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Cytomegalovirus vaccine: phase II clinical trial results

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Abstract

Cytomegalovirus (CMV) is one of the most significant viral pathogens during pregnancy and in immunocompromised patients. Antiviral prophylactic strategies are limited by toxicities, drug–drug interactions and development of antiviral resistance. A safe and protective vaccine against CMV is highly desirable in view of the potential positive impact on CMV-associated morbidity and mortality as well as healthcare costs. Unfortunately, this demand could not be met in the past four decades although development of a CMV vaccine has been ranked at the highest priority by the US Institute of Medicine. Multiple different vaccine candidates have been developed and evaluated in phase I clinical trials and few succeeded to phase II trials. Nevertheless, two different vaccines showed recently promising results in trials that studied healthy adults and immunocompromised solid-organ and bone-marrow transplant recipients, respectively. The gB/MF59 vaccine exhibited a vaccine efficacy of 50% in healthy, postpartum females. In transplant patients, gB/MF59 and the DNA vaccine TransVax both limited the periods of viraemia and consequently the need for antiviral treatment. The success of these trials is encouraging and will probably give new impetus to the development of an effective CMV vaccine. Sterilizing immunity may not be attainable in the near future and may not be necessary for a CMV vaccine to have a significant impact on health care as discussed in the present review.

Keywords

Cytomegalovirus; glycoproteins; human immunodeficiency virus; immunology; intrauterine infection; pentameric complex; transplantation; vaccine

Significance of Cytomegalovirus Infection and Emerging Risk Groups

Cytomegalovirus (CMV) is one of the most significant viral pathogens during pregnancy and in immunocompromised patients. CMV infection is the leading cause of congenital viral infection in Western countries with an overall birth prevalence of 0.64% [1]. Primary CMV infection occurs during 1–4% of pregnancies with an associated rate of congenital infection of 40–50% [2]. CMV-specific immunity does not protect from intrauterine infection as 1% of fetuses from CMV-seropositive pregnant women are infected in the course of viral

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reactivation or superinfection with a different CMV strain [2]. Infants with congenital CMV infection are symptomatic at birth in 10% of cases and a further 10–15% of infants will develop symptoms within 4 years postpartum [1,2].

The tremendous success of solid-organ and haematopoietic stem cell transplantations add another growing group of patients at risk for CMV disease. Particularly CMV-seronegative transplant recipients who receive a graft from a CMV-seropositive donor ($D^+ R^-$) are at high risk for severe CMV disease [3]. Human immunodeficiency virus-infected patients are mostly CMV-seropositive (>90%) and are therefore frequently at risk for CMV disease during periods of intense immunodeficiency [4]. Fortunately, the advent of highly active antiretroviral treatment reduced the incidence of CMV disease in these patients from being the most significant opportunistic infection before their development to a rarity [3]. Progress in the treatment of autoimmune or haematological diseases with immunomodulating drugs improved patient management but put additional patient cohorts at risk for CMV disease. For example, treatment of patients with chronic lymphocytic leukaemia with the monoclonal antibody alemtuzumab increases median survival by several years [5]. Alemtuzumab-associated lymphocyte and T-cell depletion, however, results in CMV reactivation and disease in up to 66% of patients without antiviral prophylaxis [5]. Finally, patients treated at intensive care units are also at increased risk of CMV reactivation in the absence of a known immunodeficiency [6]. The reasons for reactivation and the clinical significance of CMV viraemia is poorly defined in these patients [6]. CMV reactivation in this cohort was associated with adverse clinical outcome such as longer duration of mechanical ventilation, prolonged hospitalization and increased all-cause mortality [6].

In view of the significant impact of CMV infection on health care, a safe and protective vaccine against CMV is urgently needed. Development of a CMV vaccine is ranked at the highest priority by the US Institute of Medicine based on avoidable economic costs—estimated annual savings would be $4 billion for transplantations and congenital infections in the USA alone [7]. However, this need could not be met during four decades of CMV research.

