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The Immune Interface of Age: Neonatal and Adult Host Responses to Monkeypox Virus Infection

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ABSTRACT

The emerging zoonotic pathogen Monkeypox virus (MPXV) produces separate clinical outcomes between age groups because young and older individuals possess varying levels of immune system development. The review examines the host-specific events that occur in both adult and newborn immune systems when exposed to Monkeypox virus. Neonates experience suspicion to systemic spread, limited interferon responses and subpar viral clearance because they have underdeveloped immune systems. The immune system of adult hosts generates strong Th1-dominated defense mechanisms which result in better viral control. High-grade immune reactions in adults may create tissue damage in major infection manifestations. The evaluation investigates how aging affects skin protection mechanisms and the way cytokines work and antigen-presenting cells perform their responsibilities. Medical treatments with appropriate age considerations and vaccination administration strategies and public health policies need accurate understanding of age-specific immune properties. The understanding of immunological age interactions enables researchers to develop individualized interventions which will enhance outcomes for various patient groups throughout MPXV outbreaks.

Keywords: Monkey pox, neonates, immune system, cytokine storm

1. INTRODUCTION

MPox virus (MPXV) is a zoonotic pathogen causing monkey pox (mpox), a disease that has lately become a major worldwide health problem. Clade I & Clade II are the two genetic clades into which MPXV is categorized, Clade II is further divided into Clades IIa & IIb. MPXV historically, was limited to West and Central Africa's wooded region, but recently it has expanded beyond of these endemic areas, accusing outbreaks in several non-endemic nations. The B1 lineage-caused worldwide mpox epidemic in 2022 brought attention to the virus's capacity for extensive propagation. The World Health Organization (WHO) on 23rd July 2022 declared that mpox is considerably contributing to health crisis situation. Scientists discovered MPXV in Danish captive monkeys during 1958 yet humans did not report their initial mpox infection until 1970 through an infant, nine months old, originating from the Democratic Republic of the Congo. Human mpox case numbers remained very low throughout the period that spans from 1970 to 2021 while the disease maintained narrow geographic boundaries. MPXV triggered its first outbreak outside endemic regions when the United States documented the first cases in 2003. This development shifted how the disease spreads. Mpox clinics show similar clinical features as smallpox by causing fever and headache alongside muscle aches and swollen lymph glands and distinctive rash. The disease presents milder symptoms than smallpox yet affects immune-compromised patients and children with a fatality range of 1% to 10%. The successful elimination of smallpox in 1980 resulted in stopping smallpox vaccinations because the vaccines previously offered 85% protection against MPXV. The decreased immune defenses from ending variola vaccination programs became a factor behind the growing spread of mpox. Current research into MPXV stands limited because this virulent poxvirus follows variola virus (VARV) as the second most virulent pathogen. A complete comprehension of these areas represents an essential prerequisite for creating effective prevention methods as well as control strategies.

This paper investigates MPXV's ecology along with genomics and infectious biology and investigates its evolutionary processes while emphasizing its current worldwide expansion. The article explores present-day mpox control strategies and discusses research opportunities for increased preparedness when responding to public health outbreaks.

2. THE ORIGIN AND CLASSIFICATION OF MPXV

A double-strand (ds) virus MPXV is classifies under the genus Orthopoxvirus genus within Poxviridae family (figure 1). Medical authorities documented in 1958, the initial discovery of MPXV (MPXV) from *Macaca fascicularis* (crab-eater monkeys) in Copenhagon (Cop), Denmark [1]. Poxviridae contains two subfamily divisions: Chordopoxvirinae including 18 genera along with 52 species and Entomopoxvarinae including 4 genera and 31 species which altogether make up 22 genera and 83 species. Twelve types of Orthopoxvirus exist within the genus and this virus group causes infections in humans and animals. The prominent members of this virus group consist of MPXV and Vaccinia virus together with Takerapox virus and *Abatino macacapox* virus and Akhmeta virus and Camelpox virus and Cowpox virus and Ectromelia virus along with Raccoonpox virus and Skunkpox virus and Volepox virus [2]. In 1970, the first documented human case caused by MPXV, occurred in the Democratic Republic of the Congo [3]. MPXV functions as the pathogenic agent that produces mpox disease which mainly occurs across Central and Western Africa. Researchers have identified two separate viral clade types: West African coupled with Central African (Congo Basin) [2].

