Although following primary human cytomegalovirus (CMV) infection in many individuals no overt symptoms are observed, CMV came to medical attention due to its significant morbidity and mortality associated with congenital infection and immunosuppressed individuals. Congenital infection occurs following transplacental transmission during pregnancy as a result of primary infection, reactivation or re-infection with a different isolate. Estimates suggest at least a million cases of congenital CMV occur annually worldwide. Congenital infection is a leading cause of neurological complications such as mental retardation, cerebral palsy, developmental delay and seizure disorders and also causes permanent disabilities, such as hearing loss and vision impairment. In addition, other common manifestation of CMV infection are stillbirth, preterm delivery and intrauterine growth restriction (IUGR) and cardiovascular disease, which are risk factors for perinatal and lifetime morbidity. Recent reports have estimated that the economic costs to public health and families due to congenital CMV infection are immense, with direct annual costs of billions of dollars. An effective CMV vaccine that could prevent transplacental transmission, reduce CMV disease and CMV-associated stillbirths has been recognised as an urgent medical need. Over the past 40 years several CMV vaccine candidates have been evaluated in a series of clinical trials and found to be effective in preclinical and clinical studies. However, in spite of extensive efforts over many decades, successful licensure of an effective CMV vaccine formulation to prevent congenital CMV infection remains elusive.

The major target populations for a CMV vaccine to reduce congenital infection include women of reproductive age, infants, toddlers and adolescents. Children who attend day care represent a particularly important reservoir of CMV. Women of reproductive age exposed to children who are shedding virus in urine and saliva are 10 times more likely to seroconvert compared to women unexposed to virus shedding children. In addition, the symptomatic congenital CMV rate is very high if women acquire primary infection or CMV virus reactivates during or just before pregnancy, whilst prior natural CMV infection provides protection from transplacental transmission.

In pregnant women following natural primary infection, viral replication is controlled by the emergence of antigen-specific CD4+, CD8+ and CD45RA+ effector memory T-cells. Lower frequencies of CMV-specific CD4+ T-cells and CD45RA+ cells in mothers following primary infection is known to be associated with virus transmission to the fetus. Based on these observations it can be hypothesised that emergence of higher frequencies of CMV-specific CD4+, CD8+ and CD45RA+ effector memory T-cells may be associated with control of viremia and prevention of transplacental transmission. Therefore, an effective CMV vaccine specially designed to induce CMV-specific CD4+, CD8+ and CD45RA+ effector memory T-cells in women of reproductive age could potentially decrease CMV transmission to the fetus and vaccination of infants, toddlers and adolescents could reduce the duration of viral shedding, which may reduce child-to-mother transmission.

Clinical evaluation of active and passive immunisation strategies against CMV in the context of congenital CMV

Live attenuated virus vaccines

The initial CMV vaccine trials based on an attenuated form of CMV isolates Towne and AD169 induced humoral and cellular
immune responses in immunocompromised solid organ transplant patients. However, a study conducted in young women with children attending group day care showed no reduction in the infection rate in Towne-vaccinated mothers compared to placebo. Thus the efficacy of the Towne vaccine against congenital CMV infection was questioned\textsuperscript{13}. Subsequently several alternative approaches have been used to improve the efficacy of the live attenuated Towne vaccine, which includes generating recombinant chimeras by swapping lost genome segments of Towne vaccine with the less attenuated Toledo strain. The evaluation of safety and immunogenicity of chimeras in CMV-naive subjects is now in phase 1 clinical trials\textsuperscript{14}. However, safety concerns raised by experts in the field during an FDA review in 1999 are the major confounders to vaccination with any live attenuated CMV vaccine\textsuperscript{14}.

**Subunit vaccines**

Another vaccine strategy is based on a subunit vaccine that was developed initially by Chiron by combining recombinant glycoprotein B (gB) with an oil-in-water adjuvant, MF59. The efficacy of gB-MF59 vaccine was recently evaluated in a Phase II, double-blind, randomised, placebo-controlled trial, in seronegative women of child bearing age\textsuperscript{15}. The vaccine showed reduction in the incidence of primary maternal infection by 50% in the vaccinated group compared to the placebo group. However, the protection was not durable and it was predominantly observed within the first year after immunisation. Subsequent testing of gB-MF59 vaccine in seropositive women showed a significant boost in neutralising antibody titers and CD4\textsuperscript{+} T-cell responses\textsuperscript{16}. Nevertheless, whether such boosting will provide protection against reactivation or reinfection with a different isolate in women with pre-existing immunity is not yet known.

