Mpox (Monkeypox): The Current State of the Global Health Crisis

ABSTRACT

Mpox, formerly known as the Monkeypox Virus, is once again in the headlines announcing its comeback. While still recovering from the 2022 outbreak - the World Health Organization (WHO), for the second time in as many years has declared mpox to be a global health emergency. We now find ourselves facing the same uphill battle at the outset of this recurring threat. Mpox is a known quantity to the scientific community and has been for more than 60 years. First identified in humans during the 1970s, mpox is a viral zoonotic disease transmitted from animals to humans and is caused by the mpox virus. It is largely relegated to the tropical rainforests of Central and West Africa. It has been mostly ignored in Europe and the Americas until just recently where it has generated worldwide attention. Cases of the mpox infection first appeared sporadically amongst gay and bisexual men with Europe first reporting cases in mid-2022. Shortly thereafter, occurrences were seen in the metropolitan areas of New York, Chicago, San Francisco and Los Angeles. The 2022 outbreak was a turning point with over over 100 countries reporting cases which had not previously been seen before. Mpox infections are transmitted through close personal contact with infected individuals, infected animals or mpox-tainted materials. The WHO has declared mpox a "Public health emergency of international concern". There are two distinct clades of mpox virus - clade I and clade II. In 2022 the global outbreak was caused by clade IIb and most recently by clade Ib. Mpox is genetically similar to smallpox. Although no treatment for the mpox virus exists, supporting care, antivirals and vaccines developed for smallpox have proven effective. Because of its similarity to smallpox, individuals infected with mpox demonstrate attenuated symptoms (i.e. fever, chills, muscle aches, sore throat and cough) as compared to those infected with smallpox. After a 3-week incubation period, mpox goes away on its own in approximately 2-5 weeks. Diagnostic testing and disease confirmation is performed via RT-PCR testing of genetic material from the infected areas and through the presence of lymphadenopathy (i.e. enlarged lymph nodes). This overview serves as a point of discussion for the aforementioned areas and provides commentary on understanding the methods of disease prevention and containment.In summary, the power of viral spread causing global pandemics is not to be ignored or neglected - and much more research is needed.

Comment [TA1]: Definite year is required. For example, … for the second time in two/ten/twenty years …

Comment [TA2]: What was "first" identified? Consider writing "MPOX was first identified in humans …

Comment [TA3]: Consider re-writing this sentence.

Comment [TA4]: Re-write the two sentences to make a single sentence and meaning.

Comment [TA5]: Re-write this sentence

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Comment [TA7]: Consider "been reported".

Comment [TA8]: The article is unnecessary.

Comment [TA9]: Which overview?

Comment [TA10]: Which areas?

Comment [TA11]: This sentence doesn't make a meaningful sentence. Consider re-writing for clarity.

Comment [TA12]: This is unnecessary here.

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Keywords: Mpox, Monkeypox, Etiology, Epidemiology

Introduction

Humanity entered a new dawn in 2019 with yet another contagion that proved to be the deadliest viral outbreak the world has seen in more than a century. The world is now healing from the death grip of the novel coronavirus disease (COVID-19) [16]. All hope is not lost - through advances in modern medicine, specifically in the fields of vaccine and virology [17,18] this deadly infection is better understood and its vice-like grip on humankind is slowly giving way. What was a ravenous and untreatable disease just a few years ago is now being held at bay. We still have a long way to go in eradicating outbreaks like these, but one thing is for certain,

science and public policy working hand in hand can stop the spread and hopefully eradicate these life-threatening contagions.

Higher vaccination rates, greater vaccination availability, public awareness and public policy are all contributing factors to allay the fears associated with viral outbreaks [19-21]. Furthermore, all these factors have resulted in declining infection and death rates. While the remnants of one major pandemic have become more manageable and less deadly, the makings of another potential pandemic have now appeared on the world's radar [22,23].

Since 2022, The mpox virus has taken a foothold in countries around the world and we are now witnessing a resurgence in cases [22-25]. It first appeared in countries in which it has historically been foreign or unheard of. Like that of any such viral disease, the threat of rapid outbreak, rapid mutation, public policy response, vaccination development and availability - all driving factors from the COVD-19 playbook - are once again front and center for the mpox virus [26]. This of course begs the question; does this have the potential to become yet another epidemic of the 21st century?

Viral Outbreaks

Throughout the centuries, a constant battle with viral epidemics and outbreaks of infectious diseases have dotted our history books [1-4]. The wildfire-like spread of these pandemics have had a profound impact on the global population - causing the loss of life, laying waste to entire civilizations [6,7], bringing nations to their knees and leaving economies in ruins.

The following outbreaks represent some of the most significant infectious diseases in human history, each one exhibiting its own unique set of characteristics and consequences. Of note, many of these have been characterized by making the jump from animals to humans and humans to humans. Regardless of their characteristics, the social, cultural, religious, political and economic impact of these outbreaks is profound [5-7].

The Justinian Plague (541-542 AD): Affected the Byzantine Empire during the reign of Emperor Justinian. This pandemic is considered to be one of the first recorded in history and attributed to killing between 25-50 million people [8-11].

Black Death / Bubonic Plague (1347-1351): This famous outbreak appeared in the mid-14th century and spread across Europe, Asia and Africa. An estimated 75-200 million succumbed to its devastating grip. This outbreak was caused by the Yersinia pestis bacterium and spread through infected fleas and rats.

Cholera (1817- Present): The first cholera pandemic originated in India and spread across Asia and Europe between 1817-1824. The second cholera pandemic spread from Asia to Europe and America between 1829-1851 and most recently in South Asia (1961). It is still endemic in many countries. Cholera is characterized as an acute diarrheal iliness caused by the ingestion of food or water contaminated with the Vibrio cholerae bacteria usually found in shellfish and plankton.

Spanish Flu (1918-1920): Also known as the Great Influenza was exceptionally deadly, affecting an estimated 500 million people and killing upwards of 50 million. It was caused by the H1N1 subtype of the influenza A virus [12,13].

Comment [TA13]: Sadly, the first paragraph didn't speak about the subject matter but rather talked about covid-19.

Comment [TA14]: Can the author explain the relationship between this paragraph and the concept of this manuscript.

Comment [TA15]: Delete

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Comment [TA18]: This sentence should immediately precede the listing of the major pandemic listed below. Such as before "The Justinian plague…".

Asian Flu (1957-1958): This originated in Guizhou, China and is caused by the influenza A virus subtype H2N2. It is estimated that between 1-4 million deaths globally were caused by the Asian flu.

Hong Kong Flu (1968-1969): A decade after the Asian flu, the Hong Kong flu emerged and resulted in one million deaths. It was caused by the H3N2 strain.

