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Review Article

Monkeypox Poses A Serious Public Health Challenge, A Comprehensive Review

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Abstract

Background and Aims: Monkeypox (MPX) is a zoonotic disease due to Orthopoxvirus infection that has reemerged after decades of Smallpox eradication, raising international concern. Monkeypox virus (MPXV) was originally found in Central and West Africa in the 1970s, but it has now crossed the borders of Africa, Europe, and America and recorded the most newly infected patients at the time. Common ways of transmission could be the zoonotic and human-to-human transmission. The most common means of transmission are direct and prolonged contact with patient bodily fluids, unprotected contact with lesions, and sexual contact. Early symptoms can manifest as headache, fever, and lymph node inflammation. Despite the similarity in clinical manifestation between Smallpox and Monkeypox, swollen lymph nodes can distinguish MPX from Smallpox. MPX has five stages based on the clinical manifestation of lesions appearing on the skin, macula, papule, vesicle, pustule, and scar. Also, there are several methods for detecting, preventing, and treating MPXV. This paper provides a comprehensive review of Monkeypox and various aspects of the disease were discussed.
Keywords: Monkeypox, Poxviruses, Diagnosis, Transmission, Phylogeny, Epidemiology.

Etiology

Monkeypox virus (MPXV), a linear double-stranded DNA virus that resides in the cytoplasm of infected cells, is one of the most virulent members of the Orthopoxvirus genus in the family Poxviridae that includes Vaccinia virus, variola virus, and Cowpox; all of which can cause infection in humans. Human Monkeypox is a zoonotic Orthopoxvirus that clinically resembles Smallpox, making it troublesome to differen-tiate it from Smallpox and Varicella. MPV was first discovered in 1958 in Copenhagen and it is not a new threat. The diagnosis of the research center is a fundamental part of the disease that distinguishes detection and observation, and novel tests are expected for more accurate and faster diagnosis.

Most human contaminations happen in Central Africa, where screening is tested in remote areas with little scope but might be conducted by utilizing evidence-based methods and educational materials that educate general health workers on the crucial standards of this contamination. New drugs and vaccines have shown conclusions about the treatment. However, more examinations are expected to demonstrate their adequacy in genuine endemic settings. Subsequently, further research into infections, the study of disease transmission, environment, and science in endemic areas are required for a

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better approach and to prevent human diseases. MPXV is related to various mammalian species, including monkeys, mice, squirrels, and dogs, using African rodents as a reservoir, however, it has sporadically involved humans in zonal outbreaks (1, 2, 3, 4, 5).

Genomic Analysis

Monkeypox is a member of the poxviruses. This family has large DNA and reproduces in the cytoplasm. The best-known member of this family is Smallpox, which was eradicated about 45 years ago after the deaths of about 300-500 million people. Other species of this family still occur in nature and are pathogenic and deadly. These viruses have had genetic interactions between themselves and the environment over time, and they have diversified and the old world separated from each other following these events (6, 7, 8).

Evolution

Akhmetapox virus and Alaskapox virus, identified in 2013 and 2015 respectively, split from the other Orthopoxviruses about 10,000 to 20,000 years ago. Other species are also thought to have originated between 1700 and 6000 years ago (7, 9, 10). MPXV evolution began about 3500 years ago. The West African MPXV clade is believed to have emerged about 600 years ago (7).

Phylogeny

The family of poxviruses has 60 identified members that have been classified. Poxviruses circulate in nature and cause infections between different organisms and their classification is based on genomic amino acid sequences or poxvirus core genes (11) (Fig. 1).

Genomic Variability

Current MPVX, known as human Monkeypox virus 1 or (hMPVX1), can be divided into Lines A, and B and also divided into these sublines A.1, A.1.1, A.2, B.1, B.1.1. B.1.2, B.1.3, B.1.4, B.1.5, B.1.6, B.1.7. According to genomic sequence analysis, the 2022 outbreak is associated with the disseminated B.1 lineage (13).

Pathogenicity

After entry of the virus into the host's body via the oropharynx, nasopharynx, or intradermal routes, the study shows that MPXV replicates itself at the site of inoculation and then propagates to regional lymph nodes. After a phase of primary viremia, the virus spreads in the host's organs (3). It is difficult to distinguish the clinical exhibition of MPXV from other diseases caused by poxviruses (14). Characteristic rashes or lesions progress to papules and vesicles that eventually crust and form a fresh layer, but the scars remain on the skin's surface (15, 16). Macula: Discoloration of a small area of skin tissue (usually less than 1 cm) (17, 18). Papules: A papule is a raised area of skin tissue. After some time, spots become pulvinated and develop into papules (19). Vesicle: small bubble, usually filled with white-yellow liquid, appearing on the skin (20). Pustule: Inflamed and irritable lesions with red bumps with a white center (21). Scar: After going through all the steps listed, the lesions will crust and the scar will remain for a while.