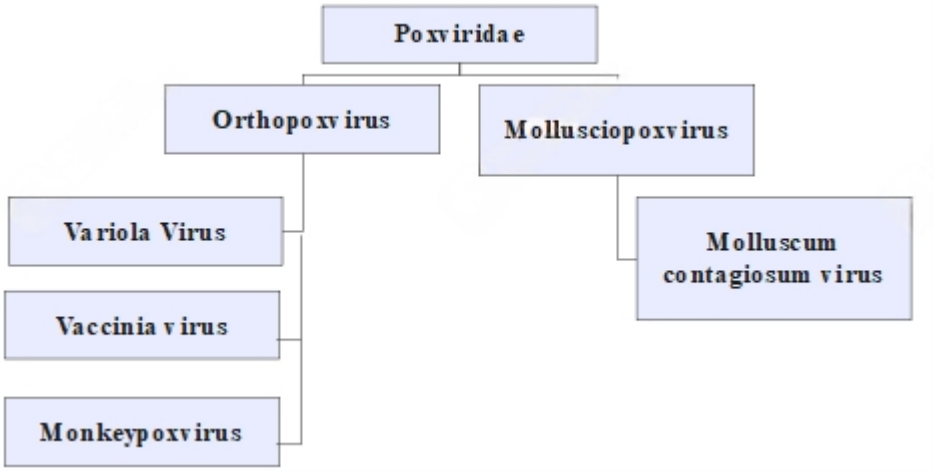

Figure 1: Taxonomy of MPXV

3. EPIDEMIOLOGY

Discovery and Animal Reservoirs

Viruses from central Africa tend to show more virulence compared to those from West Africa. The human MPX disease clade from Central Africa was accessory to amplified viremia, human-to-human transmission, illness, & mortality in the course of 2003 outbreak in the United States. According to reports, the clade of Central Africa reported much severity, showing a greater death rate of 10% as compared to that of West African clade i.e., 4%. Occurrence of variability in the organization of genome by removal of gene sections and fragmentation of gene in free reading frames are the source of variations in virulence. Therefore, gathering samples from various regions, people, and clades is essential for figuring out the MPXV's genetic characteristics as well as confirming the cases and research facilities.

When captive monkeys were transferred from Africa to Denmark (Copenhagen) for research, the initial indication of MPXV was discovered in 1958 during an epidemic of vesicular illness. As a result, "MPox." The name is inappropriate because rodents were considered to serve as the primary reservoirs of this virus, among animals, including huge pouched rats and squirrels, both of which are killed for food. There are about 1500 species of Rodents, making them the largest group of mammals. Ecological and epidemiologic studies are necessary to characterize the etiology, natural history, and breadth of the wild animal reservoir of MPox in people and animals. Several species of animals including dormice, rats, striped mice, monkeys, and squirrels (both tree and rope) have been found to harbor MPXV. MPox was carried via rope squirrel in the Democratic Republic of the Congo (1985) and a deceased baby mangabey monkey in Tai National Park, Cote of d'Ivoire. In a major outbreak, monkey pox virus was introduced by animals brought for livestock commerce, and about fourteen species of rodent were identified as the host carrying the Mpox virus. Monkeys are regarded as disease carriers, just like people. In addition to investigating the impact of pathogen-host relationships and climatic and ecological elements that influence changes in the virus between geographic regions and as a cause of human disease, more research is required for getting a clearer view with respect to the survival of the virus in nature. During the period of early human identification, Zaire recorded 282 events from 1980 to 1985 including the age span from a month to 69 years, out of which 90 percent were less than fifteen. There were no deaths among immunized patients, whereas the average fatality rate was 11% for non-immunized individuals, with elevated rates among children (15%).Vaccinia had previously been used to

produce protection against the MPXV, but the smallpox annihilation and subsequent curtailment in the immunization effort prevented the development of resistance against MPox. Due in part to the paucity of data from rural Africa, the dangerous potential of this contagious virus was underestimated. MPXV was believed to have been spread by visitors to Israel and other countries when it emerged in 2017 after 39 years of unreported occurrences in Bayelsa and Nigeria state. In 2018 and 2019, the issue was then raised.Shipping, Importation, travel, contact with sick monkeys, and associated groups at risk of acquiring MPXV were among the factors contributing to the MPXV spread outside of Africa. This may be connected to the discontinuance of the smallpox vaccine, which showed cross-resistance in defiance to MPXV and perhaps played a role in the development of inter-human transference, as was previously indicated. The MPXV outbreaks beyond the African boundaries show how this virus is connected worldwide. Although it did not end in Africa, MPXV moved to developed countries. The United States reported two MPX cases in July 2021 in people traveling back to Texas from Nigeria. Following his visit to Nigeria, a British man's case was publicized on May 6, 2022. Spanning over 43 territories, together with Europe and North America, there have been about 1500 cases reported as of June 2022. Central and western Africa are home to the MPXV, but reports of MPX symptoms spreading around the industrialized globe have also surfaced. All cases of illness were either associated with traveling to African territory or shipping livestock. The United States is now an emerging center of Mpox viral outbreak, with 80 deaths and 29,980cases. This poses a worldwide risk, demanding the development of a judiciously calculated plan of action to stop MPXV from spreading like wildfire.

