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COMMENTARY

Advancing Our Understanding of Protective Maternal Immunity as a Guide for Development of Vaccines To Reduce Congenital Cytomegalovirus Infections

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ABSTRACT Human cytomegalovirus (HCMV) is the most common congenitally transmitted pathogen worldwide, impacting an estimated 1 million newborns annually. Congenital HCMV (cCMV) infection is a major global contributor to long-term neurologic deficits, including deafness, microcephaly, and neurodevelopmental delay, as well as to fetal loss and occasional infant mortality. Accordingly, design of a maternal vaccine to prevent cCMV continues to be a top public health priority. Nevertheless, we remain without a licensed vaccine. Maternal immunity provides partial protection, as the risk of vertical HCMV transmission from chronically infected mothers is reduced compared to settings in which the mother is newly infected during pregnancy. Therefore, an understanding of the maternal immune correlates of protection against cCMV is critical to informing design of an efficacious maternal vaccine. Although vaccine development is being assiduously pursued by a large number of pharmaceutical manufacturers, biotechnology organizations, and academic researchers, some pessimism has been expressed regarding the issue of whether a vaccine to protect against cCMV is possible. This pessimism is based on observations that natural immunity is not completely protective against maternal reinfection and congenital transmission. However, we assert that optimism regarding vaccine development is indeed justified, on the basis of accruing evidence of immune correlates of protection—readily achievable by vaccination—that are associated with reduced transmission of HCMV to the fetus in seronegative women. In light of the substantial burden on society conferred by cCMV infection, even a modest reduction in the occurrence of this fetal disease is an important public health goal and justifies aggressive clinical evaluation of vaccines currently in the pipeline.

KEYWORDS congenital infections, cytomegalovirus, vaccines

Human cytomegalovirus (HCMV) congenital infection impacts 1 in every 150 live-born infants (0.7%) globally, making it the most common infectious cause of birth defects. Nearly 40,000 cases of congenital HCMV infection (cCMV) occur in the United States annually, resulting in up to 7,000 infants with permanent sequelae such as sensorineural hearing loss (SNHL), growth restriction, and intellectual disability (1). Moreover, recent work has linked cCMV to the risk for acute lymphoblastic leukemia (2) and has identified CMV infection as a contributor to a number of chronic diseases, including glioblastoma (3, 4). A maternal vaccine to prevent cCMV has been labeled a "tier 1 priority" of the National Academy of Medicine (NAM) for over 15 years, and, stimulated in part by a NAM report (5), recent years have seen an increased interest on

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the part of academic researchers, the pharmaceutical industry, and the lay public in development of a vaccine. The elimination of congenital rubella syndrome through high vaccine coverage and the recent fervor concerning congenital Zika virus infections and the rapid progress by the research community in design of a Zika vaccine to prevent such infections demonstrate that a firm societal commitment can enable rapid development of vaccines aimed at preventing infant birth defects and brain damage sustained prior to birth. And yet an HCMV vaccine should have a similarly high priority, since a successful immunization program would lead to substantial improvement of pediatric and population health.

Candidate HCMV vaccine development started in the 1970s (6) but is now truly progressing in earnest, with a number of viable candidates in clinical trials or in preclinical studies. The target populations for the vaccine are women of childbearing age (who would be immunized prior to pregnancy to prevent transmission to their fetuses) and solid-organ or hematopoietic cell transplant patients who are at risk of either primary infection (acquisition from a transplanted organ) or reactivation from latent infection in the context of immune suppression. Preliminary clinical studies of HCMV glycoprotein B (gB) subunit vaccine in postpartum (7) and adolescent (8) women, as well as in transplant patients vaccinated with the gB subunit (9) or with a DNA plasmid coding for $CD8^+$ T cell-stimulating proteins (10), have yielded promising results and yet require improvement prior to further clinical development. Further, work delineating maternal immune correlates of protection against congenital transmission after primary and nonprimary maternal infection in both humans and animal models, combined with the identification of neutralizing epitopes on the viral proteins, have provided new leads for the HCMV vaccine field. Thus, HCMV vaccine product development designed to improve on the efficacy achieved in the prior vaccine trials, including advanced stage trials, is proceeding at a rapid pace.