According to WHO information, the lesions commonly appear on the face (95% of cases), palms and soles (75%), oral mucous membranes (70%), and genitalia (30%) (Refer to: https://www.who.int/news-room/fact-sheets/detail/ Monkeypox). Experimental research has shown that these percentages are different and rashes usually manifest in the genital area (46.1%), arms (39.6%), face (38.4%), and legs (31%) (22). The rash typically appears within 1 up to 5 days after the onset of fever, and it is noteworthy that patients are contagious until the rash disappears. Although many patients reported no or few lesions with pain and bleeding, usually located in the genital area, in the last and current onset, generalized lesions in some sites can number up to several thousand. The infection is self-limiting and is treated after 2 to 4 weeks (14, 16).

Clinical Signs

Monkeypox exhibits the same symptoms as people infected with Smallpox but not as severe as them. The incubation period of this

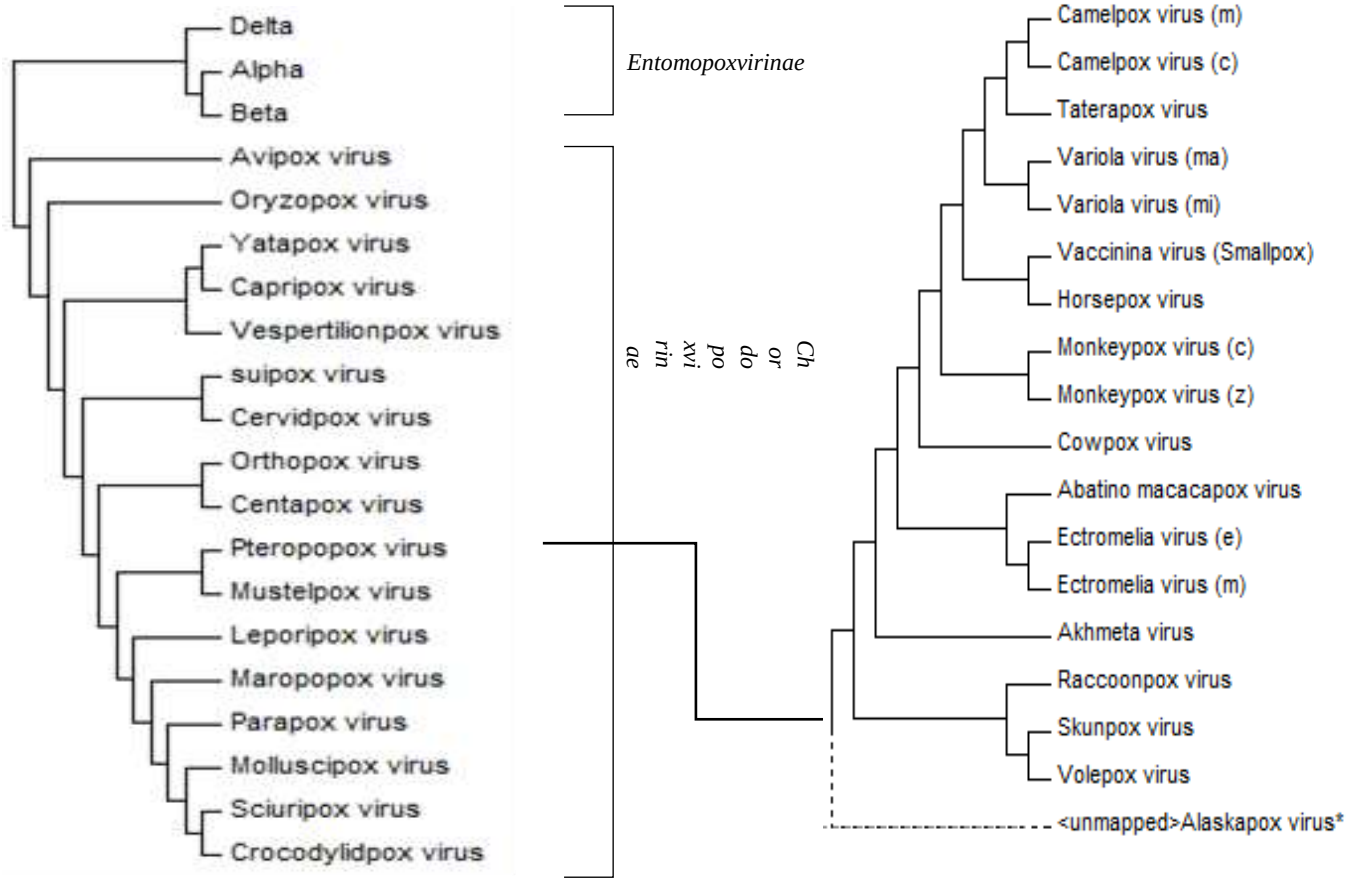


Fig 1. This taxonomy was created using the MEGA7 program and the information available in references (7, 11, 12) (Refer to: https:// ww w. ncbi.nlm.nih.gov/data-hub/taxonomy/tree/? taxon=10244). In the classification of Orthopox, phylogeny is drawn based on the core of Poxviruses genes (11). *The exact localization of this serotype is still unknown. It's hoped that the whereabouts of this member will be found in further research.Figure was prepared by Sana Yousefian Jazi & et al.