4. VIRAL GENOME AND STRUCTURE

The MPXV Zaire strain of Central Africa (NC_003310.1), also known as Clade I the reference strain, has a dsDNA genome of over 197 kb that encodes over 190 open reading frames. Although MPXV clades I and II have a very slight disparity in DNA sequence, around 0.55% to 0.56% , discrepancies in critical areas encoding significant virulence genes most likely account for the marked disparities in seriousness of the disease across the two clades [1, 4]. The coding section of the genetic makeup of MPXV, which encodes crucial elements involved in transcription, virion assembly, and viral replication, is largely conserved with those of orthopoxviruses [4]. Inverted terminal repeats (ITRs), that are similar but opposite sequences found in the variable sections at the terminal regions of the viral genomic composition, are crucial for the pathogenicity and host range of poxviruses and are susceptible to the development of hairpin ends with covalent closures. Despite having a similar genetic makeup, poxviruses appear to differ from one another. ITR regions have the greatest degree of poxvirus genome flexibility [5, 6]. Sequences of MPXV isolates from the 2003 U.S. epidemic also show notable changes between MPXV Clades I and II ITR regions, in terms of deletions and insertions. MPXV's increased dissemination, virulency, and capacity to elude immune responses are mostly due to its mutation rate, adaptability, and continuous genetic development, which might result in a global outbreak of cases. Similar to other poxviruses, MPox Virus is a big virus with an oval, rounded, or brick-shaped morphology, measuring between 200 and 250 nm in size. The lipoprotein membrane, lateral bodies, surface tubules, dsDNA, and a double-concave dumbbell-shaped core make up the MPXV virion (Li et al., 2023). Enzymes linked to the main transcription of structural genes are included in the core region of the MPXV virion.

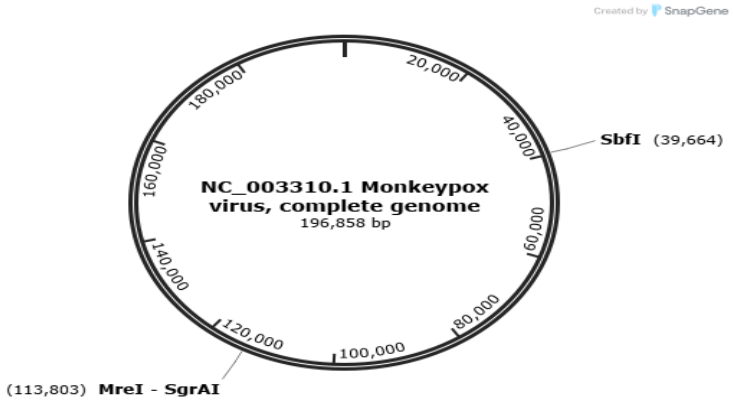

Figure 2: MPox Virus genome

5. HOST-VIRUS INTERACTIONS

i. Transmission

MPX has mostly been seen in West and Central Africa. Inter-human to human, inter-animal, and animal to human are some of the ways that MPXV might spread. Direct connection with infected animals or bodily fluids is the most frequent way that infections are spread from one animal to another [7]. Animal contact has been linked to human infections. In areas where animal interaction occurs often, rodent contagion in dwellings and the preparation or hunting of bush meat from distinct species make it heavy to pinpoint the specific way that exposed a human case [8]. In addition to monkeys, squirrels and sooty mangabey are other animals that are considered to be common reservoirs for MPV. Rodents are also believed to be the virus's reservoir hosts, while exact number of animals are yet to be confirmed. Furthermore, humans,

prairie dogs, mice and rats can be infected [9]. In West Africa and Nigeria, inter-human dissemination has been detected [10]. Infected surfaces or objects that are believed to raise the chance of transference of the virus among component of the same household include living in the similar house or use of similar dishes that has been used by infected individual. In 2003, the 1st human Monkey pox case was detected in the United States. There was still a chance of transmission from human to human even if the outbreak was connected to getting in touch with sick prairie dogs [11]. In September 2018, a patient in the UK infected a healthcare worker with the MPXV through contaminated bedding [12].