**Passive immunisation**

In addition to active immunisation strategies, passive immunisation strategies based on administration of anti-CMV immune globulin to women at high risk of transmitting CMV to the fetus also have been explored in clinical research. Initial observations suggest that CMV hyperimmunoglobulin (HIG) could inhibit viral spread in vitro\textsuperscript{17,18}, restore placental health in mothers during primary infection\textsuperscript{19} and lead to the regression of fetal cerebral ultrasound abnormalities\textsuperscript{20}. A prospective study carried out in mothers with confirmed primary infection demonstrated that monthly intravenous administration of HIG can decrease mother-to-fetus transmission significantly, from 40% to 16% and the risk of congenital disease from 50% to 3%\textsuperscript{21}. Several retrospective studies have suggested that CMV HIG can reduce intrauterine transmission of CMV\textsuperscript{22} and can protect against poor outcomes in infants\textsuperscript{23,24}. However, in a recent randomised trial, HIG treatment did not significantly modify the course of primary CMV infection during the pregnancy\textsuperscript{25}. Therefore, in our perspective more randomised studies are required to draw a firm conclusion on the efficacy of HIG therapy.

**CMV vaccines in preclinical studies**

Several additional proof-of-concept studies of various candidate vaccines have also been evaluated in clinical and preclinical studies in recent years\textsuperscript{14,26}. Vical/Astellas developed a vaccine (CyM- Vectin\textsuperscript{26}) to target congenital CMV using plasmids that encode gB and pp65 formulated with Vaxfectin adjuvant. The preclinical data from this study presented at the 5th International Congenital CMV Conference (2015) held in Brisbane showed that CyMVectin\textsuperscript{26} has the potential to induce neutralising antibodies against both fibroblasts and epithelial cells. AplhaVax developed a dual alphavirus replicon that expresses the CMV antigens gB plus an IE1-pp65 fusion protein and has evaluated its safety and immunogenicity in Phase I clinical trials. Following vaccination all vaccine recipients developed polyfunctional CD4\textsuperscript{+} and CD8\textsuperscript{+} T-cell responses and neutralising antibody response\textsuperscript{27,28}. Furthermore, several alternative vaccine strategies have shown promising results in emerging preclinical evaluations\textsuperscript{20}. These include a recombinant modified vaccinia Ankara (MVA) expressing three immunodominant CMV antigens pp65, IE1 and IE2 as a fusion protein, a dense body vaccine consisting of non-infectious, replication-defective particles formed during the replication of CMV, polypeptide vaccines comprising a replication-deficient adenoviral vector for the expression of gB antigenic domain-1 or the extracellular domain of the gB protein and 46 HLA class I and II restricted T-cell epitopes or recombinant gB and polypeptide protein formulated with TLR4 and TLR9 agonists\textsuperscript{29}. However, the safety and immunogenicity of these vaccine candidates is yet to be determined in advanced clinical studies in the context of congenital CMV.

Extensive studies in humans have revealed that the gHgL/UL128–131A pentameric complex is the most important antigenic complex for neutralising antibodies especially to restrict the entry of CMV into epithelial and endothelial cells\textsuperscript{30}. High titers of neutralising antibodies are thought to protect against transmission by blocking receptor-mediated transplacental transmission of CMV and by reducing viral replication\textsuperscript{31,32}. Therefore, it will be interesting to investigate the potential role of pentameric glycoprotein complex-specific humoral responses in both primary and recurrent infections in pregnant women.

**Major barriers in the development of effective CMV vaccines**

Conventional CMV vaccine approaches that target a single genotype may induce only partial protection due to high levels of CMV
genomic variation and recombination within infected populations. Frequent recurrence and transmission in largely CMV seropositive individuals are the major confounders for CMV vaccine development. Despite the promising results from CMV-HIG trials, the mode of action of these antibodies in limiting transplacental transmission of CMV in high-seroprevalence population remains to be determined. Finally, understanding the immune parameters that effectively protect from transplacental transmission of CMV in pregnant women as a result of primary infection, reactivation or re-infection need to be delineated for the development of an effective CMV vaccine (Figure 1).

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References


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