



REVIEW

REVISED Monkeypox (mpox) in immunosuppressed patients**[version 2; peer review: 2 approved, 1 approved with reservations]**Sirwan Khalid Ahmed ¹, Mona Gamal Mohamed ², Eman Abdelaziz Dabou², Israa Abuijlan², Deepak Chandran ³, Nahed A. El-Shall⁴, Hitesh Chopra⁵, Kuldeep Dhama ⁶¹Department of Pediatrics, Rania Pediatric & Maternity Teaching Hospital, Rania, Sulaymaniyah, Kurdistan Region, 46012, Iraq²RAK College of Nursing, RAK Medical and Health Sciences University, Ras Al Khiamah, United Arab Emirates³Department of Veterinary Sciences and Animal Husbandry, Amrita School of Agricultural Sciences, Amrita Vishwa Vidyapeetham University, Coimbatore, Tamil Nadu, 642109, India⁴Department of Poultry and Fish Diseases, Faculty of Veterinary Medicine, Alexandria University, Edfina, El-Beheira, 22758, Egypt⁵Chitkara College of Pharmacy, Chitkara University, Punjab, 140401, India⁶Division of Pathology, ICAR-Indian Veterinary Research Institute, Bareilly, Uttar Pradesh, 243122, India**v2** First published: 02 Feb 2023, 12:127
<https://doi.org/10.12688/f1000research.130272.1>Latest published: 03 Apr 2023, 12:127
<https://doi.org/10.12688/f1000research.130272.2>**Abstract**

The World Health Organization (WHO) proclaimed a public health emergency in July 2022 due to the emergence of Mpox (formerly monkeypox) while the globe was still dealing with the COVID-19 epidemic. The characteristics of mpox in immunocompetent individuals are well-characterized, despite difficulties in diagnostics, immunization, and access to treatment that persist in low-income countries. Patients with weakened immune systems are more likely to spread an illness and die from it than healthy people because they cannot mount a protective immune response against it, such as a neutralizing IgG and poxvirus-specific Th1 response. A health warning on severe mpox in people who are immunocompromised due to Human Immunodeficiency virus (HIV) and other illnesses was released by the U.S. Centers for Disease Control and Prevention (CDC) on September 29, 2022. The advice does not specifically include primary immunodeficiency, but it does define other immunocompromising disorders as "having autoimmune disease with immunodeficiency as a clinical component". Both those with healthy immune systems and those with weakened immune systems, such as those who are immunosuppressed, older people, children, etc., have encountered serious health issues, but the latter group is more likely to do so. According to the advisory, "of the people with severe mpox manifestations for whom CDC has been consulted, the majority have had HIV with CD4 counts 200 cells/ml, indicating substantial

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immunosuppression". However, new cases are still expected to be discovered, especially in low-income countries with limited access to diagnosis, treatment, and prevention, and where a large percentage of the mpox-infected population also has advanced HIV infection. Thus, further research is always needed to determine the best way to treat mpox in immunocompromised people. In this context, we discussed /reviewed the mpox clinical presentation, available treatment options and current preventive guidelines in immunocompromised patients.

Keywords

monkeypox, immunocompromised patients, autoimmune disease, human immunodeficiency virus, management, prevention, control



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REVISED Amendments from Version 1

In this version of the article, the authors made some edits as follows:

1. In the Abstract part of the paper, we made modifications depending on the suggestions of the reviewers.
2. The introduction has been revised, and more references have been included in response to the reviewers' comments.
3. In accordance to the suggestions made by the reviewers, the section relating to the ongoing 2022 mpox outbreak has been amended, and more references have been provided. Also, in response to the suggestions made by the reviewers, we added a figure that is relevant to the most recent mpox that has been confirmed worldwide.
4. The transmission and replication section has been revised, and more references have been included in response to the reviewers' comments.
5. The mpox in immunosuppressed patients' section has been revised, and more references have been included in response to the reviewers' comments.
6. The management and prevention section changed to (prevention strategies and counter-measures for immunocompromised individuals). In addition, we revised, and more references have been included in response to the reviewers' comments.
7. The conclusion and future prospects section has been revised, in response to the reviewers' comments.
8. The name of (Eman Abdelaziz Ahmed Rashad Dabou) changed to (Eman Abdelaziz Dabou).

Any further responses from the reviewers can be found at the end of the article

Introduction

The monkeypox virus (MPXV) is an *Orthopoxvirus* that can spread to humans and result in mpox (formerly monkeypox) disease quite similar to the smallpox.¹ Large respiratory droplets, inadvertent or intentional contact with bodily fluids or lesion material or contact with biota—including bedding or towels—are some of the main ways that viruses are spread. Symptoms like malaise, headache, lymphadenopathy, myalgia, and cutaneous symptoms have been documented within one to three days of the onset of fever. Macules may initially be present when a lesion first develops, followed by papules, pustules, and vesicles, which then dry up and peel off. Immunocompromised individuals should be examined for other diseases, such as primary or secondary infection with the varicella zoster virus or other pathogens such as *Cryptococcus neoformans*, *Histoplasma capsulatum*, or *Bartonella henselae*, when skin lesions arise along with viral prodromal symptoms.² Despite ongoing challenges with diagnoses, immunization, and availability to treatment in low-income countries, the characteristics of mpox in immunocompetent persons are well-characterized. Individuals with compromised immune systems are at a higher risk of spreading an infection and succumbing to it than the general population because they lack the ability to produce a protective immunological response, such as a neutralizing IgG and poxvirus-specific Th1 response. Yet, more instances will likely be found, particularly in low-income countries with sluggish healthcare systems and a high proportion of mpox-infected people who are also HIV-positive.^{3,4} Research on the most effective treatment for mpox in immunocompromised patients is, thus, an ongoing necessity. In-depth discussion of mpox disease in immunocompromised people and recommended preventative measures is provided in the current article.

The epidemiological history of the mpox revealed that the first recognition of this disease in human beings was in 1970 in the Democratic Republic of the Congo among children.⁵ The mpox disease was endemic to central and western Africa region where 12 countries were identified, including Benin, Cameroon, the Central African Republic, the Democratic Republic of the Congo, Gabon, the Ivory Coast, Liberia, Nigeria, Sierra Leone, and South Sudan.^{6–7} Since then, human cases of mpox have occurred rarely in that area.^{5,10–16} The first outbreak of the disease reported outside Africa was in the USA in 2003.¹⁷ Investigation revealed that the USA outbreak was linked to an infected Prairie dog with MPXV. These pets were housed near rodents shipped from Ghana in 2003.¹⁸ After the 2003 USA outbreak, several countries reported mpox cases with a history of travel from Nigeria in 2018,¹⁹ including Israel,²⁰ the UK,²¹ and Singapore.²² Now, some 34 years later, we find ourselves in an eerily similar predicament.²³ The World Health Organization (WHO) closely tracked human mpox cases after the 1980 eradication and subsequent end of routine smallpox immunization out of worry that decreased immunity rates to smallpox would increase population vulnerability to the MPXV. In the Democratic Republic of the Congo, 760 cases were confirmed in laboratories between 2005 and 2007, and there were three spatial clusters from 2000 to 2015 that are indicative of outbreaks of probable mpox cases. From 1981–1986 to 2006–2007, the number of instances grew by 20 (from 0.72 per 10000 to 14.2 per 10000). There has been an uptick in reported cases of mpox in Nigeria since 2017, following an almost 40-year absence of such reports.^{24,25} WHO reported in 2022 that mpox

was endemic in several African countries, including Benin, Cameroon, the Central African Republic, the Democratic Republic of the Congo, Gabon, Ghana (identified in animals only), Côte d'Ivoire, Liberia, Nigeria, Sierra Leone, and South Sudan. There were 1284 probable cases of mpox and 58 deaths reported between January and May of 2022, with the majority of cases occurring in the Democratic Republic of the Congo. The discrepancy between confirmed and suspected cases is large and concerning, suggesting insufficient laboratory testing capability. In addition to rising rates in endemic regions, mpox has been detected in non-endemic regions (e.g., the United Kingdom, the United States, Israel, and Singapore) through either imported animals or tourists. In the United States, prairie dogs were linked to 71 human infections in 2003 (35 of which were confirmed by laboratories). Seven cases of mpox were identified in the United Kingdom between 2018 and 2021, four of which were linked to international travel to endemic regions.^{26–28}