Fomites, close touch, or exposure to big respiratory droplets while in close contact to an infected person's skin lesions ca n all result in transmission [8]. Since there were initially no epidemiological links to West and Central African sites, the unexpected occurrence of MPX in several areas increases the likelihood of undetected transmission over an extended period of time. The CDC has updated its guidelines regarding potential transmission routes for MPXV, including hugging, kissing, and various forms of sexual intercourse, which may be associated with hereditary alterations that facilitate inter-human transferance [13]. The majority of confirmed cases in the 2022 outburst in Europe were derived from the West African clade, suggesting a limitation in human to human transference [14].

ii. MPXV Transmission between Animal and Human

Unlike VARV, having just a single recognized human host, MPox virus has a wide variety of hosts, which could increase its ability to adapt and spread to people. Non-human primates, dormice, squirrels and Gambian pouched rats are among the natural reservoirs of MPXV. In 2003, an outbreak of 47 human cases happened in the United States as a result of exposure to the secretions and excretions of diseased pet prairie dogs. Based on epidemiologic studies, these dogs had previously come into close contact with rodents that were brought in from Ghana [15].

iii. **MPXV transmission from humans to humans**

a. Sexual transmission

One of the main theories for MPXV transmission at the moment is sexual transmission. According to Vivancos et al., men who determined as gay, bisexual, or MSM reported 66 out of 86 confirmed MPXV cases [16]. According to a latest systematic review that included 124 MPXV cases, unsuitable sexual conduct is considered to be the main way that the virus is spread [17].

b. Non- Sexual Transmission

The main methods of non-sexual contact transmission are direct contact with infected objects, respiratory droplets, vertical transmission, and skin-to-skin contact. Orthopoxvirus entry pathways can penetrate the placenta's viral-resistant syncytiotrophoblast barriers.(is the primary barrier between the mother and fetus, regulating the exchange of nutrients and gases between the maternal and foetal circulations) [18]. Due to the broad rash seen in stillbirths delivered to pregnant women detected with MPox viral infection and the identification of MPXV DNA in foetal tissue, the placenta , and the umbilical cord , vertical transmission has been verified [19]. When individual come into close, sustained contact with one another, large/vast respiratory droplets carrying aerosolized MPXV may spread the virus from person to person [8]. For instance, a tourist not having immediate sexual interaction with an infected individual was reported to have contracted MPXV. Non-sexual interaction with many people during a packed outdoor event was his main danger factor [20]. Cynomolgus monkeys were revealed to aerosolized MPXV in a non-human primate experiment, which led to their infection and eventual pneumonia-related deaths [21]. Following intranasal MPXV treatment, same behaviour has also been noted in barking squirrels with black tails or the model of prairie dog [22]. Furthermore, close physical contact with rashes, scabs, sores, or bodily secretions of an already exposed person can spread MPXV [13]. MPXV can also be inherited via accidental exposure to tainted objects, like apparels and bedcloths. The public should therefore be aware of the need of maintaining good personal hygiene.