Strategies for the Prevention of CMV Disease

In the absence of an effective CMV vaccine, alternative strategies were devised to reduce the risk of CMV infection and disease. Hand and environmental hygiene is an essential part in every effective infection control programme and may also reduce transmission rates of CMV. CMV infection in the first 3 years of life is followed by viral excretion in urine and saliva for up to 42 months [8]. Accordingly, CMV-seronegative mothers of CMV-infected children are at 20–25% higher risk of primary CMV infection compared with CMV-seronegative mothers of uninfected children and become infected with a probability of at least 50% within 1 year after the child acquires the infection [8]. Effective hygiene measures for CMV-seronegative mothers and screening of their children for CMV infection could reduce infection rates significantly [8]. Still, effective interventions also included avoidance of intimate contact of the CMV-seronegative mother with its child, which appears to be rather drastic.

Several antiviral drugs have been licensed for treatment and prophylaxis of CMV infection and disease (reviewed in [9]). Development of viral resistance to these drugs, toxicities, drug–drug interactions and inhibition of the host's immune response to CMV may limit significantly the usefulness of these drugs in the clinical setting [9]. To limit potential side-effects of antiviral prophylaxis, the concept of pre-emptive therapy was developed [10]. Pre-emptive therapy is based on the observation that viraemia is a prerequisite for development of CMV disease. Hence, pre-emptive therapy involves serial testing for CMV-DNA in blood samples and, in contrast to antiviral prophylaxis, administration of antiviral drugs only in the case of a positive test result [10]. Drug-related toxicities may be reduced considerably with the use of pre-emptive therapy although both preventive approaches have multiple benefits and disadvantages that stirred a controversy on the most useful approach (reviewed in ref. [10]).

The CMV Vaccine Pipeline

Multiple candidate CMV vaccines have been developed during the past four decades and several more are currently under preclinical and clinical evaluation (Table 1). Phase I clinical trials were carried out on almost a dozen vaccine candidates with different antigens, formulations, adjuvants and routes of administration. The stream of vaccine candidates, however, diminishes to a trickle at advanced stages of clinical evaluation. So far, the experience with only a single CMV vaccine warranted a phase II clinical trial in healthy adults for protection from CMV infection [11]. Two further recent phase II trials aimed at modifying the course of CMV reactivation or re-infection in immunocompromised patients (therapeutic vaccination) [11,12]. Surprising to all scientists involved [13], these recent CMV vaccine trials were successful and showed for the first time some light on the horizon.

Phase II Vaccine Studies in Healthy Individuals

The gB/MF59 vaccine was developed in the early 1990s by Chiron (Emeryville, California, USA) and later by Sanofi Pasteur (Paris, France). The vaccine is based on a purified gB protein formulated with MF59, a squalene and water emulsion adjuvant [13]. In a series of phase I clinical trials including adolescents and adults as well as toddlers, the vaccine was found to be safe and immunogenic (Table 1) [14,15]. A vaccination schedule of 0, 1 and 6 months elicited the highest titres of neutralizing gB-specific antibodies [16], antibody and T-cell responses could be boosted successfully in CMV-seropositive women [24], and gB/MF59 was significantly more immunogenic than the highest dose of gB adjuvanted with aluminium hydroxide [14].

The extensive and promising experience gained in these early studies warranted a phase II trial in young women of child-bearing age. The patient population of this trial comprised postpartum, CMV-seronegative, predominantly African-American (73%) women (Table 2). The advantage of this population was a comparably high force of CMV infection. CMV-seronegative mothers in earlier studies acquired CMV between deliveries at a rate of *c.*6% per year and past CMV infection reduced the congenital infection rate by around 67% in subsequent pregnancies compared with the rate in newborns of CMV-seronegative women [25]. At months 0, 1 and 6, subjects received either the investigational vaccine or placebo

(Table 2) and were followed for a median period of 42 months. Subjects were screened for CMV infection by a commercial ELISA that used whole virus lysate. To differentiate immunity generated by the vaccine from that by infection, sera were pre-absorbed with recombinant gB to eliminate gB-specific antibodies, similar to the concept applied to the diagnosis of hepatitis B infection [26].

