Impact of Monkeypox virus on human health and its Epidemiological study

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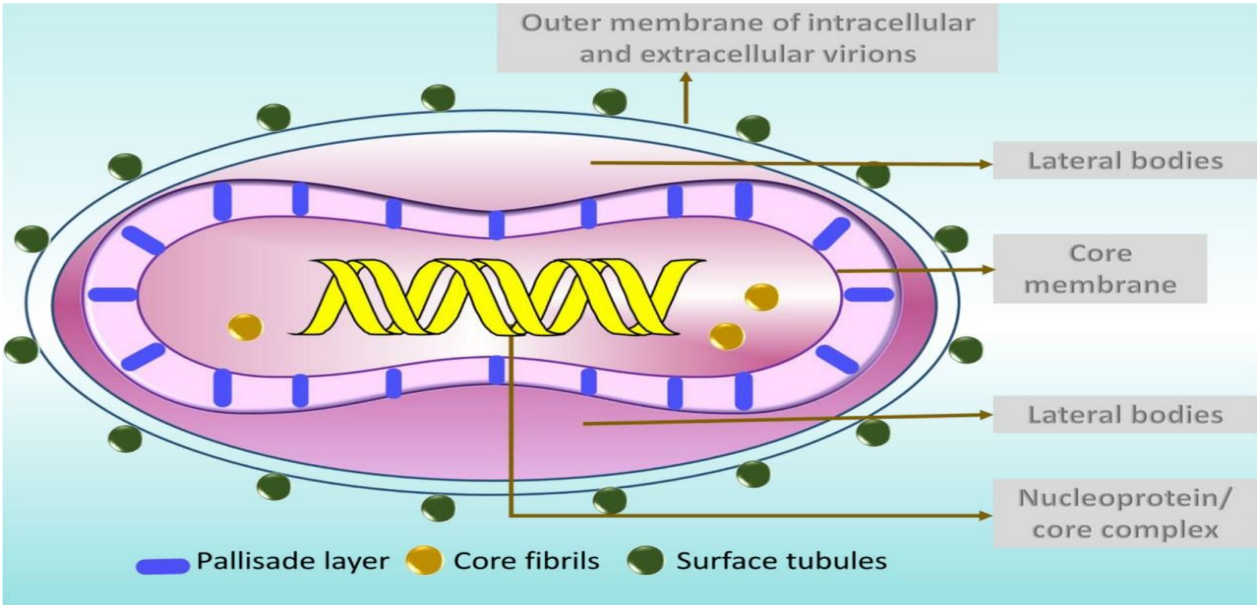
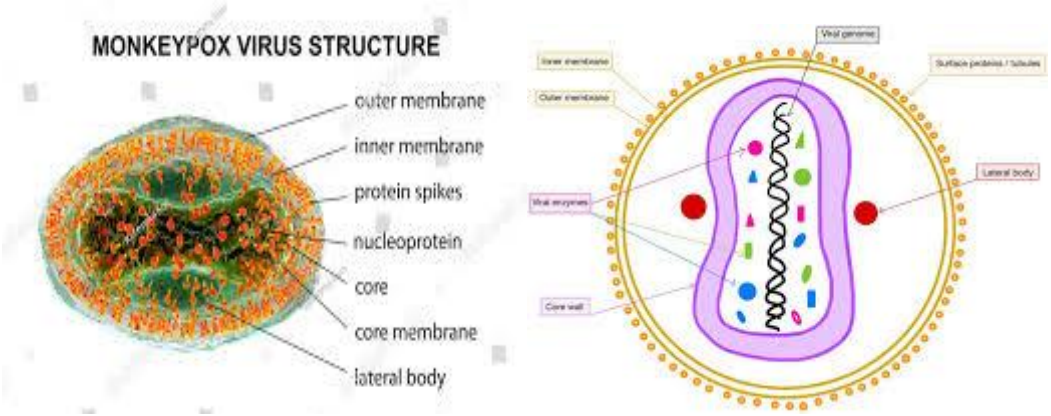
1. INTRODUCTION

