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Priorities for CMV vaccine development

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Abstract

A multidisciplinary meeting addressed priorities related to development of vaccines against cytomegalovirus (CMV), the cause of congenital CMV (cCMV) disease and of serious disease in the immunocompromised. Participants discussed optimal uses of a CMV vaccine, aspects of clinical study design, and the value of additional research. A universal childhood CMV vaccine

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could potentially rapidly reduce cCMV disease, as infected children are sources of viral transmission to seronegative and seropositive mothers. A vaccine administered to adolescents or adult women could also reduce cCMV disease by making them immune prior to pregnancy. Clinical trials of CMV vaccines in women should evaluate protection against cCMV infection, an essential precursor of cCMV disease, which is a more practical and acceptable endpoint for assessing vaccine effects on maternal-fetal transmission. Clinical trials of vaccines to evaluate prevention of CMV disease in stem cell transplant recipients could use CMV viremia at a level triggering preemptive antiviral therapy as an endpoint, because widespread use of preemptive and prophylactic antivirals has rendered CMV-induced disease too rare to be a practical endpoint for clinical trials. In solid organ transplant patients, CMV-associated disease is sufficiently common for use as a primary endpoint. Additional research to advance CMV vaccine development should include identifying factors that predict fetal loss due to CMV, determining age-specific incidence and transmission rates, defining the mechanism and relative contributions of maternal reactivation and re-infection to cCMV disease, developing assays that can distinguish between reactivation and re-infection in seropositive vaccinees, further defining predictors of sequelae from cCMV infection, and identifying clinically relevant immune response parameters to CMV (including developing validated assays that could assess CMV antibody avidity) that could lead to the establishment of immune correlates of protection.

Keywords

cytomegalovirus; congenital CMV; viruses; clinical trial endpoints; meeting report

Introduction

The development and licensure of a cytomegalovirus (CMV) vaccine has long been considered of paramount public health importance, as highlighted by CMV's inclusion among high priority targets in Institute of Medicine vaccine prioritization reports[1,2]. In 2000, a U.S. Government-sponsored meeting proposed activities to support CMV vaccine development within the disciplines of virology, immunology, epidemiology, and clinical trials[3]. Despite significant progress in these areas and the availability of multiple candidate vaccines in early development, no product is yet under consideration for licensure. On January 10–11, 2012, representatives from government, industry, academia, patient advocacy groups, and professional societies met to identify and begin to address challenges to CMV vaccine development. This manuscript summarizes available data, considerations, and proposals for future research and clinical trials discussed by meeting participants.

Background and Epidemiology

Most overt CMV-related disease occurs following transmission during pregnancy, manifesting as congenital CMV (cCMV) disease in children. Annually, cCMV causes an estimated 400 deaths and 5000 permanent disabilities among approximately 30,000 infected U.S. infants [4,5,6]. Estimates of the prevalence of cCMV infection among live-born infants range from 0.5–0.7% in the US, Canada and Western Europe to 1–2% in South America, Africa and Asia[7]. Approximately 13% of newborns with cCMV infection are symptomatic,

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with findings such as prematurity, intrauterine growth retardation, petechiae, jaundice, hepatomegaly, splenomegaly, purpura, thrombocytopenia, microcephaly, chorioretinitis, seizures, or focal neurologic deficits[4,7,8]. Rates of permanent sequelae in newborns with symptomatic cCMV infection range from 40–50% to >80%, depending on the severity of their disease[4]. Rates of sensorineural hearing loss in children without clinical findings in the newborn period (asymptomatic cCMV infection), observed at 3–4 years, range from 7.4–21%[9,10], with late-onset hearing loss in some occurring at seven years of age and older. Overall, an estimated 17–20% of infants develop permanent sequelae as a result of the infection, including the 13% of infants born with cCMV that have symptoms at birth and an additional and an additional 4–7% of infected infants who appear asymptomatic at birth[4].