The gB/MF59 vaccine was clearly more effective than placebo in protecting from CMV infection. CMV infection was diagnosed in 31/216 (14%) placebo and 18/225 (8%) CMV gB vaccine recipients (p 0.02). The rate of CMV infection was 6.6/100 person-years in placebo recipients compared with 3.3/100 person-years in vaccine recipients, an overall efficacy of 50%. Congenital CMV infection occurred in 1/81 (1%) and 3/97 (3%) babies born, respectively, to CMV gB vaccine and placebo recipients. During the first 15 months of the follow-up period, vaccinees had a significantly higher probability of remaining free of CMV infection than controls. Nevertheless, this difference remained stable for the ensuing observation period. Accordingly, the protective effect of the gB/MF59 vaccine may be short-lived in concordance with phase I trials that showed neutralizing antibody titres that declined rapidly half a year after vaccination [14,16].

The measured vaccine efficacy of 50% is clearly higher than expected and lower than wished for from a clinical perspective. Still, is sterilizing immunity essential for a CMV vaccine to have a significant impact on CMV-associated morbidity and mortality? In contrast to highly infectious viral pathogens such as measles or rubella, CMV is poorly contagious [27]. The estimated force of CMV infection ranges between 1.6 and 3.5/100 persons/year in the general population of Western countries and is considerably higher in non-Hispanic Blacks and Mexican Americans and in groups with low household income [28]. Accordingly, even modest rates of vaccination efficacy (~60%) would be sufficient to generate herd immunity, interrupt transmission and eradicate CMV from the human population [30]. Concomitant interventions such as education and levelling of social disparities would very likely decrease the force of infection further and increase the success of a CMV vaccine.

Moreover, sterilizing immunity may not be required to protect infants from the consequences of intrauterine CMV infection. The evaluation of dried blood spots from newborn biochemical screening (‘Guthrie’) cards for quantity of CMV-DNA revealed a significant positive correlation between viral load and severity of sensorineural hearing loss [31]. Vaccinating adolescent females with a CMV vaccine that does not protect from infection but from significant periods of viraemia in the child may still be a valuable prophylactic option in addition to the use of antivirals in newborns, which frequently cause significant neutropenia [32].

Phase II Vaccine Studies in Immunocompromised Patients

Three phase II clinical trials have been completed in immunocompromised patients so far (Table 2). Two decades ago, the first one was conducted in D^+ R^- kidney transplant recipients at high risk for CMV infection with the use of an attenuated Towne strain of CMV [33]. Consistent with earlier phase I studies, this vaccine did not prevent CMV infection, but severe cases of CMV disease were observed only in the placebo group [33]. Nevertheless, a

limitation of this vaccine was its apparent inefficiency to generate neutralizing antibodies [34].

In 2006, a trial of the gB/MF59 vaccine was initiated in kidney and liver transplant patients to evaluate its effectiveness with respect to reducing the incidence of end-organ disease [11]. The patient population included CMV-seropositive and CMV-seronegative recipients and donors, respectively. Patients were followed for a median observation period of 95 days post-transplantation. One prerequisite for the feasibility of this study was the use of pre-emptive therapy in contrast to universal prophylaxis, which allowed the evaluation of vaccine efficacy without confounding by the antiviral intervention. The low rates of end-organ disease observed (1/78 patients) underlined the effectiveness of pre-emptive therapy but made the definition of the co-primary endpoints—safety and immunogenicity of the vaccine—necessary [11].