The documented incubation period of mpox is 5–21 days and clinical symptoms range from widespread rashes with secondary fungal or bacterial skin infections or tissue death (necrosis) to intestine obstruction, and difficulties with the heart, lungs, urinary system, and nervous systems.^{25,27}

Since several *Orthopoxvirus* species share genetic and antigenic characteristics, getting infected with one of them may provide significant protection from getting infected with the others. The vaccinia virus vaccine offers defense against illnesses brought on by the variola major, mpox, or cowpox viruses.^{29,30} Vaccine-induced cross-protection appears to be mediated by a variety of immunologic pathways, with neutralizing antibodies among the key players.^{26,31,32} Monkeys can be immunized with the human smallpox vaccine to prevent mpox, which is consistent with the ability of the smallpox vaccine to give cross-protection for humans against mpox. Since the end of smallpox vaccinations in 1978, cross-protective immunity to different orthopoxviruses has decreased, especially in younger people without vaccinia-induced immunity, and the number of unvaccinated, susceptible people has increased globally. In fact, during the past few years, these changes have been accompanied by a rise in the number and geographic dispersion of human mpox cases.^{33,34} A health warning on severe mpox in people who are immunocompromised due to HIV and other illnesses was released by the U.S. Centers for Disease Control and Prevention (CDC) on 29th September 2022.³⁵

Notwithstanding difficulties in diagnostics, immunization, and availability to therapy in low-income countries, the characteristics of mpox in immunocompetent persons are well-defined.²⁸ Sexual contact was suspected as the mode of transmission in 95% of the 528 instances of mpox reported, with 98% of patients being gay or bisexual men. There were no fatalities, although 13% of patients needed hospitalization due to discomfort; a few patients needed hospitalization due to visual lesions, decreased oral intake, myocarditis, or acute kidney disease. The majority of patients exhibited a rash upon presentation, with the majority having less than 10 lesions and 11% having more extensive lesions. Patients had a 41% HIV infection rate, but after receiving antiretroviral medication, their viral loads dropped to undetectable levels. Most importantly, no coexisting immunocompromising diseases were observed, indicating that this is an immunologically healthy group. Hence, it is not surprising that only about 5% of people needed mpox-specific antiviral medication, as this demonstrates that mpox is self-limiting in immunocompetent people.³⁶ Although “having autoimmune disease with immunodeficiency as a clinical component” is included in the advisory’s definition of other immunocompromising disorders, primary immunodeficiency is not specifically included in it. There have been reports of widespread rashes, subsequent bacterial or fungal skin infections, tissue death (necrosis), bowel obstruction, heart, lung, urinary, and neurological problems as severe symptoms of mpox.²⁶ Serious problems have happened in both immunocompromised and immunocompetent individuals, although immunocompromised individuals are more prone to experience them. The majority of those with severe mpox presentations for whom the CDC has been contacted have Human Immunodeficiency Virus (HIV) and CD4 counts below 200 cells/ml, indicating significant immunosuppression, according to the advice.³⁷

The ongoing 2022 mpox outbreak

In the 2022 outbreak, the mpox disease was reported by numerous non-endemic countries. The first case of mpox was reported by the United Kingdom Health Security Agency (UKHSA) in the United Kingdom.³⁸ Afterwards, cases of the illness were reported in Spain, Portugal, Italy, the United Kingdom, and the United States.^{39–48} Up to January 06, 2023, the Centers for Disease Control and Prevention (CDC) confirmed 84,075 mpox cases in 110 countries worldwide with 75 deaths,⁴⁹ and clinical research has shown that the disease has distinct epidemiological and clinical features.^{36,39,40,50} Statistics show that one-third of the reported cases were highly concentrated in the USA (the highest), Spain, Germany, and the UK.⁵¹ The mortality rate of this disease is less severe as investigation revealed that the MPXV genome involved in the current outbreak belongs to West African (clade II) strain, which is less virulent than the Central African clade also known as the Congo Basin (clade I) strain.⁵² The case fatality rate of the clade I and clade II strains of MPXV are documented to be 10.6% and 3.6% worldwide.^{53,54}

The demographic characteristics of reported cases distinguished from the previous outbreak were 99% male with a median age of 37 years, and 44% were HIV-positive.⁵⁵ Furthermore, 99% of reported cases were gay or bisexual,⁵⁵

indicating sexual transmission as a new mode of transmission.³³ Interestingly, Pluart *et al.* declared that mpox occurred among healthcare workers.⁵⁶ However, the protection of healthcare workers should be a top priority during this public health emergency.^{57,58} Scientists have espoused that the affected people represent the population who did not receive smallpox vaccination due to disease eradication, indicating its possible contribution to their susceptibility to mpox disease.^{59,60}

The WHO received its first reports of the 2022 global outbreak of mpox in May, and the number of confirmed cases has steadily increased (Figure 1). Since then, many of the earliest cases were found in people who had attended a Pride celebration for LGBT+ people from all over the world. This event served as a transmission hub that spread the disease throughout several different European countries. By the end of May 2022, however, locally acquired illnesses and community transmission had become the norm throughout all impacted nations. An epidemic of mpox was labeled a Public Health Emergency of International Concern by the WHO on July 23, 2022.^{3,26,27,62,63} Even though evidence is just starting to emerge, it is possible that mpox can present with more severe symptoms in immunocompromised adults than in the general population.^{64,65} The CDC found that among 57 patients hospitalized with severe mpox infection between August and October 2022, 90% had underlying immunocompromising diseases, including 31 people with HIV who had a CD4 cell count of fewer than 50 cells/mm. Among the most striking aspects of this report is the notably high fatality rate of 21%, with at least 5 deaths directly attributable to mpox.⁶⁶

Genital lesions have been reported as one of the distinguishing features of the current outbreak.⁶⁷ The majority of confirmed cases have reported to clinics with at least one symptom, including systemic rashes, fever, or genital rashes, which is not consistent with the typical presentation of mpox disease, which usually include centrifugal rashes preceded by fever and swollen lymph nodes.^{45,53} In addition, the number of rashes is less in most cases, with the first rash occurring in the genital and perineal area followed by monographic and centrifugal distribution all over the body.^{30,68} The other sites of lesions were as follows: 55% on the trunk, arms, and legs, 25% on the face, 10% on the palms and soles.³⁶ Most rashes (58%) were identified as vesiculopustular.³⁶

In the current outbreak, there is a disappearance of an epidemiological link to the endemic region.³³ Yet, data showed that 91% of confirmed cases reported an immediate sexual exposure before symptoms started, particularly with men having sex with men,³⁰ while 98% of the patients identified as gay or bisexual.³⁶ Therefore, WHO considered sexual exposure in the 21 days before symptoms onset as a risk factor,^{51,53} especially among men who have sex with other men. Evidence showed that all confirmed cases of mpox among men who have sex with other men have a history of sexually transmitted disease (STD), hepatitis C, syphilis, and HIV.⁴¹ Epidemiologists reported that the reproductive ratio value of MPXV is between 1.10 and 2.40, suggesting the ability of an infected individual to infect one to two other persons.⁶⁸ Such value highlights the need to initiate preventive measures to contain the spread of the disease.^{57,69,70}

