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REVIEW ARTICLE

The *Mpox*, serious menace, or paper tiger?

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ABSTRACT

One of the most horrible diseases in history, Smallpox is caused by the *Variola* from Poxvirus family, has caused great morbidity and mortality along the way since it was eradicated in the 20th century. During and after the eradication program for Variola, other *Poxviruses* such as the *Monkeypox (Mpox)* virus, which causes a smallpox-like disease, became flagrant. With its long range of enzymes and proteins, poxviruses are effectively resisting hostile immune system attacks and disrupting cell signaling pathways. After *Smallpox* vaccination, cross-reaction immunity develops between *Orthopoxviruses*. *Mpox* is indeed an African endemic virus; however, increasing and emerging cases have been reported globally in recent years. According to *Smallpox* eradication in the 1970s and vaccination ceasing, nowadays centerpieces of the world population are vulnerable to *Mpox* virus. Our knowledge of *Mpox* is severely limited due to the lack of regular surveillance methods. Increasing education, boosting surveillance, and developing diagnostic competence is the most significant policies for improving identification, treatment, and restricting further virus spread. So *Mpox* can play a double-edge blade role in which without monitoring and increasing awareness it could be horrific and with public awareness and boosting surveillance it could be a paper tiger. This article reviewed previous reports about the *Mpox* merge from PubMed and google scholar from 2018 to June 2022.

Keywords: *Monkeypox*; *Mpox; Variola*; Poxviruses; *Smallpox*; *Vaccinia*

POXOVIRIDAE TAXONOMY

The *Poxviridae* are split up into two subfamilies depending on host range; viruses in the *Chordopoxvirinae* target vertebrates, while viruses in the *Entomopoxvirinae* infect insects. The *Chordopoxvirinae* includes eight genera (*Orthopoxvirus*, *Parapoxvirus*, *Avipoxvirus*, *Capripoxvirus*, *Leporipoxvirus*, *Suipoxvirus*, *Molluscipoxvirus*, and *Yatapoxvirus*) and three *Entomopoxvirinae* (*Entomopoxvirus* A, *Entomopoxvirus* B, and *Entomopoxvirus* C). Species of the same genus are genetically and immunologically related, and their structure is comparable. *Orthopoxvirus*, which contains *Variola* (VARV) and *Vaccinia* (VACV), and *Mpox* (MPXV), is the best-studied genus. *Ectromelia* virus and *Rabbitpox* virus (a type of VACV) are two other *Orthopoxviruses* worth mentioning since they are particularly pathogenic for mice and rabbits, respectively (1).

Variola virus and *Vaccinia* virus are the most well-known members of the *Chordopoxvirinae*, *Poxviridae* family. *Variola* is the causative agent of *Smallpox*, a disease that plagued the human population until it was eradicated in 1977 by a global vaccination program, using the highly associated with Vaccinia, which gives efficient and long-last-

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ing immunity. *Molluscum contagiosum* virus, which causes relatively benign wart-like lesions, and *Mpox* virus (MPXV), which cause a smallpox-like disease after uncommon zoonotic infections, are the other human *Poxvirus* diseases. Even though poxviruses have been studied extensively for many years and *Smallpox* vaccination began more than 200 years ago, there is still concern about the reappearance of *Smallpox* through leakage or its use as a bioweapon (2). Long DNA viruses such as *Poxviruses* resist hostile immune system strikes by generating plenty of gene products that systematically destroy crucial components of the inflammatory response. Several of the key mediators of innate immunity are targeted by *Poxviruses*, including interferons, tumor necrosis factors, interleukins, complement, and chemokines. Poxviruses also control a range of intracellular signal transduction pathways, including the apoptosis pathway. Many of the *Poxvirus* genes that disrupt these pathways were directly stolen from the host immune system, while others bear no relation to any known host gene (3).