The mpox (monkeypox) virus was first isolated and identified in 1959 when monkeys shipped from Singapore to a Denmark research facility fell ill.[1] However, the first confirmed human case was in 1970 when the virus was isolated from a child in the Democratic Republic of Congo suspected to have smallpox.[2] Coincident immunity to the mpox virus was previously achieved with vaccinia vaccination; however, eradicating smallpox and subsequent lack of vaccination efforts paved the way for mpox to gain clinical relevance.[3] In recent years, there has been cause for concern due to a rapid and unprecedented pandemic of Mpox infections in several countries all over the world. Rodents and primates are the hosts for Mpox, a zoonosis (a virus transmitted from animals to people) with symptoms like smallpox but less severe. When the virus was initially identified in monkeys in a Danish laboratory in 1958, the term "monkeypox" was coined [1]. The etiological agent of monkeypox, a zoonotic illness that can be transmitted to humans, is the monkeypox virus, which is a member of the Orthopoxvirus genus that was originally mainly present in Central and West Africa [2,3].



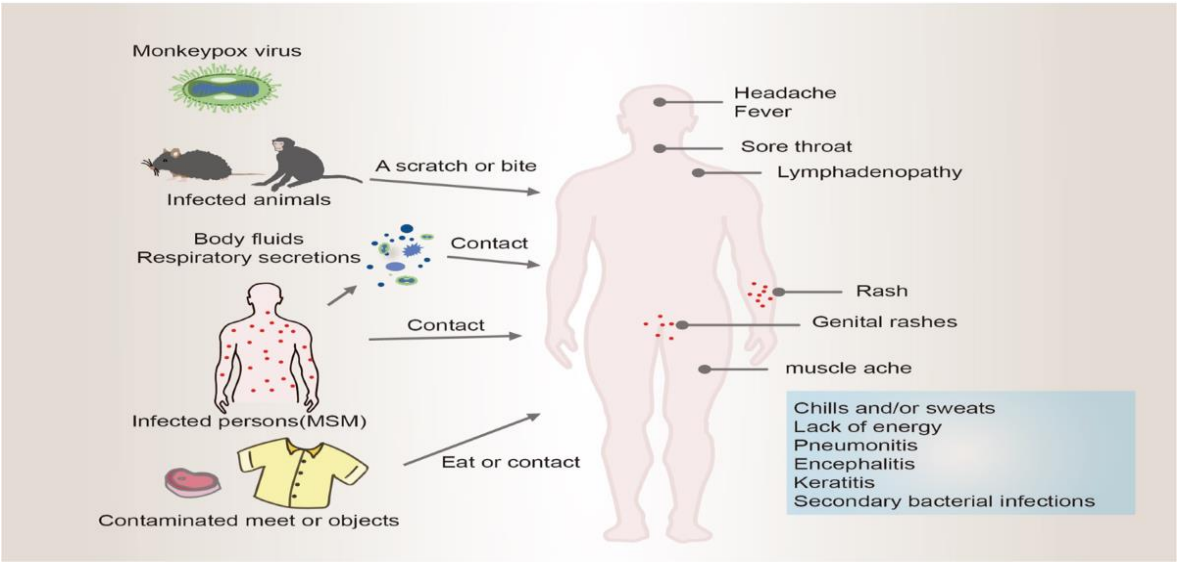


There have been numerous reports of human Mpox from various countries that are not typically affected since May 2022. With the large number of proven cases and stories of the virus passing between people and within a population, it has become a cause for concern all over the world. The large number of people confirmed to have Mpox around the world currently stands at over 85,189, and it is rapidly increasing in more than 110 nations. The WHO declared it a Public Health Emergency of International Concern on 23 July 2022 in order to alert the world of the danger it poses [4]. Since smallpox was eradicated in 1980, the Mpox virus has been found to be the most prevalent orthopoxvirus impacting people. It produces a sickness that is identical to smallpox in humans. The signs and symptoms of the present Mpox epidemic differ from those in the past, even though the virus was first identified many years ago. Traditionally, the only genital sores associated with human Mpox were ones that were all the same in