Mpox: Cumulative confirmed cases, Mar 14, 2023

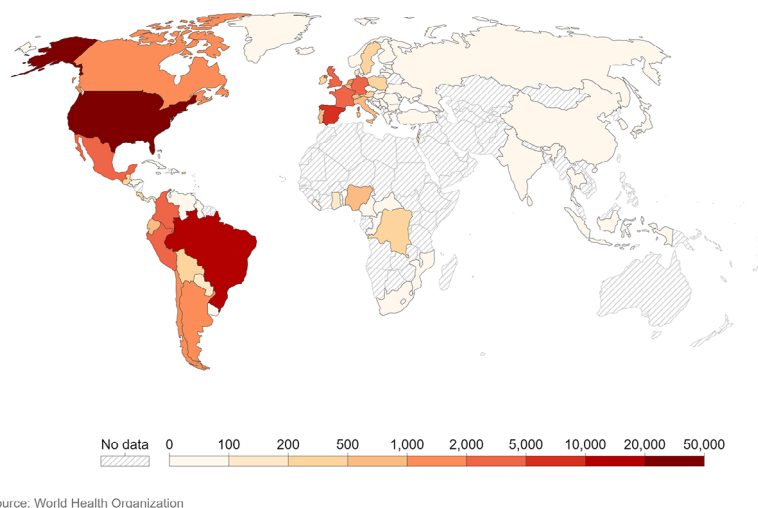


Figure 1. Geographical distribution of confirmed cases of mpox globally.⁶¹

Transmission and replication

The MPXV is considered one of the largest DNA viruses⁷² and its size ranges from 130 to 360 kbp.⁷³ It therefore stimulates the host immune system rapidly. The MPXV has two distinctive sets of modulatory proteins responsible for invading the immune system, including intracellular modulatory proteins and extracellular modulatory proteins. Another unique feature of MPXV is its exclusive replication in the cytoplasm.⁷³ The replication process of MPXV starts with viral attachment initiated by glycosaminoglycans including chondroitin, heparin sulfates, and laminin,⁷⁴ followed by viral fusion to the host cell involving 11 to 12 non-glycosylated, transmembrane proteins.⁷⁵ Once the viral entry is complete, viral transcription takes place by virus-encoded multi-subunit DNA-dependent RNA polymerase.⁷⁶ It is proceeded by the translation of proteins on the host ribosome, which occurs at three levels: early, intermediate and late translation.⁷⁶ Studies reveal that DNA synthesis and replication occur at cytoplasmic structures called factories,²⁰ proving its effectiveness in viral RNA synthesis.⁷² Each factory derives from the cell's rough endoplasmic reticulum (RER).⁷⁷ Lastly, some of the mature virions transported via microtubules and coated by endoplasmic reticulum or Golgi-derived membranes will exit the cell by fusing with the cytoplasmic membrane and become extracellular enveloped virus (EEV).⁷⁸

The orthopoxviral physical stability contributes to their varied modes of transmission.⁵² The mpox information chain includes animal-to-human transmission and human-to-human transmission. Since the virus is present in the infected host lesions, crust, and secretions, direct contact with these secretions can promote viral transmission, whether the host is animal or human. Animal to human transmission occurs when there is direct contact with the bodily fluids of affected animals, such as blood, saliva, and cutaneous and mucosal lesions of these animals. Furthermore, respiratory droplets and eating raw meat or poorly cooked meat products of affected animals can transmit the MPXV. Another transmission mode includes the bites and scratches caused by infected animals.⁷⁰ Monkeys, rats, and squirrels are the primary host of MPXV in Africa.⁵⁸

The source of MPXV has not been determined, however rats are a leading possibility. Consumption of raw or under-cooked meat or other animal products from infected animals is a possible risk factor. Also, people who reside in or near forested areas may experience low-level or indirect exposure to sick animals. Direct or indirect contact with infected body fluids or lesion materials can result in transmission of mpox, despite the disease's low transmissibility. Fomites, respiratory secretions, and skin-to-skin contact are all examples of direct exposure in the context of MPX. Patients can be exposed to you through indirect contact if you are in their room or within 6 feet of them during procedures that may produce aerosols from oral secretions, skin lesions, or the resuspension of dry exudates. Intimate contact during and after childbirth is another potential route of transmission, as is the placenta (resulting in congenital mpox).^{3,27} The virus replicates at the site of infection, where it was initially detected by mononuclear phagocytic cells after infection. Afterwards, it leaves the skin and circulates through the body before returning to the dermal layer. Once the virus has completed its initial round of replication, it spreads to nearby lymph nodes, resulting in viremia 10–14 days later (the possible incubation period). Nonspecific prodromal symptoms such as fever, chills, myalgia, headache, fatigue, and lymphadenopathy typically occur before the hallmark clinical manifestation of a vesiculo-pustular rash. It is important to note that patients are contagious from the onset of prodromal symptoms until the scabs that formed over the lesions peel off. The oropharynx is typically the first area affected, followed by the skin.^{26,79}

Similarly, transmission from human to human occurs when there is direct contact with an infected person's rashes, sores, scabs, respiratory droplets, or oral fluids.^{51,53} Furthermore, sharing the same household of infected individuals increases the risk of contamination.⁷⁰ The common mechanism used by MPXV in the 2022 outbreak is attacking the host defense by encoded proteins produced during transcriptions named MHC class II antigen presentation inhibitor, an IFN-alpha/beta receptor glycoprotein and IL-1/TLR signaling inhibitor.⁸⁰ Moreover, vertical transmission, such as from mother to fetus, was also identified.⁸¹ Another unique feature that contributed to the current outbreak is the excessive genome mutations that result from the action of apolipoprotein B mRNA-editing catalytic polypeptide-like 3(APOBEC3) enzymes.⁸⁰ The action of these enzymes results in hypermutated, viable variants of the virus as revealed by phylogenomic analysis.⁸⁰

Immunosuppression

The immune system plays a vital role in defending the body against microorganisms and other foreign bodies.⁸² Failure of the immune system to protect the body indicates the body's immunosuppressed status. Immunosuppression is defined as "a state of temporary or permanent dysfunction of the immune response resulting from insults to the immune system and leading to increased susceptibility to disease", originally proposed by Dohms and Saif in 1984.^{83,84} Immune dysfunction is classified as primary and secondary immune dysfunction. The immunosuppression status occurs due to disease condition or medication-induced immunosuppressed state. Consequently, hematologic malignancies, solid-organ transplant, chimeric antigen receptor (CAR)-T-cell therapy, or hematopoietic stem cell transplant are all common causes of

immunosuppression, as are moderate to severe levels of immunodeficiency disease, such as DiGeorge syndrome, Wiskott-Aldrich syndrome, HIV cases with CD4 cell counts less than 200/mm³, and the history of an AIDS-defining illness without immune recrudescence. The degree of immunosuppression can vary among patients.⁸⁵ Furthermore, medication that induces immunosuppression status includes high-dose corticosteroids (i.e., ≥20 mg of prednisone for two or more weeks), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, tumor necrosis factor (TNF) blockers, and other biologic agents that are immunosuppressive or immunomodulatory. Evidence has shown a steady rise in the number of acquired immunity deficiency (secondary immunodeficiency) conditions in response to an increasing number of individuals with transplantation of solid organ or hematopoietic stem cells⁸⁶ as such medical treatment requires an intensive immunosuppressive regimen which can cause the patient to develop severe adenovirus infections.⁸⁶ A US cross-sectional study revealed that 2.8% of patients experienced drug-induced immunosuppression between 2018 and 2019, particularly those who were prescribed oral corticosteroids for 30 days or longer (40.9%).⁸⁷ Oral corticosteroids, methotrexate, and other disease-modifying anti-rheumatic therapies, transplant antirejection drugs, tumor necrosis factor inhibitors, antineoplastic treatments, and other biological product medications all contribute to immunosuppression.⁸⁷ Immunosuppressive medication has a significant role in patient survival such as keeping a person from rejecting an organ transplant and treating the overactivity of the immune system in cases like autoimmune disease and allergies. On the other hand, immunosuppressant medication can negatively impact a patients' health as it increases their likelihood of having infections.⁸⁸