Variola virus (VARV). *VARV* belongs to the *Orthopoxvirus* genus. This virus's absolute human specificity is one of its notable features and its origin is unclear. The discovery of smallpox-like lesions on Egyptian mummies implies that the disease has been around for at least 3,000 years. In the fourth century CE, the first documented mention of sicknesses like *Smallpox* appeared in China. This viral disease existed in the global population, creating severe epidemics with a significant number of deaths. Fortunately, due to immunization, this virus was completely eradicated from the world population by the end of the 20th century (4-6).

Variolation was one of the early strategies for controlling *Smallpox*. Individuals who had never had *Smallpox* were treated with debris from *Smallpox* sores (pustules) by scratching the substance into their arms. People frequently acquired smallpox-like illnesses after variolation, such as fever and a rash.

The principle of vaccination was developed in 1796 by the English doctor Edward Jenner, who realized that milkmaids who had *Cowpox* were immune to *Smallpox*. In 1801 he described his treaties detailed his findings and stated hope for "the elimination of *Smallpox*." Vaccination grew generally recognized and eventually substituted with variolation. The virus used to create the *Smallpox* vaccine switched from *Cowpox* to vaccinia virus sometime during the 1800s. By the time smallpox Intensified Elimination Project started in 1967, Smallpox had been eradicated in North America (1952) and Europe (1953). By 1971, variola had been eradicated from South America, followed by Asia (1975), and lastly Africa (1977) (7).

***Vaccinia* virus (VACV).** As mentioned above, the *Vaccinia* virus has had a great role in *Variola* elimination. Since the *Smallpox* was eradicated, global vaccination programs were discontinued, and interest in VACV, the *Smallpox* vaccine, remained. Because of the VACV genome's capacity to accept extra genetic material, scientists have created a wide range of candidate vaccines that target a broad set of microbial pathogens (8).

Since structural proteins of orthopoxvirus are largely conserved, cross-protection is a unique feature in this genus, immunization with VACV gives cross-protection against *Smallpox* as well as other *Orthopoxviruses* such as *Mpox*. Genetic manipulation of VACV leads to several strategies which have been used to accomplish attenuation, including successive passage in an alternate host, deletion of particular genes, and genetic engineering of viral genes expressing immunomodulatory proteins. Some highly attenuated third and fourth generation VACVs are now being examined for stockpile in case of a bioterrorism-induced of *Smallpox*. Furthermore, now the rabies virus glycoprotein is encoded by recombinant *VACV*, which is fed orally to wild animals. *VACV* expresses several proteins that restrict the host's antiviral and inflammatory responses. Mutation or deletion of these genes frequently results in replication-competent viral constructs with reduced pathogenicity. The viral E3L gene, for example, is necessary for host suppression in IFN response. The E3L gene has been substituted with vIF2, which permits for a single round of replication in human cells but does not allow for spread and does trigger the immune response and signaling pathways. As a result, genetically modified Vaccinia vectors will not only advance our understanding of *Orthopoxviruses*, but will also empower us to maintain safety while achieving the immunogenic opportunities of replication competence (8-10).

***Poxviridae* genome.** *Poxviridae*, a family of huge eukaryotic dsDNA viruses known as Nucleo-Cytoplasmic Large DNA Viruses (NCLDVs), has been shown to infect a wide range of birds, mammals, and

insects. Poxvirus genomes are made up of linear double-stranded DNA containing termini that form covalently closed hairpin loops. The genome sequences of different poxvirus types vary greatly (130-360 kb). The *Mpox* virus appears relatively enormous under electron microscopy (200-250 nanometers). *Poxviruses* are brick-shaped, with a lipoprotein envelope (11). Although *Poxviruses* typically contain more than 150 genes, only 49 of these are found in all complete genomes of *Poxviruses*. However, there are nearly 90 genes that are shared by all *Chordopoxvirus* (ChPVs). These genes, which are involved in key functions such as replication, transcription, and virion assembly, are grouped in the core region of the genome, meanwhile, species or host-specific genes are dispersed toward the opposite edges of the genome. Many of these terminal genes produce proteins that diminish the host's anti-viral activities, such as apoptosis, antigen presentation, interferon functions, and immunological signaling pathways, and are thus referred to as virulence genes (11). *Chordopoxvirinae* genomes range in size from 135,000 base pairs (bps) (*Yaba monkey tumor* virus) to 289,000 (*Fowlpox virus*) and encode from 136 to 260 open reading frames (ORFs). *Poxvirus* ORFs are often classified as consisting of more than 50 amino acids and being non-overlapping regions. Furthermore, the noncoding sections between ORFs are frequently very short, consisting of only a few nucleotides in some situations (2).

