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# Antigen recognition and immune response to monkeypox virus infection: implications for Mpox vaccine design – a narrative review

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## SUMMARY

Monkeypox virus (MPXV) is a DNA virus from the *Orthopoxvirus* genus, sharing significant genomic similarity with the variola virus that causes smallpox. The cessation of smallpox vaccinations has contributed to recent Mpox outbreaks, with reduced immunity levels, particularly in younger populations born after the vaccine was discontinued. The virus triggers innate and adaptive immune responses, with toll-like receptors (TLRs) playing a key role in recognizing viral components and activating proinflammatory cytokines. However, MPXV evades the immune system by producing proteins that inhibit immune signaling pathways. Natural killer (NK) cells and interferons are crucial for early defense, but MPXV impairs their function. Adaptive immunity involves robust antibody and T-cell responses, similar to smallpox vaccination responses. Various mRNA-based candidate vaccines have demonstrated strong immunogenicity, with preclinical studies confirming their ability to trigger potent B-cell and T-cell responses. However, the genetic changes observed in the current outbreak strains necessitate ongoing surveillance of MPXV mutations and their impact on immunogenic proteins. This review aimed to summarize current insights into antigen recognition and immune responses to MPXV, with a focus on key antigenic proteins relevant to vaccine development.

*Keywords:* Adaptive immune response, Antigen recognition, Innate immune response, Monkeypox virus infection, MPXV.

## INTRODUCTION

Monkeypox virus (MPXV) is a DNA virus belonging to the *Orthopoxvirus* genus and is responsible for Mpox disease [1, 2]. The virus shares 90% genomic similarity with the variola virus, which causes smallpox, and smallpox vaccines and treatments have proven effective in protecting against MPXV infection [3-5]. It has two infectious forms: the intracellular mature virion (MV) and the extracellular enveloped virion (EV), and both forms contain multiple outer membrane proteins that can trigger an immune response [2, 6]. MVs are released through host cell lysis, while the EVs exit via exocytosis [7].

Several observational studies have shown that the smallpox vaccine is approximately 85% effective

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in reducing MPXV infection [8]. A substantial waning of herd immunity against smallpox is projected for the 2022 Mpox outbreak [9, 10]. The cessation of smallpox vaccination is the primary reason for viral transmission, and the median age transition of cases from children to young adults is likely due to this [11, 12]. In Nigeria, the majority of Mpox patients are under 40 years of age and lack immunity since they were born after smallpox vaccinations ceased [13]. Compared with those from younger participants, plasma samples from individuals in their early 40s and older in Korea were more reactive to MPXV and smallpox viral proteins [14]. The level of herd immunity required to halt the spread of the virus among Moscow residents was found to be less than expected [4]. Moreover, only 38% of historically vaccinated individuals in China showed a reduced level of humoral response to MPXV-specific antigens [15], and this trend was observed in both HIV-negative and HIV-positive individuals [16].

Natural MPXV infection elicits a robust immune response capable of managing the disease [17] and provoking the innate and adaptive immune systems [2, 18]. Innate immune cells, including natural killer (NK) cells and monocytes, initiate the body's defenses by producing type I interferons (IFNs) and inflammatory cytokines in response to viral invasion [19, 20]. Combinations of MV and EV surface proteins stimulate antigen-specific $CD4^+$ T-cell responses and neutralizing antibodies, protecting mice from lethal doses of vaccinia virus (VACV) challenge [7].

MPXV proteins such as M1R, E8L, H3L, A29L, A35R, and B6R trigger strong B-cell and T-cell responses [21]. Immunocompromised individuals are at increased risk of contracting an illness and succumbing to it because of an insufficient protective immune response [22, 23]. Inadequate clearance of infected cells and infection of lesion-associated fibroblasts driven by profibrotic macrophages may contribute to merging lesions and a severe, prolonged Mpox course in immunocompromised patients [24].