Ebola Virus (1976-Present): First detected in South Sudan and the Democratic Republic of Congo, it kills between 25% and 90% of those infected. Sporadic outbreaks between 1976-2016 have claimed close to 12,000 lives [14,15].

HIV/AIDS (1980-Present): Human Immunodeficiency Virus (HIV) is a retrovirus which attacks the immune system. HIV made the jump from primates to humans during the early-to-mid-20th century in west-central Africa. There is no vaccine or cure for HIV and it has been attributed to 40 million deaths and counting.

Swine Flu (2009-2010): First detected in La Gloria, Mexico. This H1N1 virus is characterized by a reassortment of bird, swine, human and Eurasian pig flu virus. It mainly affected younger populations and pregnant women.

Zika Virus (2015-2016): The Zika virus outbreak of 2015 caused only mild symptoms like fever, headache, vomiting, muscle pain and skin rash, but more alarmingly it caused birth defects like microcephaly and neurological disorders in newborns. It comes from the Flaviviridae family of viruses and is spread through mosquitoes.

Respiratory Ailments:

- SARS (2002-2004): Severe Acute Respiratory Syndrome outbreak that resulted in over 8,000 cases and approximately 800 deaths. It is a viral respiratory disease of zoonotic origin caused by the SARS-CoV-1 virus.

- MERS (2012): Middle East Respiratory Syndrome originated in the middle east attributed to over 2,500 cases and 870 deaths.

- COVID-19 (2019-Present): Perhaps the most ~~well known~~well-known respiratory ailment is COVID-19. It is a contagious disease caused by coronavirus SARS-CoV-2 with the first known case coming out of Wuhan, China. To date it has killed more than 7 million people.

Etiology

Mpox formally known as monkeypox was renamed by the WHO in 2022 to restrain what was characterized as “racist and stigmatizing language” surrounding the infection.

Mpox is a rare viral disease that is a part of the Orthopoxvirus genus in the family of Poxviridas. The virus is closely related to other orthopoxviruses, which include smallpox. It exhibits the same symptoms in humans to those seen in smallpox patients. Although clinically less severe, the vaccinia virus, cowpox virus often seen in squirrels, rats and various monkey species.

Comment [TA19]: Can the author summarize these using a table. Author may follow this format Event name/Date/Location/Total casualties…

Comment [TA20]: No need to categorize. Run off with the above listed in a table.

Comment [TA21]: Repetition. This has been said above.

Comment [TA22]: Run-off. Delete paragraph

Virus structure: The mpox virus is closely related to the variola virus which causes smallpox, as well as the vaccinia virus. Under an electron microscope the virus has a complex structure (Figure 1). The virus can be described as being a large “brick” enveloped by a lipoprotein with double-stranded DNA. Its size is noted as being between 200-250 nanometers and its mutation rate is observed to be slower than that of the coronavirus [22-24,28,39].

Animal Reservoirs: The exact and complete nature of the reservoir is unknown [22,24,25,32] Most likely, it is maintained in certain infected African rodents and non-human primates. These animals harbor the host and transmit it to other animals or humans through direct or indirect contact. The genome encodes various proteins that facilitate the virus’ entry into the host and infects and invades the immune system’s response.

Pathogenesis: The pathogen enters the body through broken skin, the respiratory tract, the mucous membrane of the eye, nose, mouth, anus or rectum. Once there, the mpox virus initially replicates at the site and then spreads to the lymph nodes and finally to the entire body through the bloodstream (Figure 3).

Epidemiology

Previously known as the Central African or Congo Basin clade and the West African clade, the strains have officially been renamed by the World Health Organization (WHO) and are now referred to as Clade I and Clade II, respectively [23]. In addition to the nomenclature adopted by the Centers for Disease Control (CDC); MPV, MPXV or hMPXV are also abbreviations used by the scientific community. The Central African (Congo Basin) strain is more severe than the West African strain.

Comment [TA23]: What is previously known as? Can you always ensure to write clearly so your readers could understand.

Mpox is a rare zoonotic disease that jumps from animals to humans and humans to humans [27] with symptoms in humans similar to those seen in smallpox patients with clinically attenuated symptoms. Despite being called the mpox virus [22,24,32], the real origin of the virus ~~is unknown~~is unknown. It is found primarily in remote parts of Central and West Africa near tropical rainforests [22,24], predominantly in animals including squirrels, rats and various monkey species. The mpox virus was first discovered in 1958 when two outbreaks of a pox-like disease occurred in colonies of monkeys from Singapore kept for research at the Statens Serum Institute laboratory in Copenhagen, Denmark [20,21,33] hence the name “monkeypox”. The first human case of mpox was recorded in 1970 in the Democratic Republic of Congo (DRC), in a ~~9-month old~~9-month-old boy. Since ~~then~~then, sporadic cases have been recorded in Central and Western African countries during the 1980s-1990s [15,16,18,19].

Comment [TA24]: Can the author be consistent? Choose between Mpox, mpox, or MPOX.

During the ~~1996-1997-time~~1996–1997-time frame, a large outbreak occurred in DRC with more than 500 reported cases. In 2003, the first outbreak outside Africa in the United States was linked to imported animals. There were 47 confirmed cases reported in six states - Illinois, Indiana, Kansas, Missouri, Ohio and Wisconsin. No deaths were recorded. In 2017, the largest documented case since the 1970s was noted in Nigeria. The 2020 global outbreak was caused by the Clade IIb (West African strain). In more recent times, eleven African countries led the case count followed by a May 2022 outbreak in the UK [34], raising international awareness and response. The UK outbreak was attributed to British citizens who exhibited signs and symptoms shortly after returning from Nigeria [35-37]. This outbreak in the UK was followed by instances in

16 countries including those on continental Europe, the United States, Canada, Australia, the United Arab Emirates, Brazil and India [26,38]. Since then, global case counts have grown dramatically, especially in the United States. WHO declared the outbreak a Public Health Emergency of International Concern (PHEIC) in July 2022 due to the rapid spread of the disease, with many cases occurring among men who have sex with men (MSM). The higher mortality variant, Clade Ib, emerged in September of 2023, with the first cases seen in sex workers of the DRC. Subvariant, Clade Ib, is responsible for the 2024 global outbreak.

As of August 2024, the global situation with mpox remains a matter of grave concern. The most severe outbreak is in DRC where the African Centers for Disease Control and Prevention (ACDC) declared it a public health emergency. There have been over 16,800 confirmed cases and more than 500 deaths. The fatality rate for this strain is between 3-4%, which is significantly higher than the global average (<1%).