MPOX VIRUS (MPXV)

History. *Mpox* is an uncommon viral disease caused by the *Mpox* virus, which is an *Orthopoxvirus.* It was only found in tropical forest regions in central and western Africa. It was first detected in laboratory monkeys in 1958, and later examination of blood from African wildlife revealed indications of *Mpox* infection in a variety of African rodents. Human *Mpox* was not considered as a separate illness in people until 1970, when the virus was isolated from a patient with probable *Smallpox* infection in Congo. Most of the clinical signs of human *Mpox* disease are similar to those of smallpox (12, 13). *Mpox* virus has identified two separate MPXV clades, WA (West Africa) and CB (Congo Basin), based on clinical presentation, epidemiologic characteristics, geographic location, and genotyping. CB MPXV has a 10% mortality rate and can be transmitted between humans. WA MPXV, on the other hand, is associated with lesser symptoms, and person-to-person transmission has never been established as the main mechanism of transmission (14).

Genome and pathogenesis. There are 190 non-overlapping ORFs over 180 nt in MPXV's linear DNA genome, which is approximately 197 kb in size. MPXV is characterized by highly conserved central coding region sequences (CRS) flanked by variable ends with inverted terminal repeats (ITRs) at nucleotide positions 56000-120000. A majority of VACV homologs to genes identified at the ends of the MPXV genome influence host range determination and pathogenicity, and most have been predicted or reported as such. In contrast to VARV, MPXV contains at least four ORFs in its ITR region (15). Comparative study has revealed that the center genomic sections of MPXV and VARV, which contain fundamental enzymes and structural proteins, are virtually comparable, meanwhile, the terminals regions, which express pathogenicity and host-range factors, are significantly different. Mutations in two interferons (IFN) resistance genes, as well as the existence of an interleukin-1 (IL-1) antagonist in MPXV, may contribute to the differences in the two viruses' characteristics. While the significant genetic variations are comforting and indicate that MPV was not a direct progenitor of VARV, they do not exclude future adaption of MPVX to humans (16).

Intracellular mature virus (IMV) and extracellular-enveloped virus (EEV) are two types of infectious virions generated in infected cells in VACV (and most likely MPXV). IMV is released upon cell lysis, but EEV is liberated from cells via interaction with actin tails, which is thought to be the reason for the virus's quick long distance transmission within the infected host. Although the abovementioned qualities are for VACV, they are most likely shared by all *Orthopoxviruses.* Cell-associated virions (CEVs) are created as a result of the microtubule-mediated transport of intracellular enveloped virus (IEV) to the periphery of the cell, wherein the IEV's external membrane merges with the cellular membranes and remains connected to the cell surface. Cell-to-cell dissemination is mostly the responsibility of CEVs. When IMV is enveloped by a double membrane produced from an early endosomal component or the trans-Golgi network, IEV is created. Aside from IEV exocytosis, another mechanism for the genera-

tion of EEV is IMV budding across the cell surface (17-19).