appearance—pustular eruptions [5,6]. The present monkeypox outbreak, however, is differentiated by genital rashes. Additionally, the vaginal rash typically comes before the widespread pustular rash in non-endemic regions outside of Africa [6,7,8,9]. An initial infection in the genital region can cause a localized rash and, in rare instances, a subsequent widespread illness. Additionally, skin lesions and prodromal symptoms are not significantly linked, and systemic symptoms are only present in around 50% of patients [10].

2. ETIOLOGY

Mpox belongs to the family: *Poxviridae*, subfamily: chordopoxvirinae, genus: orthopoxvirus, and species: mpox virus. On electron microscopy, the mpox virus is relatively large (200 to 250 nanometers). Poxviruses are brick-shaped, surrounded by a lipoprotein envelope with a linear double-stranded DNA genome.[5][6] Aside from their reliance on host ribosomes for mRNA translation, poxviruses include all necessary replication, transcription, assembly, and egress proteins in their genome.[7][5]

Mpox is a zoonosis and is spread from animals to humans. The animal reservoir for the disease is thought to include squirrels, rats, monkeys, primates, prairie dogs, hedgehogs, pigs, and mice found in the African regions from where mpox was previously widely reported.[5] The ongoing epidemic is, however, primarily driven by human-to-human transmission through respiratory droplets, fomites, and direct contact with lesions of an infected individual.[5]. Recent analysis has found that viral loads are high in bodily fluids, including urine, saliva, semen, and feces, as well as in swabs taken from the oropharynx and rectum, suggesting that sexual transmission is a major driver of transmission.[8]



3. EPIDEMIOLOGY

The Mpox virus was first reported in 1958 in laboratory monkeys employed for research purposes at State Serum Institutes in Copenhagen, Denmark, as well as in Africa [9,10,18,15]. Humans in Sub-Saharan Africa have been infected with monkeypox through intimate contact with diseased animals, suggesting that the disease has been present for thousands of years. Mpox was formally recognized as a different illness in 1970, when the smallpox-eradication campaign revealed a continuing