There is no licensed vaccine directly originating from MPXV, and vaccines from other Poxviridae family viruses have been recommended [21]. Currently, the WHO-approved vaccines for Mpox include replicating (ACAM2000), low-replicating (LC16m8), and nonreplicating (MVA-BN) types [25]. However, replication-competent second-generation smallpox vaccines are restricted by potential risks [26]. JYNNEOS is a third-generation FDA-approved vaccine recommended for adults containing the weakened Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN) virus [27, 28]. It induces neutralizing antibody response against A29, A35, B6, M1, H3, and I1 proteins of MPXV [29]. Compared with first- and second-generation VACV-based protein vaccines, this vaccine has fewer side effects [30]. However, this vaccine is not licensed for the population under 18 years of age [31]. No specific therapy currently exists for MPXV infection, and the virus has developed resistance to several antiviral treatments, highlighting the urgent need for alternative therapies for this deadly disease [32, 33].

MPXV circulates in two distinct clades: Clade I, with a case fatality rate of 10.6%, and Clade II, with a rate of 3.6% [34, 35]. The clade I lineage has Ia and Ib subclades [36], whereas clade II consists of IIa and IIb, the latter being responsible for the ongoing global outbreak [37]. Zoonotic transmission is a key factor in the spread of clades Ia and IIa, whereas clades Ib and IIb primarily spread via continuous transmission between humans [38].

The first human MPXV infections emerged as zoonoses in Central and West Africa approximately 1970, with sporadic cases reported throughout the decade [39]. The Ministry of Public Health of the Democratic Republic of Congo (DRC) reported over 11,806 cases, including more than 2,298 confirmed cases and 459 deaths as of 2024 [40]. By 2022, the virus had spread beyond Africa, reaching Europe, the Americas, Asia, and Oceania, with more than 99,500 cases globally [41-43]. Between January 2022 and November 2024, 127 countries reported 117,663 confirmed cases and 263 deaths to WHO [44].

This study aims to explore the complex dynamics of antigen recognition and immune responses to Mpox, which are crucial for developing effective vaccines and therapeutic strategies.

## METHODS

We conducted a thorough electronic search of research databases, including; Scopus, PubMed, PubMed Central (PMC), Web of Science, Google Scholar, and Cochrane Library via a combination of keyword terms for "Mpox" or "Monkeypox", "Monkeypox virus infection", "antigen recogni-

tion", "innate immune response" and "adaptive immune response". Articles written in languages other than English were excluded. The authors prioritized recently published papers, although no specific time frame was set for study inclusion. A manual search was also performed, and all articles were initially screened to identify relevant ones.

## ANTIGEN RECOGNITION AND THE INNATE IMMUNE RESPONSE TO MPXV INFECTION

### *The role of toll-like receptors (TLRs)*

TLRs are pattern recognition receptors that distinguish pathogen-associated molecular patterns (PAMPs) from viruses, including Mpox. For example, TLR3 senses viral double-stranded RNA (dsRNA), whereas TLR9 detects unmethylated CpG DNA sequences characteristic of viral genomes [20, 45]. Viral dsRNA also activates protein kinase R (PKR), which phosphorylates eukaryotic translation initiation factor-2a (eIF2α), inhibiting protein translation and triggering antiviral responses [46]. The activation of TLRs stimulates the production of proinflammatory cytokines and IFN I, which are crucial for an effective immune response to MPXV. This response involves cytokines such as IL-6, TNF-α, and IL-12 [19, 45]. The myeloid differentiation factor 88 (MyD88)-dependent pathway predominantly mediates this process for most TLRs, activating the NF-κB and MAPK signaling pathways and intensifying inflammatory responses [45]. TLR3 activation in the lungs enhances inflammation to combat viral replication, whereas TLR9 activation is key for activating dendritic cells and recruiting NK cells to infection sites and is crucial for controlling viral spread [20]. Additionally, TLR2 plays a role in activating NK cells and promoting the differentiation of memory cells into $CD8^+$ T cells. This results in enhanced production of antimicrobial peptides, such as cathelicidin (LL-37), in mast cells [19, 20]. Human tripartite motif protein 5α (TRIM5α) binds to the capsid protein L3 of MPXV and restricts viral replication [47].