Pathogenesis and clinical features. Although research on the pathology and pathogenesis of MPXV has been conducted, understanding of the innate and adaptive immune responses to MPXV infection is limited due to insufficient data. Natural killer (NK) cells, a key element of innate immunity, directly kill virus-infected cells via cytokine production to influence the functioning of other cell types such as T-cells and dendritic cells. The killing impact of NK cells is mediated through granule secretion (which contains perforin and granzymes) and cell-cell interactions. Inflammatory responses in damaged tissue are driven by IFN-gamma and TNF-alpha, which were released by NK cells during the early phases of infection, and these cytokines are also engaged in regulating dendritic cells to induce T-helper type 1 (Th1) cell polarization (20). MPXV, unlike VACV, employs cell-associated viremia to disseminate through infected hosts. Although the processes involved in *Poxvirus* immune escape against antiviral cytokines, chemokines, and antigen presentation are unknown, *Cowpox* virus CPXV interaction with intracellular transport of MHC class I correlates with the methods used by CPXV to evade antiviral CD8+ T-cell responses. Because MPXV encodes a similar homolog of CPXV203, which retains MHC class I in the endoplasmic reticulum, hypothesized MPXV to have comparable immune evasion mechanisms as CPXV. However, the MPXV evasion mechanism prevented CD4+ and CD8+ T cell activation after cognate contacts with MPXV-infected cells, protecting the viral reservoir from immune surveillance. It's worth mentioning. The lack of cross-protection generated by the *Smallpox* vaccine, combined with the likely loss of herd immunity, has resulted in an immunologically naive population that is highly vulnerable to MPXV infection. This could explain why MPXV has recently emerged (21).

The pathogenesis of *Mpox* is comparable to other mammalian pox diseases, including variola in humans. The *Mpox* replication occurs at the inoculation site and spreads to nearby lymph nodes after viral entrance via any route (Oro-nasopharynx, or intradermal). Following that, human *Mpox* infection is separated into two phases: the proforma and the rash phase. Fever, headaches, chills and/or sweats, sore throat, muscle pain, malaise, and lymphadenopathy characterize the prodrome. The rash stage, which lasts 1-3 days following the onset of fever and lymphadenopathy, is defined by a few to hundred lesions. The lesions develop at the same time and progress at roughly the same rate. Lesions develop from macules to papules, vesicles, pustules, and crusts. Their dispersion is primarily peripheral, but during a severe disease, they can cover the entire body. The sores dry and desquamate for about 2-3 weeks, based on the intensity of the disease. Patients frequently complain of abdominal discomforts like nausea, vomiting, diarrhea, and lack of appetite. Lesions of the mouth and gastrointestinal system are possible. Skin irritation caused by the rash can result in subsequent bacterial infection (common). Ocular infections with MPXV and subsequent bacterial infections can also arise, causing the patient's eye puffy, red, photosensitive, and perhaps blind. Patients may experience coughing, trouble breathing, or lung injury if their respiratory system is impacted. Encephalitis and sepsis are two further consequences. Lymphadenopathy is one of the most unique differences between MPXV and VARV. By the time lesions emerge, serum antibodies are frequently detected (14, 22, 23).

Transmission and prevention. The *Mpox* virus can be transferred both from animal to human (primary transmission) and from person - to –person (secondary transmission). The virus invades the host through breaks in the skin, mucosal tissues (eyes and mouth), and the respiratory tract. Primary animal-to-human transmission occurs by direct contact with infected animals' body fluids, lesion debris, or respiratory droplets. Viral shedding through urine and feces has also been described and could be an additional source of infection. Secondary human-to-human transmission is connected with close contact with infected people's body fluids and lesion material (24). Pulmonary transmission can also occur via continuous face-to-face exposure to big respiratory droplets. Propagation can also happen through virus-infected substances including bedding and clothing. The infection is transmitted from infected pregnant women to the baby. There is little evidence on the influence of human MPXV infection on pregnancy outcomes with the vertical transmission; however, there are case studies of abortion and fetal mortality (25-27). The early epidemiological studies indicate a relationship with sexual interaction among men who have sex with men (MSM). Sexually transmitted skin le-

sions, droplets, and fomites might pose a significant risk of transmission, regardless of whether *Mpox* is genuinely sexually transmissible (e.g. via sperm) or not. The current outbreak of *Mpox* in non-endemic countries seems to be in dramatic contrast to past episodes. The major proportion of patients have no recorded animal exposure or trip background to endemic areas. The quick increase of reported cases and geographical distribution point to significant human-to-human transmission rather than overflow from an infected animal. This also marks the first large epidemic of *Mpox*, primarily in MSM, with possible sexual transmission (28).

