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Emerging Vaccine Technologies Against Cytomegalovirus: A Narrative Review of Viral Vectors, DNA, and mRNA-based Strategies

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Abstract

Cytomegalovirus (CMV) is a globally prevalent herpesvirus that poses serious health risks, especially in immunocompromised individuals, transplant recipients, and neonates. Despite extensive efforts, a licensed CMV vaccine remains unavailable, largely due to the virus's ability to establish latency and evade immune detection. This narrative review examines three promising vaccine platforms—viral vector-based, DNA-based, and mRNA-based technologies—that are currently at the forefront of CMV vaccine development. Viral vector vaccines, such as adenovirus and vesicular stomatitis virus (VSV) vectors, utilize genetically engineered viruses to deliver CMV antigens into host cells, stimulating potent cellular and humoral immune responses. However, their efficacy can be compromised by pre-existing immunity to the vector and concerns related to safety in high-risk groups.

DNA-based vaccines offer a non-viral alternative by introducing plasmid DNA encoding CMV antigens directly into host tissues, where it initiates antigen expression and immune activation. These vaccines are stable, easy to manufacture, and inherently safe, but often require adjuvants or advanced delivery methods like electroporation to overcome their comparatively low immunogenicity. Meanwhile, mRNA vaccine platforms represent a transformative advancement in vaccinology. These vaccines encode key CMV proteins, such as glycoprotein B and immediate-early proteins, and are delivered via lipid nanoparticles. They elicit robust T cell-mediated and antibody responses, making them especially suitable for combating CMV's immune evasion strategies. While mRNA vaccines offer rapid scalability and flexibility, their instability and storage requirements present logistical challenges.

By comparing these vaccine modalities, the review underscores their respective mechanisms, advantages, and limitations, offering critical insights into the ongoing pursuit of an effective CMV vaccine. The integration of these emerging technologies with targeted immunological strategies holds promise for achieving long-term protection against CMV, particularly in vulnerable populations.

1. Introduction to Cytomegalovirus (CMV) and Its Global Impact

Cytomegalovirus (CMV), a prevalent herpesvirus, infects human beings worldwide via saliva, urine, sexual contact, and vertical transmission. Seroprevalence is region and socioeconomic-dependent and reaches 50–80% in industrialized nations and approaches universal prevalence in developing regions. Congenital CMV infection occurs in 0.5–2.5% of live births, and the prevalence is 1.42% in low- and

middle-income countries, which is three times higher than in high-income countries (0.48%). Vertical transmission continues to be a major concern with congenital infection, since it can cause sensorineural hearing impairment, intellectual disability, and blindness. The virus causes lifelong latency that is reactivated within immunocompromised hosts and presents a major risk during pregnancy in areas with compromised access to healthcare.(1)

In immunocompromised patients, including organ transplant recipients and HIV/AIDS patients, CMV induces serious complications. Transplant recipients develop graft rejection associated with CMV disease, with research demonstrating a sixfold greater risk of acute rejection after symptomatic CMV infection. Autologous bone marrow transplant recipients have high mortality due to CMV pneumonia, especially those who are seropositive pre-transplant. HIV-infected individuals are at risk of CMV retinitis, which may occur as the only opportunistic infection and cause permanent vision loss if not treated early with antiviral drugs. Even immunocompetent patients can develop serious complications of CMV, such as colitis, meningoencephalitis, and hematological conditions, requiring antiviral therapy in severe cases.(2)

The immune response of the host to CMV is focused on CD8+ cytotoxic T cells, which have extremely potent and age-related activity for inhibiting viral reactivation. Nevertheless, CMV utilizes elaborate mechanisms of immune evasion, including downmodulation of MHC class I and II molecules to evade T-cell detection and disruption of natural killer cell activity.(3) These processes facilitate viral persistence by suppressing antigen presentation and modifying surface protein expression on infected cells. The ratio of strong T-cell responses to viral immune evasion is the foundation of the difficulty in attaining viral clearance, especially among immunocompromised hosts where immune surveillance is broken.(4)

CMV places a significant global health burden, with congenitally acquired infections contributing to avoidable childhood impairments and developmental delays. In the transplant recipient groups, CMV pneumonia is associated with 16.7 times greater mortality risk, which necessitates keen surveillance. Healthcare expenditure rises because of longer antiviral treatments, readmissions to the hospital, and the treatment of complications such as retinitis-induced blindness. World Health Organization identifies congenital CMV as one of the major causes of sensorineural hearing loss, highlighting the urgency of universal screening and early intervention in high-risk groups.(5)

Vaccine production is complicated by CMV's immune evasive strategies and the unavailability of animal models that accurately mimic human infection. Existing approaches seek to promote T-cell immunity and neutralize viral mechanisms for inhibiting antigen presentation. A licensed vaccine does not yet exist, but studies are directed at taking advantage of knowledge regarding the interaction of CMV with host immunity to create new candidates. A solution to these challenges is crucial for preventing transmission, congenital disease, and improving outcomes in immunocompromised patients.(6)