In spite of this progress, vaccine development to eliminate cCMV presents unique challenges in that, unlike the responses seen in cases of rubella, natural immunity is not fully protective against maternal reinfection or congenital transmission. This recognition has led to a cloud hanging over the field, representing a point of view recently eloquently expressed in an article pointing out that cCMV infection takes place commonly in the setting of preexisting maternal immunity, raising skepticism about whether a vaccine can achieve a higher level of protection than that provided by the imperfect natural immunity induced by HCMV infection (11). In fact, the debate over whether a vaccine against cCMV infection that elicits immunity similar to natural immunity would be adequate, or whether a vaccine must provide augmented immunity over and above that conferred by natural infection, has been ongoing for decades (12–15). In this article, we consider the evidence derived from animal and human studies indicating that vaccine induction of CMV-specific immunity can protect against congenital transmission in seronegative individuals and why a better understanding of immunity in seropositive individuals could lead to progress in identifying immunologic endpoints and in targeting epitopes for vaccine development. We also summarize the status of candidate HCMV vaccines for humans.

CONGENITAL CMV TRANSMISSION IN ACUTELY AND CHRONICALLY HCMV-INFECTED WOMEN

Vertical transmission of HCMV *in utero* is thought to begin with virus in the maternal circulation, replication of virus in decidual cells, and subsequent spread of virus leading to focal infection of cytotrophoblasts in the placenta (16–19). Thus, preexisting vaccine-elicited maternal anti-HCMV immunity that impedes this initial chain of infection events could prevent cCMV transmission, and such immunity should be the goal in designing an HCMV vaccine. While ubiquitous HCMV infections occur readily in both seronegative and seropositive women (20) and superinfection can be readily achieved in nonhuman primates (21), it has been estimated that there is a lower fetal transmission rate per maternal CMV infection in the setting of preexisting maternal immunity (1, 22, 23). Up to 30% to 40% of seronegative women who acquire primary HCMV infection during

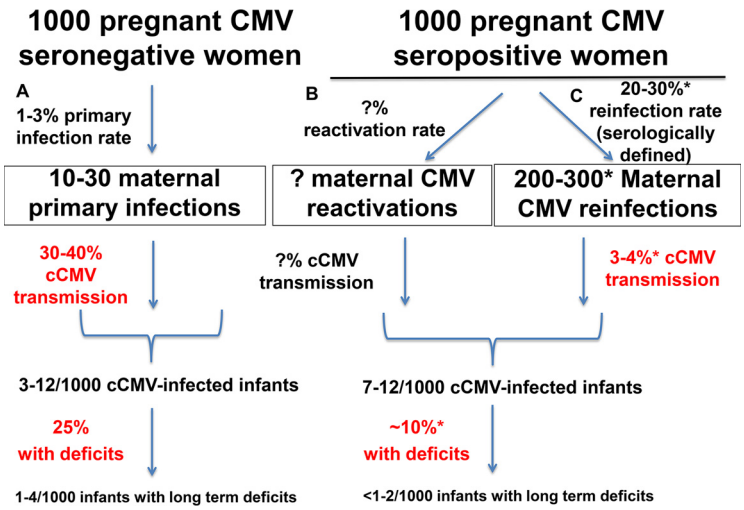

FIG 1 Congenital HCMV transmission rates in CMV-seronegative and -seropositive women. (A) Primary HCMV infection occurs infrequently (rate, 1% to 3%) in HCMV-seronegative pregnant women, but rates of cCMV transmission (30% to 40%) and infant disease (25%) are known to be high following primary maternal infection (1, 97). (B) The rate of systemic maternal HCMV reactivation in chronically infected women is not known; nor is the rate of cCMV infection in the setting of maternal reactivation known. (C) HCMV reinfection rates, identified by detection of a serologic response against a new strain of HCMV, have suggested that nearly 1 of 3 CMV seropositive women become reinfected during pregnancy (24, 39), and yet the cCMV transmission rate is up to 10-fold lower than that in primary maternal infection (3.4%) (23) and the disease rates have been reported as 10% or less (24, 29, 33, 34). Thus, similar numbers of cCMV-infected and -impaired infants occur in HCMV-seronegative and -seropositive pregnant women populations (1). *, data points where more studies are needed to further advance our understanding of the partial protective nature of preexisting HCMV immunity.