Despite its role in boosting the immune response, MPXV produces proteins that disrupt host immune pathways by inhibiting apoptosis, altering chemokine binding, and blocking complement activation, allowing it to evade immune detection more effectively [20, 48]. Binding of the viral F3L protein with its dsRNA disrupts the signaling pathways associated with PKR and decreases IFN production [49, 50]. The virus also produces proteins that interfere with the NF-κB signaling pathway, impairing the host's ability to generate an effective inflammatory response, leading to extended viral replication and more severe disease outcomes [20]. The MPXV protein p2 interacts with karyopherin α-2 (KPNA2) to promote its nuclear translocation, while competitively inhibiting KPNA2-mediated interferon regulatory factor 3

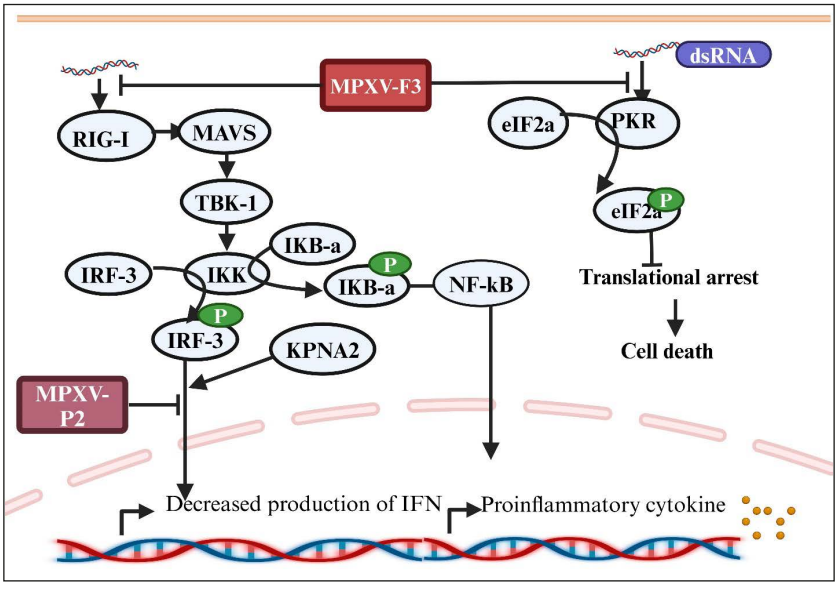


**Figure 1**

Innate immune evasion strategies of MPXV: evasion from detection, inhibition of host cell apoptosis, and disruption of host immune signaling pathways.
The figure was produced with https://app.biorender.com

Notes: RIG-1, retinoic acid-inducible gene I; MAVS, mitochondrial antiviral signaling; MPXV-F3, monkeypox virus protein F3; MPXV-P2, monkeypox virus protein 2; dsRNA, double-stranded RNA; PKR, protein kinase R; eIF2a, eukaryotic translation initiation factor 2a; TBK-1, TANK-binding kinase 1; IRF-3, interferon regulatory factor 3; IKB-a, inhibitor of kappa B alpha; IKK, inhibitor of nuclear factor-κB kinase; NFkB, nuclear factor kappa B; KPNA2, karyopherin subunit alpha 2

(IRF3) nuclear translocation and suppressing downstream IFN production [51] (Figure 1). Moreover, the viral C6 protein interacts with the host TRIM5α and is subjected to proteasome-dependent degradation [47].

### *Natural killer (NK) cell response*

The function of NK cells is essential for the host's immune defense against Mpox [52]. During MPXV infection, NK cells are activated via TLR2 signaling and express NKG2D receptors, enabling them to recognize stress-induced ligands on infected cells [20]. The release of perforin and granzymes facilitates the cytotoxic activity of NK cells [19]. Their protective role against lethal MPXV infection was demonstrated in IL-15-treated CAST mice [53].