infection is considered to be long 5-14 days (or a maximum of 21 days) and after this time the symptoms begin (14, 16, 23). Common clinical features are lesions (100% of cases), fever (62%), chills (59.1%), lymphadenopathy (58. 5%), malaise (57.1%), lethargy (41%), myalgia (31-55%), mild headache (27%), nausea, fatigue, pharyngitis (sore throat), corneal lack of transparency and drenching sweats (6, 14, 15, 16, 22, 24, 25, 26). The data shows that the rashes usually last longer than other clinical presentations and take 1 to 3 weeks to heal. Patients are no longer known to be contagious approximately 2 to 4 weeks after the lesions appear (Figure 2 & 3). This disease, unlike Smallpox, has mild symptoms and severe patients are observed in children (14, 27).

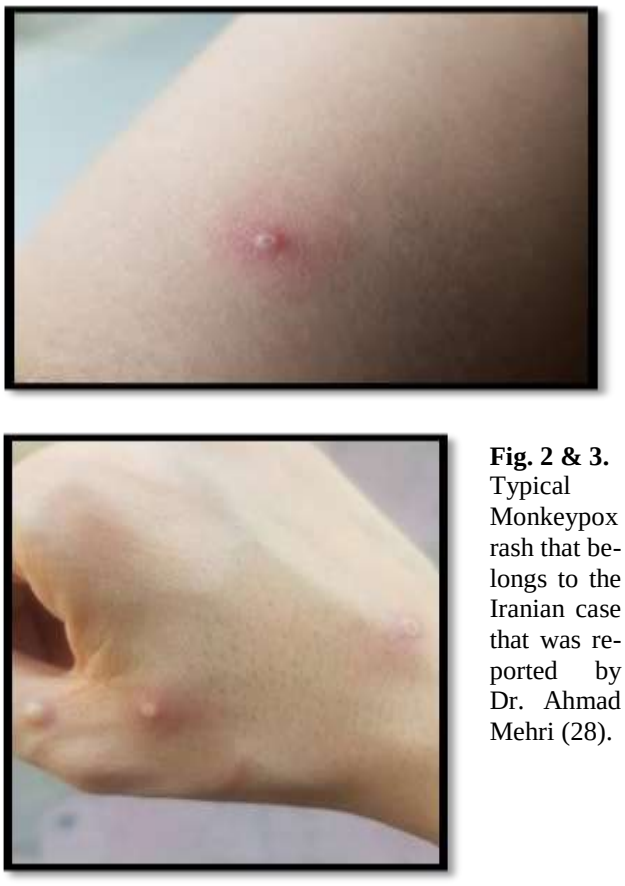


Fig. 2 & 3. Typical Monkeypox rash that belongs to the Iranian case that was reported by Dr. Ahmad Mehri (28).

Mode of Transmission

After the global eradication of Smallpox (post-eradication era), Monkeypox appears to be the most common Orthopoxvirus (OPXV) infection among humans. The term R0, which stands for a viral reproductive number, indicates the risk and potential of a disease of epidemic concern (29, 30). The R0 for Monkeypox, an eradicated disease, ranges from 3.5 to 6.07, and scientists suspect that this number should be lower due to the animal reservoir for Monkeypox. The potential risk of Monkeypox becoming a pandemic is low (29). Monkeypox is a zoonotic disease, so there are two main routes of MPXV transmission. Zoonotic transmission and human-to-human transmission. In addition to the routes mentioned that require direct contact, there are also assumptions about the transmission of the disease by routes that do not require direct contact; such as airborne transmission (31).