occurrence of smallpox-like disorders in rural regions [16,17,35]. Imported human Mpox-virus infections beyond the African continent have been infrequent in the last 50 years. Mpox has gained attention as a disease of global public-health significance since the first outbreak in the United States in 2003, which was linked to an infected pet prairie dog [18,23]. It was believed that native prairie dogs housed alongside rats from Ghana introduced in Western Africa were the main source of the pandemic. This is because most infected individuals became ill after coming into contact with pet prairie dogs [19,26] In the summer of 2003, a cluster of illnesses in the US Midwest was attributed to Mpox. The main cause of the epidemic was believed to be native prairie dogs that were kept with rats imported from Ghana in Western Africa. This conclusion was reached as the vast majority of those who became infected fell ill after being in contact with pet prairie dogs [20,26]. Since 2003, many cases of Mpox have been reported in a variety of countries, with Nigeria experiencing the worst epidemic in 2017 [28,27]. In 2018, two individuals with secondary Mpox illness were reported by the United Kingdom after they visited Nigeria [29]. Over the past five years, there have been multiple cases of human Mpox identified in areas all over Africa [28]. Mpox has also spread to other areas, such as Singapore, Israel, the United States, and the UK.On 7 May 2022, the UK Health Security Agency announced a confirmed case of Mpox in a person who had recently traveled to Nigeria [29]. By 29 January 2023, the World Health Organization had received 85,189 suspected and/or confirmed cases of Mpox from 110 countries, with the majority of cases occurring in Europe and the Americas, resulting in 86 fatalities around the world.According to an epidemiological-modeling study, the Ro value for Mpox varies from 1.10 to 2.40 in countries with little exposure to Orthopoxvirus species. Ro is also known as the reproduction ratio, and it is used to determine the disease's transmissibility. This score indicates that an Mpox pandemic is poised to break out in the case of imported human or animal cases. As previously noted, the stated Ro indicates that each infected person has the ability to infect one to two other people. Because the virus is infectious, an infected individual must take special steps to isolate themselves and prevent contact with others.Globally, the number of weekly reported new cases dropped by 2.3% in week 3 (16 January–22 January) (n = 295 cases) compared to week 2 (9 January–15 January) (n = 302 cases). The bulk of cases recorded in the last four weeks were from the Americas region (77.7%) and the African region (13.9%). The United States of America (n = 29,860), Brazil (n = 10,709), Spain (n = 7518), France (n = 4114), Colombia (n = 4066), the United Kingdom (n = 3735), Peru (n = 3723), Mexico (n = 3696), Germany (n = 3690), and Canada (n = 1460) are the ten most afflicted nations worldwide listed. These top affected nations account for 85.2% of all cases recorded worldwide. In the last seven days, 18 nations have reported an increase in the weekly number of cases, with Costa Rica reporting the largest rise. In the last 21 days, 74 nations have reported no new cases. According to the CDC, India has had a total of 22 cases and 1 death due to the Mpox virus. Mpox showed up out of the blue in several countries and regions, but there was no initial epidemiological link to areas where the Mpox virus has always been common. This suggests that transmission has been going on for a long time without being noticed. Therefore, the monkeypox epidemic needs to be looked at with an open mind and with care. The World Health Organization (WHO) reports a moderate risk to the entire world. However, the risk is high in the Americas region and moderate in the Africa, Eastern Mediterranean, Europe, and South-East Asia regions, according to the WHO. In contrast, the risk is believed to be low in the Western Pacific region [31,32].

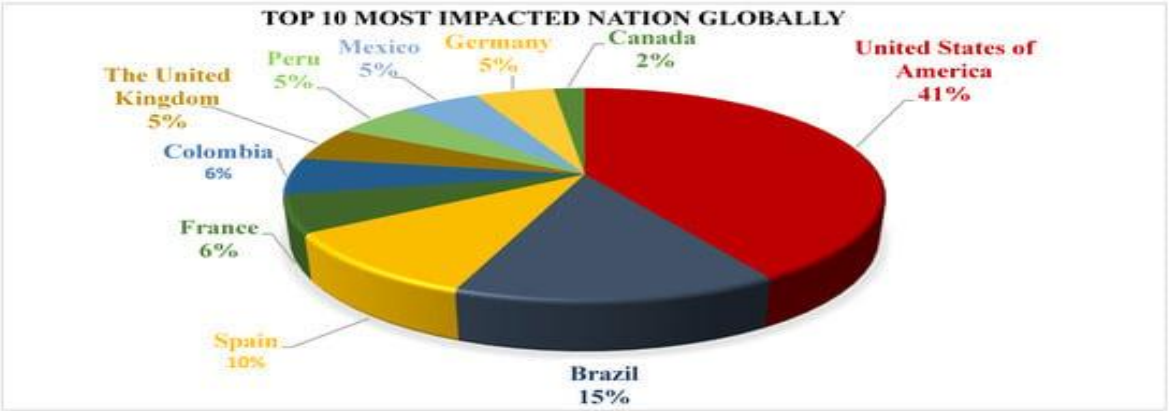


Figure 3. Top 10 most impacted nations globally are the United States of America (*n* = 29,860), Brazil (*n* = 10,709), Spain (*n* = 7518), France (*n* = 4114), Colombia (*n* = 4066), the United Kingdom (*n* = 3735), Peru (*n* = 3723), Mexico (*n* = 3696), Germany (*n* = 3690), and Canada (*n* = 1460).

