Relooking the monkeypox virus during this present outbreak: epidemiology to therapeutics and vaccines

S. CHATTERJEE¹, A.R. SHARMA², M. BHATTACHARYA³, K. DHAMA⁴, S.-S. LEE², C. CHAKRABORTY⁴

¹Department of Biotechnology, School of Life Science and Biotechnology, Adamas University, Kolkata, West Bengal, India
²Institute for Skeletal Aging & Orthopaedic Surgery, Hallym University-Chuncheon Sacred Heart Hospital, Chuncheon-si, Gangwon-do, Republic of Korea
³Department of Zoology, Fakir Mohan University, Vyasa Vihar, Balasore, Odisha, India
⁴Division of Pathology, ICAR-Indian Veterinary Research Institute, Izatnagar, Bareilly, Uttar Pradesh, India

S. Chatterjee, A.R. Sharma and M. Bhattacharya contributed equally

Abstract. – OBJECTIVE: The recent monkeypox disease outbreak is another significant threat during the ongoing COVID-19 pandemic. This viral disease is zoonotic and contagious. The viral disease outbreak is considered the substantial infection possessed by the Orthopoxvirus family species after the smallpox virus’ obliteration, a representative of the same family. It has potentially threatened the Republic of Congo’s regions and certain African subcontinent zones. Although repeated outbreaks have been reported in several parts of the world, as conferred from the epidemiological data, very little is explored about the disease landscape. Thus, here we have reviewed the current status of the monkeypox virus along with therapeutic options available to humanity.

MATERIALS AND METHODS: We have accessed and reviewed the available literature on the monkeypox virus to highlight its epidemiology, pathogenicity, virulence, and therapeutic options available. For the review, we have searched different literature and database such as PubMed, PubMed Central, Google Scholar, Web of Science, Scopus, etc., using different keywords such as “monkeypox”, “Orthopox”, “smallpox”, “recent monkeypox outbreak”, “therapeutic strategies”, “monkeypox vaccines”, etc. This review has included most of the significant references from 1983 to 2022.

RESULTS: It has been reported that the monkeypox virus shows a remarkable similarity with smallpox during the ongoing outbreak. Sometimes, it creates considerable confusion due to misdiagnosis and similarity with smallpox. The misdiagnosis of the disease should be immediately corrected by rendering some cutting-edge techniques especially intended to isolate the monkeypox virus. The pathophysiology and the histopathological data imply the immediate need to design effective therapeutics to confer resistance against the monkeypox virus. Most importantly, the potential implications of the disease are not given importance due to the lack of awareness programs. Moreover, specific evolutionary evidence is crucial for designing effective therapeutic strategies that confer high resistance, particularly against this species.

CONCLUSIONS: The review focuses on a brief overview of the recent monkeypox virus outbreak, infection biology, epidemiology, transmission, clinical symptoms, and therapeutic aspects. Such an attempt will support researchers, policymakers, and healthcare professionals for better treatment and containment of the infection caused by the monkeypox virus.

Key Words: Monkeypox, Zoonotic, Disease outbreak, Therapeutic strategies.

Introduction

The present monkeypox disease outbreak is an additional significant threat in the world that has just started to recover from the COVID-19 pandemic. A recent monkeypox case was recorded in the UK on 7th May 2022, the first case in non-African countries¹². Scientists found a travel link to
Nigeria. Following this, the disease has spread to more than 20 non-African countries such as the UK, Canada, Portugal, Spain, Italy, Sweden, and the USA (Figure 1). More than 400 suspected and confirmed infected cases have been recorded in these non-African countries.

Monkeypox virus is a class of DNA viruses belonging to the family of Poxviridae. Specifically, it is a double-stranded DNA virus with quite a large size. The first report of the monkeypox virus was made in the Republic of Congo in 1970. Like the other members of the Poxviridae family, the emergence of monkeypox is quite similar to that of smallpox, camelpox, and vaccinia. According to several reports by WHO, the emergence of the monkeypox virus was followed by the eradication of smallpox.