Cross-reactive antibodies are made by *Orthopoxviruses*, which defend against infection by other *Orthopoxviruses* species. The live *vaccinia* virus vaccine, which was employed during the *Smallpox* eradication program, was believed to be 85 percent effective against *Mpox* infection. There is no *vaccinia* vaccine available to the general population. There has been no formal investigation on the post-exposure usage of the *vaccinia* vaccine for *Mpox* diseases, however it has been used for this purpose in cases of imported *Mpox* to the UK and Singapore. Because there are no authorized vaccines for *Mpox*, the only way to avoid it is to educate health workers and the general public about the dangers of coming into touch with sick or deceased animals that may contain the virus (26, 29, 30).

Epidemiology. Human *Mpox* is common in places where people have frequent contact with infected animals. From 1970 to 2018, incidences were documented in Cameroon, Côte d'Ivoire, Central African Republic, the Democratic Republic of the Congo, Gabon, Nigeria, Sudan, and Sierra Leone. Since the 1970s, the prevalence of human *Mpox* cases has been increasing, with the most significant increases occurring in the Democratic Republic of the Congo. The median age at presentation has risen from 4 years in the 1970s to 21 years currently (2010–2019). The total mortality rate was 8.7 percent, with a notable difference between clades—Central African 10.6 percent (95 percent CI: 8.4 percent – 13.3 percent) vs. West African 3.6 percent (95 percent confidence interval: 1.7 percent – 6.8 percent) (31). The only human cases of *Mpox* outside Africa occurred in 2003 in the United States, which was caused by rodents imported from Ghana, with no human-to-human transmission but an outbreak of *Mpox* virus was reported in the United Kingdom in September 2018. Till 19 August 2022 there are more than 41960 confirmed cases of *Mpox*, and 12 confirm deaths were reported. The USA with 14594 cases, Spain with 5792 cases, Brazil with 3359 cases, Germany with 3366 cases are the most prevalent counties, and United Kingdom, France, Canada and the Netherlands have reported more than 1000 cases. Middle East prevalence of *Mpox* are limited to United Arab Emirates with 16 cases, Saudi Arabia 6 cases, Qatar 3 and Iran with 1 confirmed case (Table 1). Such a significant high prevalence from so many countries beyond Africa in such a short period has never been recorded before. Every day, new cases are reported (32, 33). Nowadays, because of the extreme disease produced by MPXV, it must continuously monitor infection rates worldwide to guarantee that it does not achieve human adaption by spontaneous or recombinational processes in the unvaccinated population.

Diagnosis. If the typical skin lesions are observed and there is a background of contact, *Mpox* can be tentatively diagnosed; nevertheless, clinical cases can mimic *Chickenpox* and may be difficult to identify clinically from *Chickenpox* disease. Because of its efficiency and specificity, PCR is the primary laboratory test. The roof or fluid from vesicles and pustules, as well as dry crusts, are ideal diagnostic specimens for *Mpox*. A biopsy is an approach where possible. Lesion samples must be maintained cool and stored in a dry sterile tube (no viral transport media). Due to the obvious brief period of viremia relative to the date of specimen collection after symptoms begin, PCR blood tests are frequently unreliable and should not be regularly collected from patients (34, 35).

Treatments. *Mpox* treatment is primarily supportive. Tecovirimat (chemical agent ST246), also known as Arestyvir (TPOXX's), has already been approved for use in humans infected with *Orthopoxviruses.* Since there is not human documentation proving TPOXX's effectiveness for the treatment of *Mpox*, as well as its safety and pharmacokinetic characteristics, the authority stated that undergoing randomized, controlled trials to evaluate TPOXX's safety in humans with *Mpox* infections is critical. However, its efficacy against *Mpox* in humans has yet to be verified. Clinical trials are underway for several potential medicines, including a cidofovir derivative (CMX001/ Brincidofovir). *Vaccinia* im-

Table 1. Prevalence of *Mpox* cases and death (updated 19 Aug. 2022)