pregnancy transmit the virus to their fetus, and yet less than 1% of women with chronic CMV infection transmit to their fetus (1). However, this stark difference in transmission rates does not account for the risk of fetal transmission per maternal HCMV exposure and could be underestimating the transmission rate in seropositive women (11). Studies are now emerging that more closely compare the rates of transmission in primary versus nonprimary maternal infection and support the notion that the risk of transmission is considerably higher in the setting of primary maternal infection (22, 23). In one such study of seropositive women with serologic and/or virologic evidence of recent reinfection, Simonazzi et al. reported a fetal transmission rate of 3.4% in the setting of nonprimary maternal infection (23), considerably lower than the 30% to 40% rate of cCMV transmission in the setting of primary CMV infection (Fig. 1). Another recent retrospective study of saliva screening in newborns demonstrated that the risk of fetal transmission is 4-fold higher in primary maternal infection than in nonprimary maternal infection (22). And yet the latter study did not take into account recent reinfection status; thus, the Simonazzi study represents a better estimate of the risk of congenital transmission upon maternal reinfection (3.4%). Together, the data from those studies indicate a partially protective role of maternal immune factors against cCMV infection.

The emerging understanding of the differing cCMV transmission rates in cases of primary and nonprimary maternal infection cannot be overlooked as the prospects for deploying prepregnancy maternal HCMV vaccines are debated (1, 23). While a number of studies have demonstrated that congenitally infected infants born to women with preexisting immunity can develop symptomatic disease (11, 24), there is also evidence that cCMV occurring in the setting of preexisting maternal immunity is less severe and less likely to result in disabilities. Placental virus pathology has been described as less severe in the setting of preexisting and robust neutralizing antibody responses (16, 25). Moreover, the major sequela of cCMV infection, hearing loss, may be less severe in the setting of nonprimary maternal infection, with a reported lower rate of severe/profound

hearing loss (26). There have also been a number of studies performed with highly seroprevalent populations that indicated a low rate of symptomatic disease compared to that described in seronegative populations (24, 27–34). However, other studies have reported rates of symptomatic disease in CMV-infected infants of seropositive women that were similar to those reported for CMV-infected infants of seronegative women (35, 36), fueling the debate over whether maternal immunity modulates cCMV disease severity. While the impact of maternal immunity on the severity of disease remains ill-defined, the established high rates of congenital transmission and disease sequelae in the absence of preexisting immunity make maternal vaccine development for this setting imperative. The impact of preexisting natural immunity on reducing the rate of placental transmission and, potentially, also disease severity suggests that CMV-specific immunity should be an effective means to reduce the effects of exposure to CMV during pregnancy.