The most commonly reported infection among immunocompromised patients is a protracted infection characterized by the intra-host viral evolution and the generation of multiply mutated viruses.⁸⁸ The common form of protracted infection is protracted bacterial bronchitis which occurs among children.⁸⁹ In addition, other types of infections associated with immunosuppression are viral, bacterial, and fungal infections of the blood, lungs, and central nervous system.⁹⁰ Furthermore, the immunocompromised status might increase patients' susceptibility to prolonged infection, resulting in a prolonged length of stay in hospital and more complications.⁹¹ Studies on immunosuppressed patients' response to infection vary in terms of mortality rate, complication, and length of stay. For example, authors of a study conducted in Spain among immunocompromised patients admitted with Influenza A (H1N1) virus in 2009 reported that immunocompromised patients had higher mortality than non-immunosuppressed individuals.⁹² In addition, the complicated cases experienced a bacterial coinfection, specifically gram-negative bacilli and *Staphylococcus aureus* infections.⁹² Inversely, a retrospective cohort study in the U.S. in 2020 was conducted on the impact of COVID-19 on drug-induced immunosuppressed patients. It revealed that the chronic use of immunosuppressive drugs was neither associated with worse nor better clinical outcomes among hospitalized cases with COVID-19 in terms of the risk of using mechanical ventilation, in-hospital mortality, or length of stay.⁹³ Similarly, another study revealed that immunosuppressed patients infected with COVID-19 are not at increased risk of severe pulmonary disease compared to other populations, highlighting the necessity of continuing patients' treatment, such as chemotherapy and radiotherapy.⁹⁴ The controversial condition of immune suppression was pregnancy. There was a debate regarding pregnancy being considered an immunosuppression state.⁹⁵ However, the authors highlight that the susceptibility of pregnant women to infection depends on the placental immune response to certain pathogens.^{95,96}

Monkeypox in immunosuppressed patients

According to studies, there is a greater chance of severe manifestation of MPXV infection in immunosuppressed patients.^{50,97-106} Immunosuppressed patients include patients who have undertaken cancer treatment, organ transplant, HIV infection, primary immune deficiency disorders, some severe autoimmune disorders, and medications to treat autoimmune diseases and other illnesses that can weaken the immune system. The disease appears to have a lethal prognosis, especially in children who have not been vaccinated against smallpox.⁹⁷ Individuals with compromised immune systems include those with HIV, hematological malignancies, usage of immunosuppressive medicines such corticosteroids, organ transplant patients, autoimmune illness, or innate immunodeficiencies.

A CDC investigation of 57 people hospitalized with severe mpox showed a substantially more dismal natural history among immunocompromised persons. Around 90% of people had CD4 counts 200 cells/mm³, and roughly 70% had CD4 levels 50 cells/mm³. Less than 10% of people were getting antiretroviral therapy. Just about 5% of patients had undergone a solid organ transplant, and another 3.5% had been diagnosed with a hematologic malignancy. Severe mucosal lesions were present in the majority of patients, and all of them had severe skin lesions. In addition, mpox often spread to other organs, affecting the lungs (21%), eyes (7%) and brain (7%). Patients were treated with tecovirimat (93%), vaccinia immune globulin intravenous (51%), or cidofovir (23%), all of which are antivirals that target mpox. Certain mpox lesions may persist even when treated with antivirals, as evidenced by two patients' individual stories. The most alarming statistic is that 21% of patients who were treated in the intensive care unit ultimately died, with 5 out of 12 deaths being directly attributed to mpox.^{36,107,108} These results paint a bleak picture of the prevalence and lethality of mpox in immunocompromised patients, who, in contrast to immunocompetent persons, are unable to mount a neutralizing IgG

and poxvirus-specific Th1 response after infection.³ Two case reports, one from a patient receiving cytotoxic chemotherapy for Hodgkin's lymphoma and the other from a patient who had undergone a kidney transplant in the context of well-controlled HIV, are published in the current edition of *Transplant Infectious Diseases*. Both patients were guys who engage in anal intercourse with other men and who did not use any form of barrier protection in the weeks leading up to the development of lesions. Large, disfiguring, and necrotic face lesions progressed in the lymphoma patient despite the early use of tecovirimat to combat the disease. When his lesions progressed, he was also given tecovirimat, cidofovir, and vaccinia immune globulin intravenous for 28 days (instead of the usual 14). The kidney transplant recipient contracted mpox despite having received a smallpox immunization as a child, indicating that the vaccine's protective effects had worn off. In response to his over 50 lesions, he was started on tecovirimat 12 days after the onset of symptoms and treated for a total of 14 days. There was at least one lesion that appeared while he was on tecovirimat and tested positive for orthopoxvirus even after treatment ended; resistance testing is currently underway. The pictures of the recovered patients show that the cancer patient's disease progressed significantly more severely than the kidney transplant patient's, despite the fact that both patients survived. This finding likely reflects the kidney transplant recipient's reduced net state of immunosuppression, given he had received his transplant 5 years prior to his illness, had not experienced any rejection episodes recently, and was only taking low doses of tacrolimus and azathioprine. Both these instances demonstrate the diversity of this infection's clinical presentation in immunocompromised patients and the difficulties in controlling them in the absence of more information.⁴ Although over 80000 instances of mpox have been diagnosed globally, including over 29000 in the United States, there is a lack of data from randomized controlled trials (RCTs) of antiviral medication.¹⁰⁷

The immunocompromised patient is more liable to get the mpox infection with severe manifestations of mpox, including extensive skin rashes with secondary bacterial or fungal infections or necrosis, bowel blockage, and heart, lung, urinary, and neurological complications.^{42,60,100} Guarner *et al.* (2022)³³ reported that an immunosuppressed patient had several scattered maculopapular rashes and pustules on the trunk, upper and lower extremities, groin, and peri-anal area and palpable cervical lymph nodes. Moreover, immunocompromised patients are more likely to develop complications, including respiratory deterioration, acute kidney injury, and multiple organ dysfunctions.⁹⁷ Simon-Gozalbo *et al.* (2022)¹⁰⁹ reported a case of a 30-year-old male patient diagnosed with HIV infection. The manifestations were maculopapular rash affecting mainly the trunk, buttocks, upper and lower extremities, and multiple demarcated purpuric macules with central umbilicated pustules and crusts, along with palpable cervical lymph nodes.

Prevention strategies and counter-measures for immunocompromised individuals

Data on mpox in HIV patients are sparse; however, early identification, treatment, and prevention may lessen the severity of potential complications and slow the disease's transmission.⁹⁷ No licensed treatment or proper evidence-based guideline is available for treating human mpox. However, the viruses belonging to the *Orthopoxvirus* genus are genetically similar. Hence, antivirals used to treat smallpox might be effective against mpox. Antiviral drugs such as tecovirimat, cidofovir, and brincidofovir can be considered mainly for those with severe symptoms or who may be at risk of poor outcomes, such as those with immune suppression.¹¹⁰

Two anti-viral medications, tecovirimat and brincidofovir, have been given the green light by the Food and Drug Administration (FDA) to treat smallpox. The CDC offers tecovirimat for use in the treatment of mumps as a first-line agent. Co-administration of tecovirimat and antiretroviral therapy for HIV infection is safe because there are no known medication interactions that would prevent it. The JYNNEOS vaccination can be used for prophylaxis both before and after exposure if necessary. Although the European Medicines Agency (EMA) has given its approval for the use of tecovirimat in mpox, there is a need for innovative therapies with different mechanisms due to the danger of resistance. In terms of effectiveness and safety, tecovirimat is the drug of choice for treating mpox. Consequently, the accessibility and diversity of effective anti-*Orthopoxvirus* medicines will be improved through the target-based design of novel antivirals. Patients who did not show a response to tecovirimat run the risk of developing resistance. An immunocompromised HIV/AIDS patient was reported to have contracted mpox by Viguier *et al.* (2022).¹⁰² He had a serious, prolonged infection that was treated with tecovirimat for 14 days after his clinical status deteriorated. Almost immediately, he began to feel better, and both the skin lesions and MPXV burdens dropped with no negative consequences. In this instance, tecovirimat shows promise as an effective treatment. The success of tecovirimat in this patient suggests that it may be used to treat other immunocompromised people who have contracted MPXV. Hernandez *et al.* (2022)¹⁰⁰ reported a case study about an immunocompromised patient and treated him with tecovirimat. Tecovirimat could effectively and safely treat severe mpox infections among immunocompromised patients. Last but not least, there is an immediate need to focus on minimizing psychological distress, particularly among immunocompromised individuals and healthcare workers.^{111–113} An overview of mpox in immunosuppressed patients, preventive measures and clinical management is presented in [Figure 2](#).