2. Pathogenesis of Cytomegalovirus Infection

Cytomegalovirus (CMV), a betaherpesvirus, uses complex mechanisms to gain entry into host cells and escape immune recognition, guaranteeing its latency and reactivation in immunocompromised hosts. In this review, recent advances on CMV's entry strategies, immune evasion mechanisms, and their role in viral latency and pathogenesis are combined. CMV begins infection by attaching to heparan sulfate (HS) proteoglycans, wherein certain sulfation patterns and degrees of polymerization are important for viral binding. Extended HS chains with 6-O- and N-sulfation augment CMV glycoprotein B (gB) binding, and desulfated HS analogs cannot compete, highlighting the structural specificity of this interaction. (6) After HS binding, CMV uses CD13 (aminopeptidase N) as a coreceptor, with anti-CD13 antibodies inhibiting viral entry in bone marrow transplant recipients. CD13-specific autoantibodies only appear during CMV viremia, connecting viral entry to autoimmune disease in immunocompromised hosts. In glioblastoma cells, CMV exploits Ephrin receptor A2

(EphA2) via the viral gH/gL/gO complex, where EphA2 knockdown reduces infection by more than 70%. EphA2's ligand-binding domain interacts with gH/gL, mirroring mechanisms seen in Epstein-Barr virus and Kaposi's sarcoma-associated herpesvirus. Notably, EphA2 is upregulated during latency by the CMV-encoded G protein-coupled receptor US28, which represses the Src-MEK/ERK-c-Fos pathway to suppress lytic gene transcription. This double function of EphA2 in entry and latency serves to underscore its centrality to CMV's lifecycle.(7)

CMV targets major histocompatibility complex (MHC) molecules by degradation through US2, a protein that binds to MHC class I, II, and nonclassical proteins (e.g., HFE) in the endoplasmic reticulum (ER). US2's cytosolic tail targets MHC proteins for proteasomal degradation without regard to the enzymatic activity of the tail, decreasing antigen presentation to CD8+ T cells by more than 90%. US2 truncation mutants that do not have the cytosolic domain still bind MHC but cannot induce degradation, validating that US2 bridges MHC proteins to ER-associated degradation machinery. UL16 glycoprotein prevents CMV-infected cells from being lysed by natural killer (NK) cells by sequestering intracellular NKG2D ligands such as MICB. Deletion of UL16 restores MICB to the cell surface, enhancing NK-mediated cytotoxicity by 3–5 fold.(8) This mechanism acts in concert with other viral mechanisms, including UL18-mediated interference with leukocyte Ig-like receptor 1 (LIR-1), to suppress NK activation. CMV's IE1-72kDa protein interferes with type I interferon (IFN) signaling by sequestering STAT1/STAT2 in the nucleus and blocking their interaction with IFN-stimulated gene factor 3 (ISGF3). IE1-deficient mutants have 4–6 fold greater IFN-responsive transcript levels, and IE1 function decreases STAT1/2 binding to antiviral gene promoters such as ISG15. This intranuclear blockade enhances US28's down-regulation of c-fos, an AP-1 subunit necessary for IFN-γ signaling, further compromising innate immunity.(9)

US28: US28 sustains CMV latency in myeloid cells through MIEP repression by downregulation of c-fos. US28 expression decreases c-fos phosphorylation by 60%, reducing AP-1 binding to the MIEP and stabilizing latency. Upon reactivation, the US28 interaction with EphA2 reverses from latency promotion to entry facilitation since EphA2 overexpression in glioblastoma is associated with increased CMV infectivity and tumor growth.(10)

Receptor-targeted therapies, including EphA2 inhibitors (e.g., dasatinib), decrease CMV entry into glioblastoma organoids, whereas heparan sulfate mimetics may inhibit initial attachment. Reversal of NKG2D ligand expression through UL16 inhibition makes CMV-infected cells sensitive to NK cells. Manipulation of US28's cytosolic tail interferes with MIEP repression, possibly compelling viral reactivation for antiviral clearance. CMV's receptor usage and immune evasion mechanisms worsen outcomes in immunocompromised hosts. In patients undergoing transplantation, EphA2-mediated entry and US2-directed MHC degradation promote graft rejection and CMV pneumonitis, which raises mortality risk 16.7-fold. High EphA2 expression in glioblastoma patients also creates poorer prognoses through increased CMV infectivity and tumor growth. US2's cytosolic domain or EphA2 signaling pathways may be targeted to interrupt viral persistence, providing new interventions for high-risk patients.(11)

CMV's mechanisms of entry and immune evasion are interdependent, with receptors such as EphA2 and US28 playing double-duty roles in viral life cycle phases. By taking over host signaling (e.g., Src-MEK/ERK) and evading immune detection (e.g., MHC degradation, NK evasion), CMV guarantees lifelong infection. New approaches that target these pathways hold promise for the control of CMV in high-risk individuals, yet hurdles exist in terms of avoiding the disruption of latency with inflammatory sequelae.(12)