Studies have shown that MPXV infection significantly increases the number of NK cells. In rhesus monkeys, the total number of NK cells in the blood increased approximately 23-fold by day 7 after infection, whereas the number of NK cells in the lymph nodes increased approximately 46.1-fold by days 8–9. This expansion was marked by the increased proliferation of different NK cell subsets, such as $CD56^+$ and $CD16^+$ cells, as indicated by increased expression of Ki67, a marker of cell proliferation. However, their functionality is greatly impaired, and the expression of chemokine receptors, including CXCR3, CCR6, and CCR7, is significantly downregulated [54].

The downregulation of chemokines likely hampers the ability of NK cells to migrate to inflamed tissues. Additionally, NK cells display reduced degranulation and decreased secretion of key cytokines, such as interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α) [19, 54]. MPXV produces the *Orthopoxvirus* major histocompatibility complex class I (MHC I)-like protein (OMCP), which binds to the NKG2D receptor on NK cells, helping the virus evade the NK cell response. Additionally, this protein reduces MHC I molecule expression in infected cells, further decreasing the likelihood of NK cell activation [20]. Moreover, the virus directly targets NK cells, reducing their number and functionality during infection [50]. Given the essential role of NK cells in controlling viral loads, the use of NK cell stimulants or enhancers and targeting specific receptors such as NKG2D may increase their ability to detect and destroy infected cells [55].

### *Interferon response*

Type I and II IFNs are critical in the host defense against MPXV infection [52]. *In vitro* experiments indicated that treatment with IFN-β significantly prevented the production and spread of MPXV.

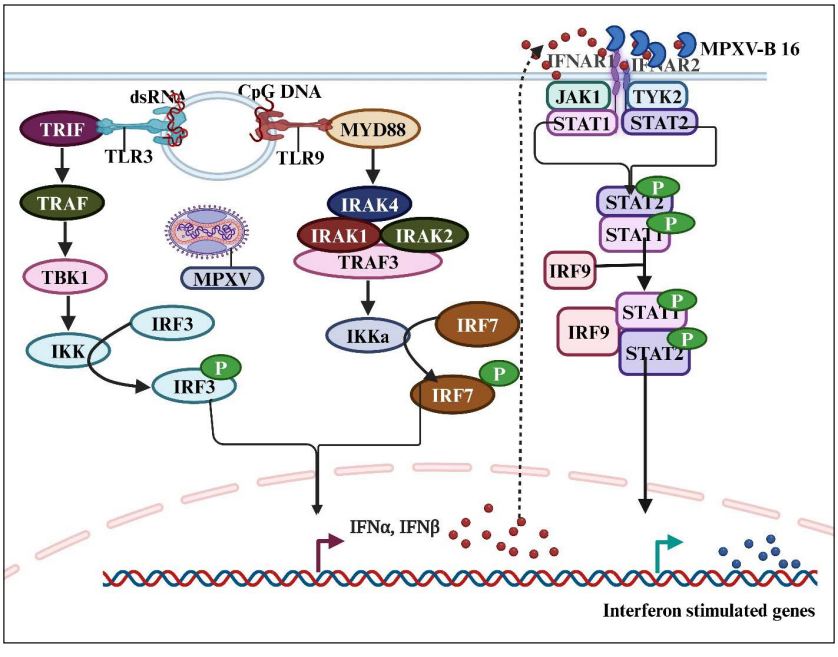


**Figure 2**

Activation of TLR signaling during MPXV infection and the mechanisms of viral evasion from the IFN response. The figure was produced using https://app.biorender.com

Notes: dsRNA, double-stranded RNA; CpG DNA, cytosine-phosphate-guanosine DNA; TRIF, toll and interleukin-1 receptor (TIR) domain-containing adaptor inducing interferon β; TLR, toll-like receptor; MyD88, myeloid differentiation factor 88; IRF, interferon regulatory factor; TRAF, tumor necrosis factor receptor-associated factor; TBK1, TANK binding kinase 1; MPXV, monkeypox virus; MPXV-B16, monkeypox virus protein B16; IKK, inhibitor of nuclear factor-κB kinase; IRAK, interleukin-1 receptor-associated kinase; IFNAR, interferon alpha/beta receptor; JAK2, Janus kinase 2; TYK2, tyrosine kinase 2; IFN, interferon; STAT, signal transducer and activator of transcription.