Because of the high global rate of HCMV seroprevalence, congenital transmission in mothers with preexisting natural HCMV is a contributor to cCMV cases that is equal in significance to or more significant than primary maternal infections in developed countries, despite an overall transmission rate of ~1% (22, 23, 37). Thus, CMV vaccine development to prevent congenital transmission should include seropositive women. However, it is unknown whether reinfection by an exogenous strain of HCMV or latent viral reactivation is responsible for transmission in the setting of natural maternal immunity, as complete molecular characterizations of maternal reinfecting strains of HCMV are still lacking. The frequency of exposure to HCMV during pregnancy is likely to be higher in settings of nearly universal seropositivity or of clustering of seropositive individuals. In support of this concept, a 20% to 30% rate of reinfection in seropositive women with an antigenically distinct strain has been reported based on serologic evidence of reinfection both in areas of high HCMV seroprevalence (24, 38) and in seropositive U.S. populations (39). This high rate of reinfection of seropositive women is in contrast to the 1% to 3% infection rate seen among seronegative women in developed countries (1). This discrepancy can be explained by the knowledge that cases of HCMV seropositivity are highly clustered among populations by ethnicity, race, and socioeconomic factors (40–42). Since HCMV is typically transmitted by close contact within households, the high reinfection rate among seropositive women versus the primary infection rate in seronegative women seems plausible. Thus, even if immunity reduces the risk of abnormalities in the infants of those women, the importance of cCMV in seropositive populations remains substantial. Of note, nearly all HCMV-seropositive women reactivate virus postpartum in breast milk (43), and yet very few transmit the virus across the placenta, indicating that preexisting maternal immunity controls systemic replication of endogenous HCMV strains at a low enough level to prevent or eliminate placental infection in the majority of cases. Defining the maternal immune correlates of protection against congenital transmission in the setting of nonprimary and reactivated maternal HCMV infection, as well as in the setting of infections that occur in the setting of experimental vaccine immunity, will iteratively inform and guide maternal vaccine development. And yet protection of seronegative women remains an important goal given the equal contributions of transmissions in the seronegative and seropositive settings to cCMV infections in developed countries.

HUMORAL IMMUNITY AND PROTECTION AGAINST CONGENITAL CMV TRANSMISSION

Maternal HCMV-specific IgG responses appear to be critical for protection against congenital transmission (16, 44–47). The impact of humoral immune responses on protection against congenital infection has been examined by comparisons of IgG responses in transmitting and nontransmitting HCMV-infected women (45, 48–50). In those studies, HCMV neutralization titer, IgG avidity, and rapidity of neutralizing antibody development, but not HCMV-specific IgG binding, were correlated with protection against congenital transmission. Application of a combination of HCMV IgM and IgG avidity testing can predict congenital transmission in primary infections but

may miss the identification of congenital CMV transmission cases in the setting of nonprimary maternal infection (51). Further support for the idea of a role of neutralizing antibodies in reducing the risk of placental HCMV transmission comes from studies demonstrating that neutralizing titers induced by the HCMV pentameric complex (PC; gH/gL/UL128-131A) against epithelial-cell-tropic viruses are strongly associated with reduced congenital CMV transmission in the setting of nonprimary congenital CMV transmission in HIV/CMV-coinfected pregnant women (48, 52). Whereas another study reported that high fetal cord blood neutralization titers were associated with sequelae of cCMV among infected infants from mothers with first-trimester primary infection (11), high neutralization titers in those mothers might have been a result of high levels of earlier maternal systemic virus replication, which is independently associated with symptomatic infection (53, 54). Together, these findings suggest that a high HCMV neutralization titer contributes to protection against congenital transmission, though there is a concern that after transmission has occurred, higher neutralization titers may be associated with poor outcome.

Results of studies of passive IgG protection against congenital CMV in animal models have been convincing in establishing the ability of virus-specific IgG to block placental CMV transmission. In a recent study in the rhesus monkey model of placental CMV transmission, provision of hyperimmune globulin to $CD4^+$ T cell-depleted pregnant rhesus monkey dams prior to rhesus CMV (RhCMV) challenge provided complete protection against fetal loss and, after adjustment for dose optimization to achieve high neutralizing titers for >1 week postinfusion, completely protected against placental transmission (55). In the guinea pig cytomegalovirus (GPCMV) congenital infection model, the passive administration of antibody targeting envelope glycoproteins was first shown to modify the risk of vertical transmission in studies in the 1980s (56). Later passive transfer studies using pooled antisera generated following immunization with purified glycoprotein preparations identified the anti-gB response as the protective component in these guinea pig pregnancy/challenge studies (46, 57). Passive antibody transfer studies in the GPCMV model have also demonstrated efficacy of a monoclonal antibody targeting the gH/gL (44). Notably, unlike current human trials assessing the role of hyperimmune globulin administered after primary maternal infection (58), passive antibody was more beneficial in improving pregnancy outcomes in animal studies when it was administered prior to viral challenge during pregnancy. These observations suggest that a greater benefit is likely to be conferred by induction of maternal antibodies (via vaccination) prior to exposure to HCMV than by passive transfer of antibody after infection has already been established (58).