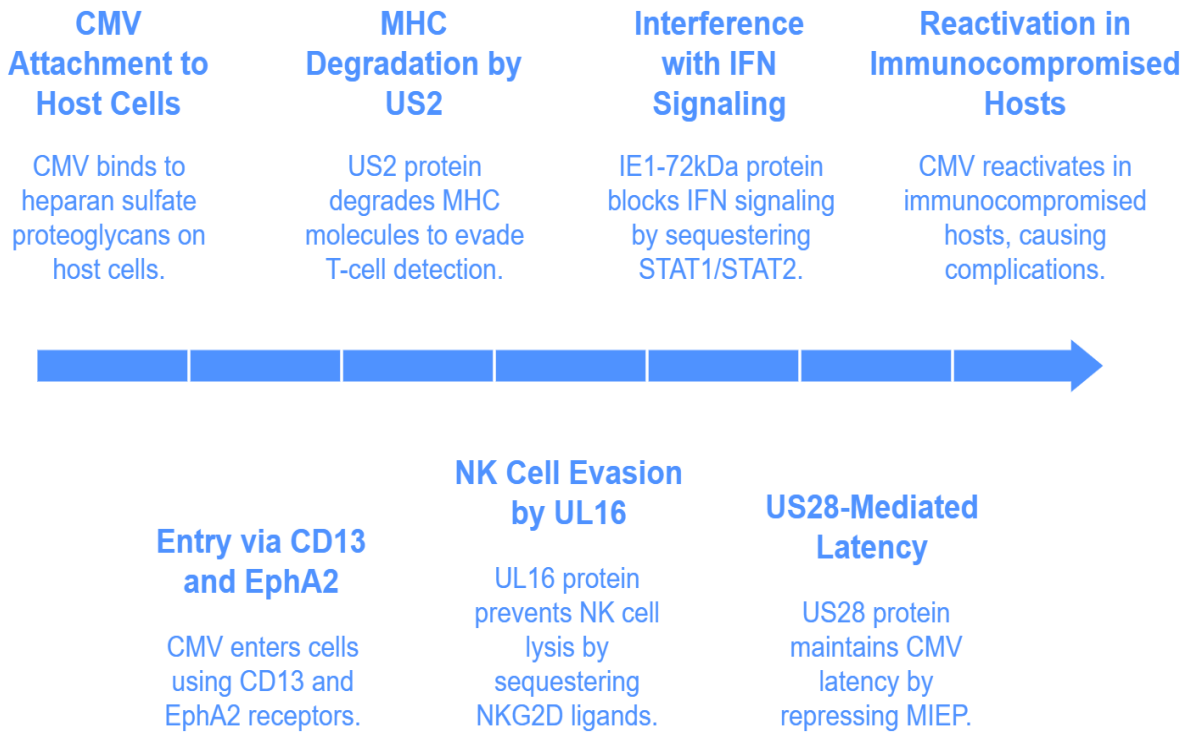

Figure 1: CMV infection and immune evasion sequence

3. Viral Vector-based Vaccines for CMV

Viral vector vaccines are a very promising method in the creation of a Cytomegalovirus (CMV) vaccine. These vaccines employ genetically modified viruses, or viral vectors, to introduce CMV antigen genes into host cells, eliciting strong immune responses. Of the viral vectors investigated for CMV vaccination, adenoviral vectors and vesicular stomatitis virus (VSV)-based vectors have been found to hold high promise because of their unique biological characteristics and immunogenicity.

Adenoviral vectors are one of the most widely used platforms in CMV vaccine development. Adenoviruses are ubiquitous viruses that cause mild respiratory infection in healthy individuals. These viruses can be made replication-defective for use as safe vaccines. The vectors harbor parts of the CMV genome that encode important antigens, which upon delivery into host cells, stimulate production of CMV proteins. This expression of intracellular antigen induces both cellular and humoral immunity (antibody response) and cytotoxic T lymphocytes (CTLs), which are essential for CMV infection control. Adenovirus type 5 (Ad5) vectors have been shown to be highly immunogenic but are vulnerable to pre-existing immunity against Ad5 in most people, thereby limiting their use on a large scale.(13)

Vectors based on VSV, which is an RNA virus, provide another strong platform for CMV vaccination. VSV vectors could be made to produce CMV antigens, triggering strong antibody and T cell responses. They have a capability to replicate naturally, which primes the immune system well. However, safety becomes an issue since wild-type VSV causes illness in humans, requiring modification very carefully to make the vector replication-deficient and safe for vaccine use. In spite of these limitations, VSV vectors have demonstrated good immunogenicity in preclinical models.(14)

Adenoviral and VSV vectors have the advantages of conventional protein-based vaccines as they induce robust cellular and humoral immunity via endogenous antigen expression. The viral vectors infect host cells to introduce CMV genes, which results in antigen expression that stimulates CTLs

and antibody-forming B cells. Adenoviral vector trials in the clinic have induced potent T cell responses against CMV-infected targets, inhibiting viral replication, particularly in immunocompromised subjects. Likewise, VSV-based vaccines have elicited robust CD4+ and CD8+ T cell responses in animal models. Nonetheless, additional human trials will be required to demonstrate long-term protection and efficacy, especially among susceptible hosts like transplant recipients and neonates.(15)