4. PATHOPHYSIOLOGY

Following viral entry from any route (oropharynx, nasopharynx, or intradermal), the mpox virus replicates at the inoculation site and then spreads to local lymph nodes. Next, an initial viremia leads to viral spread and the seeding of other organs. This represents the incubation period, typically lasting 7 to 14 days with an upper limit of 21 days.

Symptom onset correlates with a secondary viremia leading to 1 to 2 days of prodromal symptoms such as fever and lymphadenopathy before lesions appear. Infected patients may be contagious at this time. Lesions start in the oropharynx and then appear on the skin. Serum antibodies are often detectable by the time lesions appear.[34] Rash progression is described in more detail in the History and Physical section.

5. TRANSMISSION ROUTE ASSOCIATED WITH MPOX

The current research implies that monkeypox may spread in three different ways: from person to person, via direct contact with infected organisms, and from animals to people. It is well established that animals can pass the Mpox virus on to humans [35]. The majority of the animals that are known to be carriers of the virus are rodents, such as rats, squirrels, and dormice, as well as numerous kinds of primates. On the other hand, there is evidence of a human-to-human transmission that has occurred not just in Africa but also outside the continent. Direct contact with skin lesions of infected animals or people, respiratory exposure to droplets from infected humans, and consumption of contaminated bushmeat are all potential routes of transmission for the Mpox virus. During the current outbreak of the illness, researchers have shown that it is more prevalent in men who engage in sexual activity with other men. Most cases of Mpox have been identified in men who have had sex with other men (MSM). The CDC reports that transmission can occur through contact with an infected person. Furthermore, semen analysis for many patients has revealed the presence of monkeypox-virus DNA, which is a novel finding. The virus may pass from one person to another by respiratory (airborne) contact, direct contact with body fluids from an infected person, or during pregnancy from the mother to the fetus. Given that the pathogenic Mpox virus can be isolated from samples of semen, there are signs that transmission may happen during sexual intercourse. The Mpox virus could be stored in the genital area if it stays in seminal fluids for a long time. Whether the virus can spread via vaginal secretions is unknown. Even with adequate personal protective equipment, the virus may spread through fomites or by indirect contact with lesion material, such as through contaminated bedding, most commonly through inhalation [35]. Sharing a bed or room or using the same utensils as an infected individual are risk factors for transmission. Factors involving the introduction of the virus to the oral mucosa are linked to increased transmission risk. It is still unknown whether those who do not have monkeypox symptoms can transmit the virus [37]. Currently, further study is being conducted to better understand how this particular strain of the West African lineage spreads, although the general consensus is that it is not unique. As far as we know, it does not disperse in the air like COVID-19. Mpox, in contrast to COVID-19, is not communicable until the infected individual develops symptoms. Therefore, it is much simpler to keep sick people apart and stop the spread of the disease.

6. VACCINES FOR MPOX VIRUS

In order to prevent the spread of the Mpox virus and protect people from it, there are multiple steps that must be taken. Vaccines are the most effective way to achieve this goal, yet unfortunately, there is currently no specific vaccine for the Mpox virus. However, research has revealed that the same smallpox vaccine that was used to protect people against smallpox may be effective in protecting against the Mpox virus as well. Previous knowledge shows that receiving a smallpox vaccination could result in a reaction to the Mpox virus and may be able to protect from being infected by the virus by up to 85% [31]. The Food and Drug Administration has approved ACAM2000, a second-generation smallpox vaccine, to be used to prevent exposure to smallpox during an outbreak or crisis. Therefore, it has been acquired for the Strategic National Stockpile (SNS) and is available to be used for a range of demographic groups. Furthermore, JYNNEOS (MVA-BN) was authorized to be used in the United