The gB/MF59 vaccine induced significantly higher antibody titres in CMV-seronegative and -seropositive subjects than in placebo recipients. The proportion of patients who tested positive for CMV-DNA anytime during the observation period was similar in the two study groups. Still, high gB-antibody titres correlated with shorter duration of viraemia (p 0.0022) and, particularly in the $D^+ R^-$ vaccine recipients at high risk for CMV infection, duration of viraemia and number of days of ganciclovir treatment were reduced [11].

The third CMV vaccine evaluated in a phase II trial, TransVax [VCL-CB01, Vical (San Diego, California, USA)/Astellas (Tokyo, Japan)], differs from gB/MF59 with respect to formulation, antigens and target population. TransVax is a bivalent DNA vaccine encoding the two CMV antigens pp65 and gB, adjuvanted with poloxamer CRL1005 and benzalkonium chloride. CMV pp65 was included to induce T-cell responses and gB was included to induce antibody and T-cell responses. The aim of the phase II trial of TransVax was to boost pre-existing immunity in CMV-seropositive bone-marrow transplant recipients (therapeutic vaccination) [12]. Subjects received either vaccine ($n = 40$) or placebo ($n = 34$) at day –5, 21–41, 84, 196 and were followed for 1 year post-transplantation (Table 2). Similarly to the gB/MF59 trial, the main endpoint of this study was significant CMV-DNA detectable in blood from patients and requiring antiviral therapy.

Occurrence and duration of CMV viraemia episodes were significantly reduced in these CMV-seropositive patients when receiving the full vaccination schedule of TransVax. In addition, the intervals between periods of viraemia were clearly longer in vaccine recipients than in placebo recipients.

The observed efficacy of TransVax is remarkable for several reasons. (i) Donors of bone marrow were also CMV-seropositive in >50% of transplantations and therefore potential sources for CMV superinfection with an additional viral strain. Immunosuppressive or myeloablative therapies diminish the response of pre-existing immunity to antigens and immune maturation following primary infection is clearly prolonged [35]. Accordingly, it may be hypothesized that the vaccine had some protective effect also in cases of superinfection. (ii) The successful vaccination strategy was attributed to the stimulation of cell-mediated immunity to pp65, gB-specific humoral or cellular immunity was not

stimulated significantly with use of TransVax [12]. In a phase I trial in healthy CMV-seropositive and CMV-seronegative adults, Transvax induced a significant antibody and/or T-cell response only in 46% of CMV-seronegative and in 25% of CMV-seropositive participants evaluated [36]. In contrast, the success of the gB/MF59 vaccine trial in solid-organ transplant recipients was defined similarly by virological end-points but attributed to the generation of protective gB-antibody titres [11]. This difference between the two studies underlines the importance of clinical end-points in CMV vaccine trials, such as prevention of maternal–fetal transmission of CMV or of CMV disease in immunocompromised patients [13]. (iii) The equally high occurrence rate of CMV disease recorded in both TransVax study groups is a reminder that sterilizing immunity may not be attainable in immunocompromised patients. Still, a CMV vaccine may still have a significant clinical impact when the use of potentially toxic antiviral drugs may be reduced, the efficacy of established prophylactic strategies improved, and the time of first CMV viraemia delayed to periods of less intense immunosuppression, as was the case in the TransVax study.

Future Directions in the Development of a CMV Vaccine

Evaluation of the two successful CMV vaccines (gB/MF59, TransVax) will be carried on soon in phase III trials (see www.clinicaltrials.gov). Still, the use of laboratory-adapted CMV strains as templates for vaccine antigens may be problematic. AD169 and Towne have been extensively propagated on fibroblasts and harbour deletions, mutations and rearrangements in the virus genome including a large deletion in the AD169 genome encompassing all of the UL133-UL150 genes and a frameshift in the UL131 gene [37]. Wang and Shenk showed recently that an intact UL128-131 locus is important for broadening viral tropism to epithelial and endothelial cells [37]. Antibodies to the pentameric complex gH/gL/UL128-131 neutralize viral entry into epithelial cells and reduce the risk of perinatal CMV transmission [37,38]. Interestingly, the pentameric complex of rhesus and human CMV also appears to play a significant role in the priming of T cells by inhibiting responses to highly promiscuous, unconventional epitopes, which would induce a broad major histocompatibility complex class I-restricted and class II-restricted $CD8^+$ T-cell response [39].