The primary source for this monkeypox is still unexplored. According to available literature, it was isolated from two animals: the rope squirrel from the Republic of Zaire (now called Congo) and the sooty mangabey from the Ivory Coast. This zoonotic virus develops specific clinical symptoms resembling smallpox in affected human beings. However, the cases of mortality reported in this infection are much lower compared to smallpox. The virus is predominantly found in some areas of Africa. However, its presence has been reported in some regions of the western hemisphere due to trading and traveling among countries.

The size of a monkeypox virus is approximately 250 nm, as recorded from the electron microscope. The members of the Poxviridae families resemble the shape of a brick with an outer envelope region of lipoprotein. The virus comprises a linear dsDNA with all the required genes for vital processes like transcription, translation, and replication. Various tubular structures surround the viral surface, with a dumbbell-like structure in the core. The vaccination using the vaccinia, another member of Orthopoxvirus, was influential in protecting the victims of the monkeypox virus. However, the eradication of smallpox has led to the failure in organizing vaccination programs against monkeypox and can be a significant reason for its dominance. The genome sequencing data of the monkeypox virus elucidated the presence of two virus clades with a difference in virulence.

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**Figure 1.** The figure shows the recent spread of the monkeypox virus in some major non-African countries, along with the virus’ origin in African countries, such as the Republic of Congo, Nigeria, and Liberia.

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The two clades are West Africa (WA) and Congo Basin (CB)\textsuperscript{14-17}. The CB clade’s transmission rate is higher than that of WA\textsuperscript{12,18}. The computation approach was undertaken to decipher the entire genome of the monkeypox virus, illustrating that this virus contains a variety of genes that are not found in the other members of this family. However, in line with evolution, it was presumed that this virus evolved in its way from its ancestors, maybe from the cowpox virus\textsuperscript{19}. In the present article, we have tried to highlight several essential aspects of the monkeypox virus, i.e., disease outbreak, infection biology, epidemiology, transmission, clinical symptoms, and therapeutic features. Moreover, our review will support researchers, policymakers, and healthcare professionals on a global scale, leading to better treatment and containment of the infection caused by the monkeypox virus.

Materials and Methods

For review, we have searched different literatures and databases such as PubMed, PubMed Central, Google Scholar, Web of Science, Scopus, etc. The literature search was performed using different keywords from those databases. The keywords used were: “monkeypox”, “Orthopox”, “smallpox”, “recent monkeypox outbreak”, “therapeutic strategies”, “monkeypox vaccines”, etc. During the literature search, we found that it is a neglected disease, and merely 850 papers have been available in the PubMed database since 1964. We observed from the PubMed database that several new papers were published quickly within a few days of the recent monkeypox virus outbreak. Around 84 articles were listed in PubMed within a month (from 17 May 2022 to 16 June 2022). However, we have included some of the most significant references from 1983 to 2022. In this case, we have decided some criteria for the reference selection. The moderate to high impact factor journals and highly cited references are two essential criteria for reference selection.

Origin of Monkeypox Virus

The first report of the monkeypox virus was recorded in the year 1958. It was found in the cynomolgus monkeys in Copenhagen, Denmark\textsuperscript{19}. The first incidence of human infection was reported in 1970. A nine-year-old child developed symptoms similar to smallpox and was admitted to a hospital in the Republic of Congo\textsuperscript{20,21}. Until 2003, the monkeypox virus infection had been restricted to certain parts of Africa (Figure 2). During the last week of July 2003, approximately 72 monkeypox cases were observed in different parts of the USA, such as Indiana, Illinois, and Wisconsin\textsuperscript{22}. Again, some people from the USA were infected with this virus during the spring of last year. However, this viral infection was transmitted from a pet dog to a human, and it was noted that the dog had come into contact with a rodent in Africa. Several symptoms were noted in the infected individuals, which are fever, respiratory troubles, and rashes\textsuperscript{23}. However, this incident occurred last year and has no connection with the present outbreak.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{monkeypox_outbreak_timeline.png}
\caption{A schematic line diagram shows the timeline of monkeypox outbreak in different countries. The figure describes that the infection was restricted to certain parts of Africa until 2003. The virus has spread outside Africa since 2003.}
\end{figure}
Epidemiology of Monkeypox

