkeys, rats, and other mammals [92]. However, it can also spread from person to person or by direct contact with infected animals to people. Human monkeypox symptoms can range in intensity and may be similar to those of other viral diseases [93]. The symptoms and mode of transmission of monkeypox virus are shown in **Fig. 2**.

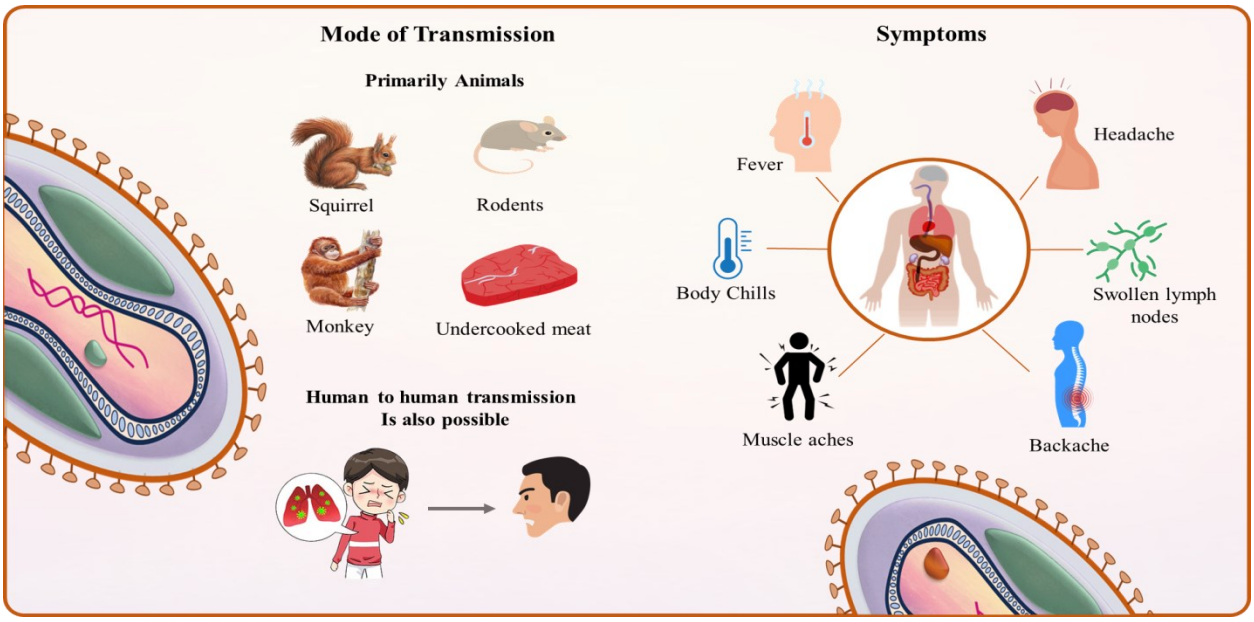

Fig. 2: Symptoms and mode of transmission of Monkeypox

Fever is the most frequent symptom before the appearance of the rash. Typically, monkeypox starts with a fever that exceeds 38.3°C (101°F). Both agitation and lymphadenopathy [94]. Clinically, human MPX resembles both conventional and modified smallpox. [95]. Various-sized rashes appear throughout the course of the next five days, initially affecting the face, it then progressing to the trunk and limbs. The soles and palms of the feet are frequently where the rashes manifest. These lesions have a diameter of roughly 0.5 cm, while some can be as large as 1 cm [96]. Once prodromal or rash symptoms appear, until lesions scab over, fall off, and a new layer of skin or mucosa forms underneath, patients are thought to be contagious. It's important to note that these skin and mucosal lesions could be misdiagnosed as syphilis, varicella zoster, molluscum contagiosum herpes simplex, or acute HIV [97].

Exanthems form over time in various stages, eventually resolving into crusts that break off during the healing stage. Future skin marking is significantly influenced by lesion co-infection, which occurs frequently [95]. Not all monkeypox patients experience these flu-like symptoms, although many do experience back and muscular aches and exhaustion. Patients typically experience a rash within 1 to 3 days after the onset of their fever, which frequently starts on the face before spreading to other areas of the body and perhaps involving the mouth, vagina, and anus. The rash initially appears as flat red dots, which develop into hard, fluid-filled, raised lumps before becoming scabs that take many weeks to recover weeks [98]. There have also been reports of severe cases of proctitis, urethritis, balanitis, and pharyngitis. When exposed to strong light, sensitivity to light (photophobia) may develop and cause discomfort.[99]. Loss of appetite (Many infected individuals experience a loss of appetite and may have a reduced interest in eating) [100]. Sore throat, (Monkeypox infection can be accompanied by a sore throat, making swallowing painful or uncomfortable) [100]. Abdominal pain, Vomiting and Nausea, Back and joint pain, Diarrhetic all are involved in the symptoms of monkeypox virus.