Statistics

The global mpox outbreak of May 2022 gained international attention and it was declared a Public Health Emergency of International Concern (PHEIC). A ~~never before seen~~never-before-seen outbreak of over 90,000 confirmed cases with over 200 deaths were recorded spanning more than 100 countries. The 2022 outbreak saw a significant number of cases emerge in the USA, Spain, Brazil, UK and India.

There have been no significant changes in mpox cases in the US during the last six months. Mpox virus affected all age groups of men, especially amongst gay men, immunocompromised individuals and pregnant women. Mortality rate for mpox is generally around 1-3%.

For the second time in two years, the WHO declared mpox a global health emergency in 13 African nations with more than 17,000 recorded cases. The 2022 global outbreak was caused by Clade II strain, which is still present in the USA and elsewhere. The 2024 outbreak is triggered by Clade I and Clade Ib.

Key Scientists in the Field of Mpox

Dr. Anne Rimoin: Professor UCLA, School of Public Health, Los Angeles CA. Epidemiologist experienced in infectious diseases, with an understanding of the various aspects of mpox in Central Africa and Democratic Republic of the Congo.

Dr, Daniel Bausch: President of the American Society of Tropical Medicine and Hygiene. Expert in infectious disease, worked extensively on viral hemorrhagic fever in zoonotic diseases especially all aspects of mpox.

Dr. Inger Damon: Virologist and key figure in the U.S. Centers for Disease Control and Prevention (CDC). Made significant contributions and provided expert opinion and guidance during the mpox outbreak.

Dr. Anthony Fauci: Director of the National Institute of Allergy. Pre-eminent scientist and virologist. Provided expert opinion and guidance on prevention, vaccinations, public health administration during mpox outbreak.

Comment [TA25]: Citation needed

Comment [TA26]: Incomplete sentence. What is the case fatality rate in the last six months which hasn't had a significant difference?

Comment [TA27]: Citation needed

Comment [TA28]: Can the author give an explanation on why this section is important to this chapter. The list of scientists that has contributed to Mpox eradication in which aspect or direction; clinical intervention, ecological, social or education wise? Also, the authors stated Field of Mpox. What does that mean?

Dr. Tedros Adhanom Ghebreyesus: Director General of the World Health Organization (WHO). Played a vital role during the 2022 mpox outbreak. Declaring mpox a Public Health Emergency of International Concern (PHEIC). His leadership is exemplary to global health, raising awareness, detection, vaccination and public health administration to control the spread of the virus.

Comment [TA29]: I suggest this should be removed.

Key Public Health Agencies

World Health Organization (WHO): The WHO has been front and center to the world's response to mpox. It provided expert opinion, guidence and technical support globally during the outbreak. In 2022, the WHO declared the mpox outbreak a Public Health Emergency of International Concern (PHEIC).

Centers for Disease Control and Prevention (CDC): Played a vital and crucial role during the mpox outbreak in the USA and globally. Provided excellent support services to healthcare providers including raising public awareness, research, vaccination guidance and public health administration to prevent the spread.

European Centre for Disease Prevention and Control (ECDC): Provided total guidance during the mpox outbreak of 2022.

National Institute for Communicable Diseases (NICD), South Africa: Monitored Mpox cases especially in South Africa where the disease is prevalent.

Comment [TA30]: This section has no importance or does not enhance the quality of the manuscript. I suggest the authors should delete.

Signs and Symptoms

Mpox exhibits symptoms that are similar to that of smallpox, but less severe in nature. The outward appearance of the mpox virus is similar to that of chickenpox. However, these two diseases are very different and are caused by two distinct viruses [26,42,49-52].

The Incubation period of mpox (time from infection to symptoms) is typically between 6 and 13 days. In certain ~~cases~~cases, incubation periods of between 5 to 21 days have been observed. Even though mpox exhibits milder symptoms than smallpox, it is accompanied by painful pustules and rashes [53]. These symptoms usually last between 2 and 4 weeks.

Symptoms are divided into two phases:

1. Invasion (0-5 days): This period is characterized by fever (often the first sign) [32,42], intense headaches (a common occurrence during this period), lymphadenopathy (swelling of the lymph nodes of the neck, armpit or groin), intense back pain, muscle pain (myalgia) and an extreme lack of energy (asthenia) [34,43,44]. Other possible symptoms include, blood in the stool, swollen penis, anal/rectal pain and difficulty when urinating. (Figure 2). In severe cases development of pneumonia or a bacterial infection leading to sepsis. Clinical Chemistry shows high levels of liver enzymes (ALT and AST) and low levels of BUN, hypoalbuminemia, leukocytes and thrombocytopenia [79].

2. Skin Lesions: Within 1-3 days after a fever, skin lesions or skin rashes occur. These lesions become pus-filled and are often painful or itchy. The rash typically develops on the face and then migrates to the rest of the body (hands, feet, chest, eye, genitals, rectum and inside of

the mouth). Some people may develop 1 or more skin lesions while others may develop 100 or more (Figure 5,6). Mpox progresses through several stages of skin eruptions over the course of 2-4 weeks. Patients are contagious right from the onset until new skin has formed. Stages associated with skin eruption are (Figure 7).

- Macules: Often flat, reddish or dark, usually small and circular - these appear on the skin and last for a period of 1-2 days
- Papules: These develop from macules and signal the beginning of inflammation which lasts for 1-2 days. Papules are described as bumps on the skin, small and typically red or flesh colored
- Vesicle: Papules turn into vesicles. They are small, often filled with fluid, itchy and painful. They last for 1-2 days
- Pustules: Vesicles turn into pustules. Pustules last for 5-7 days and are described as painful, large, pus-filled, inflamed, dimpled or umbilicated.
- Scabs: Pustules eventually dry up and form dark colored scabs which in turn fall off as the skin heals.

The above signs and symptoms vary from person to person. In certain ~~cases~~cases, patients may also experience sore throat, cough, nasal congestion, nausea, vomiting and diarrhea. Generally, infected individuals develop a rash followed by symptoms and in some ~~cases~~cases, it is completely the opposite; symptoms are followed by a rash. Some infected individuals develop a rash only and no symptoms. Symptoms can vary from mild to severe, depending on the patient's health, age and exposure level. In most cases the illness lasts for 2-4 weeks. Children, pregnant women and those with compromised immune systems are at greater risk. The latest research indicates that individuals who are asymptomatic (i.e. have the virus but show no outward symp Run-off. Continue the next paragraph here.toms) can spread the mpox virus [54-57].

Comment [TA31]: Re-write as "Recent research opined/indicated/revealed that individuals who are asymptomatic can spread the Mpox virus".