As per the database of WHO (until 21 May 2022), 98 cases of the monkeypox virus have been reported across various nations. Though, no mortality has been reported. The monkeypox outbreak was reported on 13 May 2022 in the regions where the virus was not dominant. The virus is mainly found in rodents and a few primates (not human beings). After 1970, several reports of transmission from human beings have been released. Moreover, evidence of infections in rats, squirrels, mice, and monkeys is also recorded. Out of the two reported clades, i.e., CB and WA, several reports highlight that the CB clade is one of the primary causative agents in case of human transmission compared to WA. Parker et al. reported the main reasons that hampered some epidemiological surveillance studies of the monkeypox virus. The monkeypox’s clinical symptoms are similar to Varicella-Zoster Virus (VZV) virus. The major problem in assessing the epidemiological trend of the monkeypox virus is the prevalence of different data from different sources, which creates unavoidable confusion. Besides, some major hindrances that affected the accurate epidemiological study are the lack of reporting of several cases and the shutting down of the vaccination camps after smallpox eradication. From 2003, a surge in the monkeypox virus infections has been registered. Recent data provided by the WHO discuss a positive case of infection in Massachusetts of a patient who traveled from Canada. Other cases have been from the UK. The significant factors indicating people’s susceptibility to this infection are the unhealthy practices due to their natural habitat and contact with someone who may be a monkeypox victim or unvaccinated against smallpox.

Transmission of Monkeypox

The major routes of monkeypox virus transmission are from human to human or animal to human through the respiratory droplets or certain fluids discarded from the infected patients. The communal spread between humans can also be due to the exchange of skin cells from an infected person. The transmission from the animals to humans occurs when the human is in direct contact with the animal (positive for the virus) or during feeding these infected hosts. The other ways of transmission mentioned from human to human are also valid in this case. The Ro or the contagious disease rate for the CB clade ranges between 0.6-1. The Ro for the WA clade is unknown, although it is anticipated to be much lower than CB. By seeing the maximum limit in the case of CB, it can be concluded that the infection will not only be restricted to a single person but is likely to prevail in the community of human beings. Besides all these transmission routes, humans might be affected by the infected animals’ leftover feces. The transmission in the case of humans is predominant from the primary victim with lesser evidence of secondary means. The transmission of the monkeypox virus can be attributed to many causes. Notably, the transmission landscape of the virus from animals to humans is unclear. In several reports, the exact source could not be identified. However, some of the research highlighted that some of the natural practices of the human being in their habitat involving infected animals might be a reason for the spread of infection. Beer and Rao have elucidated the importance of providing surveillance to patients at high risk to curb the nosocomial infection of the virus.

Virus Structure

The monkeypox virus under the genus of Orthopoxvirus is structurally the same as the cowpox and smallpox viruses. This virus resembles the shape of a brick as examined under the electron microscope. The outer region is encapsulated by a layer of lipoprotein, the virion part is encapsulated, and the linear core contains a double-stranded (ds) DNA genome and enzymes responsible for viral replication and uncoating. Additionally, all the interconnecting bonds, the dsDNA genome, and the central region of the virus also comprise different transcriptional factors, are protected by the outer lipoprotein-rich layer. The central region resembles a biconcave disc with two lateral regions on each side of the disc. The size of the monkeypox virus genome is nearly equal to 197 kb. Several palindromic hairpin structures form covalent bonds with the bases are present at the end of the genomes. Besides, there are other structural attributes like the tandem repeats, the inverted terminal repeat (ITRs), and the open reading frame. The ITRs constitute several hairpin loop-like structures. All the necessary proteins required for the vital life processes of the monkeypox virus are present in the central part of the genome. The housekeeping genes common to all the viruses of the orthopoxvirus species are also located at the core. The entire genome constitutes 190 ORFs, and each of the ORFs contains more than
60 amino acids. Out of 190 ORFs, four ORFs can be identified in the ITR region\(^\text{39}\). Monkeypox virus-encoded structural proteins and other important enzymes show 96.3\% identical genome sequence with the smallpox virus, while there are significant variances between the monkeypox virus and smallpox virus in the regions responsible for encoding the host-range factors and host cell virulence (closer to the terminal genomic part)\(^\text{41}\). Compared to monkeypox, the smallpox virus contains 10 enzymes that regulate the viral gene expression, and nearly 100 nucleoproteins are involved in the viral DNA transcription function of viral DNA\(^\text{42}\).