Congenital CMV infection can occur as a result of transplacental transmission of virus in the setting of primary infection (the pregnant woman's first encounter with CMV) or of non-primary infection (either reactivation of a previously established latent infection or re-infection with a newly acquired virus in a previously infected woman). Non-primary maternal infections may account for three-quarters of cCMV infections in the United States[11], and the proportion of cCMV infections due to non-primary infections in countries with higher maternal CMV seroprevalence is probably even higher. A significant proportion of non-primary infections during pregnancy in Brazil were found to be re-infections[12]. Although rates of measurable hearing loss may not differ substantially in children born to mothers with primary vs. non-primary infections[13], primary maternal infection typically results in more severe cCMV disease, including greater neurological damage manifesting as more severe hearing loss. The relative contributions of reactivation and re-infection to cCMV disease are not yet clear, and the role of antibody or cellular immunity in preventing them is unknown.

Among women of reproductive age, approximately half are CMV-seropositive in the U.S., Australia, and Western Europe, while almost all are CMV-seropositive in South America, Asia, the Middle East and Africa[14]. U.S. seroprevalence rates are generally lower among non-Hispanic whites than other ethnic groups[5]. Young maternal age is a risk factor for both primary and non-primary infection.

In healthy adults and children, CMV infection may cause a mild infectious mononucleosis syndrome, but is usually asymptomatic. Despite its generally silent nature, CMV infection has been associated with long-term consequences, including earlier immunosenescence during aging[15] and increased all-cause mortality[16,17]. Additional research is needed to confirm and address potential mechanisms for these outcomes.

CMV is commonly spread via saliva and urine, especially from young children who often shed asymptomatically for months, contributing to higher CMV exposure among adults exposed to children attending daycare. In addition to transplacental transmission leading to congenital infection, CMV is readily transmitted to infants via breast milk, but this typically causes disease only in premature infants[18]. CMV can also be sexually transmitted. Transmission also may occur via solid organ or hematopoietic cell transplantation and, rarely, by transfusion of blood products from seropositive individuals.

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Persons with immunosuppression, typically associated with transplantation-related medications, highly immunosuppressive cancer chemotherapy, or advanced HIV infection, are at increased risk of CMV disease. Allogeneic hematopoietic stem cell transplant (HSCT) and high risk solid organ transplant (SOT) recipients often require treatment with drugs that exhibit significant toxicity to prevent potentially fatal CMV disease. CMV-associated sequelae among HIV-infected individuals have been substantially reduced by the availability of highly active antiretroviral therapy.

Virology, Immunology, and Previous CMV Vaccine Experience

Because natural immunity can reduce the severity of CMV disease[19,20], development of an effective CMV vaccine is likely to be feasible. Identification of immunological markers that can predict protection from CMV disease would be useful to evaluate potential vaccine candidates in preclinical, Phase I, and Phase II studies, to assess the duration of vaccine protection, and to “bridge” demonstration of vaccine effectiveness between populations.

Antigens that evoke humoral and cell-mediated immune responses are considered as targets for a vaccine because immune responses against these targets are readily detected in naturally infected individuals. Antibody is considered more likely to prevent or attenuate primary infection, while cell-mediated immunity (CMI), including cytotoxic T cells, is considered more likely to mediate life-long control of virus replication once infection has been established.

In a non-randomized, uncontrolled clinical study, CMV hyperimmune immunoglobulin administered to pregnant women soon after detection of primary infection was reported to reduce congenital transmission of CMV and to provide a therapeutic benefit to CMV-infected infants[21]. The results of two ongoing double-blind randomized placebo-controlled trials of immunoglobulin will provide further insight into the role of humoral immunity in preventing transplacental transmission (NCT00881517, NCT01376778).

A randomized placebo-controlled trial of a recombinant CMV envelope glycoprotein B (gB) vaccine formulated with MF59 (an oil-in-water emulsion adjuvant) showed 50% efficacy in preventing CMV acquisition of primary CMV infection in young mothers[22]. However, vaccination did not appear to yield long-term protection and the studies were not powered to evaluate protection against transplacental transmission. This vaccine induces primarily humoral responses, suggesting a role for anti-gB antibodies in reducing acquisition of CMV infection. In a randomized phase II study of MF59-adjuvanted gB vaccine in CMV-seronegative patients awaiting SOT, vaccinees who received grafts from CMV-seropositive donors had higher titers of gB specific antibodies, shorter duration of viremia and fewer days of antiviral treatment than placebo recipients[23]. Thus, anti-gB antibodies alone may also suppress primary CMV infection in SOT recipients. Cinical studies showed that this vaccine also boosted pre-existing immune responses in seropositive transplant candidates and seropositive women[24]. Another adjuvanted gB-based vaccine has also demonstrated immunogenicity in clinical trials (NCT01357915).