Country	Cases	Deaths
Andorra	4	0
Argentina	72	0
Australia	89	0
Austria	217	0
Bahamas	1	0
Barbados	1	0
Belgium	624	0
Benin	3	0
Bermuda	1	0
Bolivia	31	0
Bosnia and Herzegovina	3	0
Brazil	3359	1
Bulgaria	4	0
Cameroon	7	0
Canada	1112	0
Central African Republic	8	2
Chile	189	0
Colombia	129	0
Costa Rica	3	0
Croatia	17	0
Curacao	1	0
Cyprus	4	0
Czechia	36	0
Democratic Republic of the Congo	163	0
Denmark	163	0
Dominican Republic	6	0
Ecuador	19	1
Estonia	9	0
Finland	22	0
France	2889	0
Georgia	2	0
Germany	3266	0
Ghana	47	1
Gibraltar	6	0
Greece	50	0
Greenland	2	0
Guadeloupe	1	0
Guatemala	3	0
Honduras	3	0
Hungary	62	0
Iceland	12	0
India	9	1
Iran	1	0
Ireland	113	0
Israel	194	0
Italy	689	0
Jamaica	4	0
Japan	4	0
Latvia	4	0
Lebanon	6	0
Liberia	2	0
Lithuania	5	0
Luxembourg	45	0
Malta	31	0
Martinique	1	0
Mexico	252	0
Moldova	2	0
Monaco	3	0
Montenegro	1	
Morocco	1	0
Netherlands	1087	0
New Caledonia	1	0
New Zealand	4	
Nigeria	157	4
Norway	76	0
Panama	4	0
Peru	937	0
Philippines	1	0
Poland	104	0
Portugal	810	0
Qatar	3	0
Republic of the Congo	3	0
Romania	33	0
Russia	1	0
Saint Martin	1	0
Saudi Arabia	6	0
Serbia	23	0
Singapore	15	0
Slovakia	10	0
Slovenia	43	0
South Africa	4	()
South Korea	1	0
Spain	5792	2
Sudan	1	0
Sweden	139	0
Switzerland	392	0
Taiwan	3	0
Thailand	5	0
Turkey	1	0
United Arab Emirates	16	0
United Kingdom	3081	0
United States	14594	0
Uruguay	2	0
Venezuela	1	0

mune globulin, which was once used to treat *Smallpox*, could possibly be investigated, especially in immunocompromised patients (23, 36, 37). Although several medicinal prevention for *Orthopoxviruses* include *Mpox* are on hand. JYNNEOS (live, replication incompetent vaccinia virus) and ACAM2000® vaccines are now available. Following the Advisory Committee on Immunization Practices (ACIP) suggested ACAM2000 in 2015, JYNNEOS authorized preexposure prophylaxis as a replacement to ACAM2000 for certain persons at risk of *Orthopoxvirus* and especially MPXV encounter in 2019. According to historical statistics, *Smallpox* immunization with vaccinia virus was around 85% efficient preventing *Mpox* (38-40).

CONCLUSION

Mpox virus is an emerging pathogen that causes a potentially epidemic disease about which little is understood. Health professionals are frequently unfamiliar with the concept and characteristics of *Mpox*, and lack of regular surveillance methods to monitor *Mpox*, providing considerable gaps in our knowledge, epidemiology and prevalence of this disease. At the same time, clinical isolates of *Mpox* have been rising in Europe and North America, which is most likely due to a mix of environmental and anthropogenic factors. Climate change, urbanization, tourism, and war, among other factors, enhance human interaction with infected wildlife.

Currently, patients can only receive symptomatic and supportive treatments; nevertheless, preliminary evidence of the efficacy of many medicines against MPXV infection is hopeful. Some of the most significant policies for improving identification, treatment, and restricting further virus spread are improving education, boosting surveillance, and developing diagnostic competence. Furthermore, research initiatives are required to create knowledge and lead to future improvements in *Mpox* prevention and control. Clinical trials for current vaccines and antivirals for *Mpox* are included.

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