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Advances in monkeypox: exploring vaccines and therapeutic drugs for prevention and treatment

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Abstract

The most extensive monkeypox outbreak in history commenced in 2022 and has swiftly disseminated globally. This review aims to succinctly outline host immune reactions to orthopoxviruses, present an insight into available vaccines to counteract the epidemic, and delve into clinical research and animal studies examining induced immunity against monkeypox induced via the vaccinia virus-based monkeypox vaccines. It addresses current concerns about the outbreak and suggests optimal vaccine utilization as a control measure. During the 1980s, surveillance studies in Central Africa and subsequent outbreaks demonstrated that smallpox vaccines were approximately 85% effective against monkeypox. These findings are substantiated by numerous animal studies, primarily in primates, involving live virus challenges through different inoculation methods, consistently showcasing high levels of protection and immunity post-vaccination. Smallpox vaccines emerge as effective countermeasures for managing monkeypox outbreaks, although they do entail adverse effects, and second-generation, replicative vaccines have prohibited usage. Third-generation vaccines pose a challenge for rapid responses as they require 2 doses, which can be difficult for people with weak immunity. Insights from the COVID-19 outbreak must guide our collective approach to addressing the monkeypox outbreak and future outbreaks.

Introduction

The outbreak of monkeypox in human

The epidemic of a poxvirus-related illness in monkeys at an institute in Copenhagen, Denmark was initially reported in 1959 and identified as the Monkeypox virus (MPXV). The first recorded human case of MPXV occurred in the autumn of 1970 when a 9-month-old infant was referred to Basankusu Hospital in Congo, and MPXV was isolated (1).

MPX is endemic in Western and Central African countries (2). So far, five significant MPXV outbreaks are documented: one in 1970, another in 1996-97, one in 2003, and the most recent ongoing outbreak in 2022. This current outbreak has affected over 50 non-endemic countries across multiple continents, resulting in more than 6000 cases (3). MPXV has been categorized into two primary clades based on its genome architecture, namely the Central and West African clades. A novel classification proposal has been introduced to

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categorize MPXV isolates into three clades (4). These clades exhibit unique clinical, genomic, geographical, and epidemiological variations (5). These clades are associated with various epidemiological rashes of MPXV. The two main clades of MPXV isolates associated with outbreaks in Congo and West Africa are the MPXV Clade 1 and MPXV Clade 2, respectively. These clades, responsible for most of the regular spread of infection and indigenousness in Africa, exhibit varied transmission and pathobiology patterns and distinct clinical outcomes, which additionally reveal their differentiation (6). Clade 1 (Congo Basin Clade) has a particularly severe disease, with higher mortality rates and more transmissibility. Notably, clade 3 (MPXV Clade 3) consists of isolates from the 2017-2019 epidemics and genomes from the last 2022 epidemic that are constantly undergoing assessment as they diverge into emerging lineages (7).

The virus primarily spreads by being exposed to droplets of respiratory tracts or through close contact and exposure to infectious body fluids (1). There is also a possibility of uncommon transmission by touching feces and feces on the flies, which has been proposed as a source of infection in wild chimpanzees (8). Additionally, a new form of spread has emerged within sexual networks, particularly among male homosexual sex workers, highlighting sexual contact as a significant route for virus transmission, along with other potential sources (4).

The Poxviridae viruses are composed of large, complex, enveloped, and linear dsDNA viruses. These viruses infect a wide range of animals, with some being specific to humans, such as the variola virus and Molluscum Contagiosum virus. The poxviruses are classified into two subcategories: the Chordopoxvirinae, which infects vertebrates, and the Entomopoxvirinae, which infects insects. There are eighteen genera in the subfamily Chordopoxvirinae, including the Orthopoxvirus genus. Orthopoxviruses are typically large, ranging from 140 to 450 nm, and have brick or oval-shaped forms (9).