Several proteins are responsible for enhancing the virulence of the monkeypox virus, whereas some function in the opposite ways. One of the most virulent genes in the monkeypox virus genome is homologous to the BR-203, which does not permit the infected lymphocytes to undergo apoptosis\(^\text{43,44}\). Some of the other homologous genes are BR-209 and MOPICE (monkeypox inhibitor of complement enzymes). The BR-209 affects the defense mechanism of a host by blocking the IL-1\(\beta\) from interacting with the inflammatory cytokine IL-1, hindering virus entry to the host cells\(^\text{45}\). Some genes, like MOPICE, block several enzymes’ activation in the complement pathway, downregulating the immune response\(^\text{46}\). Besides that, the monkeypox virus also encodes the complement-binding proteins, consisting of merely three consensus short repeats, whereas in other orthopoxviruses (smallpox, cowpox), there are four sequences. The study also found that the monkeypox virus translates IL-1\(\beta\)-binding protein, which could be the main reason for its lower ability to infection, compared to the smallpox virus\(^\text{41}\). The clinical comparisons of smallpox and the monkeypox virus raised questions about the genetic relationships of these viruses. It is considered that the monkeypox virus could develop into a smallpox-like virus through a higher transmission frequency in humans.

**Mechanisms of Infection**

A member of the Poxviridae family, the vaccinia virus contains a protein named E3, which is responsible for obstructing the activation of the innate responses of the host cells after infection and continues the replication process. Similarly, the monkeypox virus contains a protein homologous to E3 and has similar functions\(^\text{47}\). The infection of the monkeypox virus can be via two virions. One is with the help of intracellular machinery virus (IMV), and the other can be through the external envelope virion (EEV)\(^\text{48}\). Studies have proved that the virus’ rapid spread inside the host’s body is due to this EEV virion. The intracellular envelope virus is transported into the host cell with the help of certain microtubules. They also facilitate a stronger virus attachment to the host cell’s surface. The intercellular spread of the virus is made possible through another kind of virion called CEV, or the cell-associated virion\(^\text{49}\). One of the notable facts given by Hutson et al\(^\text{52}\) depicts the possibility of tissue tropism. The isolates from the dead animals who were the victims of the disease confirmed increased viral load and the infection through many virions. The variability of the animal source makes it difficult to understand the exact mechanism of action. Due to this difference, the interaction of the virus may be different with the host, triggering the immune system in different ways\(^\text{52}\).

**Immunological Responses**

The scarcity of data makes it difficult to comment on the immediate response of the innate and adaptive immune systems to protect the body against the monkeypox virus\(^\text{49}\). Song et al\(^\text{50}\) highlighted the variation in the quantity of the natural killer (NK) cells triggered when the monkeypox virus evades the host immune system. The number of NK cells decreases, suggesting that the infected cells are not eliminated, an essential function of the NK cells\(^\text{50}\). Hammarlund et al\(^\text{51}\) stated that the infection of this virus restricts the function of the MHC-I receptors and disrupts the activation of the CD8\(^+\) and CD4\(^+\) cells, keeping the virus protected from the action of various immune cells. This, in turn, provides the insight that the virus is potent in blocking the release of several types of cytokines and can infect the monocytes\(^\text{51}\). Antibody-dependent augmentation is one of the most common phenomena observed in the case of a series of viral infections. This effect is mainly due to the involvement of the IgM and IgA antibodies. However, a similar view in the case of the monkeypox virus has not been reported\(^\text{52}\).