Differential Diagnosis: Mpox, Smallpox and Chickenpox

Mpox, smallpox and chickenpox are all viral infectious diseases caused by different viruses. They have distinct clinical features that cause systemic and skin rash.

The symptoms of mpox, smallpox and chickenpox are very similar and can be difficult to differentiate at first glance [47]. Mpox is caused by the mpox virus, a member of the Orthopoxvirus. Lymphadenopathy or swollen lymph nodes is one of the hallmarks of mpox, which distinguish it from chickenpox or smallpox. The other symptoms are back pain, myalgia and intense fatigue. Mpox has an incubation period of 6-13 days. 1-3 days after the onset of the fever, a rash starts on the face and spreads to the palms, trunk and other parts of the body. An analysis of the skin rash provides insight into viral diagnosis. Visually, the rash produced by the mpox virus has many similar cues to the ones caused by secondary syphilis, herpes simplex and varicella-zoster viral infections. A simple RT-PCR (real time polymerase chain reaction) test from skin lesions or from open sores produce answers. Interestingly enough, a blood test is not deemed reliable due to the fact it produces inconclusive results as to the virus type. Supportive care, smallpox vaccines, antivirals like cidofovir and tecovirimat (ST-246) may be used.

Comment [TA32]: Run-off. Continue the next paragraph here.

Comment [TA33]: Repetition, consider deleting.

Comment [TA34]: Repetition, see "sign and symptom" above.

Differential Diagnosis: Mpox, Smallpox and Chickenpox

Comment [TA35]: How is the headline different to the previous headline?

Both mpox and smallpox belong to the Orthopoxvirus family - they have many similarities and many differences. Smallpox is caused by variola virus, which belongs to Orthopoxvirus. An Incubation period of 10-14 days, 2-4 days after the fever is noted. Initial sypmptoms include high

fever, malaise, severe headache, severe back pain and no lymphadenopathy. Smallpox begins and is concentrated on the face, then it spreads to other parts of the body. Smallpox is much more contagious, easily transmissible, quite severe and often fatal.

Diagnosis is carried out by PCR and electron microscope - to accurately diagnose mpox, a tissue sample of the lesion/rash or fluid from the rash must be taken and sent to a qualified lab. Samples collected from the skin, saliva, urine or rectum can also be used in emergencies. Supportive care, smallpox vaccine for prevention and antivirals like cidofovir and tecovirimat (ST-246) may be used. Smallpox has been eradicated globally, whereas incidents of mpox are on the rise [50].

Differential Diagnosis: Mpox and Chickenpox

The symptoms of Mpox and chickenpox are very similar, the only difference being the presence of swelling of the lymph nodes in mpox cases. Mpox is caused by the orthopoxvirus while chickenpox is caused by herpes, the varicella-zoster virus, a member of the Herpesvirus family [51]. The mpox virus is highly contagious and faster spreading in nature than the chickenpox virus. Chickenpox causes mild fever, malaise, upper respiratory symptoms and is less intense than mpox or smallpox. Rashes first appear on the face and then spread to the rest of the body for incidents of mpox. Conversely, rashes for chickenpox start on the trunk, chest, back, face and then spread to other parts of the body. Both viruses are transmitted from skin-to-skin contact. Rashes caused by the mpox virus tend to appear at the same time and disappear at the same time after a 2-4 week period. Rashes caused by the chickenpox virus appear in waves and tend to disappear in approximately 2 weeks. Fatalities attributed to chickenpox are very rare, while fatalities attributed to mpox have a 1-11% case to fatality rate.

In general, an accurate diagnosis to help in the effective treatment and management of mpox, smallpox and chickenpox is needed. This medical assessment of clinical symptoms spans observation (rashes, lymph nodes), lab tests and general patient health considerations.

Comment [TA36]: As far as I know, smallpox has been eradicated. Why is effective treatment and management needed?

Complications

Just as the long-term effects of many viral outbreaks are slowly becoming known, mpox too is demonstrating its lasting impact on infected individuals. Mpox for all intents and purposes is still very new to the Americas and Europe. As case counts increase and more observational data is gathered, mpox's existence is defined by some very real physical, psychological and neurological disorders. More long-term studies are needed to understand the true impact of the virus - but a clear indication of what is to come leaves no question as to this uphill battle.

From a physical standpoint, complications from the mpox virus can include secondary bacterial infections of the skin and other organs; these include bronchopneumonia, sepsis and infections of the cornea (which may lead to vision loss) [58-60]. Additional symptoms may also include nausea, vomiting and diarrhea, all resulting in severe dehydration [34]. The CDC states that proctitis has also been observed in more than 10% of those infected. Damage to other sensitive internal tissue (i.e. anorectal, urethral) is also a hallmark which can lead to persistent long-term pain, physiological functions, neurological functions and other such arduous symptoms (Figure 3).

Comment [TA37]: Full meaning at the first mention.

In rare cases neurological complications such as encephalomyelitis (inflammation of the brain and spinal cord) have also been observed by the CDC. These neurological conditions may lead to seizures, weakness, difficulty walking, headaches, confusion and memory loss. In ocular complications, lesions of the eye can cause conjunctivitis, potentially leading to vision problems.

A more interesting and often overlooked symptom is the impact that physical scarring has on the individual's psychology [60]. Although it is not a "gay disease", mpox is a virus that for the most part is transmitted through sex between men. Physical scarring from lesions and rashes may persist for several months or perhaps even years. In certain communities where body dysphoria, hypersensitivity and stigmatization are prevalent, the psychological impact caused by permanent "cosmetic imperfections" can be devastating to an individual's mental ~~well-being~~well-being. This in turn can trigger other stressors and/or anxieties which may lead to yet more physical disorders.

Comment [TA38]: Re-write this sentence

Comment [TA39]: In certain communities in "Europe, Asia, Africa or America". Be specific.

Mortality

In recent years, thousands of mpox cases have been reported from Central and Western Africa and a growing number of cases are being reported from Europe and North America [25]. The case fatality ratio (CFR) is the yardstick of measurement and serves as an index of disease severity. The CFR for mpox varies by viral clade and affected persons. Recovery from mpox can be measured in a few weeks. Historically the CFR of the Central African Clade (Congo Basin) has been higher, around 1-10%. In contrast, for the West African Clades the CFR is much lower, less than 1%. Of note, the West African clade is rarely fatal with a 99% survivability rate [61,62] compared to the Central African clade. According to the CDC, higher mortality rates are observed in those who are immunocompromised, HIV/AIDs cases, children under 8 years old, women who are pregnant or breastfeeding, individuals with a history of eczema, individuals that have prolonged exposure to the virus or individuals with severe symptoms. In all these instances, there is a greater risk for serious illness or death [38]. Furthermore, the CDC states the following incident rates: men (96%), women (2%) and transgender/"undeclared" (2%).