Animal-Human Transmission

Although the host reservoir of MPXV has not been entirely determined, some groups of primates, African rodents such as Gambian rats and squirrels are known to be hosts for the virus and can transmit the virus to humans. This usually occurs via direct contact with contaminated animals or their bodily fluids, blood and skin lesions, and even bites from an infected animal. Eating improperly cooked animals is also known to be associated with zoonotic transmission (6, 14). Transmission of the disease through hunting and international trade of infected animals has been documented and this issue has raised global concerns (32).

Human-Human Transmission

According to the MPXV R0, it seems that this way of transmission is not easy and requires close and long-term physical contact with the patient, direct proximity with their lesions or virus-contaminated objects or surroundings such as patients' clothing or bedding (6, 14, 33, 34). Exposure to patients' bodily fluids or their viral respiratory droplets can also result in the distribution of the virus among humans (6, 14). This disease can be transmitted through the placenta, to the fetus, or through close contact after birth. New research suggests that the MPXV can also be transmitted through sexual interaction, as the virus has been detected in semen, but transmission by this way is still unknown. MPXV can also be transmitted by creating reservoirs in the urinary tract, even after the lesions have healed (35).

Human-Animal Transmission

This mode of transmission is not predominant and is of concern, however, according to the CDC, mammals can also be infected. Based on a new study, it has been confirmed that dogs may be diagnosed with MPVX, yet the risk is low (Refer to: https://www.who.int/news-room/questions-and-answers/item/Monkeypox?gclid=CjwKCAjws--ZBhAXEiwAv-RNL9UaWN7Cs4-jTsyM_aGFBle1BUToU2886iT7ZyW5hrb-ExLWTY-LxoCZW0QAvD_BwE) (Figure 3).

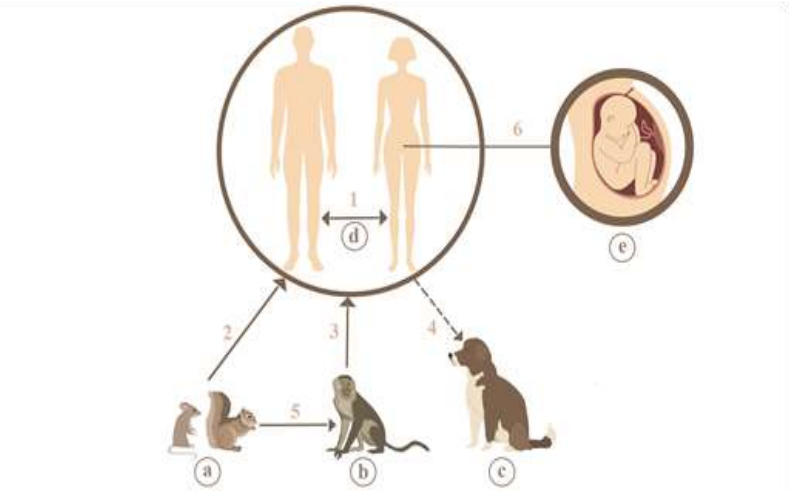


Fig. 3. Mode of transmission: a. Rodents and mammalian b. Monkeys c. Dogs or Domestic animals d. Human e. Fetus 1. Close interaction, sex, Bodily fluids 2. Animal trading, Direct contact 3. Spillover 4. UN 5. Close contact 6. Congenital UN: Unknown (Figure was designed by Sana Yousefian Jazi).

Risk Factors

The clinical indication of Monkeypox is generally less severe than that of the Vaccinia virus and its mortality rate is 6-11% in adults and 15% in children. Several factors have been

recognized to be a significant driving force in increasing the likelihood of infection, including Prolonged physical contact with patients and family members, Unsafe sex, Male gender, Breastfeeding (in newborns), Men who have sex with men (MSM), Teenagers (under 15 years), dealing with animals (slaughter workers or pet lovers) and living in rainforests (14, 36, 37, 38). There are some assumptions that urbanization in West Africa may increase the risk of infection (26). Immunodeficiency, pregnancy (due to immune susceptibility), and pre-existing comorbidity can also influence the morbidity of the disease (2, 39).