In recognition of the immunological significance of the pentameric complex of CMV, part of the pentameric complex is incorporated as antigen in two vaccines that are currently under development. One vaccine is based on an alphavirus replicon particle vaccine platform that generated in mice broadly cross-reactive complement-independent CMV neutralizing antibodies at higher titres than those elicited by gB [40]. The other vaccine is based on a CMV virus with restored expression of the pentameric complex (AD169-based revertant) which showed a significant increase of neutralizing antibodies in rhesus macaques in comparison to the AD169 strain [41].

Recent CMV vaccine designs even focus on turning the virus' own immunomodulatory strategies against itself. For example, NKG2D is a potent immune-activating receptor expressed on NK cells, NKT cells, γδ T cells and CD8 T cells. CMV has evolved numerous mechanisms to evade NKG2D-mediated immune response. Generation of recombinant

CMV encoding the ligand for an activating NK cell receptor, however, results in a profoundly attenuated virus strain that induces long-lasting immunity [42].

In conclusion, the success of recently completed clinical trials is encouraging and is likely to give new impetus to the development of a CMV vaccine. The low hanging fruits of vaccine development against smallpox, polio, measles, mumps or rubella have been picked but should not serve as standards for a CMV vaccine. Nevertheless, the recent clinical trials underline the fact that the development of a CMV vaccine with a significant impact on health care is feasible. Novel vaccine technologies along with identification of additional and potentially even more immunogenic CMV epitopes carry a high potential to improve CMV vaccine efficiency further.

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Table 1

Phase I clinical trials of CMV vaccines

						Study population and design									
Vaccine	**Vaccine formulation**	**CMV-antigen(s)used in vaccine**	**Adjuvant**	**Parameters evaluated**	**Manufacturer/ Sponsor**	**Study cohort**	**CMV serostatus of subjects**	**Age (years)**	**No.**	**Randomization**	**Blinding**	**Placebo**	**End date**	**References**	**ClinicalTrials.gov Identifier**
VCL-CT02	Plasmid (trivalent)[a]	gB, pp65, IE1	None	Antibodies and T cells	Vical/Astellas	Healthy adults	Neg.	18–45	12	Yes	Open-label	None	02/2008	Jacobson *et al.*, [17]; *Vaccine*	NCT00373412
VCL-CT02	Plasmid (trivalent)[a]	gB, pp65, IE1	None	Antibodies and T cells	Vical/Astellas	Healthy adults	Neg.	18–45	17	None	Open-label	None	08/2007[g]	Jacobson *et al.*, [17]; *Vaccine*	NCT00370006
GSK1492903A	Recombinant, sub-unit	gB	Proprietary	Antibodies and T cells	GlaxoSmithKline	Healthy male adults	Neg.	18–40	40[f]	None	Open-label	None	08/2008	n.a.	NCT00435396
Towne-Toledo (1, 2, 3, 4)	Chimeric virus strains	Whole virus	None	CMV detection in urine, blood, saliva	Saint Louis University School of Medicine, St. Louis, Missouri	Healthy adults	Pos.	18–60	25	Yes	Double-blind	Yes	05/2002	Heineman *et al.*, [18]; *Journal of Infectious Diseases*	n.a.
Towne-Toledo (1, 2, 3, 4)	Chimeric virus strains	Whole virus	None	CMV detection in urine, blood, saliva	Virginia Commonwealth University	Healthy male adults	Neg.	30–50	36[f]	Yes	Open-label	None	Recruiting	n.a.	NCT01195571
AVX601	Bivalent alphavirus replicon	gB, pp65, IE1	None	Antibodies and T cells	AlphaVax	Healthy adults	Neg.	18–45	40[f]	Yes	Double-blind	Yes	07/2008	Bernstein *et al.*, [19]; *Vaccine*	NCT00439803
Tetanus-CMV fusion peptide	Peptide vaccine[b]	n.a.	PF-03512676 DNA	T cells	City of Hope Medical Center/ National Cancer Institute (NCI)	Recipients of allogeneic HCT	Pos.	18–75	36[f]	Yes	Open-label	None	Recruiting	n.a.	NCT01588015
PADRE-CMV fusion peptide	Peptide vaccine[c]	n.a.	PF-03512676 DNA[e]	T cells	City of Hope Medical Center/ National Cancer Institute (NCI)	Healthy adults	Pos. & neg.	18–55	69[f]	No	Open-label	Yes	04/2012	La Rosa *et al.*, [20]; *Journal of Infectious Diseases*	NCT00722839
CMVpp65-A[a]0201	Peptide vaccine[c]	pp65	None	T cells	City of Hope Medical Center/ National Cancer Institute (NCI)	Healthy adults	Pos. & neg.	18–65	46[f]	Yes	Double-blind	Yes	04/2009	n.a.	NCT00712634
CMV gB/MF59	Recombinant, sub-unit	gB	MF59	Antibodies	Chiron Corp.	Healthy adults	Neg.	18–50	95[f]	Yes	Double-blind	None	n.a.	Frey *et al.* [16]; Journal of Infectious Diseases	n.a.
CMV gB/MF59	Recombinant, sub-unit	gB	MF59	Antibodies	Chiron Vaccines	Healty adults	Neg.	21–50	46	Yes	Double-blind	Yes	n.a.	Pass *et al.* [14]; *Journal of*	n.a.