The success of viral vector-based CMV vaccines is contingent upon multiple factors such as vector selection, immune status of the recipient, and target CMV antigens selected. Adenoviral vectors can be less efficient in the presence of pre-existing vector immunity, whereas VSV vectors are superior for promoting T cell responses. Antigen content—glycoproteins, capsid proteins, or early CMV proteins—affects the quality and scope of the immune response. To overcome vector immunity and promote long-term durability of the vaccine, scientists are investigating alternative vaccines such as modified vaccinia Ankara (MVA) and chimpanzee adenoviruses with reduced pre-existing immunity prevalence. In addition, heterologous prime-boost regimens involving other vectors or multiple doses are being explored to maximize immune memory and protection.(16)

5. DNA-based Vaccines: A New Frontier in CMV Prevention

DNA vaccines are a new and promising approach for CMV vaccine development and have numerous advantages such as stability, ease of production, and induction of humoral and cell-mediated immune responses. The only distinguishing feature of DNA vaccines and traditional vaccines is the fact that DNA vaccines utilize plasmid DNA, which carries the viral antigens and when the DNA is exposed to the host cells it results in an immune response. It is a method that allows for direct delivery of genetic material into the host and acts as a replacement for protein or viral vector vaccines. In the case of CMV, DNA vaccines aim to deliver precise CMV antigens, such as glycoproteins, capsid proteins, and immediate-early proteins, in order to evoke protective immune responses.(17)

The creation of DNA vaccines involves a few key aspects including the selection of the appropriate antigen(s) and the construction of a plasmid DNA vector capable of encoding them. The genetically modified DNA must be effectively delivered into host cells, which is most often done employing advanced techniques, e.g., electroporation or liposomal delivery systems. Electroporation involves the application of an electric field to the skin or muscle tissue, which temporarily disrupts the cell membrane so that the DNA plasmids may be taken up into the cells more efficiently. This approach significantly enhances DNA uptake, leading to increased immune responses. Liposomes are small lipid vesicles that can encapsulate the DNA and facilitate the introduction of the DNA into host cells by fusing with the cell membrane. Liposome-mediated delivery systems are attractive since they are biocompatible and involve less invasiveness than electroporation. In addition to these delivery systems, naked DNA (no delivery vehicle) is also administered directly into the host, even though this process is less effective than with electroporation or liposomal preparations.(18)

DNA vaccines possess various benefits such as ease of manufacture, stable shelf life, and the ability of inducing both humoral and cell-mediated immunity. The DNA itself is recognized by the host immune system as a foreign molecule, leading to antibody production as well as activation of cytotoxic T lymphocytes (CTLs) able to recognize and kill CMV-infected cells. Clinical trials of CMV therapy with DNA vaccines are only now starting to be underway, but initial encouraging results have been observed. These vaccines have demonstrated the potential to elicit both T cell and antibody responses, in which CTLs are crucial in destroying CMV-infected cells. As an example, a phase I trial of a DNA vaccine to the CMV glycoprotein B (gB) showed that the vaccine induced robust gB-specific T cell immunity and humoral immune response in healthy volunteers. Similarly, another clinical trial of a DNA vaccine that encodes CMV immediate-early protein 1 (IE1) demonstrated to induce strong T cell-mediated immunity, which is crucial in CMV infection control. These findings suggest that DNA

vaccines are likely to provide protection against CMV infection, especially for immunocompromised persons.(19)

Clinical trial effectiveness data show that DNA vaccines against CMV are safe and well tolerated with the only adverse reactions being mild local reactions at the injection site. The vaccines have been found to induce antibody responses in addition to cytotoxic T cell responses, which are central in controlling CMV infection. Activation of T cell immunity, particularly CD8+ T cells, plays a crucial role in controlling CMV because they are capable of directly recognizing and killing virus-infected cells. The immune system can also generate antibodies that will neutralize the virus and prevent it from infecting additional cells. While early-stage clinical trial data are promising, further work will be needed to assess the long-term protection, effectiveness, and safety of DNA-based CMV vaccines in larger populations.(20)

6. mRNA Vaccine Platforms for Cytomegalovirus

The advent of mRNA vaccine technology has revolutionized vaccine development into a speedier, more agile, and very effective means for combat against infectious diseases like Cytomegalovirus (CMV). As opposed to traditional vaccines, which utilize inactivated viruses or protein subunits, mRNA vaccines instruct the body's cells to produce viral proteins, which subsequently cause an immune response. This new approach makes it possible to design and produce vaccines at high speed, with the additional benefit of not requiring the live virus itself. For CMV, mRNA vaccines can induce very specific immunity by encoding specific CMV antigens such as glycoproteins playing a central role in viral attachment and entry into host cells. The success of SARS-CoV-2 mRNA vaccines spurred investigations into similar platforms for CMV and other viruses, highlighting the disruptive potential of this technology to transform vaccine development.(21)