On the other hand, another immunological component that interferes with the cell signaling pathway is the NF-\(\kappa\)B, and it also influences the pathway concerning programmed cell death and inflammatory responses. Most importantly, the monkeypox genome contains eight Ankyrin (ANK) genes responsible for inhibiting the role of NF-\(\kappa\)B\(^\text{53,54}\). A closer look at the genome or-
ganization of the monkeypox virus informs us that numerous proteins can inactivate various elements of the innate and adaptive immune systems\textsuperscript{55}, making it a difficult task for the immune system to eliminate and promote viral clearance, as observed in the case of most viral infections.

**Clinical Symptoms**

As discussed earlier, the monkeypox virus' clinical symptoms are similar to that of smallpox\textsuperscript{56}. The incubation period for this disease ranges between 10-14 days, accompanied by a prodrome period in which the infected host has no rashes over the body. However, the observable clinical symptoms at that phase are sore throat, fever, breathing troubles, chills, and the inflammation of the lymph (Figure 3a)\textsuperscript{57,58}. The process occurs within 2-3 weeks on average. Inflamed lymph nodes, mainly in the cervical or the submandibular region, constitute a significant point differentiating the clinical symptoms from smallpox. Almost 90% of all human

![Figure 3. Different clinical symptoms and different stages of rash development during the infection of monkeypox. A, A schematic diagram depicts various clinical symptoms in monkeypox infected individuals. B, Different stages of rash development which usually dries and, finally, fall off.](image)
infections account for this symptom. After this phase, the host can observe the maculopapular rashes, which vary in size. The significant transmission probability from the infected host happens during this developmental phase. The maculopapular rashes undergo four stages of development from the face to the toe. They also start originating in the palms and the toes. During the healing time, in the end, these rashes become dry and fall off like flakes.

In some cases, it has been noted that lesions begin after a rash appears, and the process takes 2-3 weeks on average (Figure 3b). The evolution of lesions progresses through four stages which happen before scabbing. In line with these clinical symptoms, certain health complications are also found associated. For instance, severe dehydration due to the growth of lesions inside the mouth hinders one from drinking, or pneumonia and sepsis can also occur. In extreme conditions, there may be a complete loss of skin pigmentation and encephalitis.

**Diagnosis**

The effective diagnosis method should be employed in the case of monkeypox because it is often misdiagnosed with several other diseases where the development of the rashes is a common symptom. The monkeypox virus was misdiagnosed as chickenpox in the Republic of Congo outbreaks. Other instances suggest that monkeypox infected cases demonstrate symptoms identical to the case of syphilis, smallpox, cutaneous anthrax, fungal diseases, rickettsialpox, etc. Thus, effective diagnosis methods should be designed to identify the monkeypox virus. A similarity with the symptoms of smallpox and resemblance of the viral genome with the variola virus makes it hard to distinguish the monkeypox in a laboratory. In recent times, the use of real-time PCR has been successful in identifying this virus. Certain limitations are arising for the development of specific techniques that can help access the immune profile of the infected host even after viral clearance. However, the generalized cross-reactive antibody detection method cannot be considered in the case of the monkeypox virus. An ELISA technique can be helpful, since it can differentiate by identifying an antigenic epitope in the monkeypox virus that is not present in variola species. Using a smaller fragment from the antigenic peptide can be a superior method in identifying the patients vaccinated against smallpox and those who tested positive for the monkeypox virus. Erez et al. mentioned a process involving imaging the patient swab using TEM and PCR and confirming the results using the ELISA technique and immunofluorescence-based assay. This assay was performed in Israel in 2018 and could detect the high titers of the virus in the patients, as it employs multiple methods to diagnose and confirm the presence of the monkeypox virus.

**Vaccination**

Vaccination is one of the significant ways to fight against the virus. It was observed that WHO declared the smallpox free world in May 1980. Presently, two smallpox vaccines are available, which are ACAM200 and JYNNEOSTM. However, several countries still preserve stockpiles of smallpox vaccines after eradication of smallpox.