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						Study population and design									
Vaccine	**Vaccine formulation**	**CMV-antigen(s)used in vaccine**	**Adjuvant**	**Parameters evaluated**	**Manufacturer/ Sponsor**	**Study cohort**	**CMV serostatus of subjects**	**Age (years)**	**No.**	**Randomization**	**Blinding**	**Placebo**	**End date**	**References**	**ClinicalTrials.gov Identifier**
														Infectious Diseases	
CMV gB/MF59	Recombinant, sub-unit	gB	MF60	Antibodies	Chiron Corp.	Toddlers	Neg.	1–3	18	Yes	Double-blind	Yes	n.a.	Mitchell *et al.* [15]; *Pediatric Infectious Disease Journal*	n.a.
CMV gB/MF59	Recombinant, sub-unit	gB	MF59	Antibodies and T cells	Sanofi Pasteur MSD	Healthy females	Pos.	14–40	150	Yes	Double-blind	Yes	n.a.	Sabbaj *et al.* [24]; *Journal of Infectious Diseases*	n.a.
ALVAC-CMV (vCP139)	Attenuated canary pox-based	gB	None	Antibodies	Pasteur-Mérieux	Healthy adults	Pos. & neg.	18–50	20	None	Open-label	None	n.a.	Adler *et al.*, [21]; *Journal of Infectious Diseases*	n.a.
ALVAC-CMV (vCP139)	Attenuated canary pox-based + live-attenuated virus[a]	gB	None	Antibodies	Pasteur-Mérieux	Healthy adults	Neg.	20–43	20	Yes	Double-blind	Yes	n.a.	Adler *et al.*, [21]; *Journal of Infectious Diseases*	n.a.
vCP260	Attenuated canary pox-based	pp65	None	Antibodies and T cells	Aventis Pasteur	Healthy adults	Neg.	18–35	23	Yes	n.a.	Yes	n.a.	Berencsi *et al.*, [22]; *Journal of Infectious Diseases*	n.a.
vCP260 + CMV gB/MF59	Attenuated canary pox-based and recombinant sub-unit	pp65, gB	MF59	Antibodies	Aventis Pasteur	Healthy adults	Neg.	18–45	105	Yes	n.a.	Yes	n.a.	Bernstein *et al.*, [23]; *Journal of Infectious Diseases*	n.a.
ASP0113 (TransVax)/VCL-CB01	Plasmid (bivalent)	pp65, gB[d]	None	Antibodies and T cells	Vical/Astellas	Healthy adults	Pos. & neg.	18–43	44	None	Open-label	None	n.a.	Wloch *et al.* [36]; *Journal of Infectious Diseases*	n.a.