Perhaps the biggest advantage of mRNA vaccine technology is that it can both elicit humoral immunity (antibody production) and cell-mediated immunity (particularly T cell responses). The latter is crucial in CMV infection, considering the virus's ability to evade antibody-mediated immunity and gain life-long latency in host cells. T cell immune responses, particularly from CD8+ T cells, play a critical role in regulating CMV replication and prevention of reactivation. Through the encoding of CMV proteins such as glycoprotein B (gB) or immediate-early proteins (IE1 and IE2), mRNA vaccines can induce robust T cell responses as well as neutralizing antibodies, giving a complete immunity protection against the virus. This bidirectional immune stimulation is the key advantage of mRNA vaccines relative to traditional vaccine candidates, which have a tendency to focus on antibody induction alone and often are incapable of eliciting sufficient T cell-mediated immunity.(22)

Clinical experience with mRNA vaccines, particularly those for SARS-CoV-2, has provided us with highly specific information on mechanisms of action and on issues for mRNA vaccines against CMV. In the clinic trials, the mRNA vaccines were highly effective, eliciting strong immune responses with minimal side effects. The trials highlighted the possibility of mRNA technology to be rapidly adapted to target multiple pathogens, such as CMV. Science has established that the mRNA platform provides flexibility for the selection of the antigen and the ability of scientists to design vaccines that code for different CMV proteins. In the case of CMV, determination of the best combination of the ideal antigens needed for stimulating the best immune response is vital, and immediate-early and glycoproteins have been found to be important targets in strategies for vaccinating against it.(23)

Despite these advantages, mRNA CMV vaccines also come with their own set of challenges, most notably delivery system and vaccine stability. mRNA is inherently unstable and can be degraded, meaning that advanced lipid nanoparticles (LNPs) must be used to stabilize the mRNA and deliver it into host cells. While LNPs are already being employed successfully in COVID-19 vaccines, optimizing their use for CMV vaccines, especially long-term storage and stability of vaccines in supply chains, is especially important, especially in low-resource settings. Additionally, the immune response against lipid nanoparticles themselves could potentially be an issue because some populations may

result in immune responses against such delivery vehicles, leading to reductions in vaccine efficacy or side effects. Addressing these challenges will be of paramount significance in the successful development of CMV mRNA vaccines.(24)

Prior immunity to CMV, especially among individuals who have been previously infected, represents an additional serious challenge. Such immunity memory can be a hindrance to vaccine efficacy as the immune system will most likely identify the vaccine as belonging to the body's normal response to latent infection. Moreover, in already CMV-seropositive individuals, the immune system is less powerful in reacting to the vaccine, and its efficacy decreases. Understanding how previously existing immunity influences the development of mRNA vaccines against CMV and finding a way to overcome this bottleneck will be most important in making these vaccines work, especially in populations at high risk, such as organ transplant recipients, neonates, and individuals with HIV infection.(25)

Table 1: mRNA Vaccines vs Traditional vaccines for CMV

Characteristic	mRNA Vaccines	Traditional Vaccines
Antigen Presentation	Viral proteins produced by host cells	Inactivated viruses or protein subunits
Speed of Development	Rapid design and production	Slower development process
Immune Response	Humoral and cell-mediated immunity	Primarily humoral immunity
Antigen Specificity	High specificity via antigen encoding	Less specific, broader immune response
Delivery Challenges	Requires advanced lipid nanoparticles	Established delivery methods
Impact of Prior Immunity	Can be hindered by prior immunity	Less affected by prior immunity

7. Comparative Analysis of Vaccine Technologies: Viral Vectors, DNA, and mRNA

Comparison of vaccine technologies—viral vector, DNA, and mRNA—gives key insights into how they prevent Cytomegalovirus (CMV) infection. Each has its strengths and weaknesses, which decide their ability to provoke a desired immunological outcome and compatibility for mass production and dispensing. Analysis of the strengths, weaknesses, and immune response provoked by each of the vaccine technologies makes it clearer how they may hold up against CMV and which populations would be benefited most by each platform.(26)

Viral vector vaccines, such as adenovirus or vesicular stomatitis virus (VSV) vaccines, have several key strengths. They are very well established in vaccine development and have been shown to induce robust cell-mediated immunity, especially CD8+ T cell responses, that are essential in the control of CMV infections. These vaccines can potentially deliver genetic material coding for CMV antigens into the host cells and induce the viral proteins to express that lead to humoral and cellular immune response. But the worst weakness of viral vector vaccines is the possibility of pre-existing immunity in the population. If an individual has already been exposed to the vector virus (e.g., adenovirus), his or her immune system can recognize the vector and react against the vector itself, lessening the efficacy of the vaccine. Also, safety concerns with respect to the use of live viral vectors must be addressed appropriately to avoid untoward reactions in immunocompromised individuals, a critical problem for CMV vaccine candidates.(27)