Epidemiology

The first documented cases of Monkeypox among humans were in the 1970s. Monkeypox is believed to have originated in the Democratic Republic of the Congo (DRC). It is now known as an endemic disease in this country (24, 40, 41). Since 2016, hMPX has been confirmed in 13 African countries such as Congo, Libya, the Central African Republic, Nigeria, and Sierra Leone (42). Genetically, the virus is divided into two clades: West African and Central African. The Central African group is more pathogenic and deadly, despite the similarity in clinical symptoms (30). A recent study indicates that the 2022 outbreak originated from the West African clade (23). The first outbreak outside Africa's borders occurred in the USA in 2003, and then several outbreaks occurred sporadically in multiple parts of the world, the epidemiological connection of which is not clear (40, 43). New cases have been detected in Israel, Singapore and the UK due to travel and the introduction of disease from Nigeria. MPXV was reported outside of Africa, in North and South America, Europe, Asia, and Oceania (30, 33, 44). Due to a lack of diagnostic capacity, it is not fully possible to record the spread of the virus in all countries where this virus is suspected to be an unknown form in almost 44 countries (45). From the beginning of the emergence of MPXV to October 26, 2022, most of the reported cases were observed in North America and Europe. The European continent has the most countries affected by the disease. Also, about 42% of deaths occurred in Africa. In Asia, the number of new infections is low compared to other continents. About 82 percent of cases are detected in Western Asia (Table 1) [Refer to: www.cdc.gov/poxvirus/monkeypox/response/2022/world-map.html;www.worldometers.info/geography/7-continents/].

Table 1. Comparison of prevalence rate in various continents (From the first detected case until October 26, 2022)

Location	Cases	Deaths	Number of countries involved	The country with the highest prevalence rate
North America	32,377	7	19	USA (28,087 cases)[1]
Europe	25,006	4	40	Spain (7,317 cases)
South America	17,013	9	12	Brazil (9,026 cases)
Africa	921	15	13	Nigeria (552 cases)
Asia	393	1	22	Israel (260 cases)[2]
Oceania	168	0	3	Australia (140 cases)
Total	76,510	36	109	USA

[1]The highest prevalence rate compared to the population;
[2] The lowest prevalence rate compared to the population

Host Immune Responses to MPXV

To date, several studies on the Monkeypox virus have been carried out, however, the immune response of this virus is not sufficient, the Monkeypox virus has made immune system responses to infection the worst because it uses various mechanisms to evade it (46, 47). Host cells recognize virus infestation and develop powerful antiviral responses, thus, the identification of viral pathogens and the host's defense against the Monkeypox virus are provided by the adaptive and innate immune systems. Pattern recognition receptors (PRRs) for instance Toll-like receptors (TLRs) and (RIG-I)-like receptors (RLRs) can detect DNA and single-stranded RNA, double-stranded RNA, and viral proteins (48). First, natural killer (NK) cells directly kill the infections that caused the Monkeypox virus, IFN- γ and some

pro-inflammatory cytokines such as TNFα indirectly caused inflammatory responses in the infected cells (49, 50). The Monkeypox virus evasion mechanism inhibited the activation of CD4+ and CD8+ T cells to protect the viral reservoir from immune observation, recognition of CD4+ and CD8+ T cells is decreased due to the Monkeypox virus evasion mechani-sm, and IFN or TNF production through virus-specific T cells is reduced, as a result, the Monkeypox virus reduced the activity of T cells and caused the immune system to become weak (6, 51). One of the biological features of PXV is its envelope; it can help the virus to survive better or evade the host's immune system (44). (Refer to:https://www.cancer.gov/publications/dictionaries/cancer-terms/def/enveloped-virus).

The Natural Host of MPXV

A variety of animal species have been identified as vulnerable to the Monkeypox virus, most mammalian species have been infected with this virus, showing that the host range is broad, and some of the infected animals in table 2 are considered to be infected with the MPXV (51).

Table 2. Animals infected with the Monkeypox virus (MPXV).

Natural host species	Location	Ref.
African hedgehogs (Atelerix sp.) Gambian-pouched rat (Cricetomys gambianus)	Africa	52, 53
African dormice (Graphiurus spp.) Shot-tailed opossum (Monodelphis domestica) Woodchucks (Marmota monax) Prairie dogs (Cynomys spp.)	USA	54, 55, 56, 57
Sun squirrel (Heliosciurus sp.)	Zaire	58
Giant anteaters (Myrmecophaga tridactyla)	Rotterdam	59
Rhesus macaques (Macaca mulatta)	Copenhagen	60
Southern opossum (Didelphis marsupialis)	South America	61