Comment [TA40]: Citation needed.

Morbidity

The severity of the diseasevaries from mild to severe depending on several criteria such as viral load (higher viral load equates to greater severity), patient age, immune system health, dietary factors, access to timely and competent healthcare, etc. All these factors are determinants in positive patient outcomes.

Detection and Diagnosis

Comment [TA41]: Diagnosis has been discussed extensively above.

The most relevant and reliable step in detection and diagnosis is to recognise the clinical signs, symptoms and rash progression. The initial signs and symptoms are fever, intense headaches, myalgia, severe back pain and fatigue. The most distinguished features are enlarged lymph nodes (lymphadenopathy) - more specifically, the submental, submandibular (jaw), cervical and inguinal nodes [47]. Both smallpox and chickenpox do not display these visual characteristics.

A diagnosis of the mpox virus is conducted using several methods including: patient profile (age, type and date of symptoms, contact tracing, etc.) and travel history (travel to "hot spots", contact/interaction with infected animals). Mpox must be differntiated from other diseases with similar presentations like: smallpox, chickenpox, allergic skin rash, syphilis, scabies, measles and bacterial infections.

Comment [TA42]: Verbose! This has been discussed in Differential Diagnosis subheading above.

The next clinical feature is understanding the rash progression. It begins 1-3 days after the fever onset. It starts on the face and spreads to the other parts of the body - especially on the palms, soles, trunk, genitals and mucous membrane of the mouth and eyes. The progression of rash lesions is as follows: macules, papules, vesicles, pustules and finally scabs. Lesions are typically in the same stage of development on any given part of the body.

Comment [TA43]: Verbose! This has been discussed in detail under sign and symptoms

The most common diagnostic tool is the RT-PCR test (real-time polymerase chain reaction). The RT-PCR test is the “gold standard” as it is the preferred method due to its accuracy, sensitivity and turn-around time. Of note, blood tests are not used to determine the presence of the mpox virus as they are deemed to have results that are inconclusive and lack accuracy [63-76].

Comment [TA44]: Delete, it has been defined at the first mention. See Differential diagnosis.

To determine the presence of the mpox virus, diagnostic samples from rash lesions & fluids, throat culture and skin biopsies are used for viral DNA detection which distinguish mpox virus from other orthopoxvirus. The handling of these specimens is critical – they should be stored in a cool, dry and sterile environment and sent to a qualified laboratory for RT-PCR testing [64].

Comment [TA45]: Repetition

The other diagnostic methods are electron microscopy, virus isolation, serology and a host of other newer methods:

- Electron Microscopy: It visualizes the virus from lesion samples and provides rapid results but is less accurate than a PCR test.
- Virus Isolation: Is a process that involves culturing the virus in a cell culture media to confirm the diagnosis. This method is time consuming.
- Serology: It detects antibodies against the mpox virus in the blood. This method is used mostly in retrospective diagnosis and epidemiological studies but cross reactivity with other orthopoxviruses is of concern.
- Next-Gen Sequencing: It uses an in depth analysis on the viral genome to investigate its evolution.
- Antigen Detection: The detection of viral antigens in tissue samples using immunohistochemistry techniques are more relevant to post-mortem cases.

Histopathology, Immunohistochemistry (IHC) and Electron Microscopy (EM)

Histochemistry, immunohistochemistry and Electron Microscopy are important tools in the diagnosis study of mpox. They provide valuable information on changes inside the tissue and the cellular response of the infection. This assists in the diagnosis accuracy and provides a deeper understanding of the pathophysiolgy and treatment of the disease.

Histopathology: Histopathology provides important information into cellular changes caused by the virus. It sheds light on the pathology of the disease and can assist in diagnosis and post-mortem studies.H&E (hematoxylin and eosin) staining shows changes in epidermal, dermal and viral cytopathic effects. Epidermal changes show a ballooning degeneration of keratinocytes, spongiosis, the presence of acanthosis, epidermal and keratinocyte necrosis. Dermal changes show a dense infiltration of inflammatory cells, dilated blood vessels and in severe cases, necrosis of blood vessels. Viral cytopathic effects show eosinophilic intracytoplasmic inclusion bodies in keratinocytes and multinucleated giant cells [67-69]. H&E histological staining of the mpox virus is nonspecific and similar to other viruses [67-69].

Immunohistochemistry (IHC): IHC staining for Orthopox viral antigens is done in reference laboratories and uses antibodies to detect specific antigens in tissue samples to confirm the presence of a virus (i.e. mpox). Viral antigens are detected within the lesions of the epidermal keratinocytes, follicles, eccrine epithelium and other dermal mononuclear cells [63]. Key markers include orthopox virus antigens and cellular markers like cytokeratins and lymphocytes.

Electron Microscopy (EM): Electron microscopy reveals round-to-oval, sausage shaped virions measuring between 200 to 300 um within the keratinocyte cytoplasm in various stages of assembly [67,69].

Using RT-PCR assay for the extracellular-envelope protein gene of the mpox virus can be distinguished by IHC and EM [67].

How Does Mpox Spread?

The mpox virus can spread in any number of ways. Mpox is primarily zoonotic disease meaning it is transmitted to humans from animals. Transmission can also occur from human to human, which can lead to an outbreak. Knowing the mode of transmission is important in controlling and preventing the spread of the disease.

Animal to Animal Transmission: The main mode of transmission is through direct contact with infected animals. This occurs through direct contact with the blood, bodily fluids or cutaneous or mucosal lesions. Viral transmissions also occur by being bitten or scratched by an infected animal. This can also happen through handling, hunting or eating the meat of an infected animal [70,71], particularly in areas with poor public education/awareness.

Human to Human Transmission: Can take place in many forms once it is introduced to the human population and degrees of contact. Prolonged exposure to an infected individual by face-to-face contact through respiratory droplets (coughing, sneezing or talking), hugging, cuddling or massage. Direct contact with an infected individual's rash, saliva, lesion, scab or bodily fluids. It can also spread through sexual contact, intimate exposure through kissing, oral/anal/vaginal sex, skin contact of the genitals (male & female). Indirect contact with items like clothing, linens, bedding, towels, or surfaces that were previously touched or used by an infected individual may also transmit the mpox virus. Individuals who are asymptomatic can spread the mpox virus as well [73].

Risk mitigation through fewer or limited sexual partners may decrease exposure risk to the mpox virus. For infected males, leading research indicates the detection of the mpox virus in the semen; however, the transmissibility of the mpox virus through the semen, vaginal fluids, urine or feces has not been established [72].