The presence of cytotoxic and helper T cell immunity correlates with protection from CMV disease in HSCT and SOT recipients. A landmark study performed 20 years ago and several

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subsequent studies showed that adoptive T cell immunotherapy benefits allogeneic HSCT recipients[25]. Key cellular immune targets include the viral proteins pp65 and IE1.

The latency-deficient live-attenuated Towne strain CMV vaccine, which lacks more than a dozen viral genes, prevented severe disease in renal transplant recipients, but did not prevent infection with natural strains[26]. Anti-CMV neutralizing titers after Towne vaccine were comparable to those observed after natural infection in one study[27], but were lower in another[28]. CMI, including cytotoxic T cells, was also induced by the live-attenuated vaccine.

A series of Towne/Toledo strain chimeric candidate vaccines, designed to be more immunogenic than Towne, appeared to be attenuated when administered to CMV-seropositive individuals[29]. These chimeras are currently undergoing Phase I trials in CMV-seronegative individuals. Although Towne virus did not become latent and reactivate, owing to its lack of the ULb' region of the genome, concern over the potential consequences of administering a live virus vaccine that might develop latency and potentially reactivate has limited further exploration of this approach to CMV vaccination.

A randomized phase II study with a DNA vaccine expressing gB and pp65 showed CMI responses and reduced rate of viremia in CMV-seropositive HSCT recipients. This study was not powered to demonstrate potential effects on CMV disease, which was also infrequent in placebo recipients[30]. Other candidate vaccine approaches under clinical development include CMV antigenic peptide-based vaccines[31] and vaccine vector approaches to express CMV antigens, including canarypox[32] and alphavirus replicons[33].

The ability of CMV to reactivate and of new CMV strains to re-infect previously infected individuals suggests that the immunity induced by primary infection is insufficient to completely prevent subsequent infections, although it may be sufficient to prevent severe cCMV. Maturation of the immune response, repeated asymptomatic reactivations, and declining antibody or cellular responses over time may also influence the level of immunity after primary infection. Thus, different candidate vaccines may have different abilities to prevent CMV infection, reactivation, or shedding in seronegative vs. seropositive individuals. Further study of both viral and host factors, including antibody avidity, that influence transmission and infection-associated pathology should aid rational vaccine design.

Use of a CMV vaccine in different target populations to prevent cCMV

The Advisory Committee on Immunization Practices (ACIP) and other recommending bodies influence U.S. vaccine usage. Key factors considered by ACIP include disease burden, vaccine effectiveness and safety, feasibility of additional recommendations in the context of the existing vaccination schedule, equity of access, and whether or not vaccination is a good use of public funds[34]. Assuming an effective vaccine were available, relative advantages of potential vaccination strategies targeting adult women, adolescent girls, and/or young children to reduce cCMV were considered by meeting participants in the context of age-specific CMV seroprevalence rates (Table 1). Determining the likely target population for a vaccine to prevent cCMV would help vaccine manufacturers assess the potential market for a CMV vaccine.

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A vaccine targeted at women of reproductive age would need to induce protective immune responses before the first trimester, when cCMV disease risk is greatest. Logistical barriers to achieving high vaccination coverage in women of reproductive age prior to the first pregnancy would thus need to be addressed. Historically, vaccination coverage for vaccines recommended for adults have been lower than levels achieved for children or adolescents. Efforts would be needed to ensure awareness among the general public of CMV disease and availability of a CMV vaccine, especially considering that nearly half of U.S. pregnancies are unplanned and many women do not seek preconception counseling. Currently, fewer than 15% of women of reproductive age report having heard of CMV[35]. Potential liability issues are a consideration for a vaccine strategy targeted at women with childbearing potential. Of note, the issue of whether *in utero* injuries are compensable under the Vaccine Injury Compensation Act has not been resolved[36].