Diagnosis

At the time, certain diagnostic methods have been confirmed and used. The specimens for the laboratory include skin lesions, crusts, fluid in vesicles or pustules that may contain the virus, the patient's blood, etc (62). One of the features of MPXV is swollen lymph nodes; following this event C-reaction protein (CRP) proliferates, which can be confirmed in clinical tests. This method is not entirely reliable since this protein increment can also be seen in cancer, inflammatory diseases, and viral and bacterial diseases (63). Other methods are:

Molecular Method:

PCR (Polymerase Chain Reaction)

Two of the most accurate diagnostic methods are Polymerase Chain Reaction (PCR) and Real-time PCR (RT-PCR), samples should be collected in sterile containers so the tests can be conducted on them (11). In this method, multiple copies of a particular sequence of DNA are made to make the test more definite (Refer to: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/pcr). According to experiments, RT-PCR is more reliable and authentic than the conventional PCR method (Table 3).

LAMP (Loop-Mediated Isothermal Amplification)

This unprecedented method, amplifies RNA with sensitivity, output, and fast function up to isothermal situations. Several methods have been used for MPXV for instance, RT-PCR and conventional PCR, these methods require special tools, despite the LAMP method being functional without using these tools. There are three LAMP methods such as C-LAMP, COM-LAMP, and WLAMP for the detection of the Congo Basin genome and the West African MPXVs and to distinguish between the two clads with three LAMP tests. Six primers have been used in this method including (F3, b3), (FIP), (BIP), and (LF and LB), what that's called the 6-primer-based LAMP. (C-LAMP), (W-LAMP) and (COM-LAMP) tests are used for the amplification of the Congo Basin genome, West African genome, and West African MPXV and Congo Basin genomes, respectively. For these three assays, the primers based on the nucleotide sequences of the (ATI) from

Table 3. Types of PCR methods for Monkeypox detection (80).

Method	Gene target	Accuracy	Oligo nucleotide	Sequence	Ref.
RT-PCR	E9L-NVAR	100%	F	TCAACTGAAAAGGCCATCTATGA	(78, 79)
			R	GAGTATAGAGCACTATTTCTAAATCCCA	
			P	TET-CCATGCAATATACGTACAAGATAGTAGCCAAC-QSY7	
RT-PCR	B6R	100%	F	ATTGGTCATTATTTTTGTCACAGGAACA	(78, 79)
			R	AATGGCGTTGACAATTATGGGTG	
			P	MGB/DarkQuencher-AGAGATTAGAAATA-FAM	
LC-qPCR	ATI (Congo)	90%	F	GAGATTAGCAGACTCCAA	(80, 81)
			R	GATTCAATTTCCAGTTTGTAC	
			P1	GCAGTCGTTCAACTGTATTTCAAGATCTGAGAT-Fluorescein	
			P2	LCRed640-CTAGATTGTAATCTCTGTAGCATTTCCACGGC-Phos	
LC-qPCR	ATI (West African)	90%	F	GAGATTAGCAGACTCCAA	(80, 81)
			R	TCTCTTTTCCATATCAGC	
			P1	GCAGTCGTTCAACTGTATTTCAAGATCTGAGAT-Fluorescein	
			P2	LCRed640-CTAGATTGTAATCTCTGTAGCATTTCCACGGC-Phos	
RT-PCR	A39R	100% (One patient)	F	5'-TGGGATAACG AATCCAATGTCA-3'	(82, 83)
			R	5'-GCGTGC TTCCAGCAACACT-3'	
			P	probes for the Real-time PCR are designed based on the *A39R* gene of the genus *Orthopoxvirus*	
RT-PCR	N3R	58%	F	AACAACCGTCCTACAATTAAACAACA	(80, 84)
			R	CGCTATCGAACCATTTTTGTAGTCT	
			P	FAM-TATAACGGCGAAGAATATACT-MGBNFQ	
RT-PCR	F3L	58%	F	CTCATTGATTTTTCGCGGGATA	(80, 84)
			R	GACGATACTCCTCCTCGTTGGT	
			P	6FAM-CATCAGAATCTGTAGGCCGT-MGBNFQ	
RT-PCR	O2L	100%	F	5'-TAGTGAGTTCGGCGACAAAG-3'	(11)
			R	5'-GTATCGCATCTCTCGGGTATTC-3	
			P	6-FAM-5'-ACCGGTAATCTTGTCGAGGAGGACA-3'-ZEN-IBFQ	
PCR	B2R	100%	F	5'-CTGATAATGTAGAAGAC-3'	(82, 83)
			R	5'-TTGTATTTACGTGGGTG-3'	
			P	NA	
MuRT-PCR	B7R	NA	F	ACGTGTTAAACAATGGGTGATG	(80, 85)
			P	AACATTTCCATGAATCGTAGTCC	
			R	TAMRA-TGAATGAATGCGATACTGTATGTGTGGG-BHQ2	