Pregnant women can transmit the mpox virus to the fetus via the placenta. Additionally, individuals whose jobs expose them to orthopoxviruses may be at risk as well (eg. first responders, lab workers, public safety officers, healthcare professionals, etc.).

Risk Factors for Transmission

There are many factors which increase the risk of transmission of mpox. These include close contact with household members who are infected, health care workers, sexual contact,

community settings like overcrowded mass gatherings (i.e. refugee camps, dormitories). Others who are at greater risk are veterinarians, laboratory personnel and animal handlers.

Comment [TA46]: This information should be under Epidemiology of Mpox

Treatment

There are no medicines or specific cures available to treat the mpox virus. The virus usually goes away on its own after it runs its course of between 2 to 4 weeks. Most therapies concentrate on treating and alleviating symptoms during the infection period. ~~A combination of supportive care, antiviral medication and vaccines can effectively manage the disease.~~ Once the viral infection goes away, individuals usually start feeling better. Symptoms can be managed through [22-24,28,74].

A combination of supportive care, antiviral medication and vaccines can effectively manage the disease.

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1. Supportive Care: Helps alleviate symptoms and prevents complications. There are many over the counter medications available for symptom relief, complication mitigation and secondary bacterial infection containment. Analgesics for pain relief (i.e. Ibuprofen, Advil, Motrin) and antipyretic for fever reduction (i.e. Acetaminophen, Tylenol) are just a few examples. Proper hydration and a proper nutrient intake ensure a healthy immune system. A personal hygiene regimen that keeps the skin clean, dry, smooth along with the application of antiseptic cream mitigates the chance of a bacterial infection. Oxygen therapy for patients with lung and respiratory problems can also be of assistance.

2. Antiviral Drug Therapy: Since the mpox and smallpox virus are genetically similar, antiviral drugs tecovirimat, cidofovir and brincidofovir developed to protect against smallpox can be used to prevent and treat mpox infections. Despite the lack of thorough clinical studies, they have been shown to be effective in the treatment of mpox cases [40,75,76]. Figure 8.

    - Tecovirimat: Also known as TPOXX or ST-246 is the first antiviral drug is approved in Europe and in the USA for the treatment of smallpox and mpox,is an intracellular viral release inhibitor for smallpox which has demonstrated efficacy against the mpox virus as well. This was first shown to be effective in animal studies and approved by the FDA for treatment of smallpox. The drug works by inhibiting the viral envelope protein VP37 that the poxvirus needs to spread from the infected cell.Tecovirimat be administered orally or intravenously is available through the US federal Strategic National Stockpile.The antiviral drug is recommended for patients with severe illness.
    - Cidofovir: Is a DNA polymerase inhibitor that prevents viral replication. Initially used for the cytomegalovirus infection, it is currently not approved by the FDA for use in mpox virus cases. Cidofovir is toxic to the kidneys.
    - Brincidofovir: This is a lipid conjugate of cidofovir, which is available as Tembexa. It has shown promise in animal studies and has been approved by the FDA for use in mpox cases. Brincidofovir also works by inhibiting DNA polymerase, preventing DNA replication. Brincidofovir is considered safer than cidofovir.

~~3.~~ Vaccinations: although no specific treatment for mpox exists, controlling the severity and spread is possible. Smallpox vaccine development has been shown to be about 85% effective for controlling outbreaks. The CDC encourages the use of smallpox vaccines to protect against the mpox virus for those individuals who are at higher risk due to lifestyle factors and immunocompromised profiles. ACAM2000, Jynneos Intravenous Vaccinia

Immune Globulin (IMVANEX) are effective vaccines to prevent, control and reduce viral infection outbreaks [77,78].

3. Vaccination given within 4 days of exposure can prevent the onset of the disease and vaccination given within 14 days may reduce the severity. These vaccines offer greater benefit if given before for preventing the disease and soon after exposure to reduce symptoms and severity. According to studies carried out by the WHO, smallpox vaccines have an 85% efficacy rate at preventing mpox. If smallpox vaccines are given to children, mpox symptoms may be milder if contracted at a later stage in life.

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It is recommended by the CDC that individuals aged 18 years and older and who have been exposed to mpox be vaccinated to prevent a viral infection and to lessen any potential symptoms. While vaccination is primarily a first preventive measure, the treatment protocol known as Post-Exposure Prophylaxis (PEP) plays a crucial role. PEP can also be administered to individuals who are unaware of their personal exposure, community affiliations or who live in areas where mpox exists.

Mpox Prevention

Preventing the spread of mpox involves several strategies that focus on reducing the risk of transmission. It is of the utmost importance that a healthcare provider be contacted immediately if an individual experiences signs or symptoms of the mpox virus. Healthcare providers will diagnose the infection through testing and a physical examination. In the event of exposure or infection, healthcare providers will administer treatment protocols that prevent an infection or decrease the severity of it [52,70,71,75-78].

Telltale signs and symptoms of the mpox infection include feeling feverish, body aches and pains, swollen lymph nodes and the appearance of new sores or rashes. If an individual experiences something more critical like trouble breathing, chest pain, confusion, loss of consciousness or seizures - seek emergency room treatment immediately.

It is best to take appropriate safeguards to prevent exposure to the mpox virus. These safeguards are multi-dimensional and depending on an individual's demographic profile, one or more of the following prevention mechanisms may be appropriate.

Animal to Human Transmission:Avoid handling wild animals, use gloves and protective clothes. Refrain from eating their meat; when it is used, ensure it is properly cooked.

Human to Human Transmission: **I**solate or quarantine the infected individual in a negative pressure room to prevent further spread. Use personal protective equipment (PPE) - gloves, mask and gowns. Regularly wash hands with soap or ~~alcohal~~alcohol based sanitizers. Regularly disinfect the contaminated areas and surfaces in use.

If you are infected with the mpox virus, alert your sexual partners or any individuals you have had close contact with. Ensure all parties involved closely monitor themselves for new and emerging signs and symptoms. Seek medical attention immediately so as to contain the spread of the virus and to mitigate new or worsening health conditions. It is best to avoid all acts of

intimacy (i.e. kissing, hugging, cuddling or engaging in sexual acts) with infected individuals or those who display signs or symptoms of the mpox virus.

Screening: If an individual identifies with or belongs to the LGBTQ community, screening for the mpox virus is recommended as the majority of cases in the current mpox outbreak are from this demographic. The incubation period for the mpox virus is between 5 and 21 days and as such monitoring for emerging symptoms or changes in temperature should be done twice daily. All medical service providers and first responders should use personal protective equipment (PPE) when interacting with individuals infected with the mpox virus.