Challenges in obtaining high adolescent coverage levels with other vaccines, including HPV vaccine, might also apply to a CMV vaccine. U.S. uptake of HPV vaccine has been slow, likely due to a combination of the delayed benefit of vaccination, its indication to prevent a sexually transmitted disease, and the requirement for three doses (single dose adolescent vaccines have achieved better uptake). With increased experience and recognition of the importance of adolescent vaccination, these challenges may decline. Ideally, the duration of protection from an adolescent CMV vaccine would cover most reproductive years, although if necessary, booster immunization could prolong duration of immunity.

Use of a CMV vaccine among women or adolescents likely would require assessment of risks and benefits both for CMV-seropositive and seronegative vaccinees. Serological testing before vaccination, if needed, could present logistical challenges in implementing vaccination programs. Because CMV seroprevalence among U.S. adolescents averages ~40% (higher among lower income adolescents), a CMV vaccine indicated only for seronegatives would need to be administered before age 13 years to have the greatest influence on cCMV disease. Thus, a cCMV disease vaccine candidate targeted at adolescents or women would ideally prevent cCMV infection among children born both to seronegative and seropositive vaccinees.

Universal administration of effective CMV vaccines in early childhood could also reduce cCMV disease rates. Because exposure to toddlers, who excrete CMV in their urine and saliva for months after primary infection, is an important source of both primary infection and re-infection in pregnant women, reducing infections among toddlers would likely reduce CMV transmission to their seronegative and seropositive mothers during subsequent pregnancies. It could also reduce transmission among children in daycare, indirectly protecting additional families. While a vaccine given at later ages would likely need to be effective both in seronegative and seropositive vaccinees, a vaccination strategy targeting toddlers may not require a vaccine that provides protection to seropositives in order to substantially reduce cCMV transmission. For rubella vaccine, vaccinating male and female toddlers was superior to vaccinating only seronegative women in reducing viral circulation and the incidence of congenital disease. Preliminary modeling of the effect of various immunization strategies predicts that even a CMV vaccine with a relatively short duration of

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efficacy of a few years administered to 12–18 month-olds would substantially reduce cCMV incidence[37, 38].

Although there may be resistance to vaccinating healthy children who are not at risk for serious CMV disease, the precedent of rubella vaccines, the use of "cocooning" (i.e., vaccinating those with close contact with newborns) as a strategy to protect infants against pertussis, and interest in developing transmission-blocking malaria vaccines, demonstrate the acceptability of vaccines that do not directly prevent serious illness in recipients. Preventing cCMV in a family could also directly benefit vaccinated children by reducing the impact on a family of caring for severely affected siblings. Recent reports of increased all-cause mortality among CMV-seropositive adults[16,17] may suggest another potential direct benefit of CMV vaccination for both sexes.

A CMV immunization program might most rapidly reduce cCMV by vaccinating both toddlers and adolescent girls. Improved surveillance to estimate the burden of cCMV disease and population-wide age-specific infection rates would help in further predicting the likely effect of different immunization strategies on public health[39,40] and could provide a baseline for population-based studies of vaccine effectiveness.

Considerations in clinical development of a vaccine to prevent cCMV disease

Pre-licensure studies using prevention of cCMV disease as a clinical endpoint to demonstrate vaccine efficacy are impractical given the complexity, number of participants needed, and years of follow-up needed to detect hearing loss (the most common cCMV manifestation) and other later sequelae. Resolution of uncertainties regarding study endpoints likely to be acceptable to regulatory agencies could increase the likelihood of investment by manufacturers in development of CMV vaccines. Meeting participants discussed and identified acceptable endpoints for CMV vaccine trials (Table 2).

Prevention of cCMV infection is considered to be the most relevant and practically achievable endpoint for Phase III efficacy trials to support licensure of a vaccine indicated for prevention of cCMV disease. Virus isolation or real-time PCR assay of urine or saliva samples from newborns are sensitive and specific and would be the most practical tests for diagnosing cCMV infection. Such samples would need to be taken within 2–3 weeks after birth, since CMV may be acquired during delivery or soon after birth[41]. The link between prevention of cCMV infection and prevention of cCMV disease could be studied separately in post-licensure studies that directly confirmed impact of vaccination on cCMV disease.