Complicating the role of antibody responses in protection against congenital HCMV infection, preexisting, nonneutralizing maternal IgG has been implicated in facilitation of placental transmission. IgG-CMV virion complexes can be transported across the syncytiotrophoblast by FcRn and epidermal growth factor receptor (EGFR) (59). Indirectly supporting the data concerning this mechanism of placental transmission, congenital CMV risk is only 30% during the first trimester when FcRn and EGFR are not fully expressed compared to a 72% transmission risk during the third trimester, when the placental IgG transfer peaks (59–61). To assess the role of maternal antibody function, placental transmission was further assessed in an *ex vivo* human placental model (16) which demonstrated that the presence of weakly neutralizing monoclonal IgG, but not potently neutralizing monoclonal IgG, resulted in placental HCMV infection. While the results of administration of CMV hyperimmune globulin to acutely CMV-infected pregnant women to protect their fetuses have been mixed, partial benefit may have been achieved, even though the antibodies were administered days to weeks after maternal infection (58, 62).

Critical to vaccine development is defining which glycoprotein targets are important to protection against placental transmission, as multiple HCMV surface glycoproteins are involved in viral entry into host cells and contain neutralizing epitopes (63). Within gB, distinct regions have been characterized as targets for neutralizing antibodies, including antigenic domain 1 (AD-1), AD-2, domain I (AD-5), and domain II (AD-4)

(64–67). Additionally, the PC has been identified as the target of the most potently neutralizing antibodies (50). In sera from transmitter and nontransmitter mothers with primary infection, adsorption with the PC, but not gH/gL or gB, resulted in a dramatic reduction in neutralizing activity in epithelial cells at all postinfection time points. Importantly, anti-PC and anti-gH/gL IgG titers, but not anti-gB IgG titers, were higher in magnitude in nontransmitting mothers than in acutely infected transmitting mothers within 30 days postinfection (50). Identified immune correlates of protection against primary cCMV transmission (i.e., immune correlates of risk for cCMV [68]) were as follows: delayed antibody response to gB; higher and more-rapid antibody response to PC; broad and rapid antibody response to neutralizing epitopes on PC; rapid plaque formation-inhibiting antibody response; the presence of gamma interferon IFN-γ-producing $CD4^+$ and $CD8^+$ T cells; higher levels of reverted effector memory cells (T_{EMRA}); rapid virus-specific lymphocyte proliferation; rapid virus-specific interleukin-2 (IL-2) production by $CD4^+$ T cells; and higher levels of $1L\text{-}7R^+$ $CD4^+$ T cells. (Note that all of the immune correlates listed above pertain to responses in women who did or did not transmit CMV to their fetuses.)

However, several recent studies have suggested that gB-directed antibodies remain important to prevent viral spread. Monoclonal antibodies against gB, but not the PC, have been reported to block placental trophoblast infection, and an HCMV mutant strain lacking the PC was able to infect human trophoblast progenitor cells, suggesting the PC is not essential for placental cell entry (69). Furthermore, in the setting of nonprimary cCMV transmission in HIV-infected women, a weak association between protection and maternal IgG binding to gB AD-2 was observed, but not with the PC, gH/gL, or gH/gL/gO (48). Eliciting antibody responses to multiple epitopes may be essential for vaccine-mediated protection against cCMV, with the best-established targets consisting of neutralizing epitopes within gB and the PC.