DNA vaccines, on the other hand, offer advantages such as ease of production and stability. Because DNA vaccines are not live pathogens, they can readily be made and kept at normal temperatures, making them well-suited for distribution in large quantities. DNA vaccines induce a robust humoral response by promoting the production of antibodies against CMV antigens. They also induce cell-mediated immunity, although typically to a lower extent than viral vector vaccines. One of the biggest

pluses of DNA vaccines is their safety profile—because they don't contain live virus, the risk of causing disease is very low. But the biggest minus of DNA vaccines is their immunogenicity, which is usually weaker than that of other platforms. Electroporation or liposome-delivery systems are used to facilitate DNA uptake and augment immune responses, but using such systems, DNA vaccines are adjuvant dependent or require the use of multiple booster doses to exhibit sufficient immunogenicity. Furthermore, DNA vaccines are not capable of inducing the robust T cell-mediated response necessary for CMV control, especially among high-risk populations such as organ transplantation recipients or HIV-seropositive individuals.(28)

The mRNA vaccine technology is a new vaccine platform whose initial widely effective use is via SARS-CoV-2 vaccines. One of the strengths of mRNA vaccines is their versatility and rapid manufacturing capability. The mRNA platform can be quickly adapted to express multiple CMV antigens, enabling tailoring of vaccines to specific viral strains or variants. Moreover, mRNA vaccines can also induce both humoral immunity (antibodies) and strong cell-mediated immunity, including the induction of CD8+ T cells, which is of most importance in CMV infection control. It has been shown by clinical trials that mRNA vaccines can elicit strong immune responses with minimal side effects and hence are very promising for prevention of CMV. In spite of this, the most important problems with mRNA vaccines are delivery platforms. The mRNA is unstable and requires lipid nanoparticles (LNPs) to stabilize and assist in the delivery into host cells. While LNPs have performed well in COVID-19 vaccines, maximizing their performance for CMV vaccines, including ensuring long-term stability and scalability, is an issue. Additionally, pre-existing immunity to the lipid nanoparticles or the CMV antigens may restrict the effectiveness of the vaccine, particularly among individuals with prior exposure to CMV.(29)

In their immune response, each vaccine platform has a distinct advantage. Viral vector vaccines are also reported to induce strong cell-mediated immunity due to their ability to elicit cytotoxic T lymphocytes (CTLs) that can kill CMV-infected cells. This makes viral vector vaccines highly effective in controlling viral replication and reactivation of CMV, especially in immunocompromised individuals. Alternatively, DNA vaccines induce primarily antibody responses but also some T cell activation, albeit in generally lower magnitudes than viral vectors. The response to the DNA vaccine is generally late, and efficacy can be a function of the presence of adjuvants or boosters. mRNA vaccines, in contrast, are characterized by their capacity to induce both humoral as well as cell-mediated immunity, and as such, are especially appealing for prevention of CMV. By directly encoding antigens into the host cells, mRNA vaccines can trigger a robust T cell-mediated response in combination with neutralizing antibodies, which are critical for long-term protection against viral infections.(30)

Table 2: Comparative Overview of CMV Vaccine Platforms

Feature/Parameter	**Viral Vector-based Vaccines**	**DNA-based Vaccines**	**mRNA-based Vaccines**
Platform Mechanism	Uses engineered viruses to deliver CMV genes	Delivers plasmid DNA encoding CMV antigens	Delivers mRNA encoding CMV proteins via lipid nanoparticles
Immune Response	Strong humoral and cellular (CD8+ T cells)	Moderate to strong cellular & humoral	Strong humoral and cellular (CD4+/CD8+)
Antigen Targets	gB, pp65, IE1, IE2	gB, pp65, IE1	gB, IE1, IE2
Delivery System	Adenovirus, VSV, MVA	Electroporation, liposomes, naked DNA	Lipid nanoparticles (LNPs)

Immunogenicity	High, but varies with pre-existing immunity	Moderate (requires adjuvants/boosters)	High (boosted by LNPs)
Production Complexity	Moderate to high	Low to moderate	Moderate to high
Safety Profile	Generally safe with replication-defective vectors	Safe, well-tolerated	Safe, but LNPs may elicit immune responses
Stability and Storage	Stable under standard conditions	High stability, long shelf life	Needs cold chain; mRNA prone to degradation
Clinical Trial Stage	Several in phase I/II	Early-phase human trials	Preclinical/early clinical for CMV

8. Immunological Mechanisms Induced by CMV Vaccines

CMV is particularly dangerous to immunocompromised patients, newborns, and transplant recipients because it can cause latency and avoid immune detection. A successful vaccine should activate both branches of the adaptive immune system to avert primary infection, reinfection, and reactivation. Induction of virus-specific T-cell responses, especially cytotoxic CD8+ T lymphocytes, for clearance of infected cells and B-cell responses with neutralizing antibodies to prevent viral entry are critical. Hence, CMV vaccine strategies need to address both cellular and humoral immunity for robust and long-lasting protection.(4)