IFN-β enhances the expression of the antiviral protein myxovirus resistance protein A (MxA) in infected cells, thereby assisting in the inhibition of MPXV [56]. The protection of IFN-γ against lethal MPXV infection has also been demonstrated in mouse models [57]. During viral infections, $CD4^+$ and $CD8^+$ T cells are the main producers of IFN-γ. As NK cells kill virally infected cells [58], IFN-γ increases the cytotoxic activity of NK cells and supports the differentiation of T cells into Th1 cells, both of which are crucial for strong antiviral defenses [59]. It also aids in the elimination of infected cells by increasing the expression of MHC molecules, which display viral antigens to T cells [19, 48].

However, MPXV evades the IFN I response [52, 60]. The virus produces a protein known as B16 (an orthologue of VACV B19), which functions as a decoy receptor by binding to IFNs. This prevents IFNs from binding to their actual receptors, thereby blocking downstream IFN signaling and antiviral effects [52, 61] (Figure 2). The virus also evades the host immune response by releasing proteins that antagonize the functions of host IFN-γ [62].

## ANTIGEN RECOGNITION AND ADAPTIVE IMMUNE RESPONSE TO MPXV INFECTION

### *B-cell response*

MPXV infection triggered antibody responses to various poxvirus antigens similar to those observed in Smallpox-vaccinated individuals, reflecting the antigenic similarity between VACV and MPXV [48, 63, 64]. The MPXV-2022 sequences present an average genetic similarity of approximately 84% to the VACV reference sequence, and VACV proteins recognized by neutralizing antibodies exhibit high sequence similarity with MPXV-2022 orthologs [65]. Preexisting monoclonal antibodies from the vaccinia vaccine demonstrated broad binding to epitopes on the B6 protein of MPXV and orthologs of variola and cowpox viruses [66]. Neutralizing antibodies against the A29, A35, B6, M1, H3, and I1 antigens of MVA-BN also demonstrated cross-reactivity against MPXV in mouse models [29, 67]. A subset of individuals in China vaccinated with the historic VACV Tiantan (VTT) strain demonstrated cross-reactivity to the MPXV surface proteins A35R, B6R, A29L, and M1R [68, 69]. Recombinant versions of these proteins stimulate the production of neutralizing antibodies in mice, significantly suppressing viral replication [6]. Additionally, those vaccinated with VTT strains before 1980 presented with cross-reactive IgG antibodies against MPXV [70, 71].

Despite the antigenic homology among *Orthopoxvius* antigens, previous studies highlighted that differences in amino acid sequences can affect cross-protection, as observed in A33R orthologs, underscoring the need for an MPXV-specific vaccine [72]. Furthermore, studies on MVA vaccine immunogenicity indicate low levels of neutralizing antibodies against MPXV, reflecting antigenic variability among poxvirus targets [73]. Comparisons between 2022-2023 MPXV strains and smallpox vaccine strains revealed amino acid changes in B-cell epitope regions, raising concerns regarding vaccine effectiveness [74]. Compared with classical strains isolated from 218–2019, the 2022 outbreak strain also exhibited an unexpected level of genetic divergence, with an average of 50 single nucleotide polymorphisms, exceeding predictions based on the estimated *Orthopoxvirus* substitution rate [75]. In the presence of these changes, the effectiveness of existing vaccines in the context of the current multi-country outbreak still needs to be verified [25]. On the other hand, three monoclonal antibodies (9F8, 3A1, and 2D1) produced against A29L protein of MPXV were found to effectively neutralize *Orthopoxviruses* [76]. The B16 protein B-cell epitopes are more specific to MPXV, allowing differentiation between MPXV-infected individuals and those vaccinated with MVA-BN [77].