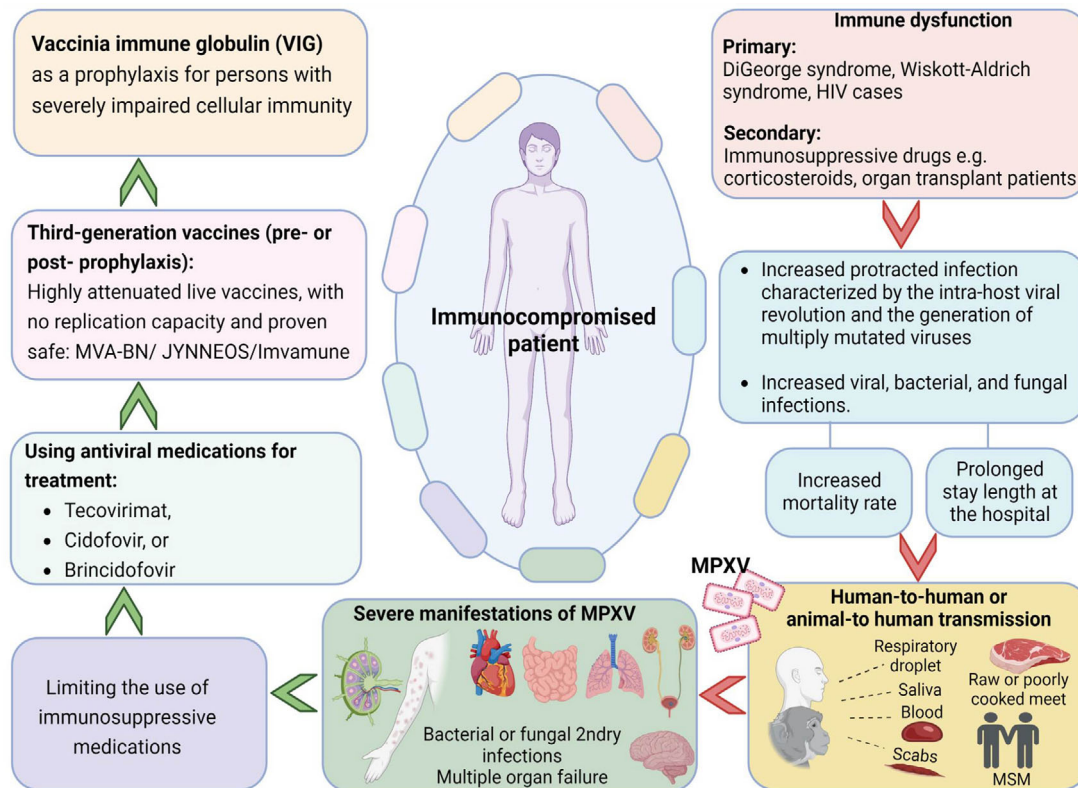


Figure 2. An overview on monkeypox in immunosuppressed patients, prevention and clinical management (Designed with Biorender premium software; <https://app.biorender.com/>).

Patients with immune impairment run the risk of contracting serious illness. As a result, efforts should be undertaken to strengthen their immune system in addition to using tecovirimat (e.g., limiting the use of immunosuppressive medications, initiating antiretroviral therapy for those with HIV). Following a tecovirimat 14-day therapy, certain individuals with significant immunocompromise may continue to develop lesions.¹¹³ If viral resistance is suspected in this situation, physicians may think about sending a second swab for sequencing. As long as there is no sign of viral resistance, it is reasonable to continue tecovirimat (with emphasis on the need for a fatty meal for optimal absorption) until there is clinical improvement, but no longer than 90 days.¹¹⁵ In contrast, if there is sign of viral resistance, a second anti-viral medication, such as cidofovir (or brincidofovir, if it becomes available), can be added. An infectious disease expert or public health official should be consulted for the management of such patients (e.g., the CDC mpox consultation team in the United States.^{32,35,70,110}

Prevention is essential for the immunocompromised patient to protect them from infection. There are two types of vaccines: second and third generation. Second-generation vaccines called replication-competent vaccinia virus vaccines due to their replication capacity in mammalian cells (examples include ACAM2000 and APSV approved for >18 years old) are associated with complications among immunocompromised patients.¹¹⁶ This type of vaccine is not recommended for any group of immunosuppressed patients, especially those with inflammatory/autoimmune diseases of the central nervous system where there can be an outbreak of the disease. Third-generation vaccines, for example, MVA-BN/ JYNNEOS/Imvamune, are highly attenuated live vaccines. In contrast to replication-competent smallpox vaccines, these replication-deficient vaccinia vaccines pose a lower risk of side effects, making them suitable for use in healthy people as well as those with immune system deficits, HIV infection, atopic dermatitis, or allergic rhinitis. However, those with compromised immune systems may not respond as well to the vaccine.^{117,118} The vaccination of those with immunosuppression, who are at high risk for developing mpox sequelae, should proceed with a 0.5 ml SC/IM dose. People living with HIV whose CD4 count is greater than 200 cells/mm³ can get MVA-BN through intradermal administration.¹¹⁹

JYNNEOS (also known as Imvamune and Imvanex) is a vaccine against a modified Vaccinia Ankara virus that does not replicate. In the US, it was approved for use in preventing both mpox and smallpox.¹¹⁰ Because JYNNEOS does not cause the development of live viruses in vaccinated patients, it is safer for use in immunocompromised individuals than ACAM2000. Importantly, however, immunocompromised persons may have a lower immunological response to the

JYNNEOS vaccination. Thus, protection can be weaker than in immunocompetent people. Both vaccines can legally be administered to those aged 18 and up. However, information on JYNNEOS's ability to protect humans from MPXV infection is scant.^{32,53,121} There is a lack of information regarding the efficacy of vaccinia immune globulin (VIG) in the treatment of mpox sequelae. In severe cases of human mpox, VIG may be considered, albeit its efficacy is uncertain. In the case of an exposed person with significantly compromised cellular immunity, for whom smallpox vaccination is not an option, VIG may be considered as a prophylactic measure.¹

Evidence from other immunosuppressive diseases suggests that people with HIV who are getting antiretroviral medication and have healthy CD4 cell counts are not at elevated risk for most infections, including opportunistic infections like mpox. The approved first-line treatment for mpox is tecovirimat, and clinicians should consider taking this drug when determining a patient's risk of serious illness due to both HIV and mpox. Tecovirimat and antiretroviral therapy can be used together, if necessary, because of the low risk of medication interactions. Pre- and post-exposure prophylaxis with a mpox vaccination are options that clinicians should consider. The JYNNEOS vaccine, which is licensed for the protection of smallpox and mpox, is recommended for patients with HIV since it uses a live, nonreplicating modified vaccinia Ankara virus.^{25,122}

To sum up, the 85% efficacy offered by cross-immunity means that the current smallpox vaccinations are also licensed for mpox. However, before recommending or not vaccinating immunosuppressed patients, it is essential to be well informed of the type of vaccine that local authorities are obtaining. If it is a second-generation live attenuated vaccine, these patients should not receive it. If it is a third generation live attenuated vaccine with no replication capacity and proven safe in immunosuppressed patients. In that case, vaccination should be advised, always considering that the underlying disease should not be active at the moment of the inoculation.^{2,123}