T-cell responses, particularly CD4+ and CD8+ subsets, are primarily involved in the long-term control of CMV. CD8+ T cells directly lyse CMV-infected cells, while CD4+ T cells provide essential help for B-cell maturation and memory formation. Studies have shown that transplant recipients lacking strong CMV-specific T-cell responses are more susceptible to viral reactivation, emphasizing the need for vaccines to induce effective cellular immunity. Some of the CMV vaccine candidates, including those based on pp65 and gB antigens, are designed to be primarily a booster of T-cell activity to impede viral replication.(31)

B-cell-mediated responses are also essential in CMV immunity. Neutralizing antibodies, which are mainly against the gB and pentameric complex of CMV, inhibit viral entry into epithelial and endothelial cells. A landmark report on a gB-based CMV vaccine demonstrated antibody titers correlated with decreased maternal-fetal transmission, emphasizing the role of humoral immunity. Antibody response alone is not enough for full protection, which again points to the fact that there is a need for an immunogen eliciting both branches of the adaptive immune system.(32)

Viral vector vaccines, including those based on modified vaccinia Ankara (MVA) or adenoviral vectors, have shown to be capable of inducing strong T-cell immunity. These platforms introduce CMV genes into host cells and induce antigen expression and presentation through MHC class I molecules, efficiently priming CD8+ T cells. Clinical trials involving adenovirus-based CMV vaccines have demonstrated increased CMV-specific T cell frequencies, while the risk of pre-existing immunity to the vector and vector-induced inflammation is still a concern.(33)

DNA vaccines provide a stable and immunogenic platform for CMV immunization by delivering plasmid DNA encoding viral antigens like pp65 or gB. These vaccines are well tolerated and can stimulate cellular and humoral immunity. Nevertheless, their immunogenicity tends to be lower than other platforms and requires the use of adjuvants or sophisticated delivery technologies like electroporation. Clinical trials have proven that DNA vaccines are capable of eliciting low levels of antibodies and T-cell responses, making them a promising though still developing candidate in CMV vaccine development.(34)

mRNA vaccine platforms recently rose to fame with their success against COVID-19 and are currently being investigated for CMV as well. These vaccines express CMV proteins that are host-cell translated and shown to the immune system, generating robust CD8+ T-cell and antibody responses. The Moderna mRNA-1647 CMV vaccine, currently undergoing clinical trials, is targeting both gB and the pentameric complex and has demonstrated encouraging immunogenicity and safety findings. The mRNA platform also supports quick updates and scalability, which makes it a favorable choice for CMV.(35)