MF59, microfluidized adjuvant 59; HCT, haematopoietic (stem) cell transplant.

[a]Boost with Towne live-attenuated vaccine.

[b]Tetanus fusion peptide.

[c]Containing PADRE/tetanus peptides.

[d]Formulated with the non-ionic copolymer (poloxamer) CRL1005 and a cationic surfactant benzalkonium chloride (BAK).

[e] PF 03512676 DNA (=CpG 7909 adjuvant).

[f] Estimated number of participants/enrolment.

[g] Estimated completion date.

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Table 2

Phase II clinical trials of CMV vaccines

						Study population and design									
Vaccine	**Vaccine formulation**	**CMV-antigen(s)**	**Adjuvant**	**Parameters evaluated**	**Manufacturer/ Sponsor/Collaborator**	**Study cohort**	**CMV serostatus of subjects**	**Age**	**No.**	**Randomization**	**Blinding**	**Placebo**	**End date**	**References**	**ClinicalTrials.gov Identifier**
ASP0113 (TransVax)/ VCL-CB01	Plasmid (bivalent)	pp65, gB[a]	None	Viraemia	Vical/Astellas	HCT recipients	Pos. (recipient)	18–65	108[b]	Yes	Double-blind	Yes	11/2009	Kharfan-Dabaja *et al.* [12]; *Lancet Infectious Diseases*	NCT00285259
ASP0113 (TransVax)/ VCL-CB01	Plasmid (bivalent)	pp65, gB[a]	None	Viraemia	Astellas	HCT recipients	n.a.	20+	8[b]	None	Open-label	None	Recruting	n.a.	NCT01903928
CMV gB/ MF59	Recombinant, sub-unit	gB	MF59	Antibodies, CMV infection	Chiron Corp./Sanofi Pasteur	Healthy females	Neg.	14–40	464	Yes	Double-blind	Yes	06/2007	Pass *et al.* [13]; *Journal of Clinical Virology*	NCT00125502
CMV gB/ MF59	Recombinant, sub-unit	gB	MF59	CMV in urine or blood (PCR)	National Institute of Allergy and Infectious Diseases (NIAID)	Healthy females	Neg.	12–17	409[b]	Yes	Double-blind	Yes	03/2013[c]	n.a.	NCT00133497
CMV gB/ MF59	Recombinant, sub-unit	gB	MF59	Antibodies, viral load	University College/ National Institute of Allergy and Infectious Diseases (NIAID)	Solid-organ recipients	Pos. & neg.	18+	140	Yes	Double-blind	Yes	09/2009	Griffiths *et al.* [11]; *Lancet Infectious Diseases*	NCT00299260
vCP260	Attenuated canary pox-based	pp65	None	T cells	Sanofi (Aventis) Pasteur MSD	HCT recipients	Pos. & neg.	18–80	38[b]	None	Open-label	None	03/2008	n.a.	NCT00353977
Towne	Live-attenuated whole virus	Whole virus	None	CMV disease	Pasteur-Méerieux	Renal transplant recipients	Neg.	n.a.	177	Yes	Double-blind	Yes	03/1990	Plotkin *et al.*, [29]; *Transplantation*	n.a.

MF59 = microfluidized adjuvant 59; HCT = haematopoietic (stem) cell transplant.

[a] Formulated with the non-ionic copolymer (poloxamer) CRL1005 and a cationic surfactant benzalkonium chloride (BAK).

[b] Estimated number of participants/enrolment.

[c] Estimated end-date.