Prevention of CMV infection in pregnant women was considered a less useful endpoint to support CMV vaccine licensure. This is because completely preventing maternal infection may be less readily achieved than attenuating transplacental transmission. A vaccine that did not protect mothers against CMV infection could nonetheless protect against cCMV. Also, reduced maternal infection rates may not necessarily lead to reduced cCMV disease if vaccination prevented only the mildest maternal infections. Because current serological tests

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cannot readily identify new infections in previously seropositive women, the ability of a vaccine to prevent these infections during pregnancy would be difficult to determine.

A CMV vaccine could be studied in women of reproductive age who are planning pregnancy, although there are a number of logistical challenges associated with recruitment and follow-up. Women contemplating future pregnancy do not necessarily routinely seek pre-conception medical attention, so they could be difficult to recruit to a vaccine clinical trial. Women recruited at the time of a delivery, however, have both a high likelihood of subsequent pregnancy and an increased risk of exposure to CMV from the infant just delivered (because young children often transmit CMV acquired at daycare to their mothers[42]), with possible maternal-fetal transmission during those subsequent pregnancies, and thus may be better vaccine trial candidates. Even in this group, time to subsequent pregnancy is uncertain and long-term follow-up may be difficult due to the mobility of young families. Awareness of CMV and advice given to women in a clinical trial about how to avoid acquiring CMV infection may decrease seroconversion rates relative to those observed in the past, potentially increasing the number of subjects required for the study. Both seronegative and seropositive women should be considered for vaccine trials, depending on the ability of the candidate vaccine to induce protective immune responses in both groups.

Adolescents have a high rate of primary CMV infection, but could be a challenging clinical trial population due to the difficulty of long-term follow-up as they move away from their childhood homes and to their low incidence of pregnancy. Thus, a vaccine intended for use in adolescents may best first be studied in older females. A correlate of protection could then be used to bridge evidence of efficacy to adolescent girls.

Clinical trials evaluating vaccination of healthy children to prevent transmission of CMV to mothers should consider outcomes both in the immunized child and in household members, potentially including the outcome of subsequent pregnancies. Attack rates in mothers with children in day care can be measured directly by seroconversion of seronegative mothers, and the relationship between strains of viruses in children and mothers could be investigated.

Considerations in development of a CMV vaccine for transplant patients

In allogeneic HSCT patients, CMV serological status of donor and recipient is associated with important clinical outcomes including transplant-related mortality, secondary infections, and overall graft survival[43]. CMV-seropositive recipients of stem cell transplants are at greatest risk[44,45]. Detection of CMV in blood, either by pp65 antigenemia or by nucleic acid amplification testing (NAAT), is a useful predictor for development of CMV disease[46,47]. Preemptive therapy of CMV viremia with antivirals, based on monitoring with quantitative PCR, is the most commonly used strategy to reduce CMV-associated morbidity, and is currently recommended by international guidelines[48–50]. Currently available antivirals with activity against CMV are associated with significant toxicity—the first-line agents ganciclovir and valganciclovir may cause bone marrow toxicity, a particularly important adverse event in HSCT patients requiring repeated or prolonged therapy. Antiviral

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prophylaxis with currently available antiviral agents is expensive and risks toxicity and is only partially effective, although new drugs with improved toxicity profiles are in clinical development.

A recently performed large randomized phase III trial with the antiviral drug maribavir showed a background incidence of CMV end-organ disease in the placebo group of 4.8% over six months follow-up[51]. Although the study started at donor cell engraftment and thus might have missed a few early cases, this low attack rate makes using CMV end-organ disease as a phase III vaccine trial endpoint in HSCT recipients impractical, due to the number of patients that would need to be enrolled. Thus, additional endpoints that predict the development of CMV-associated end-organ disease should be considered in evaluating CMV vaccines in the HSCT population.