As discussed earlier, severe monkeypox outbreaks were observed after the eradication of smallpox and the break from the regular vaccination programs against smallpox. Jezek et al. implied that the vaccinated individuals against smallpox are resistant to the infection caused by the monkeypox virus. More precisely, the same vaccination strategy was helpful for both the viruses of the Poxviridae family. However, the prior use of the vaccines was not considered as it might have induced severe health effects.

There are no effective therapeutic intended particularly for treating monkeypox outbreaks. The critical observation and management of the symptoms is the primary way that is usually followed in the case of monkeypox infection. The smallpox vaccine can be a potent agent for the protection against monkeypox. Vaccinia, an independent species belonging to Orthopoxviruses, includes camelpox, cowpox, smallpox, monkeypox, etc. The vaccinia virus vaccine has eliminated smallpox. However, the exact origins of the vaccinia virus are unclear. The vaccinia might be a hybrid of the variola and cowpox viruses. We all know that the variola virus is the causative agent of smallpox. The incidence of getting infected by the monkeypox virus is lower if the individual gets a last shot of the smallpox vaccine. It has been reported that the vaccine given against smallpox can confer up to 85% protection against the monkeypox virus.

The clinical manifestation, including the disease's signs and symptoms, gets curbed down to a greater extent. The doses of the Ankara vaccine, a live vaccine conferring resistance to
both smallpoxes and monkeypox, can be suitable for use. Taking two doses of the vaccine within four weeks will render good results compared to the primitive vaccinia one. Notably, three essential vaccines licensed to be administered against smallpox have not been tried for exposure to monkeypox. One of them is the IMVAMUNE, the replication-deficient, attenuated form of third-generation improved vaccinia Ankara (MVA) vaccine, approved by USFDA (United States Food and Drug Administration) and EMA (European Medicines Agency). The second one is JYNNEOS, the non-replicating, live vaccinia virus vaccine (approved by USFDA in 2019). The other one is ACAM2000, which contained a live vaccinia virus that received approval from the CDC (Centers for Disease Control and Prevention) after the major outbreak in the USA in 2003. The current vaccines and antiviral therapeutics used against the monkeypox virus have been enlisted in Table I.

**Antiviral Therapeutic**

Besides vaccination, antiviral agents against monkeypox can be an effective treatment. Implementing Cidofovir has given promising results in treating infections caused by the herpes virus and cytomegalovirus. Cidofovir is a nucleotide analog administered through the nose and has given good results in the African dormice, which were the victims of the CB clade of the monkeypox virus. Tecovirimat is another drug tested on prairie dogs, and it has been given orally and found more effective than cidofovir.

Cidofovir has a wide range of antiviral activities and is a nucleotide analog. It is used for the treatment of the infection of cytomegalovirus. Another significant antiviral molecule is Brincidofovir, which is a hexadecyloxypropyl lipid conjugate of Cidofovir. It has been observed that Brincidofovir is active against dsDNA viruses.

This drug is approved for the treatment of smallpox. At the same time, the efficacy of Brincido-

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Vaccines and antiviral therapeutics</th>
<th>Country where the vaccines/therapeutics have been origin and year of development</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Vaccines</td>
<td>IMVAMUNE Democratic Republic of the Congo, USA (2013)</td>
<td>This is an attenuated strain of the vaccinia virus, unable to replicate in human cells without any serious side effects.</td>
</tr>
<tr>
<td>3.</td>
<td>ACAM2000</td>
<td>France (2008)</td>
<td>This vaccine is a second generation smallpox vaccine. It was derived from the clone of Dryvax, purified, and prepared using modern cell culture technology.</td>
</tr>
<tr>
<td>4.</td>
<td>Antiviral agents</td>
<td>Cidofovir USA (1996)</td>
<td>This antiviral component blocks the viral replication by selectively inhibiting viral DNA polymerases.</td>
</tr>
<tr>
<td>5.</td>
<td>Tecovirimat</td>
<td>USA (2008)</td>
<td>This antiviral component prevents the cellular transmission of the virus by inhibiting the functions of major envelope protein.</td>
</tr>
<tr>
<td>6.</td>
<td>Brincidofovir</td>
<td>USA (2010)</td>
<td>This antiviral component released the cidofovir which acts as inhibitor of viral DNA polymerase.</td>
</tr>
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</table>
fovir has been demonstrated against the monkeypox virus in animals.