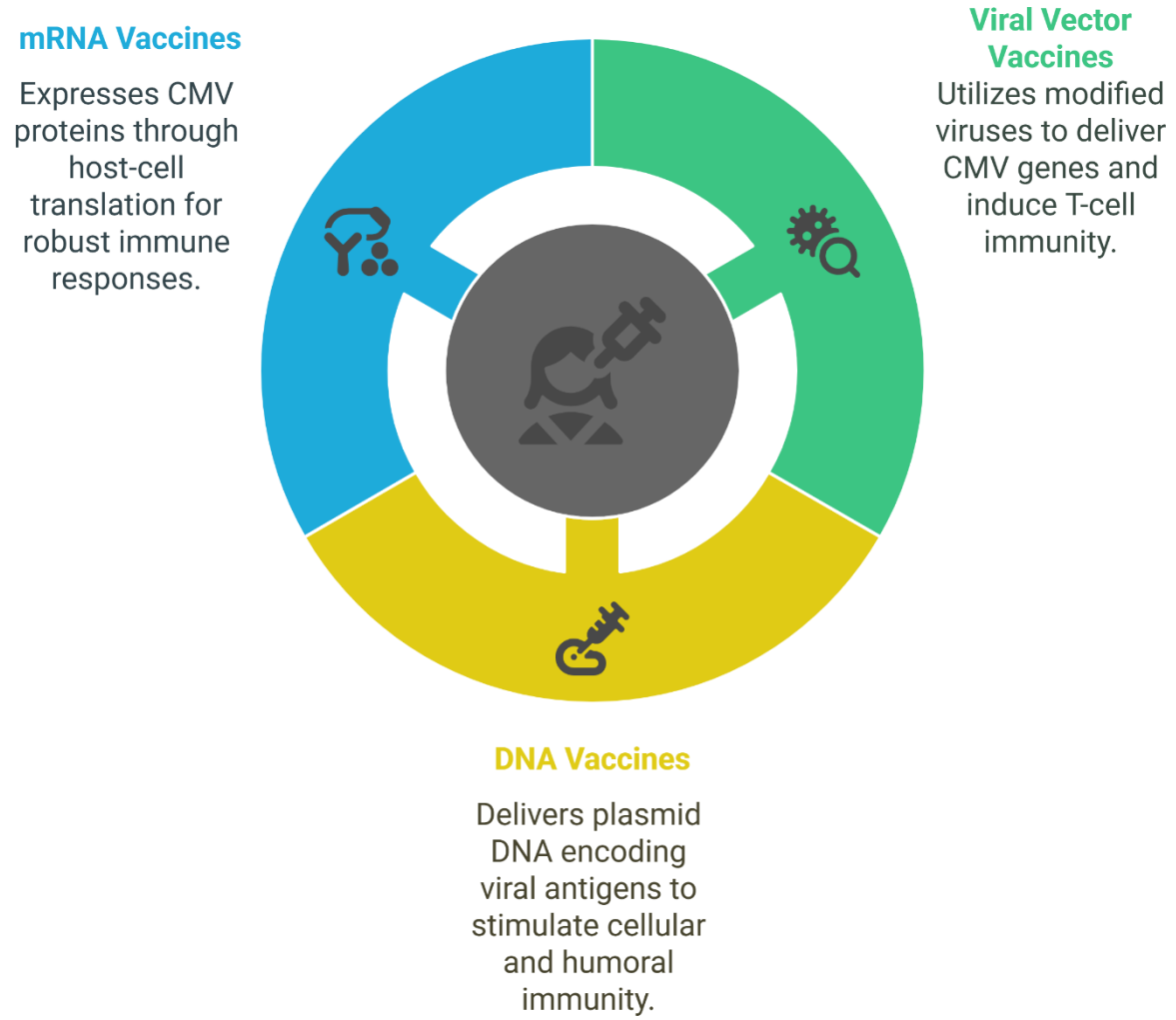

Figure 2: CMV vaccine strategies

9. Challenges and future direction of CMV Vaccine Development and Implementation

Development of cytomegalovirus (CMV) vaccine has been hampered by various scientific and immunological hurdles. One of the foremost difficulties is that the virus can develop latency and re-emerge, which makes it challenging to develop durable immunity. Another complication arises because CMV has a high degree of genetic variability and can evade immunity by downregulation of MHC molecules, making it challenging to develop universally effective vaccines. Vaccine candidates must target multiple antigens (e.g., gB, pp65, pentameric complex) to elicit robust and broad immunity. These complex requirements have made the development process slow and scientifically demanding.(36)

Safety issues are another major obstacle. Although viral vector, DNA, and mRNA platforms have been promising, each of them has its limitations. Pre-existing immunity to viral vectors such as adenovirus,

for example, decreases vaccine efficacy and provokes unwanted inflammatory reactions. DNA vaccines are safer in nature but require adjuvants or delivery improvements such as electroporation because of their relatively poor immunogenicity. mRNA vaccines, being very immunogenic, are a concern regarding long-term safety, particularly in pregnant women and those who are immunocompromised—the very groups that need protection against CMV the most.(37)

Regulatory issues further complicate the road to CMV vaccine licensure. There are no licensed correlates of protection for CMV, making vaccine efficacy challenging to assess for regulatory bodies. Clinical trial designs are also hindered by varying CMV seroprevalence rates worldwide and the necessity of testing in particular high-risk groups like seronegative pregnancy women. Also, since CMV infection can be asymptomatic in healthy persons, the assessment of relevant endpoints for the determination of vaccine efficacy in trials is attendant with needing large populations and prolonged follow-up periods.(38)

Public health implementation is not without its own challenges. The expense of vaccine production, development, and distribution can be prohibitively expensive, particularly in LMICs (low- and middle-income countries) where CMV burden is usually highest. Vaccine delivery infrastructures must be modified for populations with minimal access to healthcare infrastructure. Cold chain storage, multiple doses scheduled, and long-term follow-up require logistical challenges that may impact uptake and efficacy in the real-world setting.(39)

Table 3: Advantages and Limitations of Each Vaccine Type

Vaccine Type	Advantages	Limitations
Viral Vector-based	- Strong T cell responses- Mimics natural infection- Versatile antigen expression	- Pre-existing immunity (e.g., Ad5)- Safety concerns with live vectors- Complex manufacturing
DNA-based	- Stable, easy to produce- Elicits CTL and antibody responses- No need for live virus	- Low immunogenicity without adjuvants- Delivery methods require optimization
mRNA-based	- Rapid development- High immunogenicity- No integration risk- Safe and flexible	- Requires cold storage- Delivery system immunogenicity- Stability issues

Ongoing clinical trials reflect a diversification in vaccine platforms, including viral vectors, DNA constructs, protein subunits, and mRNA technologies. Moderna's mRNA-1647 CMV vaccine, which encodes six CMV proteins including gB and components of the pentameric complex, is currently in Phase 3 trials. Early data have shown promising immunogenicity and safety, positioning it as a leading candidate for the first licensed CMV vaccine. Similarly, VBI Vaccines is developing an enveloped virus-like particle (eVLP) vaccine that mimics the native virus structure, potentially improving both T-cell and B-cell responses.(40)

Future directions also emphasize personalized vaccination strategies. Given that CMV infection risk and severity vary among different populations—such as pregnant women, transplant recipients, and HIV patients—tailored vaccine formulations or booster regimens may become necessary. Advances in genomic and systems biology could help identify biomarkers that predict vaccine responsiveness, guiding such personalized approaches. Moreover, real-world data collection through post-marketing surveillance will be essential for refining vaccination programs and ensuring long-term safety.

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