T CELL IMMUNITY AND PROTECTION AGAINST CONGENITAL CMV TRANSMISSION IN HUMANS

A major issue in the field of congenital HCMV prevention research has been whether vaccine-elicited maternal T cell responses would be required to effectively prevent congenital CMV transmission. Studies comparing cellular immune responses in transmitting and nontransmitting mothers after primary HCMV infection resulted in the observation that an early lymphoproliferative response to HCMV was associated with nontransmission (70; see also the list of immune correlates given above). Moreover, Lilleri and colleagues found that classical HCMV-specific $CD4^+$ and $CD8^+$ T cell responses correlated with peripheral viral clearance and that delayed $CD4^+$ T cell responses, but not delayed $CD8^+$ T cell responses, were associated with congenital transmission (71), a finding that was confirmed in a distinct pregnancy cohort (72). This finding was further bolstered by studies in the nonhuman primate model of cCMV transmission in which $CD4^+$ T cell depletion prior to maternal RhCMV infection led to more-frequent transmission and a high rate of fetal loss. These studies indicated a protective role for HCMV-specific $CD4^+$ T cell frequency and/or proliferation in preventing congenital transmission of HCMV. Thus, induction of T cell responses remains a goal for vaccine-elicited protection against placental HCMV transmission, as the T cell response would both contribute to eliminating virus-infected cells and support the B cell responses, and yet their role seems to be secondary to that of robust humoral immunity for cCMV prevention.

TIMING OF IMMUNE CONTAINMENT OF PRIMARY VIRUS REPLICATION AND CONGENITAL TRANSMISSION

As the virus that inoculates the placenta is thought to originate in the maternal blood, rapid containment of systemic virus replication after primary infection is likely key to protection against congenital transmission. In fact, in the setting of isolated preexisting humoral immunity in pregnant rhesus monkey dams, the plasma viral load in the nontransmitting dams was significantly lower than that seen in the transmitting

TABLE 1 CMV vaccines currently under development

Vaccine	Developer	Antigen[a]			Reference no.
		gB	Pentamer	pp65	
Adenovirus vector	Queensland Institute	X			73
Alphavirus replicons	GSK	X		X	74
Canarypox vector	Sanofi			X	75
Dense bodies	Vaccine Project Management, Serum Institute, India	X	X	X	76
DNA plasmids	Astellas, Inovio	X		X	77, 78
Lentivirus particles	Variations Bio	X		X	79
Live attenuated	Medimmune	X		X	80, 81
Live replication-defective	Merck	X	X	X	82
LCMV vector	Hookipa	X		X	83
mRNA	GSK, Moderna	X		X	84
MVA vector	City of Hope	X	X		85
Peptides	City of Hope, University of Heidelberg			X	86
Soluble pentamer	Humabs, Redbiotech GSK		X		87
Subunit gB	Sanofi, GSK	X			8, 9, 88
VSV vector	Yale	X			89

[a]LCMV, lymphocytic choriomeningitis virus; VSV, vesicular stomatitis virus. An "X" indicates that the antigen is included in the vaccine candidate.

dams. Furthermore, the peak viral load in plasma of transmitting dams predicted the peak viral load in amniotic fluid (55). Immune analysis of human primary maternal infection also suggests that rapid induction of immunity, which could predict rapid viral containment, is an important factor in protection against congenital transmission (50). As natural immunity to HCMV is not completely protective against virus acquisition or placental transmission, the goal of designing a vaccine eliciting sterilizing immunity that can always prevent virus acquisition may be unrealistic. A more achievable goal for vaccine development might be a moderate reduction of virus acquisition, as achieved in the previous gB/MF59 vaccine trials, plus the induction of responses that can rapidly contain virus replication soon after infection and reduce the chance of spread to the placenta, which may require responses to the viral PC. Importantly, the dynamics of rapid viral containment or prevention of placental infection, as opposed to maternal virus acquisition of infection assessed by indirect means (such as seroconversion), has implications for clinical vaccine trial design.