However, new cases are still expected to be discovered, especially in low-income countries with limited access to diagnosis, treatment, and prevention, and where a large percentage of the mpox-infected population also has advanced HIV infection. Thus, further research is always needed to determine the best way to treat mpox in immunocompromised people. First, it is crucial that all occurrences of mpox infection in immunocompromised individuals continue to be recorded so that we may learn more about mpox's ability to spread and kill in this patient population. To further define the host immune response to mpox in patients with and without underlying immunodeficiency, the duration of viral infectivity, and the prevalence of treatment-emergent resistance, all providers caring for immunocompromised patients with mpox infection in settings where resources are available should attempt to enroll these patients into biorepositories.¹²⁴ Third, there is a need for prospective research to determine appropriate therapeutic approaches of immunocompromised patients with mpox, including treatment duration and the impact of combination antivirals. While a randomized controlled trial (RCT) of tecovirimat for mpox infection is currently being conducted with funding from the National Institutes of Health (NIH) (NCT05534984), the declining number of mpox cases worldwide makes it unlikely that RCTs focusing solely on immunocompromised patients will ever be conducted. Similar to the feasibility of conducting trials of cidofovir, brincidofovir, vaccinia immune globulin intravenous, or combinations thereof, their implementation is highly improbable. Thus, any application of tecovirimat should be documented as part of observational research to fill this data vacuum, whether through currently established procedures or once the NIH-sponsored trial (hopefully) proves clinical efficacy. Fourth, further information is needed on the safety and immunogenicity of the smallpox and monkeypox, non-replicating vaccine (JYNNEOS), notwithstanding the fact that clinical efficacy trials of this vaccine cannot be undertaken in immunocompromised persons. In the same way as COVID-19 vaccination data were generated by academic medical centers, so too should JYNNEOS data about the safety and immunogenicity of the vaccine in immunocompromised individuals.^{4,108,122}

Conclusion and future prospects

Immunotherapeutics and preventative strategies are critical public health interventions that complement rigorous contact tracing in stopping the spread of mpox. In a similar manner, serology-based investigations are effective surveillance tools for tracing contacts and determining exposure histories. However, given that vaccination provides a baseline of protection against poxviruses, these serological diagnostic approaches must be MPXV-specific. Expanding the surveillance network and identifying gaps are also crucial for an efficient ring-fencing system. Importantly, there is a fundamental need in public health to alert individuals who may be exposed about the advantages and hazards of vaccination.

Numerous important scientific queries are yet unanswered. The mechanisms of immune defense against the MPXV will need to be better understood, which will necessitate more research on the human systemic and mucosal immune responses during MPXV infection. It is significant to note that it is not yet known whether previous exposure to variola, mpox, or smallpox vaccine results in any type of mucosal immunity. Understanding the mucosal immune responses will be critical due to the respiratory aerosol transmission of MPXV and other poxviruses. To further understand the respiratory

difficulties produced by MPXV, it would be especially necessary to understand the functions of tissue-resident memory T cells and IgA in infection. Because MPXV DNA has been detected in semen, it is also necessary to define the immunity of the preputial mucosa. A key objective for assessing more recent vaccines, particularly those intended for the at-risk populations of immune compromised populations such as older people, pregnant women and children, is defining the immunological correlates of protection. What other factors, such as those related to behavior, geography, nutrition, health, immunology, or genetics, besides not having received a vaccine, could be at play? Recent research suggests that the severity of a viral respiratory infection in young children is tied to the efficiency of their innate immune responses. Children who are infected typically have weaker T cell and B cell responses than adults, similar to reports for SARS-CoV-2 infections. Children with MPXV tend to manifest a more severe disease and have lower vaccine effectiveness, which may be explained by the characterization of adaptive immune responses in these children. Understanding the risks of vaccination in immunocompromised populations, particularly children and expectant women, is also crucial.

It is feasible for MPXV to co-infect with any of the several infectious diseases that are endemic at global level. A co-infection with malaria and an alphavirus, for instance, can drastically alter host immunity and influence the course of an illness. Co-infection with other illnesses that disproportionately affect the group of men who have sex with men makes it especially important to understand mpox disease and immunization, especially given the continuous transmission among these communities in non-endemic countries. This is especially true for HIV-1, which can significantly inhibit adaptive immune reactions. Additionally, it is important to identify the risk factors for severe MPXV. The most vulnerable groups are known to be unvaccinated people, pregnant women, and young children. Other immunocompromised populations, such as older people, those using long-term drugs, and those with underlying metabolic illnesses that may exhibit the disease in a different way, also need to be characterized though.

Patients, including immunocompromised humans such as geriatric patients or babies born to mothers infected with MPXV should be closely monitored for the development of chronic health problems. The Zika virus epidemic provided evidence that children who were exposed to the virus in utero may be at risk of developmental issues later in life.¹²⁵ Evidence suggests that just 25% of pregnant women infected with MPXV would be successful in giving birth¹²⁶; there should be a higher priority placed on this area of research. Furthermore, infants and young children appear to be more vulnerable to severe mpox.^{127,128} Data on fetal development after congenital MPXV infection are currently missing. The ability to determine whether MPXV infection can have long-term repercussions, as was seen after SARS-CoV-2 infection during the current pandemic, would also be made possible by longitudinal surveillance of patients with the MPXV.

Because mpox has not previously been documented in many countries, there is a lack of clinical experience with the infection, inadequate diagnostic resources, an unclear illness course, and an incomplete understanding of both therapeutic and preventative approaches. Physicians should keep a high index of suspicion for this disease, record cases according to protocol, and isolate them to reduce public worry and misinformation. Even though the disease in the nonendemic nations has garnered international attention, it is in Africa that the vast majority of new cases and fatalities have been reported. To avoid making the same mistake in the future, we must not overlook neglected tropical diseases. Nowadays, when the world is so interconnected, the phrase “no one is safe unless everyone is safe” rings especially true. There is a need for more study into the length of mpox treatment and the efficacy of antivirals.

The scientific community needs to rapidly gather data, especially in extremely vulnerable communities that are unlikely to be included in clinical trials, as this second worldwide pandemic in as many years demonstrates the need for more strong infrastructure for diagnosis, treatment, and prevention. Many more pandemics are likely to strike within our lives. Well coordinated multicenter networks, with early backing from the Centers for Disease Control and Prevention, the Food and Drug Administration, and the National Institutes of Health, are necessary for generating evidence while simultaneously delivering clinical care. Local IRBs at individual hospitals should be consulted on the feasibility of rapid observational data gathering, and hospitals as a whole should work together to develop uniform guidelines for the prospective collecting of data in advance of any potential pandemic. These methods could speed up our understanding of how to deal with new infectious risks in immunocompromised individuals, which would be especially useful given the time lags experienced in responding to COVID-19 and mpox.

Data availability

No data are associated with this article.

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 **Jawad Basit** 

Department of Medicine, Rawalpindi Medical University, Rawalpindi, Pakistan

The recent revisions by the authors have added quality to the paper. The authors have incorporated all the feedback in the revised manuscript. This article would be a clinically relevant addition to the existing literature on the given topic. My final verdict is 'Accept'. No minor or major revisions are required.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Cardiology, Novel infections, Malignancies and hematology, gastroenterology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 18 April 2023

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 **Dattatreya Mukherjee**

International School, Jinan University, Guangzhou, China

Authors have updated the manuscript as per my review comments.

All my review comments are addressed. Thanks to all the authors for updating the manuscript as per my review comments. Also, thanks to the editor for selecting me as a reviewer.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Public Health, Infectious Disease

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 13 April 2023

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Osaretin Okonji 

School of Pharmacy, University of the Western Cape, Cape Town, South Africa

The authors' revision have improved the manuscript. The update and the additional information makes the review article more relevant. There are still minor edits issues in the manuscript, so I recommend that the authors closely evaluate for these. I suggest proper editing of the manuscript. Below are few issues and editing issues.

Third paragraph under transmission and replication: 'The source of MPXV has not been determined, however rats are a leading possibility'

- The authors' should revised for clarity, stating that the evidence of mpox virus infection has been observed in animals including rats, squirrels, monkeys.....

Prevention strategy section

- Paragraph 5, please revised 'up' for clarity- those aged 18 and up.

Immunosuppressed patients

- Second paragraph: Please put the reference - A CDC investigation of 57 people.....