Vaccination: If an individual believes to have been exposed to the mpox virus or identifies with the LGBTQ community, Mpox vaccinations are available. A mpox vaccination will assist in containing the virus, help reduce its spread and help attenuate its severity if contracted.

Comment [TA47]: vaccines

Isolation: If an individual is infected with the mpox virus, self-isolation is the recommended course of action. Ensure all lesions and sores are covered and make certain they do not come into contact with bedding, linens, clothes or surfaces. Keep lesions and sores covered until they scab over and fall off naturally. Wait until a new layer of skin has formed. Do not allow sores or rashes to come into contact with non-infected individuals.

Travel: Avoid travel to locations where mpox is known to exist. Central and West Africa appear to be the hotspots. It is also best to avoid contact with live, sick or dead animals that are known spreaders of the mpox virus (e.g. rodents and primates). This also pertains to ingesting these types of animals.

Social Norms and Protocols: Follow the appropriate social norms and protocols to help mitigate the risk of contracting and spreading the mpox virus. Although mpox is not as deadly or transmissible as COVID-19, the same care must be taken in social settings. It is best that infected individuals wear a well-fitted mask which covers the mouth and nose; cover any rashes or sores with clean, dry clothing; avoid skin-to-skin or close contact; wash hands frequently with soap and water; frequently clean and disinfect surfaces and do not share bedding, towels, linens or clothing with others. Infected individuals should not donate blood or any other genetic material. These social norms and protocols also apply to individuals that are not infected.

These safeguards have been in place through the COVID-19 pandemic and have proven to be effective. The same safeguards should be employed during the mpox outbreak to contain and stop the spread of infection. Preventive measures and timely medical intervention are the keys to controlling an outbreak.

Healthcare Professionals

This group of highly qualified individuals come from a multidisciplinary healthcare services background. Their expertise focuses on infectious diseases, treatment, research, support services and large scale healthcare administration. The following provides insight into their specific roles and responsibilities [80-84]:

1. Infectious Disease and Infection Control Specialist: Their role is to diagnose all aspects of the mpox virus - providing guidance on treatment, establishing disease prevention protocols,

research and development of antiviral drugs and defining viral containment protocols (PPE, decontamination, contact tracing, etc.)

2. Urgent Care / Primary Care / Mental Health Care Physician: Their primary role is to diagnose and treat the viral condition. Their secondary role is to assemble a team of support care professionals to manage the patient case via referrals to specialists, psychological support services to manage anxiety and stress, urgent care services should the need arise and other counseling and support services.

3. Public Health Administrators and Health Educators: Their role is to manage large scale viral outbreaks through data collection, data monitoring and information dissemination. They identify outbreaks, monitor the viral spread, monitor case counts, work closely with infectious disease specialists to identify the disease, identify medical treatment protocols, establish prevention, quarantine and containment protocols, prepare education materials and launch public education/awareness campaigns.

4. Dermatologists: Their role is to diagnose the cause of skin lesion and recommend the appropriate treatment for skin symptoms.

5. Nurse Practitioners: They provide patient care and support services. They provide ongoing monitoring of signs and symptoms and provide the proper care. They also provide educational material.

6. Clinical Chemistry Lab: Laboratories provide a very critical role in identifying the disease (and its strains) through sophisticated testing such PCR tests, analyzing blood chemistry and serology. They work closely with medical professionals to conduct “test, diagnose, treat and repeat” cycles until a positive patient outcome is achieved.

7. Pharmacist: They play an important role in dispensing medication, advising patients on the safe use of antiviral drugs and alerting them of any potential adverse drug interactions.

8. Spatial epidemiologists

9. Disease ecologists

Take Home Message

The mpox virus in many ways resembles the same outbreak profile humanity has seen over the centuries. It is a viral zoonotic disease which spreads from animals to humans and through ~~human to human~~human-to-human contact. The difference being that modern science, public policy, financial resources and political fortitude have been the saving grace in shaping viral containment and eradication. Understandably, countries with the willingness and ability to deploy these resources have fared better during these times of crisis.

Mpox is a zoonotic viral disease caused by mpox virus, spread from animals to humans through direct contact with infected animals. Human to human transmission occurs through respiratory droplets, bodily fluids or contaminated objects. Genetically similar to smallpox, both are part of the orthopoxvirus family. From a transmissibility and severity perspective, mpox is less contagious and demonstrates symptoms far less severe than smallpox. Recognizing the clinical assessment for mpox is crucial for proper diagnosis and treatment. In typical cases, a 5 to 21 day incubation period is followed by symptoms that range from fever, muscle aches and

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lymphadenopathy. It is similar to smallpox but generally less severe, however, serologic studies point to evidence that show it may be more infectious than originally thought. Fluid filled rashes/sores on the face, chest and other extremities appear and eventually dry up and fall off. The entire course of infection runs between 2 to 4 weeks.

Accurate diagnosis involves laboratory testing, PCR testing for viral DNA, electron ~~miccroscopic~~microscopic and serological studies. Additional support is provided by histopathology and immunohistochemistry. There is no specific treatment for mpox. Because of its genetic similarity, vaccines and antivirals developed to combat smallpox can also be used to control and contain mpox. ACAM2000, Jynneos and Tecovirimat are just a few examples of smallpox vaccines and antivirals. Other antiviral medications like cidofovir, tecovirimat and brincidofovir guard against mpox with very good results.

Comment [TA52]: Revisit this sentence. It contradict the statement above that individual with Mpox (especially LGBT) should immediately report for treatment using Mpox Vaccine.

In addition, supportive care is also important. Ensuring hydration and providing balanced and nutritional diet assists the immune system. Preventive measures include avoiding contact with infected animals or humans. Other measures include the use of personal protective equipment and good hygiene practices. Top priority should be given to the latest developments in treatment, prevention and public health guidance.

Unlike smallpox, mpox cannot be fully eradicated due to the existence of an animal reservoir. Because of this, incidence of mpox cases require rapid diagnosis, treatment and an effective public health response for outbreak containment. Vaccinations, antivirals, pandemic-inspired social protocols are all critical components of a viral outbreak containment.

The mpox virus was not on America's radar. It is mind boggling just how quickly a perfect storm of a few sporadic cases in Europe, coupled with making it to the American shores, where no immunity to orthopoxviruses exist - and all of a ~~sudden~~sudden, a full-blown potential pandemic is on hand. The nature of mpox and by extrapolation, any potentially deadly virus - understanding its transmission, treatment protocols and prevention strategies can better help manage the disease and reduce its impact on humanity and public health.

Comment [TA53]: Unclear.

This democratized approach is the only hope mankind has for navigating the magnitude and severity of future viral outbreaks. Simply put, this responsibility falls on the shoulders of every man, woman and child - "no one is safe until everyone is safe" [27,32,70].