Antibody responses are crucial in protecting against MPXV, with infected individuals generating strong responses to MPXV proteins [19, 78]. During the 2022 MPXV outbreak, antibody profiles, including IgG, IgM, IgA, and neutralizing antibodies, were observed across individuals regardless of prior vaccination status [79]. High IgG and IgA levels are correlated with quicker viral clearance. However, HIV-positive individuals show a more rapid antibody decline and lower neutralizing antibody levels over time compared to those without HIV [80, 81]. The rapid decline in the antibody titer could result from HIV-induced disruption of the coordination between humoral and cellular responses [80]. Moreover, IgG and IgM antibodies were detected 3–5 days later in HIV-positive MPXV patients than in HIV-negative MPXV patients [82]. High seropositivity rates for A29L and H3L were noted in men experiencing

acute infections [83]. Individuals who recovered from MPXV infection presented stronger antibody and B-cell responses to H3L and A35R than those vaccinated with vaccinia-based vaccines did, indicating that these protein markers are associated with natural MPXV infection [84]. Additionally, compared with the MVA-BN vaccine, MPXV infection elicited stronger antibody responses to A29L, A35R, A33R, B18R, and A30L [85, 86].

Complement proteins enhance neutralizing antibody production against MPXV, and this enhancement was more effective in those with a history of smallpox vaccination [87]. Clade I MPXV encodes a complement control protein (CCP), which prevents the classical and alternative pathway of complement activation. The removal of CCP from these strains reduces Mpox disease morbidity and mortality without significantly altering the viral load in prairie dogs [88]. However, the loss of CCP expression has been reported to restrict the adaptive immune response to MPXV infection in rhesus monkeys [89].

***T-cell response***

The immune response to MPXV infection involves a complex interplay of T-cell activation and immune evasion mechanisms [50, 86]. *Orthopoxvirus*-specific T cells are crucial for eliminating MPXV and can persist over time [80]. In a study of 17 patients with confirmed Mpox, a rapid and robust T-cell response was observed, marked by increased inflammatory mediators, regardless of HIV status [90]. MPXV infection activates $CD4^+$ and $CD8^+$ T cells, which contribute to a Th1-type response essential for viral clearance [80, 91, 92]. These T cells produce a range of inflammatory cytokines, including IL-1β, IL-8, IL-6, TNF, MCP-1, and IFN-γ [93]. Notably, protective T-cell responses were observed in HIV-positive patients, with significantly greater IFN-γ and IL-2 responses in MPXV-infected individuals than in those vaccinated with smallpox [94]. Additionally, histopathological analyses of Mpox skin lesions revealed a balanced presence of $CD4^+$ and $CD8^+$ T cells in dermal inflammatory infiltrates [95].

Research has demonstrated that IFNγ-producing Th1 effector memory cells safeguard the skin against pox virus infections [96]. Most epitopes from VACV vaccines are conserved in MPXV and can trigger memory T-cell responses [97, 98]. The F8L protein and its analog F9L are pox virus-specific proteins with a common $CD8^+$ T-cell epitope for all pox viruses and a unique epitope conserved in MPXV and VACV [99]. Over four decades after VACV exposure, older individuals presented long-lived memory CD8+ T-cells that targeted conserved VACV/MPXV epitopes. Additionally, strong effector memory MPXV-specific CD4 and CD8 responses were observed in mild Mpox cases [100]. Analysis of MPXV-specific T-cell responses in recovered Mpox patients revealed a significant presence of Th1 and Th2 memory cells in response to MPXV and VACV antigens compared with healthy donors [101]. Historic smallpox vaccination protects against MPXV infection via T-cell responses, and significant preexisting $CD8^+$ T-cell reactivities were found toward both conserved and variant epitopes between VTT and MPXV [17, 71]. Notably, studies on nonhuman primate MPXV infections have revealed the development of immune memory in gamma-delta (γδ) T-cells, which may play a role in protecting against secondary infections [102].