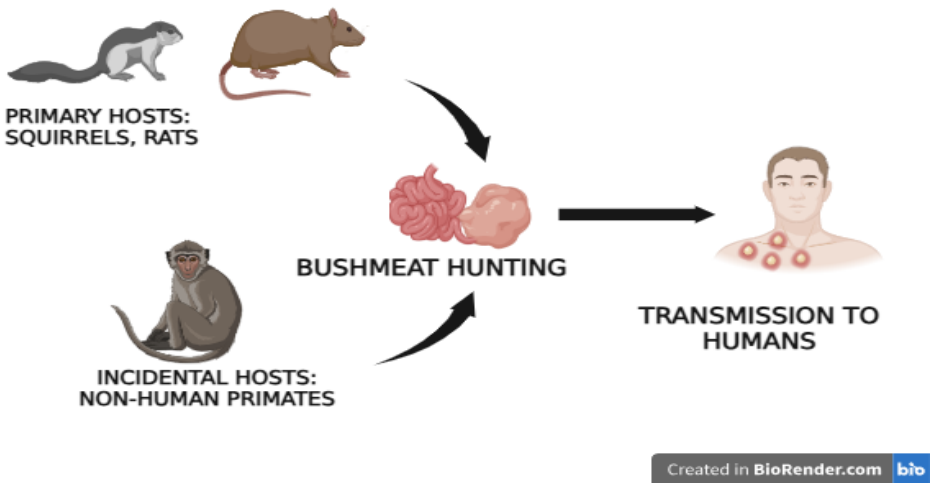

Figure 3: Transmission of MPXV

6. VIRAL PATHOGENESIS

Mpox can enter the host cells through a variety of channels, including direct contact, bodily secretions, eliminations through bowels, penetration past by the nasal route, pharynx, nasopharynx, subcutaneous, mucosal surfaces, intramuscular, or intradermal routes into the skin. In order to enter host cells and replicate at the infection site, micropinocytosis, endocytosis, and fusion mechanisms are employed [23]. The virus enters the lymphatic system from the circulation and begins to impact other critical organs, including bone marrow, lymph nodes, the spleen, and tonsils. In the host, it gradually grows and manifests as a disease linked to mpox. Furthermore, investigations have shown that mpox infections are separated into two versions because the virus causes two different forms: enveloped virion (EV) & mature virion (MV) that vary based on layers of the membrane and glycoproteins resent on the surface. While EVs have their external membrane removed ahead of combining with host cells, MVs enter host cells through micropinocytosis or fusion processes. In order to release their distinct proteins and viral genomes into the cellular environment, both forms thereafter go through a replication process inside the host cytosol. After early genes are expressed, transcriptional regulatory factors and intermediate genes follow, producing viral dsDNA. After completing the phases of immature viral DNA creation, the replication, transcription, and translation processes aid in the assembly of the intracellular mature virion (IMV). The Golgi apparatus then provides IMV with outer wrapping so that it can change into intercellular enveloped virions (IEVs). When discharged from the cell, extracellular envelope viruses (EEVs) are formed when IEVS subsequently bind with inner cellular membranes to generate cell associated viruses (CEVs).Eventually, these viral types—like IMV, CEV, and IEV—are escape the host cell to lyse the host and infect cells nearby. They form a second membrane during this discharge, which precedes their departure from the host cell. The complicated replicating cycle of monkey pox is explained by these events.

7. PATHOGENESIS IN NEONATES VS. ADULTS

MPXV is an animal to human transmissible viral infection brought about by a member of the *Orthopoxvirus* genus within *Poxviridae* family, the Monkeypox virus. While monkeypox typically presents as a mild disease in young adults and grown-ups, it can cause much severe and complicated disease in neonates due to their underdeveloped immune systems [24]. The pathogenesis of monkeypox in neonates and adults differs significantly, mainly due to the differences in immune responses, organ systems, and viral replication.

8. IMMUNE SYSTEM DIFFERENCES IN NEONATES AND ADULTS

The immature and underdeveloped immune system of neonates affects their weak ability to fight infections including monkeypox. The defense system in newborns functions poorly because they have reduced numbers of functional dendritic cells along with macrophages and natural killer cells that normally identify and combat pathogens [25]. A lack of effective pattern recognition receptor activation specifically toll-like receptors (TLRs) within neonates prevents them from properly detecting viral elements present in MPXV. The activation process for CD4+ helper and CD8+ cytotoxic T-cells operates at reduced levels in cases of neonatal immunological responses [25]. The insufficient adaptive immune response takes longer to activate thereby permitting the virus to replicate without restraint throughout the body. The B-cell immunity of new-borns remains immature while passive immunity from maternal antibodies does not guarantee comprehensive protection against MPXV especially when maternal exposure to or vaccination against MPXV is absent [26].
Due to their mature state adults own immune systems remain robust while adults possess strong defensive capabilities. Intrinsic immune responses of adults function more effectively by rapidly producing interferons and pro-inflammatory cytokines which control viral replication. Viral infection management through the adaptive immune response reaches peak efficiency in adults [27]. Immune cells named T-cells act swiftly on infected cells yet B-cells generate precise antibodies which deactivate the virus. Before the onset of adolescence the immune response works in a coordinated manner at rapid speed effectively allowing adults to better handle and eliminate viruses and thus produce a milder illness that brings reduced possibilities of developing complications.

9. CLINICAL MANIFESTATIONS IN NEONATES VS. ADULTS

Neonates' compromised immune systems sometimes result in a much extreme and complex clinical presentation of monkeypox compared to that in adults. After being exposed to the virus, neonates frequently have a shorter incubation time and show symptoms sooner [28]. Given that newborns' immune systems react more slowly, this rapid start is probably caused by ineffective management of early viral replication in these patients. While fever, rash, and lymphadenopathy—the classic signs of monkeypox in infants—are comparable to those in adults, they are frequently more severe and noticeable in neonates. Additional nonspecific signs that newborns may have, such poor eating, lethargy, and irritability, might complicate early diagnosis [29]. The principal monkeypox symptom among babies presents with a rash which appears later or less noticeable than older patients yet develops into more serious extensive pustules which result in joining together. Secondary bacterial infections tend to develop more frequently in monkeypox lesions thus leading to both worsened illness and new complications [30]. One of the main symptoms of monkeypox is a rash that can be less distinct

or delayed in newborns, but when it does show up, it can be more severe and widespread, frequently taking the form of big, deep pustules that have the potential to confluence. Additionally, secondary bacterial infections are more likely to occur in these lesions, which can exacerbate the illness and cause new problems [30].