P: probe R: reverse primer RT-PCR: Real-Time PCR
F: Forward primer NA: Not Available LC-qPCR: Light Cycler Real-Time quantitative PCR

the Congo Basin and West African MPXV were developed from the D14L gene and ATI genes. The Loopamp DNA Amplification kitTM formed the LAMP reaction and the reaction combination 25 ml including, BIP, FIP, 5 pmol of B3 and F3, LB, and LF. To control the LAMP amplification products they electrophoresed in agarose gel 3% also the COMLAMP, LAMP, and W-LAMP products were digested by TaqI and BglII (64, 65).

CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats)

At present, there are various methods for diagnosing MPXV, some of them such as Real-time PCR considered the golden and standard method and others such as enzyme-linked immunosorbent assay (ELISA) and loop-mediated isothermal amplification (LAMP) are accurate and sensitive but have some difficulties in some low-income and poor countries. Also, ELISA has negative and false positive results, especially after vaccination, it will not be able to distinguish produced antibodies caused by natural infectious from cases after vaccination. Meanwhile, LAMP's disadvantages are related to a complicated primer design and weak quantitative performance. Therefore, fast, accurate, and economical methods that can diagnose the disease on-site are more than needed (Table 4) (66, 67).

Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) represent a family of nucleic acid sequences that are found in prokaryotic organisms, such as bacteria. These sequences can be recognized and cut by a set of bacterial enzymes, called CRISPR-associated enzymes, exemplified by Cas9, Cas12, and Cas13. Certain enzymes in the Cas12 and Cas13 families can be programmed to target and cut viral RNA sequences. This new technology can be considered a precious tool for the diagnosis of some RNA viruses such as SARS-CoV-2 (68). Also, the CRISPR-Cas technique is recently developed as an effective method that has the potential to distinguish a very low 1.7 fM concentration of nucleic acid in 15 min (69).

According to the conducted research, this method has also been used to detect Monkeypox, which has many positive points compared to other methods, including the sensitivity is about 1000 times higher than PCR, the process at a mild temperature (37°C) without thermal cycling, very fast and simple diagnosis with the naked eye without the need for laboratory equipment using combining the lateral flow strip within 5 minutes. In a study using the polA gene, MPXV was distinguished from other Poxviruses (67, 70).

Other Method:

Cell-Culture

Since the 1950s, various methods have been used to diagnose infectious diseases. One of the most common methods is cell culture. The advantage of this method is the production of live viruses, but it has disadvantages such as being time-consuming, which increases the possibility of contamination of the sample with bacteria. using cellular or chick chorioallantoic membrane isolation along with assays on DNA, assist in the detection of the monkeypox virus (71, 72). This method is recommended only for laboratories that have complete containment/safety facilities (73).

Serology

The two factors (immunoglobulin M) IgM and (immunoglobulin G) IgG increase in the serum about 8 days after the onset of symptoms and can be detected by enzyme-linked immunosorbent assay (ELISA) (6, 74). The research proved that the amount of anti-Orthopoxvirus IgG was much higher in persons who received Smallpox vaccination in childhood, and it can be said that IgG is a stable response. The serum used to detect IgM after 5 days of rash or the serum used to detect IgG after 8 days is the best time for serology. In general, IgG was observed more frequently in vaccinated individuals (74, 75). IgG was detected in 94.5 percent of people who tested positive for MPXV, and IgG was observed in 80.5 percent (74).

Immunofluorescence (IF)

An important immunochemistry diagnostic method that is classified into two main methods: Direct (primary) and indirect (Secondary).