Similarly, tecovirimat is used to treat the infection of the monkeypox virus. It is the first smallpox antiviral therapeutic molecule, and this molecule was used to treat smallpox. Now, these two molecules are used to treat the monkeypox infection. However, the efficiency of Brincidofovir and tecovirimat in treating monkeypox infection is not known.

Pathology

Pathological results have indicated the presence of the monkeypox virus in the various tissues of the lungs, ovary, heart, kidney, brain, etc. Among all these organs, the maximum viral load was found in the ovarian tissues suggesting that these tissues are prone to be infected by the monkeypox virus. Besides, detecting the virus from Macacafascicularis (the Cylogenous monkeys) has indicated a well-developed tropism between the virus and the monkeys, especially the lymph tissues. The presence of the virus was noted in several tissues. Interestingly, the involvement of the lymph tissues in the tonsil and mandibular regions highlights the early infection sites and initiation of replication from these organs to other tissues. The virus can enter the host cells, and these are transdermal, nasopharyngeal, and oropharyngeal.

It has been observed that the monkeypox virus can spread to the body’s organs via blood. During the incubation phase, the primary replication of the monkeypox virus occurs in the lymphatic organs leading to the blood. After that, via blood, it spreads to other body organs. These pathophysiological events occur during the incubation period before the prodromal phase. The seeding process goes on to the other secondary organs during the prodromal period, followed by fever and chills. The infectivity rate is maximum at this phase, and the development of rashes can be observed. Rashes are first developed in the oropharyngeal regions before they are visible on the skin. The spread of the rashes is not predictable, and it may be significantly less or, in some cases, highly concentrated.

Conclusions

For the past few decades, especially after the eradication of smallpox, the world has seen some monkeypox outbreaks. The recent data illustrates that it is no more restricted to the endemic zones. It is spreading worldwide, and the symptoms are similar to smallpox. The main concern is that very scarce is known about this disease. The population is not aware of the consequences of these outbreaks, especially in the non-endemic regions.

Most importantly, the population is unaware of the significant causes of the disease. The rapid progression of the disease has not reported any mortality, but the researchers should be on the frontline to make people aware of the disease and its implications. Literature has indicated that there has been no proper therapy specially intended to confer resistance against this virus. The therapeutic agents employed in the case of the smallpox virus may provide resistance, but this should not be a permanent solution.

Some of the evolutionary evidence suggests that the mutations in the viral genome of the virus impart the capability to escape the immune system despite having performing antibodies. Recently, the world has seen several mutations in the SARS-CoV-2 virus and the creation of variants from time to time in the last two and half years. The viral variants had shown their capability of immune escape and vaccine escape. Scientists should explore the capability to immune escape and vaccine escape for the monkeypox virus. At the same time, the scientific community should aggressively come up and explore the information essential to be known about the disease to protect the population from widespread infections. Effective vaccine constructs should be invented to have specificity and protection against the monkeypox virus. More research is needed to understand better the changing pattern of epidemiology, animal reservoir(s), genomic evolution, and immune escape of this virus. Besides, surveillance programs should be conducted to educate the population about the harmful effects of the disease and the significant ways to prevent any future outbreaks.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Ethical Approval

Not required.

Informed Consent

Not required.
S. Chatterjee, A.R. Sharma, M. Bhattacharya, K. Dhama, S.-S. Lee, C. Chakraborty

**Funding**
This study was supported by Hallym University Research Fund and by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (NRF - 2020R1C1C1008694 & NRF - 2020R1I1A3074575).

**Authors’ Contribution**
Writing – original draft: Srijan Chatterjee; Writing, review, and editing: Ashish Ranjan Sharma; Writing, validation: Manojit Bhattacharya; Validation, review: Kuldeep Dhama; Validation; visualization; fund acquisition: Sang-Soo Lee; Conceptualization; review and editing: Chiran-jib Chakraborty.

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