Neonates generally experience greater frequency and worse consequences of systemic MPXV infection. The underdeveloped respiratory systems of neonates enhance their risk of developing pneumonia along with respiratory distress while increasing their chances of developing fast breathing and limited oxygen flow. The second brain system of neonates represents a weak point so MPXV infection can result in encephalitis that may create permanent neurological harm. The sepsis risk for neonates becomes higher due to two factors: bacterial infections spreading from skin lesions and viral infections causing organ damage leading to multiorgan failure [31]. The occurrence of these monkeypox complications improves the chance of fatality in neonates above the numbers observed in adult patients.

Adults usually face a standard illness duration because their case typically develops slower than neonates with longer incubation times. The rash associated with adult monkeypox patients tends to be contained on specific surfaces of the body while the fever presents as localized breaks showing a typical progression of maculopapular lesions from papules to vesicles then pustules before healing into crusts [32]. Lymph node swellings are frequent in patients but systemic problems tend to be less severe than in newborns. Adults commonly endure a light to moderate form of monkeypox illness which typically requires no intensive medical treatments. Adults experience fewer complications of pneumonia or encephalitis during monkeypox infections since these occurrences appear less often and have less serious outcomes compared to newborns. Supportive care adequately treats adult monkeypox patients since their death rate is lower than the rate observed in neonates.

10. TREATMENT

i. Treatment and Management of Monkeypox in Neonates and Adults

The specific treatment for neonatal monkeypox requires specialized care because of their susceptible immune system along with higher possibility of severe outcomes. The principal therapeutic approach for neonates consists of supportive care because there are no accessible antiviral therapies available for monkeypox [33]. The main aspects of supportive care involve hydration maintenance because electrolyte balance requires stability and prevention of dehydration particularly among neonates who struggle to eat due to their illness. The proper nutrition of neonates becomes crucial because illness might cause feeding problems while nutrition directly supports both growth and immune development. Supportive care for neonatal monkeypox patients requires proper fever management as an essential measure. The use of acetaminophen as an antipyretic medicine enables individuals infected with monkeypox to reduce high temperatures while preventing compensatory issues and discomfort [34]. Adult patients with monkeypox need supportive care as treatment that focuses on controlling fever and discomfort while maintaining proper intake of diet and water. Adults who display moderate monkeypox symptoms do not require critical care because health care providers treat symptoms through medicines that reduce rash pain and fever temperatures [35]. Heavy monkeypox infection which progresses to pneumonia or encephalitis may require supportive therapies including antivirals such as tecovirimat and supplemental breathing care. Right medical care leads to enhanced survival opportunities for adults who face less death risk compared to newborns and achieve recovery more likely [36]. Both adult groups need continuous observation to identify potential secondary conditions including bacterial infections of their skin sores. Adults experience a limited illness duration with limited treatment needs while newborns need aggressive care because their health risks can become potentially fatal.

11. DRUGS AND VACCINES

i. **Tecovirimat:** Tecovirimat, sometimes referred to as ST-246 also known as, TPOXX, is the 1st anti-viral medication to be authorized as a preferred course for smallpox treatment in kids and adults who weigh a minimum of 3 kg [37]. Dual therapy with brincidofovir and tecovirimat could be employed to patients having severe illness. Tecovirimat inhibits viral spread by blocking viral envelope protein VP37 inside the affected host, that stops the final phase of virus maturation and discharge from the tainted cell [38]. Although the drug's ability to prevent MPox from infecting humans is still under study, researchers have revealed that animals given tecovirimat during variable stages of the illness had a greater chance of surviving fatal infections with the MPXV than animals given a placebo [39]. Patients with MPox can now receive therapy with tecovirimat under a CDC and FDA-developed Expanded Access Investigational New Drug (EA-IND) program. Additionally, the Centers for disease control collected data from 1001 documented cases of this antiviral medication. According to the most recent report, a number of clinical trials are either planned or presently in progress to assess the efficancy and safety of tecovirimat in treating individuals with MPox [40].

ii. **Brincidofovir**: Brincidofovir, sometimes referred to as Tembexa or CMX001, is a lipid conjugate of cidofovir (CDV), an acyclic nucleotide phosphonate. Following entrance into the targeted cells, a phospholipase enzyme breaks down the lipid esters bond in brincidofovir, releasing CDV [41]. This is followed by two successive phosphorylations that produce cidofovir diphosphate (CDV-PP) and cidofovir monophosphate (CDV-P).Viral DNA synthesis is suppressed by CDV-pp either by attaching to the viral DNA strand as an acyclic nucleotide or inhibiting the DNA polymerase activity of various dsDNA viruses [42]. Numerous investigations on animal have shown that brincidofovir is a

successful antiviral treatment for double-stranded (ds) DNA viruses, such as poxviruses like the MPXV. It is also presently being studied in human clinical settings to treat various double-stranded DNA viruses [24].