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Figures

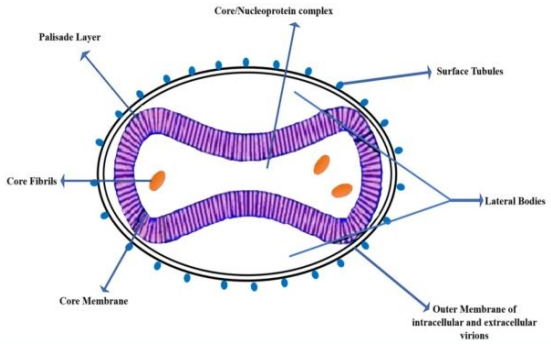

Figure # 1. Structure of the Mpox Virus under microscope
Adopted from VirusDis. 34, 191–203 (2023)

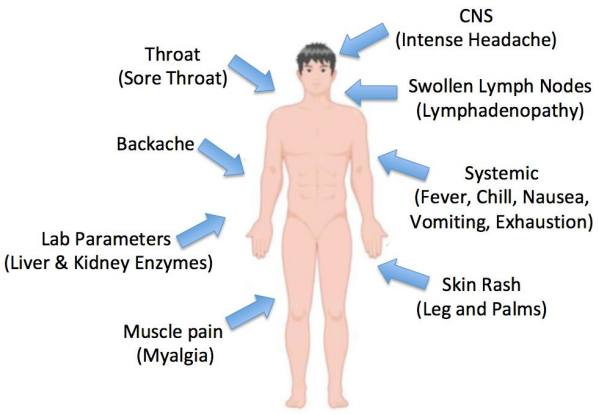

Figure # 2. Symptoms caused by the Mpox virus in the body of an infected person

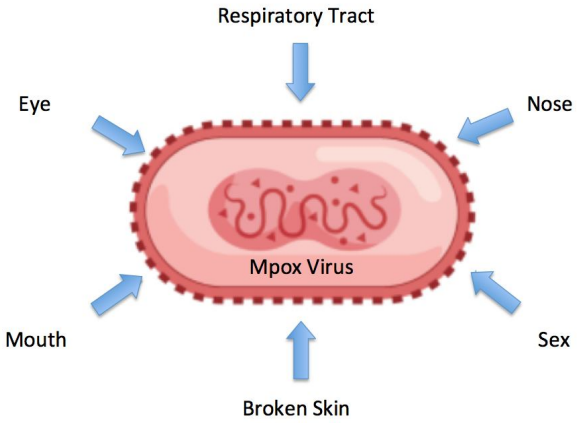

Figure # 3. How the Mpox virus enters the body.

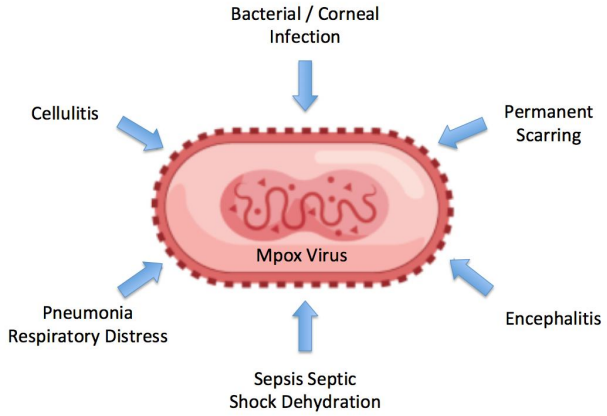

Figure # 4. Complications of the Mpox virus.

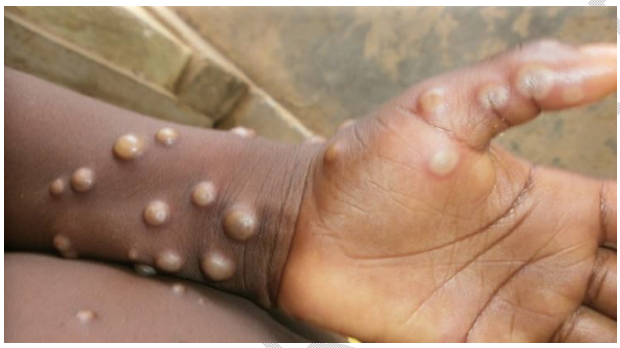

Figure # 5. Palm lesions of a person infected with the Mpox virus.
Adopted from the World Health Organization - Nigeria Center for Disease Control

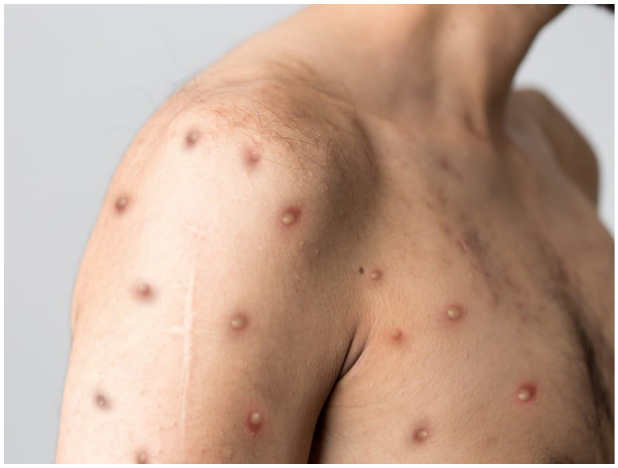

Figure # 6. Body lesions of a person infected with Mpox virus. Adopted from the National Capital Poison Control Center, Kelly Johnson-Arbor, MD, Medical Toxicologist

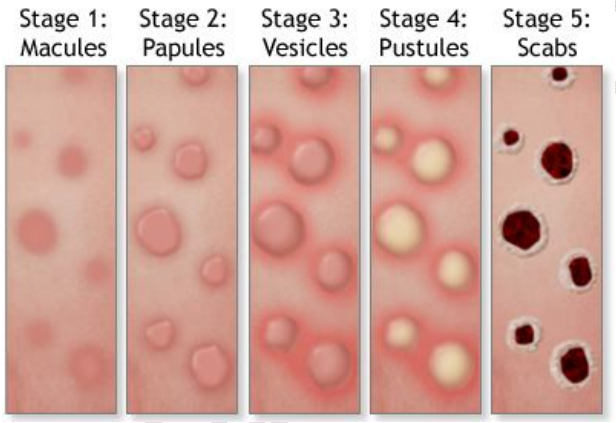

Figure # 7. Stages of skin eruption associated with the mpov virus. Adopted from Mount Sinai Hospital, New York

Figure # 8. Chemical Structure of Antiviral Drugs for Mpox

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