CURRENT STATUS OF CMV VACCINE DEVELOPMENT

In view of the evidence that natural immunity is at least partly protective against congenital CMV infection, the critical issue is how that immunity can be reproduced or improved on through vaccination. Currently, three CMV antigens appear to be of greatest interest for a vaccine: the gB glycoprotein, the PC, and the pp65 tegument protein. Table 1 lists the candidates according to their ability to induce responses to each of these targets. Antibodies to gB are thought to primarily prevent entry into fibroblasts (90), but note that some of the gB candidates are claimed to block epithelial cell entry as well as fibroblast cell entry (79), perhaps because those gB constructs have a structure different from those of the gB subunit vaccines that do not prevent entry into epithelial cells (91). Interestingly, a gB vaccine has been shown to be highly effective in preventing CMV disease in organ transplant patients (9).

The role of pp65 as an important inducer of T cell responses is recognized for protection of transplant patients (78). Immediate early (IE) proteins are also important inducers of T cell responses and have been included in modified vaccinia Ankara (MVA) and alphavirus vectored vaccines (74, 85). The role of these T cell targets, and of T cell responses in general, in preventing transmission from mother to fetus requires more study (72). However, as preliminary data suggest that T cell responses to pp65 peptide epitopes can reduce reactivation (1, 22, 23) of CMV in seropositive hematogenous stem cell transplant recipients (86) and as $CD4^+$ T cell helper function is important to

antibody production, T cell responses continue to be an important goal in designing HCMV vaccine candidates. Notably, two candidates that provide all three main vaccine antigens of interest (gB, pentamer, and pp65) are currently in the clinical trial pipeline: replication-defective virus V160 and a purified dense-body vaccine (92, 93). An IE1/pp65 fusion protein-expressing alphavirus has been assessed (74), while a Triplex MVA currently in clinical testing includes pp65 IE1 and IE2 (85). Subsequent efficacy studies are required to determine whether a combination of these antigens would be effective in preventing HCMV acquisition or cCMV.

With regard to demonstration of efficacy in clinical trials, it is notable that an attenuated virus has prevented HCMV disease in renal transplant patients and that subunit gB has been found to both moderately reduce acquisition of HCMV by seronegative women and to reduce CMV disease in recipients of solid-organ transplants (7–9). As mentioned above, pp65 protein has been shown to reduce reactivation of HCMV in hematopoietic stem cell transplant recipients (10), and peptides from pp65 have also given preliminary positive results in those patients (94). The pentamer has not yet been tested for efficacy against HCMV infection or disease. Results of these trials with efficacy outcomes should continue to be reevaluated with an eye toward defining vaccine-elicited immune correlates of protection, similarly to what has been pursued with partially effective HIV vaccine trials (95). It is also important that a HCMV vaccine that does not prevent infection of women, but does prevent transmission to the fetus, would still be valuable.

The path to licensure of a HCMV vaccine is relatively clear. For transplant populations, it will be necessary to show a reduction in the levels of viremia and disease. For seronegative women of child-bearing age, the FDA has recommended a placebo-controlled vaccine study in women prior to establishment of pregnancy, with subsequent evaluation of acquisition of HCMV infection in vaccinees and of acquisition of cCMV infection in their newborn infants (96). Prevention of cCMV infection was considered to be the most relevant and practical outcome endpoint for a putative phase III efficacy study; however, it was noted that a vaccine that demonstrated high efficacy in preventing acquisition of HCMV by women in the community could achieve licensure, since, by definition, the developing fetus of uninfected women would remain uninfected. The vaccine strategies for seropositive women remain uncharted and should be informed by studies of immune deficits that permit reinfection or cCMV transmission in the setting of preexisting immunity (24). Thus, the priorities for HCMV vaccine development remain 3-fold: (i) early-phase testing of novel vaccine candidates, comparing responses to natural immunity and to that previously elicited by partially efficacious vaccines; (ii) defining the immune correlates of congenital HCMV transmission, particularly in seropositive women and vaccine recipients; and (iii) continuing to develop and utilize animal models that can provide the proof of concept that specific immune responses can block placental CMV infection. Continued progress in these areas will ensure that an effective vaccine to eliminate cCMV as a major cause of infant birth defects and brain damage is within reach.

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