It is worth noting that there is cross-protection and cross-reactivity among Orthopoxviruses, which means infection with a member of the genus can offer some level of defense against other members of the same genus. Before the rash appears, the most frequently observed symptoms include fever, restlessness, and lymphadenopathy (10). Human MPXV exhibits symptoms that are similar to both regular and modified smallpox, although usually less severe (11). Swollen lymph nodes, which are not typically associated with smallpox but are present in 90% of MPX patients, are considered a distinguishing feature of MPX (10).

Immune system activation after MPXV infection

The immunity to MPXV infection and vaccination involves both innate and adaptive immune mechanisms. When the MPXV enters the body, the innate immunity serves as the body's initial defensive mechanism (12). Pattern recognition receptors (PRRs) on various cells, such as macrophages and dendritic cells, recognize viral components and trigger an immune response. Antigen-presenting cells (APCs), such as dendritic cells, phagocytose the MPXV (13). They process viral antigens and present them on their cell surface in conjunction with major histocompatibility complex (MHC) molecules. The innate immune system activates inflammatory pathways to contain and eliminate the virus. This involves the release of cytokines and chemokines, which attract immune cells to the site of infection. The adaptive immunity to MPXV involves the activation of specific immune cells and the production of antibodies, providing a targeted and long-lasting defense against the virus. $CD4^+$ T cells recognize the viral antigens presented by APCs (14). This interaction activates the $CD4^+$ T cells, which play a central role in coordinating the immune response. They release cytokines that help regulate the activity of other immune cells (15).

$CD8^+$ T cells recognize and directly target cells infected with the MPXV. They become activated and differentiate into cytotoxic T lymphocytes (CTLs). CTLs are responsible for killing virus-infected cells, limiting the spread of the virus within the body. B cells recognize viral antigens either directly or with the help of $CD4^+$ T cells (16). The interaction between the B cell receptor and the viral antigen activates the B cell. Activated B cells undergo clonal expansion, producing a large population of identical cells (17). Some of these cells have the ability to differentiate into plasma cells, which are designed to produce antibody. Plasma cells release antibodies specific to the monkeypox virus. These antibodies can neutralize

the virus by binding to its surface proteins, preventing it from infecting host cells (18).

A subset of B cells becomes memory B cells, providing long-term immunity. Memory B cells "remember" the specific viral antigens, enabling a faster and more robust response upon re-exposure to the virus. Antibodies produced by plasma cells neutralize the monkeypox virus by binding to its surface proteins (19, 20). This prevents the virus from entering host cells and establishes an early defense mechanism. Antibodies can also tag virus particles for destruction by phagocytic cells, enhancing the clearance of the virus from the body. Both $CD4^+$ and $CD8^+$ memory T cells are generated during the adaptive immune response. These memory T cells "remember" the viral antigens, ensuring a quicker and more effective response upon subsequent encounters with the monkeypox virus (21). Memory B cells circulate in the bloodstream and reside in lymphoid tissues (22). If re-exposed to the virus, these cells can rapidly differentiate into plasma cells, producing a swift and targeted antibody response. The adaptive immune response to monkeypox is essential for clearing the virus, preventing the spread of infection, and establishing long-term immunity to protect against future exposures. Vaccination aims to induce a similar immune response, conferring immunity without causing severe disease (23).

Monkeypox treatment

Many patients infected with monkeypox can recover without the need for medical intervention. However, individuals experiencing gastrointestinal symptoms such as vomiting and diarrhea will need oral or intravenous rehydration to prevent excessive loss of fluids in the digestive system.

Currently, there is no targeted therapy available for monkeypox. However, certain antiviral medications originally intended for smallpox or other orthopoxviruses have been adapted for the treatment of monkeypox infection (24). Some of these drugs are listed below:

1) Tecovirimat

Tecovirimat, also recognized as TPOXX or ST-246, is the preferred antiviral treatment for monkeypox in adults and pediatric patients over 3 kg weight. It is the first drug specifically indicated for this purpose (25). The successful replication of a virus results in the creation of various infectious forms of the virus. The intact viral particles are infectious but still stay inside the cell pending the cell lysis. However, enveloped virions are formed as the viral particles cover themselves with late endosomal membranes. The process of creating a cover for enveloped virions is facilitated by the orthopoxvirus P37 protein (26). These enveloped virions, which are capable of being released from the cell without causing cell lysis, play a crucial role in the spread of the virus within the host, both between cells and over long distances. The gene responsible for encoding the P37 protein is highly conserved in all orthopoxviruses (27). The P37 protein has interactions with the Rab9 GTPase and TIP47, both of which are components of transport vesicles derived from late endosomes. This interaction between Rab9 GTPase, P37 and TIP47 results in the formation of a definite wrapping complex for enveloped virions. Tecovirimat is a blocker of P37, as it prevents the interaction between P37 and Rab9 and TIP47, thus hindering the formation of the enveloped virus. As a result, it inhibits the fabrication of extracellular viruses and reduces their spread to other areas (26).

2) cidofovir (CDV)

CDV is currently only FDA-approved for treating cytomegalovirus related retinitis, despite being effective against several DNA viruses, such as orthopoxviruses. Cidofovir is a prodrug that needs to enter the cells first and then be converted into its active form, CDV diphosphate (CDV-pp), by cellular enzymes (28). Once phosphorylated, CDV-pp remains active for a long time within the cells. It works by incorporating into the elongating DNA strand through the replication, thereby slowing down DNA synthesis (29). Additionally, cidofovir diphosphate can also suppress the activity of DNA polymerase 3′–5′ exonuclease (30).

3) Brincidofovir

Brincidofovir is a CDV analogue with lipid-conjugation sold under the product name Tembexa (Chimerix). Brincidofovir obtained FDA-approval in 2021 as a medication for smallpox (30). It is believed to have a better safety profile, specifically with a decreased risk of kidney toxicity, compared to cidofovir. The mechanism of action of these drugs is to inhibit the viral DNA polymerase (31). Brincidofovir exhibits greater cellular uptake and more efficient conversion to the active form by intracellular enzymes, in contrast to cidofovir (32).

4) VIG

VIG, or hyperimmune globulin, is produced by collecting pooled plasma from healthy individuals who experimented a vaccinia vaccine and have excessive levels of anti-vaccinia antibodies. These antibodies can attach to the poxvirus virion, effectively blocking the virus transmission to other cells. VIG has received FDA approval as a treatment, for complications that can arise after receiving the vaccinia vaccine (24). These complications comprise vaccinia, eczema vaccinatum, severe generalized vaccinia, vaccinia infections in individuals with skin complications, and unusual infections caused by the vaccinia virus. However, there is information about the efficiency of VIG toward smallpox and monkeypox, and its application for these diseases has not been verified on humans. In cases where immunodeficiency in T cell function prevents vaccination with the vaccinia, VIG may be an alternative (33). It is crucial to highlight that VIG treatment should only be pursued under an IND application.

5) NIOCH-14

The State Research Center of Virology and Biotechnology, Russia, has recently developed a new compound called NIOCH-14. It is an orally bioavailable tecovirimat analog that has shown similar results to tecovirimat research in vitro. This makes it a suitable candidate for the next generation of anti-orthopoxvirus medications (34). Animal studies showed that NIOCH 14 can significantly reduce the infection in infected mice and reduce the virus load in their lungs (35).

Monkeypox vaccines

MPXV is a member of the Poxviridae family, Orthopoxvirus genus, which is similar to the smallpox virus. As a result, smallpox vaccines can protect MPXV due to cross-reactivity (36). According to previous reports from Africa, the smallpox vaccine has demonstrated at least 85% effectiveness in preventing monkeypox (37). The smallpox vaccine has undergone three generations of medical technology, but only the second and third generation vaccines, ACAM2000 and IMVANEX, are presently approved. ACAM2000 is a replicating smallpox vaccine, while IMVANEX (also known as IMVAMUNE or JYNNEOS) is a live, nonreplicating vaccine developed by Bavarian Nordic in Denmark. These vaccines are suitable for use in two scenarios: pre-exposure to avoid infection and spread of virus among high-risk individuals, or post-exposure (ideally within 4 days) to improve disease and virus replication consequences (38).