Table 4. The comparison of various diagnosis methods of MPXV

Method / Features	RT-PCR	LAMP	CRISPR	Immunofluorescence (IF)
Accuracy	High	High	High	Low
Time	4-6 hours	1 hour as standard	about 1 hour	5-6 hours
Specificity	High	High	High	Low
Price	High	Low	High	Moderate
Thermal cycling	Required	No required	No required	Required
Target	Different Sequences of DNA	RNA	Nucleic acid sequences	IgM/IgG against OPXV
Disadvantage	requires expensive equipment	In development stages	It is not yet developed and requires high technology and expensive facilities	It can be used about 8 days after infection

Table 5. Clinical features comparison of poxviruses

Disease / Feature	Monkeypox	Smallpox	Chickenpox	Cowpox	References
Incubation period	5-21days	7-17days	10-14 days	8-12 days	16, 86, 87, 88 (Refer to: www.who.int/health-topics/Smallpox#tab=tab_2)
fever	often between 38.5°C and 40.5°C	often >40°C	+	up to 39° C	4, 6, 88, 89
Skin lesion	+	+	+	+	6, 86, 87, 88
lymphadenopathy	+	_	_	+	6, 86, 88, 90
Self-limiting	+	+	+	+	16, 86, 88, 91
lethality	6 -11%	30%	<0.01%	34%	86, 92, 93 (Refer to: www.who.int/health-topics/Smallpox#tab=tab_2)

The virus is identified through marked antibodies (marked with Fluorophore) (76). This method is not exclusively used to detect the Monkeypox virus, but there are special antibodies to identify Orthopox, with which Monkeypox is also detected (77). However, it is the least effective way to detect MPXV since it can get misdiagnosed with other OPX viruses (78).

Phenotypic Methods

In people who are suspected to be infected and are in the period of the disease, it is possible to diagnose the disease based on the exhibition of symptoms. It is necessary to pay attention to the similarities between MPV rashes and other

members of the Pox family (Table 5). Observe the specific manifestations of Monkeypox such as lymphadenopathy (6).

Treatment

While MPXV is re-emerging as a threat and raising international concern, most patients recover without specific therapy (usually after 4 weeks), however, public information and education are crucial (5, 6). The clinical signs of MPXV are mild and known to be self-limiting (94). However, there are treatments for viral diseases that are mentioned in the Table 6.

Table 6. Antivirals medications

Antiviral	Description	Ref.
Cidofovir	This antiviral drug can act as an inhibitor of DNA polymerase. The complete and definite clinical results are still unclear.	3, 39
Tecovirimat	Approved by FDA and EMA, also can be given orally	3, 95
Vaccina immunoglobulin intravenously (VIGIV)	It can be used to treat Monkeypox infection (but it is not yet tested on humans). Observed studies have proven that it can reduce the possible side effects of the Cowpox vaccine.	3, 92

Control and Prevention

Multiple measures that assist the infection from spreading include the isolation of infected persons in separate rooms and avoiding any physical contact with them, also health care professionals should be equipped with standard gloves, masks and gowns. Common approaches to safety such as washing hands frequently can be effective too (3, 25, 32). There are some ways to control or prevent the spread of the disease, one study shows that vaccination is an effective way (87). Two recommended vaccines are discussed in the Table 7.

Conclusion

In the post-eradication of Smallpox era, MPXV is described to be the most prevalent Orthopoxvirus, and the newborn generation after the eradication of Vaccinia is more susceptible to the virus due to the termination of the vaccine, so the information the professional world and the public are indispensable (16, 90).

The clinical picture of the disease is remotely indistinguishable from Smallpox or chickenpox, so we need laboratory tests for the persistent diagnosis (90). Avoiding close contact with infected individuals or animals suspected of being infected is crucial for prevention, and patients should be quarantined (3). Pregnant women, those with compromised immune systems, children and adolescents, and healthcare professionals who are on the front lines of

Table 7. Recommended vaccine

Vaccine	Description	References
Vaccinia	One of the most effective ways to protect communities is the Smallpox vaccination. Based on new studies, injection after 4 days of close contact, can play an important role in disease prevention. There are still conflicts about how long the given immunity lasts but pieces of evidence report that after Smallpox eradication, vaccination has been discontinued, thus new gene-rations are more susceptible to infection. After almost 3 decades, vaccinated populations against Smallpox have a lower likelihood of infection.	45, 96, 97 (Refer to: www.who.int/health-topics/Monkeypox#tab=tab_3)
Monkeypox Vaccine	Can be administrated for persons with a high risk of infection like healthcare workers or populations with large numbers of new cases, since 2019, JYNNEOS a 2-dose series vaccine approved by the FDA has been administrated**.**	26, 98

medical care are at the highest risk of infection and should be the focus of attention (2, 3, 36). MPXV will not be more than one defined endemic infection due to recent outbreaks in Europe, America, Singapore, and Israel, although the risk of a pandemic is low, governments and global public health should not ignore the dangers (6, 90).

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Conflict of Interest

The authors declare that they have no known competing financial or non-financial, professional, or personal conflicts that may have influenced the work described in this review.

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