iii. **Trifluridine:** Trifluridine, a topical antiviral agent, has been used to treat mpox ocular disease patients and has demonstrated in vitro action against orthopoxviruses, although the lack of observational data regarding its effectiveness [43]. While critically ill mpox patients have been treated with combinations of these medicines, no clinical trial data has shown that combination therapy are helpful for Mpox. In comparison to cidofovir, brincidofovir exhibits better antiadenoviral activity, no nephrotoxicity, excellent oral bioavailability, and higher intracellular levels of the active medication [44].

12. VACCINES

BNT166, a MPXV vaccine with a multivalent mRNA, proving protection against orthopoxvirus disease to mice and macaques

We created BNT166 to provide a next-gen vaccination in defiance of MPXV and associated orthopoxviruses that is highly immunogenic, safe, scalable, and accessible. This was done in response to the 2022 mpox epidemics brought on by the MPXV virus's unprecedented inter-human transmission. In order to identify distinct variations and elevate the scope of the immune response, preclinical evaluation of two potential multivalent mRNA vaccines was performed: a trivalent vaccination (BNT166c; missing H3) and a quadrivalent vaccine (BNT166a; encoding A35, H3, B6, and M1 antigens of MPXV). In challenging research. MPXV, vaccinia, and clade I were all neutralized by BNT166a and BNT166c. Additionally, BNT166a vaccination was 100% effective in suppressing lesions and preventing mortality in a fatal clade I MPXV challenge in cynomologus macaques. They assist the continuous clinical testing and analysis of BNT166.

The main ways by which Mpox spreads intra-personally are via contaminated items, body fluids, respiratory droplets, skin lesions of exposed animals or humans. The cell membrane of mpox virus is bi-layered having a shape of bricks. It replicates inside the host's cytoplasm by taking advantage of its double -stranded DNA. Hairpin termini are present in the linear, around 197000bp long mpox virus genome. There are $\geq$ 198 open reading frames (ORFs) that do not overlap are included. The clinical presentation of mpox is quite similar to smallpox, despite the fact that it is milder and has three distinct phases. The first phase, referred to as the incubation period, lasts seven to fourteen days.

In the second phase, there is a temperature that ranges from 38.5 to 40.5 degrees Celsius, along with chills, headaches, backaches, muscle aches, and lymphadenopathy. This stage separates it from chicken pox and smallpox. Macular rash, which progresses through vesicular, papular ,and pustular stages, culminating in crusts that eventually come off, is the hallmark of the third (rash) stage .Myocarditis ,epiglottitis and septic shock are uncommon but dangerous side effects that might cause death due to an overreaction of the immune system.

13. VACCINES AGAINST MPOX: MVA-BN AND LC16M8

In 2022, the outbreak of Mpox spread around the, causing many people to be hospitalized. Many recent cases of MPOX have been seen in children in Africa. Two vaccines called MVA-BN and LC16M8 can help prevent MPOX.

MVA-BN vaccine: Protects against lethal doses of mpox and similar viruses in animals. During outbreak, MVA-BN lowered the chance of MPOX illness by 62%to 85%.in people who came contact with MPOX, MVA-BN lowered the risk of illness by 20%.MVA -BN safe even for children due to its non-replicative nature. Over 1 million people including thousands living with HIV have received MVA-BN [45].

LC16m8 vaccine: LC16m8 saved animals from lethal doses of mpox and other similar viruses. There is not much data available about LC16m8 that was used during the MPOX outbreak. Significant safety signals were not found after these doses.LC16m8 should not be given to people who have a supressed immune system, who have a certain skin conditions or who are pregnant [46].

MPOX vaccine recommendations

Health officials recommend the mpox vaccine for people at high chance of contracting the virus including children.A third vaccine ACAM2000 utilizes a replicating vaccina virus, which presents a more comlpex safety profile compared to other vaccines [47].

14. A29L, B6R, A35R, AND M1R RECOMBINANT PROTEINS IMMUNIZATION PROVIDING PROTECTION TO MICE IN DEFIANCE OF MPOX VIRUS CHALLENGE.