1) ACAM2000

ACAM2000, classified as a second-generation vaccine, is a live attenuated vaccinia vaccine that is made from a single clonal viral isolate from Dryvax.This isolate has been shown to have reduced neurovirulence in animal models. Unlike the traditional method of growing the virus in the skin of animals, ACAM2000 is produced using modern cell culture techniques. When administered within three days of contact, it is believed to be 80-93% effective in preventing VARV infection as a post-exposure prevention measure for smallpox (39). Adverse events associated with ACAM2000 include common symptoms such as fever, malaise, headache, muscle pain, and adenopathy. Although rare, there have been reports of more serious adverse events including vaccinia gangrenosa, skin infection, generalized vaccinia, inflammatory cardiomyopathy, Stevens-Johnson syndrome, idiopathic pericarditis, acute brain failure, post-vaccination encephalitis, and acute disseminated encephalomyelitis (40). Using it is not advised for individuals with a weak immune system, such as those with pregnancy , HIV, and individuals with skin conditions like eczema, due to the possibility of severe side effects resulting from its potential for replication (41).

2) IMVANEX (also known as JYNNEOS or IMVAMUNE)

IMVANEX, a third-generation vaccine, utilizes the replication-deficient modified vaccinia Ankara (MVA) (25). Actually, it has been derived from over 570 passages of the strain in primary chicken embryo fibroblast cells and has become limited in its ability to replicate to avian and certain mammalian cells (42). In clinical trials, no serious adverse events were observed, and overall peak neutralizing antibody levels after two doses of MVA vaccine were comparable to those seen after a single dose of ACAM2000 in human volunteers (43). However, a study revealed lower levels of monkeypox-specific neutralizing antibodies (44). These vaccines have an improved safety profile due to their attenuated nature, making them suitable for immunocompromised individuals such as patients with HIV and atopic dermatitis (45).

3) LC16m8

During the 1970s, Japan developed a novel smallpox vaccine called LC16m8. This vaccine is live, attenuated, and cell-cultured, derived from the Lister (Elstree) strain of vaccinia. LC16m8 is a third-generation vaccine that replicates and attenuates the virus. The high level of attenuation is achieved through a single nucleotide deletion mutation in the B5R viral gene, leading to a truncated B5 protein of membrane, which is highly immunogenic. Various studies on human subjects have confirmed the safety of LC16m8, showing mild to moderate local and systemic adverse events as common occurrences (45). Though, severe adverse events such as encephalitis and symptomatic myocarditis have not been observed in clinical trials and cohort studies. It is not recommended to widely administer this vaccine to individuals with compromised immune systems or those with atopic dermatitis (46). Nevertheless, preclinical evidence suggests that the LC16m8 vaccine may still be suitable for use in these specific populations (47).

Conclusion

In conclusion, a comprehensive approach involving the development and deployment of effective vaccines and therapeutic drugs is required to combat monkeypox. The historical efficacy of smallpox vaccines in providing significant protection against monkeypox underscores their role as a crucial tool in outbreak control. However, the presence of side effects and contraindications in certain vaccine formulations prompts the exploration of alternative solutions. The promising results from animal studies, particularly in non-human primates, provide encouraging evidence for the development of vaccines targeting monkeypox. While second-generation, replication-competent vaccines may pose challenges, third-generation vaccines offer a safer option for immunocompromised populations, albeit with the drawback of requiring a two-dose regimen. In parallel, the investigation into therapeutic drugs for the treatment of monkeypox remains a vital avenue of research. The quest for antiviral agents and targeted therapies aims to enhance patient outcomes and mitigate the severity of the disease.

As we navigate the complexities of the monkeypox landscape, drawing lessons from the COVID-19 pandemic becomes imperative. Collaborative efforts, accelerated research, and strategic vaccine deployment strategies are essential for an effective response to the current monkeypox outbreak and preparedness for future challenges. The dynamic interplay between scientific innovation and public health measures will ultimately shape our ability to control and overcome the threat posed by monkeypox.

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Conflict of Interest

Authors have no conflict of interest to declare.

Ethical Approval

Not Applicable.

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