States and Canada in 2019 after a series of animal studies. Clinical trials have also demonstrated its strong effectiveness and safety, which can be used to protect people in many different age groups from getting infected with the Mpox virus. The approval was due to the effectiveness in animals, the safety profile in humans, and the evidence that JYNNEOS had a similar immunogenicity to existing smallpox vaccinations. In addition, due to the verified protective effects in animal studies and the immunizing action seen in human trials, the US Food and Drug Administration's emergency investigational new drug program approved LC16 both in the US and in Japan. No data exists on the efficacy of LC16 for avoiding Mpox-virus infections, even though it is the only smallpox vaccine available for kids. It is essential to note that when taking pre-exposure precautions, these vaccinations can often stop Mpox-virus infection. Yet, experts have demonstrated that post-exposure immunization may be able to stop the onset of serious diseases or reduce the intensity of the issues experienced by those who have been infected with the Mpox virus. In this scenario, it is recommended to get vaccinated promptly after being exposed. The Centers for Disease Control and Prevention (CDC) has confirmed that vaccination within four days of exposure can prevent the onset of illness. If this window is missed, the disease may still occur, but immunization in the first two weeks can help to avoid more serious consequences. Currently, three vaccines for orthopoxviruses are accessible: ACAM2000, JYNNEOS, and LC16. The initial vaccine, ACAM2000, is a replicating vaccine; however, the other two vaccines are either non-replicating or minimally replicating. In 2015, the Food and Drug Administration (FDA) and the United States government gave ACAM2000 a permit to treat smallpox and monkeypox. From 2015 to 2019, it was the only monkeypox vaccine that could be purchased in the United States. Cell-culture techniques were utilized in both France and the USA to create ACAM2000. Those aged from 18 to 64 were allowed to use it. Emergent BioSolutions manufactured this second-generation, replication-capable, live-attenuated, plaque-purified vaccine. The scarification technique with a bifurcated needle is used to deliver the vaccine percutaneously by repeatedly injecting it into the surface of the skin. This single-dose vaccine grants maximum immunity 28 days after immunization. People exposed to highly virulent orthopoxviruses require booster doses every three years, whereas those exposed to low-virulent orthopoxviruses (e.g., vaccinia virus or cowpox virus) must be administered booster doses every 10 years. The MVA-BN vaccine created by Bavarian Nordic is a third-generation, live-attenuated, nonreplicating Ankara vaccine. It is a two-dose vaccination that must be taken 28 days apart in order to generate immunity. Clinical trials indicated that a substantial antibody response was seen after the initial dosage. Following the second dose, immunity was established. Those exposed to highly virulent Ortho poxviruses need to receive a booster shot every two years, whereas those exposed to low-virulence strains need one every 10 years. In 2019, this vaccine was given the green light by the FDA for use in Canada to prevent smallpox and monkeypox in adults aged 18 and older who are at high risk. KM Biologics created a third-generation vaccination called the LC16 vaccine, which was granted a license for use against smallpox in Japan in 1975 and against monkeypox in the USA in 2014. This live-attenuated, minimally replicating vaccine was made using cell-culture techniques and has an immunogenic-membrane protein B5R that has been eliminated. A bifurcated needle is used to percutaneously administer the multidose vaccination, which is suitable for individuals of all ages, including newborns and toddlers. It is essential to look into the reactogenicity, safety, and any possible adverse effects of the vaccine in order to ensure the most effective selection, especially for those in high-risk and vulnerable groups. For example, there are various vaccines that can be used for healthy individuals, such as those that are nonreplicating (e.g., JYNNEOS), slightly replicating (e.g., LC16), and replicating (e.g., ACAM2000). Researchers need to make a vaccine specifically for the monkey-pox virus to increase protection against the virus.