CMV DNA detected in blood by quantitative PCR alone or in combination with initiation of antiviral therapy is a more practical primary endpoint. A composite endpoint could also include other potentially CMV-associated clinical events such as graft-versus-host disease and overall mortality. Even though it is rare, because some CMV disease occurs without preceding PCR positivity, CMV disease should also be included in a primary composite endpoint (Table 2). A recently adopted WHO standard could be used to improve standardization of NAAT for viremia[52].

In SOT patients, the CMV serological status of donor and recipient is one of the most important factors predicting development of symptomatic CMV infections. CMV infections in this population may cause CMV end-organ disease, the so-called CMV syndrome (CMV viremia in the presence of fever and neutropenia or thrombocytopenia, in the absence of other causes) and indirect effects such as graft rejection and secondary infections. In SOT patients, seronegative recipients of organs from seropositive donors are at greatest risk, because of the significant amount of virus that can be present in a donated organ[20]. Other important risk-related factors are the type of organ transplanted and the use of anti-T cell therapy. In SOT, the most commonly used practice for CMV prevention is antiviral prophylaxis with valganciclovir for 3–6 months after SOT (and one year for lung recipients), although preemptive therapy is also used[53,54]. Current recommendations support both strategies[55]. An effective vaccine administered pre-transplant could potentially reduce the toxicity and cost associated with administration of antiviral drugs.

Recent studies suggest that the combined frequency of CMV end-organ disease and CMV syndrome is high enough, even with current prophylactic regimens in CMV D+/R-SOT patients, to allow CMV end-organ disease and CMV syndrome to be used as a primary composite endpoint in a phase III study. The donor/recipient serological status and the organ type of SOT patients are important considerations for clinical studies.

A vaccination strategy that reduced CMV infection rates in the general population might also reduce CMV-associated morbidity in transplant recipients by reducing the risk for primary infections from the donor grafts.

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Summary

Due to relatively low public awareness of CMV transmission and disease, work by public health officials and advocacy groups remains critically important for increasing awareness and an understanding regarding CMV infections and their impact on public health.

In addition to using an effective CMV vaccine to immunize adolescents, consideration of CMV vaccines as universal childhood vaccines, which based on modeling might impart the greatest reduction in cCMV disease, was endorsed. Immunization of young boys and girls could have a significant and immediate effect on cCMV disease because they are sources of transmission to seronegative and seropositive mothers. Additional study could help to better predict the potential benefits of this strategy. Based on the discussions at the meeting, the most appropriate efficacy endpoints for phase III vaccine trials to address cCMV and immunization of transplant recipients are summarized in Table 2. The ability of a vaccine to prevent CMV transmission within households could be directly demonstrated in a study. Efficacy of a vaccine intended to prevent cCMV disease could be inferred by demonstrating prevention of cCMV infection at birth. Prevention of CMV viremia (at a level that triggers prescription of preemptive therapy) was considered a useful and feasible study endpoint in stem cell transplant recipients, likely predicting effect on end-organ disease. In solid organ transplant recipients, prevention of CMV-associated disease (including CMV syndrome or the need for preemptive therapy) was considered the best available study endpoint.

Several areas were identified for further study, research, and policy development (Table 3). These included collection of additional epidemiological data, including on fetal loss due to CMV and more detailed age-specific incidence and transmission rates, to improve understanding of the potential effect of vaccination. A standardized case definition for cCMV disease would facilitate these and other studies. Further study should also define the relative roles of reactivation and re-infection in cCMV and the mechanisms involved in placental transmission. Elucidation of CMV pathogenesis and the development of assays that could detect and distinguish between reactivation and re-infection in seropositive vaccinees would facilitate evaluation of the full potential of a vaccine. Improved understanding of immune responses to CMV (including developing validated assays of CMV antibody avidity that could potentially permit comparison of neutralizing responses among recipients of different vaccines) could lead to the development of immunological markers useful to evaluate vaccine immunogenicity, evaluate duration of protection, and bridge evidence of efficacy between populations.