Etiology

The MPXV, or Monkeypox Virus, is an orthopoxvirus that causes monkeypox [101]. Camelopox, cowpox, variola (smallpox), and vaccinia (used in the smallpox vaccine) are additional orthopoxviruses that can infect people. The Congo Basin and West Africa are the two monkeypox clades identified by genome sequencing, and differences in human pathogenicity and mortality have been seen in the two geographical areas [102]. The virus has lateral bodies ranging in size from 22 to 450 nm in length and 140 to 260 nm in diameter, with a slightly pleomorphic core size from 22 to 450 nm in length and 140 to 260 nm in diameter, with a core that is slightly pleomorphic. It is an enveloped double-stranded DNA virus. Low pH and polar lipophilic solvents like chloroform render it inactive and resistant to phenolic disinfectants. The nearly

related vaccinia virus completely inactivates at 60°C in a couple of hours or minutes at 22°C following exposure to 20 nm caprylate [103]. Moreover, investigations into the cause and genomic sequencing have revealed instances of human-to-human transmission. These cases encompass infections in healthcare workers and family members of a patient whose initial illness was identified in the United Kingdom (UK), all of which took place in Nigeria. The possibility of disease transfer from one individual to another is a source of worry for the families and caretakers of the afflicted individuals. The UK Health Security Agency (UKHSA) asserts that monkeypox can be transferred during sex even though it has never been acknowledged as a sexually transmitted disease. Being near someone who has monkeypox can also spread it, as can their clothing or bed linens [104]. The monkeypox virus (MPXV), a double-stranded DNA virus, is one of the most virulent members of the Orthopoxvirus genus, the Poxviridae family [101]. The cowpox, variola, and vaccinia viruses, which are all seen in humans, are some of the other dangerous viruses in this genus. Smallpox disease is generated by the variola virus, and the live virus used in orthopoxvirus vaccines is the vaccinia virus [105]. The Congo Basin clade and The West African clade are the two clades that make towards the MPXV species. The MPXV virus, which has African rodents as its reservoirs, infects a wide range of mammalian species, including mice, squirrels, dogs and monkeys. But on occasion, it also results in human epidemics in specific areas [106].

Techniques for diagnosis of Monkeypox

In BSL-2 facilities, MPXV diagnostic testing and the handling of materials suspected to contain MPXV should be performed as a minimum requirement [107]. According to classification, the biological agent MPXV falls within safety the third category. As a result, only tasks requiring the handling of MPXV should be performed in working environments that at least meet level three confinement [108]. Real-time polymerase chain reaction (PCR) is a technique for laboratory studies and has been extensively used to detect the monkeypox virus [109]. PCR testing is very sensitive and efficient for viral DNA analysis of patient materials. Scabs or lesion exudates may be used as examination specimens. The use of techniques like virus isolation, immunohistochemistry, IgM and IgG enzyme-linked immunosorbent assays (ELISA), and electron microscopy is also an option, though these techniques unquestionably require more advanced equipment and specialized facilities, such as a high enough biosafety level for handling viruses [110]. Any person who exhibits an inexplicable rash on any part of their body together with one or more additional MPXV infection symptoms, including localized or generalized lymphadenopathy, a fever higher than 38.5 °C, headache, backache, or tiredness, PLUS one of the following: 1) A positive orthopoxvirus infection test result; 2) an epidemiological link to an MPX case that was either verified or suspected to have been present in the 21 days before symptom onset [111].

Diagnosis of Monkeypox by ELISA

Enzyme-linked immunosorbent assay (ELISA) formats for assessing antibodies that bind to VACV and MVA have previously been established using pure intracellular mature virions (IMVs) or infected cell lysates. In the current experiment, an ELISA based on an MPXV isolate from a Dutch patient was used in conjunction with an ELISA that contained VACV Elstree-infected cell lysate and an MVA-based neutralization test [112]. Orthopox viruses' highly conserved genomes result in significant antibody cross-reactivity. However, vaccinia also has genes that are absent, altered, or decreased in viruses like monkeypox; these gene products can be used to differentiate between infections with monkeypox and vaccinia. The viral antigen concentration used in the ELISA's adsorption step was determined using high-titer plasma from two recently immunized individuals that were obtained at the anamnestic response's peak (day 21) and had ELISA titers that were 10-fold higher than the highest convalescent-phase specimens used in the other experiments [113].