7. TREATMENT FOR MPOX

A total of 85,189 cases of Mpox infection as of 29 January 2023 have alarmed the world. Historically, immunization against the vaccinia virus could safeguard against Mpox; however, since smallpox was eradicated, this type of vaccination has ceased. Consequently, therapeutic options for those already infected are of considerable importance. No antiviral drugs that have been approved by the American Food and Drug Administration are specifically created to target the Mpox virus. However, other medications such as tecovirimat (TPOXX/ST-246) and

brincidofovir, both of which are effective against smallpox, as well as cidofovir, an antiviral approved to fight CMV, have been shown to be effective against orthopoxviruses in laboratory experiments. In 2018, the US Food and Drug Administration (FDA) approved tecovirimat (TPOXX) for the treatment of smallpox in adults and children. This medication works by preventing VP37, a viral-envelope-wrapping protein, from functioning properly and blocking viral replication and release. It is currently available in the US free of charge under an expanded-access investigational new drug protocol (EA-IND). Tecovirimat can be taken orally or intravenously. Although there is not enough evidence yet to show how effective it is for treating Mpox, it has been reported to have mild side effects like headache, nausea, vomiting, abdominal pain, and neutropenia in one trial participant.The use of an intravenous formulation may lead to redness, pain, and swelling at the area of infusion. In June 2021, the FDA approved the use of brincidofovir against smallpox in both adults and children. This prodrug of cidofovir comprises a lipid conjugate and is converted to cidofovir diphosphate (CDP) within the cells, which inhibits the viral DNA polymerase, eventually stopping the replication of the virus. Although there is a dearth of data on the use of brincidofovir against MPXV, animal studies have revealed that when treatment was administered at the appropriate time, infected prairie dogs had survival rates of between 29 and 57% [39]. Adler et al. reported three cases of human Mpox that were addressed by administering brincidofovir. However, the treatment was discontinued due to a rise in the levels of liver enzymes. An advantage of brincidofovir over cidofovir is that it is available in both pill and liquid forms and is smoother on the kidneys. Cidofovir and its prodrug, brincidofovir, have the same method of working. There is a lack of evidence from humans on the effectiveness of cidofovir against monkeypox, but there are animal studies that show that it is useful against orthopoxviruses such as cowpox, vaccinia, ectromelia, and rabbitpox. Thornhill et al. mentioned cases from the 2022 Mpox outbreak being treated with cidofovir, which is only obtainable as an intravenous formulation but can carry a risk of severe renal toxicity. In the treatment of the Mpox virus there is no specific treatment available in the current outbreak, so researchers should work on a treatment strategy. In figure below, the life cycle of Mpox virus inside the host-cell cytoplasm is illustrated to elicit the mechanism of action of three different antiviral therapies: cidofovir, brincidofovir, and tecovirimat [40].