MPXV-specific $CD4^+$ and $CD8^+$ T-cells recognize VACV-infected monocytes and produce inflammatory cytokines such as IFNγ and TNFα but mostly do not respond to MPXV-infected cells [50]. MPXV-infected cells were demonstrated to inhibit antigen-specific T-cell activation via the T-cell receptor (TCR) [50, 64]. Recent studies have shown that the M2 protein of MPXV binds to the B7 molecule on antigen-presenting cells, disrupting the B7-CD28 interaction and inhibiting T-cell costimulation during activation [103] (Figure 3). This blocks inflammatory cytokine production and likely aids in the spread of MPXV within the host [50, 104].

A dominant Th2 response rather than a Th1 response during MPXV infection increases disease severity, as the virus evades the immune system by promoting a Th2 response that suppresses the Th1 response necessary for effective virus elimination [105, 106].

***Immune response heterogeneity in different groups***

Although data on immune response variability specific to MPXV across age, sex, and different groups are lacking, sex-based differences were observed in MVA-BN smallpox vaccine recipients, with males exhibiting an average of 27% higher anti-MVA titers [107]. However, prior studies on the immune response to the Dryvax® vaccine re-

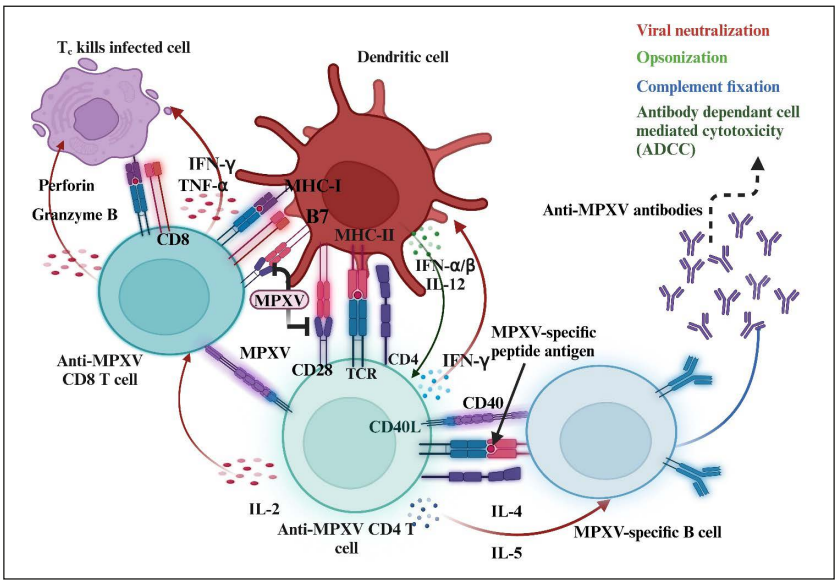


**Figure 3**

Adaptive immune response against MPXV and inhibition of T-cell costimulation. The figure was produced using https://app.biorender.com

Notes: MPXV, monkeypox virus; IL, interleukin; TNF-α, tumor necrosis factor alpha; IFN-γ, interferon-gamma; IFN-α/β, interferon-alpha/beta; TCR, T-cell receptor; MHC, major histocompatibility complex.

vealed that although no significant differences were observed based on race or ethnicity, females presented significantly higher neutralizing antibody titers than males did [108]. On the other hand, the Dryvax® vaccine-induced T-cell response indicated that males presented a strong T-cell response, and statistically significant differences in the secretion of IL-2, IL-1β, and IL-10 were observed. Moreover, Caucasians had higher levels of IFNγ-producing CD8 T cells, IL-2, and TNF-α than African Americans and Hispanics [109].