Treatment of Monkeypox

Most victims of monkeypox infection recover on their own. To reduce gastrointestinal fluid loss, those with gastrointestinal symptoms (such as vomiting or diarrhea) need oral or intravenous rehydration [100]. Although they have been licensed for the treatment of smallpox in animal models, a number of antiviral medications can be useful in treating monkeypox infection [5].

Tecovirimat

The first antiviral to be authorized in May 2022, Tecovirimat (also known as TPOXX or ST-246), is

demonstrated for the treatment of smallpox in adults and pediatric patients weighing at least 3 kg. It is regarded as the preferred course of treatment. Both PO and IV formulations are available [114]. In addition to smallpox and MPXV, this antiviral medication has been proven to be effective against a number of other orthopoxviruses, including cowpox, rabbitpox, ectromelia, and vaccinia virus [115, 116]. It was first discovered in 2002 through high-throughput screening. It is possible to employ dual therapy with tecovirimat and brincidofovir. To prevent the virus from spreading within an infected host, Tecovirimat disrupts the viral coat protein VP37, which prevents the latter stages of virus maturation and release from the infected cell. This protein is thought to be encoded by every orthopoxvirus species [117]. In patients with smallpox vaccination effects such as vaccinal eczema [118, 119] and progressive vaccinia, tecovirimat has been combined with vaccinia immunoglobulin (VIG). Headaches, nausea, abdominal pain, and vomiting are all side effects. With the IV form, infusion site responses may take place [120].

Brincidofovir and cidofovir

Since June 2021, brincidofovir has been authorized in the USA for the treatment of smallpox [121]. This is a conjugation of the cidofovir alkoxy alkyl lipid ester (CDV). An analog of the medicine cidofovir that is injected intravenously, brincidofovir (oral) may have a better safety profile, i.e. less renal toxicity, than cidofovir. Oral pills and suspensions are also available as alternatives [122]. Consequences include nausea, vomiting, diarrhea, and stomach pain. Reduced serum bicarbonate, proteinuria, neutropenia, infections, ocular hypotension, iritis, uveitis, nephrotoxicity, and fever are among the side effects of cidofovir. In contrast to CDV, only a very tiny amount of the drug reaches the kidney after intravenous administration since it is not substantially absorbed by transporters [123, 124]. This reduces the risk of nephrotoxicity.

Vaccinia Immune Globulin (VIG)

An FDA-approved hyperimmunoglobulin called VIG is used to treat some vaccine-related side effects. Passive immunity is a function of antibodies produced from pooled human plasma from smallpox vaccination recipients, according to the mechanism of action. These include aberrant vaccinia virus-induced infections, progressive vaccinia, severe generalized vaccinia, vaccinia infection in people with skin diseases, and eczema vaccinatum (apart from isolated keratitis, such as an eye infection) [125]. The IMVAMUNE and LC16m8 vaccines are third-generation smallpox vaccinations. Modified Ankara-Bavarian Nordic vaccinia (MVA-BN; Germany), JYNNEOS (USA), and IMVANEX (European Union) are some of the other names under which IMVAMUNE is marketed. IMVAMUNE has not encountered any issues related to first-generation smallpox vaccines, in contrast to first- and second-generation vaccines. In order to prevent smallpox and other smallpox viruses, a safe and effective vaccine is currently being developed. Higher dosages, however, could be necessary for IMVAMUNE [126, 127].

Monoclonal antibodies

Monoclonal antibodies were investigated in the study by Mucker et al. (2018) for the treatment of severe MPXV inflammation. The antibodies c8A & 7D11 from BioFactura were utilized [128]. These antibodies work by focusing on the mature virion (through C7D11) and the extracellular virion (via c8A), which ultimately prevents the virions from continuing to function [129].

Interferon-beta

Another stated medication was interferon-beta, which the FDA had approved as a treatment for multiple sclerosis. IFN beta promotes the expression of IFN-stimulated genes. As a result of the activation of these genes, natural killer cells and macrophages can actively work to suppress protein synthesis by triggering apoptosis. These genes also increase the expression of the major histocompatibility complex 1/II on the outermost layers of antigen-presenting cells [130]. [131] identified this active component in 2012.

Tipranavir and cefiderocol

The initial instance of a virtual display and computational drug repurposing investigation for the monkeypox virus encompassed medications such as tipranavir, cefiderocol, doxorubicin, and dolutegravir. These particular drugs were chosen due to their notable affinity for the two designated proteins within the monkeypox virus. The structural information from documented crystalline formations of corresponding proteins in the vaccinia virus was employed as the foundation for constructing the three-dimensional configurations of the TMPK enzyme in the simian-pox virus and the D9-cleaving enzyme. After being subjected to MD simulations to determine their

stability, the modeled protein structures were then fixed to a specially chosen library of 202 antibiotics and antivirals that have been approved by the US FDA. The four prospective monkeypox protein inhibitors must then undergo experimental in vivo and in vitro evaluations using the interaction and binding energy limits [5].