The MPXV comes in two forms. The first form called intracellular mature virus (IMV) builds up inside infected cells and released when those cells die. The second form, extracellular enveloped virus (EEV) undergo egress via exocytosis from the plasma membrane of the cells to improve dissemination inside the host & are fundamentally extra membrane IMVs [48]. Both the extracellular and intracellular forms of MPXV contain several proteins of external membrane that can encourage immune responses. In this study, we scrutinized the protectiveness provided by structural protein of MPXV, including A291, B6R, A35R, & M1R, as an amalgamated vaccine. Additionally, we examined the shielding efficacy in defiance of the mpox 2022 variant in BALB/c mice. The vaccine proved highly effective in mice, generating antibodies

that powerfully suppressed the MPXV ability to replicate and restrict pathological injury of organs. This data may be useful for future mpox vaccine development [49].

15. PREVENTIVE MEASURES

Although sexual contact and physical contact between infected individuals and healthy individuals. Person to person transmission of Mpox can therefore be prevented by minimizing contact with individuals exhibiting symptoms of the virus, taking personal safety into account, and adhering to standard procedures for STDs (sexually transmitted disease) [50]. Mpox transmission can also be decreased by maintaining a healthy environment for respiratory practices and regularly washing your hands with the proper hand rub [51].

Controlling the disease in society mostly depends on public education on risk factors, safety precautions, and the channels of Mpox transmission. The quick spread of infection can be stopped by identifying outbreaks early and taking the necessary action [52]. Another crucial element of prevention initiatives that are presently being studied is vaccination, which will be covered in the section that follows [53]. Additionally, fewer sexual partners are thought to be able to decrease the chance of Mpox transmission, especially in areas where infection rates are high. Healthcare workers who come into contact with infected people are regarded as being at a high risk. It is recommended that they adhere to safety protocols and use appropriate personal protection equipment, such as long-sleeved gowns, respirator masks, disposable gloves, and face shields [54].

16. CONCLUSION AND FUTURE DIRECTIONS

The worldwide reappeared MPXV situation highlights the importance of developing a full grasp of biological aspects together with transmission characteristics and treatment weaknesses. This paper conducts a thorough evaluation of MPXV by merging findings from molecular virology research with host-pathogen interaction studies and data on clinical course and public health actions. The paper presents several new findings that differentiate its research from other accomplishments in viral clade identification and pathogenesis studies and diagnostic and vaccine developments.

The review brings attention to purinergic signalling mechanisms during MPXV-induced cytokine storms because this represents a previously overlooked dimension of immune evasion and inflammatory processes. The comparison of MPXV Clades I and II through genomic research reveals distinct patterns in virulence-related genetic areas which aids scientists to study genotype-phenotype relations better. The article examines advanced vaccination technology platforms featuring subunit components along with mRNA and circular RNA techniques as they represent efficient routes to create targeted immunological defences. Additionally this review presents a predictive drug repurposing model which identifies beneficial FDA-approved drugs that act as MPXV replication enzyme inhibitors for faster antiviral development. The research provides new insights into the immunological effects of JYNNEOS vaccination through single-cell immune profiling data that remains obscure in the current literature.

The research agenda needs extension to include neonates and pregnant women because they stand among the most susceptible groups facing MPXV infection. Current medical research requires prompt investigation of MPXV impact on pregnant women along with neonates along with their transmission routes and treatment effects on both groups. The need for neonatal-safe vaccines and immunotherapeutics becomes essential because newborns suffer from higher severe disease risks along with vertical transmission possibilities due to their immature immune systems. Medical interventions need direction from the research findings which include studies of host-pathogen interactions and immune evasion methods explained in this review. The research needs to document vertical transmission routes of MPXV while developing clinical guidelines for treating exposed infants during pregnancy. Genomic surveillance needs enhancement to track the development of viral mutations in pediatric and neonatal cases to discover special pathogenic characteristics or transmission methods. Perinatal healthcare settings must implement point-of-care diagnostic tools in maternal and neonatal areas to detect MPXV early and contain the infection better particularly in epidemiologically sensitive regions. Numerous future research directions work together to link existing scientific voids which protect young people at high risk from MPs infections equitably.

The scientific knowledge and surveillance efforts regarding MPXV require inclusion of neonatal patients. This demographic group represents an essential indicator which reveals how MPXV spreads vertically between parents and their newborns in addition to evaluating population-level immunity. The condition of neonates reveals serious consequences of decreasing orthopoxvirus immunity which requires immediate creation of universal public health systems protecting the entire population. Future research requirements include following all neonatal MPXV cases over time using detailed placental pathological testing with immunological assessments of infected newborns particularly when maternal infections occur during pregnancy. Researchers should create both in vitro placentals models and neonatal animal models for revealing viral preferences and exploring transmission pathways and therapeutic timing frames. Knowledge of MPXV behavior patterns among neonates contributes to better neonatal treatments and reveals vital information about viral transformation mechanisms while exposing probable human-to-human virus reservoirs.

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