"Sexual contact was suspected as the mode of transmission in 95% of the 528 instances of mpox reported, with 98% of patients being gay or bisexual men. There were no fatalities, although 13% of patients needed hospitalization due to discomfort; a few patients needed hospitalization due to visual lesions, decreased oral intake, myocarditis, or acute kidney disease. The majority of patients exhibited a rash upon presentation, with the majority having less than 10 lesions and 11% having more extensive lesions. Patients had a 41% HIV infection rate, but after receiving antiretroviral medication, their viral loads dropped to undetectable levels. Most importantly, no coexisting immunocompromising diseases were observed, indicating that this is an immunologically healthy group."

- Please include a reference, and indicate where this result came from, is it a global report or CDC, or WHO... for clarity.

"bedding or towels—are some of the main ways that viruses are spread."

- please be more specific here 'that viruses' do you mean mpox virus

Third paragraph under. Transmission: "Patients can be exposed to you through indirect contact if you are in,,"

- Please be specific for clarity

"Repetition of consumption of raw meat, body fluids....." in the second and third paragraph in the transmission and replication.

- Succinctly join the 2 paragraph as 1.

"A CDC investigation of 57 people hospitalized with severe mpox showed a substantially more dismal natural history among immunocompromised persons. Around 90% of people had CD4 counts 200 cells/mm³, and roughly 70% had CD4 levels 50 cells/mm³. Less than 10% of people were getting antiretroviral therapy. Just about 5% of patients had undergone a solid organ transplant, and another 3.5% had been diagnosed with a hematologic malignancy. Severe mucosal lesions were present in the majority of patients, and all of them had severe skin lesions. In addition, mpox often spread to other organs, affecting the lungs (21%), eyes (7%) and brain (7%). Patients were treated with tecovirimat (93%), vaccinia immune globulin intravenous (51%), or cidofovir (23%), all of which are antivirals that target mpox. "

- This please write succinctly only important details relevant to this report and add reference.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Version 1

Reviewer Report 21 February 2023

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Dattatreya Mukherjee

International School, Jinan University, Guangzhou, China

Thank You for Giving me the opportunity for reviewing the manuscript. This is a very nicely described article. My comments are given below:

1. Introduction is written in detail. In the introduction please add about the MPOX in immunocompromised patient (in short). If there is any published cases on it, then authors can write it in short in the introduction part.
2. "The first case of Mpox was reported by the United Kingdom Health Security Agency (UKHSA) in the United Kingdom." Please add a reference.
3. An image of mechanism can be added at Transmission and replication part. (Pathophysiology).

4. In Ongoing MPXV outbreak 2022 part, one image of world map can be added with the color differentiation of cases.
5. In HIV, can we see CD4 count before injecting the vaccine? In that case, in what CD4 count, we can give vaccine? Is there any study on it? If not this paper can recommend this idea for the future. (If authors support my concept of CD4).
6. Conclusion and future aspects are written very well.
7. The paper has a good discussion on Mpox Vaccine. If authors agree my idea about CD4, can add as a recommendations
8. Is it possible to have an info graph on the topic? The Clinicians will get to know the treatment procedure quickly in ward. Like if an immunocompromised patient got admitted with Mpox. How the treatment should be given. What are the drug of choices. PCR is the test of Choice, please add that also in the management and info graph parts.

This is a nicely written and detail review on this topic. Information are written nicely with proper citations. This is a much needed discussion and the paper has filled that void successfully. This paper will be very much helpful for the scientific societies.

Is the topic of the review discussed comprehensively in the context of the current literature?

Yes

Are all factual statements correct and adequately supported by citations?

Yes

Is the review written in accessible language?

Yes

Are the conclusions drawn appropriate in the context of the current research literature?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Public Health, Infectious Disease

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 23 Mar 2023

Sirwan Ahmed

This is a nicely written and detail review on this topic. Information are written nicely with proper citations. This is a much-needed discussion and the paper has filled that void successfully. This paper will be very much helpful for the scientific societies.

Answer: Authors are very thankful to the reviewer for devoting time for improving the quality of the manuscript. The inputs and suggestions from the reviewer have been taken under consideration and have been implemented in the manuscript.

1. Introduction is written in detail. In the introduction, please add about the MPOX in immunocompromised patient (in short). If there is any published cases on it, then authors can write it in short in the introduction part.

Answer: The authors have carefully revised 'Introduction' section as per the suggestions of reviewer.

2. "The first case of Mpox was reported by the United Kingdom Health Security Agency (UKHSA) in the United Kingdom." Please add a reference.

Answer: The appropriate reference (as given below) is added, as suggested by reviewer. Ward T, Christie R, Paton R S, Cumming F, Overton C E. Transmission dynamics of monkeypox in the United Kingdom: contact tracing study BMJ 2022; 379 :e073153 doi:10.1136/bmj-2022-073153

3. An image of mechanism can be added at Transmission and replication part. (Pathophysiology).

Answer: The authors have revised the manuscript. However, the pathophysiology is still unknown accurately.

4. In Ongoing MPXV outbreak 2022-part, one image of world map can be added with the color differentiation of cases.

Answer: The authors have carefully revised as per the suggestions of reviewer.

5. In HIV, can we see CD4 count before injecting the vaccine? In that case, in what CD4 count, we can give vaccine? Is there any study on it? If not this paper can recommend this idea for the future. (If authors support my concept of CD4).

Answer: The authors have carefully revised as per the suggestions of reviewer.

6. The paper has a good discussion on Mpox vaccine. If authors agree my idea about CD4, can add as a recommendations

Answers: Whatever scientific literature is available in the databases have been added.

7. Is it possible to have an info graph on the topic? The Clinicians will get to know the treatment procedure quickly in ward. Like if an immunocompromised patient got admitted with Mpox. How the treatment should be given. What are the drug of choices. PCR is the test of Choice, please add that also in the management and info graph parts.

Answer: Dear reviewer, Thanks again for your kind suggestion. We described this information in the figure 2.

Competing Interests: None

Reviewer Report 13 February 2023

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Osaretin Okonji

School of Pharmacy, University of the Western Cape, Cape Town, South Africa

The abstract section looks quite vague. Some more explicit details are necessary

- Please the first 2 sentences in the abstract should be revised and get straight to the point about mpox global outbreak that started in 2022 putting immunocompromised individuals at increased risk.
- Please be consistent- use mpox the new recommended name by the World Health Organization (WHO) in the whole of the manuscript.
- Please remove the symptoms of mpox in the abstract, move to the introduction section or delete. 'The documented severe signs of monkeypox include widespread rashes with secondary fungal or bacterial skin infections or tissue death (necrosis), intestine obstruction, and difficulties with the heart, lungs, urinary system, and nervous system'.
- It will be good to revise this sentence to: We discussed /reviewed the mpox clinical presentation, available treatment options and current preventive guidelines in immunocompromised patients. 'The current article goes into great detail about monkeypox disease occurring in immunocompromised patients and preventive guidelines'.

Introduction

- First sentence: please use the new name recommended by WHO, which is mpox
- Please include that WHO has recommended the name mpox to reduce negative stigma linked with the previous name.
- Please include the incubation period of mpox 5–21 days in the first paragraph.
- It will be good to describe the recent outbreak of mpox in 2022 in that first paragraph, but I noticed overlapping of the symptoms of mpox in the abstract and in the other section of the manuscript.
- Please start a new paragraph about the epidemiology of mpox- 'The epidemiological history of the mpox revealed that...
- In the epidemiology of mpox please include clade 1 and clade 2 strain.
- The second paragraph in the introduction is not necessary, please delete or move below-
- This first paragraph should also highlight the importance of the review- since there are very few reviews conducted on mpox in immunosuppressed patients.

The ongoing 2022 mpox outbreak

- First paragraph, the authors should update the viral strain that are now referred to clade 1 and 2 to be consistent with the World Health Organization recommendation. Also include the case fatality rate of 10.6% for clade 1 and 3.6% for clade 2.
- Second paragraph: please include clinical characteristics of the recent mpox outbreak such as HIV infection, sexual transmitted disease

Transmission and replication

- Last paragraph should be moved to the ongoing 2022 outbreak of mpox section and the repetition----- mpox among gays, men to men sex should be taken out.
- Immunosuppression section is not necessary, I suggest it can be briefly written or taken out.