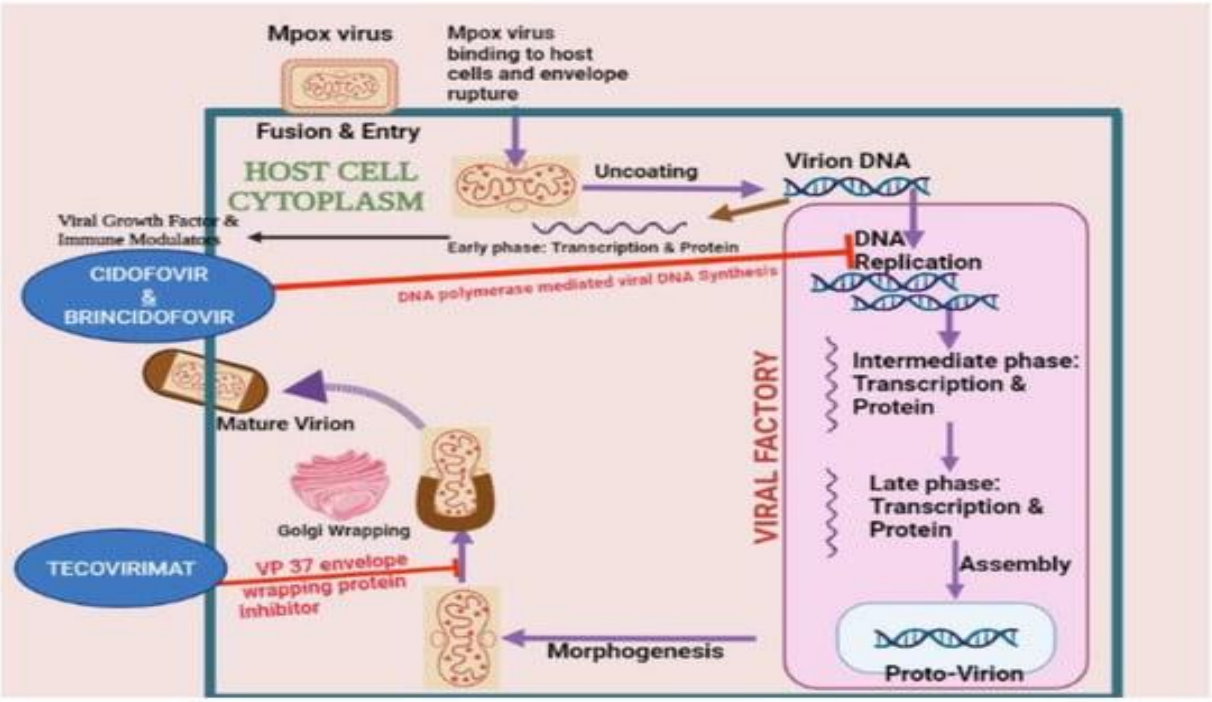


Figure: An illustration of the life cycle of the Mpox virus inside the host-cell cytoplasm to elicit the mechanism of action of three different antiviral therapies: cidofovir, brincidofovir, and tecovirimat.

8. CHALLENGES

Currently, operational research faces challenges in understanding the dynamics of monkeypox transmission and control due to limited resources for

detailed case investigations and contact follow-up in affected communities. A serious issue is the lack of adequate diagnostic facilities in laboratories. The difficulty in diagnosing the Mpox virus arises from the insufficiency of laboratory-diagnosis capacity and access, making it challenging to identify any underlying etiology. To comprehend the epidemiology and subclinical infection among contacts in communities, a seroprevalence study is crucial. However, currently available serological assays are generic orthopox tests, and they cannot specifically identify the Mpox virus due to cross-reactivity between the Mpox and smallpox viruses. Hence, it is challenging to distinguish between Mpox-virus infection and prior smallpox vaccinations or other orthopoxvirus infections. Moreover, these assays are not available on the marketplace. Data collected from Nigeria reveal that approximately 20% of 70 monkeypox-negative patients with a rash illness that had similar antigens also had orthopox antibodies. In addition, there is no specific antiviral treatment for Mpox. Treatment is primarily supportive, focusing on managing symptoms such as fever and rash. Vaccination with the smallpox vaccine can provide some protection against Mpox, but the vaccine is not widely available in many countries. Further research, including molecular and genomic approaches, is necessary to identify other orthopoxviruses transmitted in human and animal populations.

9. CONCLUSIONS AND FUTURE PROSPECTIVE

Mpox is a viral disease that is closely related to smallpox and primarily found in remote parts of Central and West Africa. There is currently no specific vaccine for Mpox, but the smallpox vaccine provides some protection against the disease. However, the smallpox vaccine is no longer routinely administered, and many younger people in Africa may not have received it. Several vaccines are being studied for their potential effectiveness against Mpox, including live-attenuated Mpox vaccines, DNA vaccines, and recombinant vaccines. Synthetic peptide-based prototype vaccines have also shown promise in preclinical studies, and researchers are investigating the use of mRNA vaccines for booster purposes in those who have received the mRNA vaccine for COVID-19. Overall, the development of effective vaccines for Mpox is an ongoing area of research, and scientists are working to develop new vaccines that can protect against this rare but potentially serious disease.

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