CMV is an important pathogen for which a vaccine would address a significant unmet public health and medical need. Discussions and conclusions reached by the experts at the 2012 CMV vaccine meeting likely will reduce barriers to development of CMV vaccine and increase the likelihood that one or more vaccines will become available to protect against CMV and its serious sequelae.

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A January 2012 meeting addressed priorities for development of vaccines to prevent disease caused by cytomegalovirus (CMV).

CMV causes serious disease, including congenital CMV and life-threatening infections in immunocompromised patients.

Discussions identified appropriate target populations for vaccine use and appropriate endpoints for vaccine studies.

Participants at the meeting also made specific suggestions for further research that could facilitate CMV vaccine development.

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Table 1

Potential vaccination strategies to reduce the disease burden of cCMV

Target Population	Advantages	Disadvantages
12–18 months (boys and girls)	Age at which universal immunization is most readily achieved. Rapid reduction of cCMV rates, if vaccination prevented infection or shedding in this age group (an important source of maternal infection). Potential for “herd immunity” that could prevent additional exposures, if vaccine reduced transmission to other children.	Potential resistance to adding additional doses to childhood vaccine schedule. Potential ethical issue of immunizing infants/toddlers with vaccine in absence of direct serious disease risk. Would require a vaccine that either prevents infection or eliminates CMV shedding if infection occurs. Would not have an effect on sexual transmission unless protection persists for 15 or more years. Vaccine effect in seropositives vs. seronegatives may be different; If required, serological screening may complicate vaccine delivery. Would not address CMV infections and transmissions from children who acquire CMV infection during birth or through breast milk.
Adolescent girls	Immunization of target population prior to pregnancy.	Might require longer vaccine duration of effect than toddler vaccine to lead to benefit, or may require a booster dose later in life Challenges in achieving high vaccination coverage for adolescent vaccines. Vaccine effect in seropositives vs. seronegatives may be different. If required, serological screening may complicate vaccine delivery.
Women before pregnancy	Population with most direct likely impact on cCMV.	Same as adolescent girls, May be difficult to identify at-risk women and vaccinate before pregnancy (though catch-up immunizations could be offered to women after delivery).

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Table 2

Proposed endpoints for CMV vaccine clinical trials in different target populations

Target Population	Objectives	Endpoint
Children <2 yrs of age	Prevent maternal and congenital CMV infection by removing an important source of maternal infections. Prevent primary CMV infection which may have long-term deleterious consequences to the host	Rate of CMV infection in vaccinees.
Adolescent girls	Prevent infection in future mothers and their children (preventing congenital infection) Prevent primary CMV infection which may have long-term deleterious consequences to the host	Rate of CMV infection in vaccinees.
Women of childbearing age (women likely to become pregnant)	Prevent maternal and congenital CMV infection	Rate of CMV infection in vaccinees. Rate of cCMV infection in their children.
Hematopoetic stem cell transplant recipients	Prevent CMV disease by reducing the rate of occurrence of surrogate markers	Prevention of CMV viremia (and associated antiviral use) Composite endpoints including CMV disease
Solid organ transplant recipients	Prevent CMV disease	Prevention of CMV-associated disease (including CMV syndrome) Prevention of CMV viremia (and associated

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Table 3

Areas for further research, study, and policy development

Epidemiological studies
• Develop standardized case definition of cCMV disease
• Determine rates of CMV-associated fetal loss
• Better define age-specific incidence and transmission rates
• Better define burden and costs of sequelae of cCMV disease and infection
• Further define predictors of outcome in cCMV
Virological/Immunological studies
• Further study the role of maternal reactivation vs re-infection in CMV-seropositive individuals and resulting burden of cCMV disease
• Develop improved serological assays to differentiate between re-infection and reactivation in CMV-seropositive individuals
• Identify and develop a mechanistic correlate of protection that could predict vaccine effect, which would have value in studies of vaccine immunogenicity and duration of protection. The correlate may differ between protection of seronegative women and seropositive women.
• Develop improved assays to assess CMV antibody neutralization, avidity, and functionality
Policy
• Resolve potential liability issues associated with inadvertent immunization of pregnant women
• Reduce uncertainties regarding potential recommendations for use of a CMV vaccine
• Increase public awareness of CMV infection and disease