## CURRENT VACCINE CANDIDATES

Multiple vaccine candidates for MPVX are available, with various platforms focusing on potent immunogens such as M1R, E8L, H3L, A29L, A35R, and B6R proteins to trigger strong B-cell and T-cell responses [110]. Two mRNA vaccine candidates, BNT166a (quadrivalent, encoding MPXV antigens A35, B6, M1, and H3) and BNT166c (trivalent, lacking H3), were evaluated pre-clinically and elicited strong T-cell and antibody responses. Both vaccines confer complete protection against vaccinia, as well as clade I and clade IIb MPXVs in animal models, and are currently undergoing clinical evaluation (NCT05988203) [111]. Two multiantigen mRNA vaccine candidates encoding either four MPXV antigens (M1, A29, B6, and A35; designated Rmix4) or six antigens (M1, H3, A29, E8, B6, and A35; designated Rmix6) were developed. Both multiantigen mRNA vaccines induced strong cross-neutralizing responses against VACV, with Rmix6 generating significantly stronger cellular immunity than Rmix4 in mice [112]. Three mRNA vaccines encoding the MPXV proteins A35R and M1R were developed, including A35R extracellular domain-M1R fusions (VGPox 1 and VGPox 2) and a formulation with encapsulated full-length A35R and M1R mRNAs (VGPox 3). These vaccines induce early anti-A35R antibodies and protect against lethal VACV challenge in mice [113]. Recently, Mucker *et al.* tested a novel Mpox mRNA-1769 vaccine encoding MPXV surface proteins in a lethal nonhuman primate MPXV model and compared it with MVA strain 572, which is closely related to the standard-of-care MVA-BN vaccine. The authors reported comparable protection against lethality but superior efficacy in preventing disease [43]. Moreover, the mRNA-1769 vaccine protects mice from intranasal and intraperitoneal MPXV infections, while bioluminescence imaging demonstrated that vaccination markedly reduces VACV replication and spread at inoculation sites [114]. A phase I/II clinical trial is currently assessing the safety and efficacy of this novel mRNA-1769 in humans under a clinical registration number (NCT05995275).

Researchers developed a polyvalent mRNA candidate vaccine (MPXVac-097) against Mpox and

evaluated the immune response in mice. Five MPXV viral antigens, A29L, E8L, M1R, A35R, and B6R, were tandemly connected via 2A peptides and optimized through codon modification. This vaccine induces a broad neutralizing antibody response, MPXV-specific T-cell activation, and protection against VACV challenge. The administration of this vaccine did not result in considerable pathological alterations in mice [115].

## LIMITATIONS OF THE STUDY

This work is presented as a narrative review. Consequently, its scope is limited and does not offer a comprehensive review of the subject matter. The authors did not conduct a systematic literature review or directly compare studies. Therefore, the included material and conclusions drawn are not exhaustive and may reflect the author's perspective.

## CONCLUSIONS AND FUTURE PERSPECTIVES

The recent rise of Mpox as a global concern underscores the need for deeper understanding and preparedness in combating this virus. While the smallpox vaccine offers significant cross-protection against MPXV, waning immunity due to the cessation of smallpox vaccination has contributed to the spread of the virus, affecting previously protected demographics. Immune responses to MPXV are complex and involve innate and adaptive mechanisms, with crucial roles played by NK cells, B cells, and T cells, alongside specific viral proteins that facilitate immune evasion. Although third-generation vaccines such as JYNNEOS provide safer options for at-risk populations, age restrictions and a lack of direct antiviral treatments leave vulnerable groups at greater risk. Several MPXV-specific mRNA-based vaccines have shown promising clinical efficacy in protecting against MPXV; some are currently under clinical evaluation. However, the genetic divergence observed in the current outbreak strain may hinder vaccine efficacy. Therefore, ongoing surveillance of MPXV mutations, targeted vaccine development, and vaccine efficacy verification in the context of the current outbreak strain are recommended.

**Authors' contributions**
All the authors directly participated in the preparation of this manuscript. Conceptualization: D. A., Y. A., A.A., M.J., and A.A.; Literature search: D.A., Y.A., A.A., Z.H.T., A.F, G.A.A., M.J., T.B., and A.A.; Original draft preparation: D.A., Y.A., A.A., Z.H.T., B.A.T., A.F., G.A.A., M.J., T.B., and A.A.; Critical review: D.A., Y.A., A.A., Z.H.T., B.A.T., A.F., G.A.A., M.J., T.B., and A.A.; Supervision: D.A., Y.A., M.J., A.A., and A.A. All the authors have read and approved the final manuscript.

**Conflict of interest**
All the authors declare that they have no competing interests.

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Nothing to declare.

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