Monkeypox in immunosuppressed patients

- Please update monkeypox to mpox
- Also state detailed information of clinical presentation of mpox among immunosuppressed individuals with regards to the recent outbreak in 2022. This information you can get from CDC website.
- Second paragraph- Please move to prevention and treatment section
- Last paragraph- Please add more studies that have reported the clinical presentations of mpox among immunosuppressed patients, include CDC published findings and other studies from Europe, there are many studies, this is to improve this section because it is an important area of this paper.

Management and prevention

- The title needs to be revised: Please change to prevention strategies and countermeasures for immunocompromised individuals.
- Please include- creating awareness of the risk factors and educating people about the measures they need to take to reduce exposure to mpox- which is the main prevention strategy for mpox.
- Please move the fourth paragraph to the first paragraph, it should be placed at the first line after prevention strategy.
- Third paragraph- 'In conclusion- please revise
- The fifth paragraph should be moved to the first and second paragraph.

Conclusion and future prospect

- Please indicate further research needed to determine the efficacy of antivirals and also the duration of mpox treatment.
- Please include mpox vaccine efficacy -is necessary to understand the current vaccine efficacy among immunocompromised individuals from the recent vaccination
- Please indicate clinical trials that are currently ongoing for mpox particularly if there is any one for immunocompromised individual's
- The importance of equitable global distribution of mpox countermeasures and high burden regions/countries should be prioritized.
- Please the conclusion should be succinctly written, and focus should be on the topic.

Is the topic of the review discussed comprehensively in the context of the current literature?

Yes

Are all factual statements correct and adequately supported by citations?

Yes

Is the review written in accessible language?

Yes

Are the conclusions drawn appropriate in the context of the current research literature?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Infectious diseases

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 23 Mar 2023

Sirwan Ahmed

Authors are very thankful to the reviewer for devoting time for improving the quality of the manuscript. The inputs and suggestions from the reviewer have been taken under consideration and have been implemented in the manuscript.

The abstract section looks quite vague. Some more explicit details are necessary
Answer: The authors have revised the abstract and have made it more updated as well as precise, as suggested by the reviewers.

Please the first 2 sentences in the abstract should be revised and get straight to the point about mpox global outbreak that started in 2022 putting immunocompromised individuals at increased risk.

Answer: The authors have revised the abstract and have made it more updated as well as precise, as suggested by the reviewers.

Please be consistent- use mpox the new recommended name by the World Health Organization (WHO) in the whole of the manuscript.

Answer: The authors have incorporated the suggestion of reviewer throughout the manuscript.

Please remove the symptoms of mpox in the abstract, move to the introduction section or delete. 'The documented severe signs of monkeypox include widespread rashes with secondary fungal or bacterial skin infections or tissue death (necrosis), intestine obstruction, and difficulties with the heart, lungs, urinary system, and nervous system'.

Answer: The authors have revised the abstract, as suggested by the reviewers.

It will be good to revise this sentence to: We discussed /reviewed the mpox clinical presentation, available treatment options and current preventive guidelines in immunocompromised patients. 'The current article goes into great detail about monkeypox disease occurring in immunocompromised patients and preventive guidelines'.

Answer: The authors have revised the abstract, as suggested by the reviewers

Introduction

First sentence: please use the new name recommended by WHO, which is mpox

Answer: The mistake has been rectified by the authors.

Please include that WHO has recommended the name mpox to reduce negative stigma linked with the previous name.

Answer: The mistake has been rectified by the authors.

Please include the incubation period of mpox 5–21 days in the first paragraph.

Answers: The authors have revised the 'Introduction' section

It will be good to describe the recent outbreak of mpox in 2022 in that first paragraph, but I noticed overlapping of the symptoms of mpox in the abstract and in the other section of the manuscript.

Answer: The authors have rectified all these mistakes and updated the manuscript with best of the efforts.

Please start a new paragraph about the epidemiology of mpox- The epidemiological history of the mpox revealed that...

Answer: The authors have incorporated the suggestion of the reviewer.

In the epidemiology of mpox please include clade 1 and clade 2 strain.

Answer: The authors have updated the manuscript as per the suggestion of the reviewer.

The second paragraph in the introduction is not necessary, please delete or move below-

Answer: The authors have updated the manuscript as per the suggestion of the reviewer.

This first paragraph should also highlight the importance of the review- since there are very few reviews conducted on mpox in immunosuppressed patients.

Answer: The authors have updated the manuscript as per the suggestion of the reviewer.

Mention about the ongoing 2022 mpox outbreak

Answer: The authors have updated the manuscript as per the suggestion of the reviewer.

First paragraph, the authors should update the viral strain that are now referred to clade 1 and 2 to be consistent with the World Health Organization recommendation. Also include the case fatality rate of 10.6% for clade 1 and 3.6% for clade 2.

Answer: The authors have updated the manuscript as per the suggestion of the reviewer.

Second paragraph: please include clinical characteristics of the recent mpox outbreak such as HIV infection, sexual transmitted disease

Answer: The authors have updated the manuscript as per the suggestion of the reviewer.

Transmission and replication

Last paragraph should be moved to the ongoing 2022 outbreak of mpox section and the repetition----- mpox among gays, men to men sex should be taken out.

Answer: The authors have revised the manuscript and rectified the mistakes as per the suggestion of the reviewer.

Immunosuppression section is not necessary, I suggest it can be briefly written or taken out.

Monkeypox in immunosuppressed patients

Answer: Dear reviewer, we believe it is preferable to include this part; kindly accept our suggestion.

Please update monkeypox to mpox

Answer: The authors have rectified the mistakes as per the suggestion of the reviewer.

Also state detailed information of clinical presentation of mpox among immunosuppressed individuals with regards to the recent outbreak in 2022. This information you can get from CDC website.

Answer: The authors have revised the manuscript as per the suggestion of the reviewer.

Second paragraph- Please move to prevention and treatment section

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Please include- creating awareness of the risk factors and educating people about the measures they need to take to reduce exposure to mpox- which is the main prevention strategy for mpox.

Answer: The authors have revised the manuscript as per the suggestion of the reviewer

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Third paragraph- 'In conclusion- please revise

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Conclusion and future prospect

Please indicate further research needed to determine the efficacy of antivirals and also the duration of mpox treatment.

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Please include mpox vaccine efficacy -is necessary to understand the current vaccine efficacy among immunocompromised individuals from the recent vaccination
Please indicate clinical trials that are currently ongoing for mpox particularly if there is any one for immunocompromised individual's

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The importance of equitable global distribution of mpox countermeasures and high burden regions/countries should be prioritized.

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Please the conclusion should be succinctly written, and focus should be on the topic.

Answer: The authors have revised the manuscript as per the suggestion of the reviewer

Competing Interests: None

Reviewer Report 09 February 2023

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Jawad Basit

Department of Medicine, Rawalpindi Medical University, Rawalpindi, Pakistan

This literature review beautifully explains the recently discovered monkeypox infection in the context of immunocompromised patients. The article has given authoritative references for different figures and all the data has been comprehensively put forward and has a natural flow and coherence. The figure is well made and is up to mark. However, I would like to recommend to add more details on the underlying mechanisms of pathophysiological details in immunocompromised individuals. Moreover, the current epidemiological status of monkeypox needs to be more stressed in the introduction^{1,2,3}.

References

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Is the topic of the review discussed comprehensively in the context of the current

literature?

Yes

Are all factual statements correct and adequately supported by citations?

Yes

Is the review written in accessible language?

Yes

Are the conclusions drawn appropriate in the context of the current research literature?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Cardiology, Novel infections, Malignancies and hematology, gastroenterology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 23 Mar 2023

Sirwan Ahmed

Reviewer: 1

Comments to the Author

This literature review beautifully explains the recently discovered monkeypox infection in the context of immunocompromised patients. The article has given authoritative references for different figures and all the data has been comprehensively put forward and has a natural flow and coherence. The figure is well made and is up to mark.

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Answer: The authors have updated the manuscript using the information gathered from following references

References

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Competing Interests: None

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