Current treatment approaches

At present, the medical community lacks the endorsement of any targeted antiviral therapy for the management of monkeypox virus infections. Supportive care is the cornerstone of treatment in this particular context. It encompasses a range of interventions aimed at effectively managing symptoms, ensuring adequate hydration, and addressing potential complications, specifically bacterial superinfections of skin lesions [132]. Investigation of Antiviral Agents for Diverse Poxviruses: Several antiviral agents that have exhibited notable effectiveness against various poxviruses, including the notorious smallpox virus, have been subjected to scrutiny in order to ascertain their potential utility against the monkeypox virus. Nevertheless, the efficacy of current interventions in combating monkeypox remains inadequately substantiated, necessitating further comprehensive investigations to ascertain their true potential [133]. The treatment options for Monkeypox include ACAM2000 & Tecovirimat, a medication composed of ACAM2000 and Tecovirimat administered at a recommended dose of 2.5-12.5 x 10 PFU. Its mechanism of action involves the use of a live attenuated smallpox vaccine. Another option is Cidofovir and Elstree RIVM, a combination of 5 mg/kg Cidofovir and 2.5 x 10 mg, administered through intraperitoneal and intracutaneous routes. This treatment functions as a nucleotide analog and DNA polymerase inhibitor. A subunit recombinant vaccine, with components (VACV L1R, A27L, A33R, and B5R), administered at (4,3,2,1) mg/kg intramuscularly in vivo, facilitates immunomodulation. RNA Interference with siA6-a and siE8-d, at a dosage concentration of (100 & 200) M, exhibits in vitro inhibition of viral replication. The summary of treatment options for monkeypox disease is shown in **Table 3**.

Limitations

The absence of targeted antiviral therapeutics for the monkeypox virus presents formidable obstacles in effectively controlling and treating the infection. Furthermore, it is crucial to acknowledge the zoonotic characteristics of monkeypox, which refers to its ability to be transmitted from animals to humans. This aspect highlights the significance of earmarking sweat towards the development of robust antiviral strategies and vaccines that can effectively combat this contagious complaint. Given the eventuality for global dispersion, it becomes imperative to prioritize exploration and invention in order to alleviate the pitfalls associated with monkey pox and guard public health on a global scale [138].

Conclusion

In conclusion, this comprehensive study has completely examined several aspects of monkeypox and handed precious perceptivity into its complex nature. The review covers inheritable sequencing, mechanistic base, global frequency and specific impacts in Pakistan and includes individual styles, symptoms and different treatment modalities. From Tecovirimat to monoclonal antibodies to interferon-beta and further, the composition highlights the innovative strategies to combat this grueling contagious complaint. Advances in inheritable sequencing have strengthened our understanding of the contagion and clarified its transmission and pathogenesis. The global and original spread underscores the critical need for robust surveillance and preparedness measures. It highlights the significance of PCR for early discovery, revolutionizing our capability to snappily manage cases and alleviate the impact on individual and public health. The different clinical instantiations of monkeypox punctuate the significance of timely intervention. Examination of different treatment approaches reveals a range of remedial options that target different aspects of the complaint progression. A comprehensive, multidisciplinary approach is pivotal to our unborn approach. Ongoing exploration, transnational collaboration and knowledge sharing will upgrade individual styles, optimize treatments and develop preventative measures. Public mindfulness and education are critical to precluding the spread of the contagion. Basically, this composition provides a holistic perspective that deepens our understanding and guides us toward further effective ways to alleviate the goods of monkeypox. The collaborative sweats of scientists, health professionals, policymakers and the global community are critical in our ongoing fight against

Table 3: Treatment options for monkeypox.

Sr. #	Drug	Route of administration	Study Type	Mechanism of Action	References
1.	ACAM2000 & Tecovirimat	Intrascapular administration	*In vivo*	Live attenuated smallpox	[117]
2.	Cidofovir and Elstree RIVM	Intraperitoneal/Intracutaneously	*In Vivo*	Vaccine	[134]
3.	CMX001	Intranasal	*In Vivo*	Nucleotide analog & DNA polymerase inhibitor	[135]
4.	ST246	Oral	*In vivo*	Antiviral	[136]
5.	Subunit recombinant vaccine (VACV L1R, A27L, A33R, and B5R)	Intramuscular	*In Vivo*	Immunomodulation	[136]
6.	RNA interference (siA6-a and siE8-d)		*In Vitro*	Inhibition of viral replication	[137]

rising contagious conditions. Through commitment and collaboration, we can fight for a healthier, safer future for all.

Conflict of interest

The authors declare no conflict of interest.

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