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Vaccine Prevention of Maternal Cytomegalovirus Infection

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Abstract

BACKGROUND—Congenital infection with cytomegalovirus (CMV) is an important cause of hearing, cognitive, and motor impairments in newborns.

METHODS—In this phase 2, placebo-controlled, randomized, double-blind trial, we evaluated a vaccine consisting of recombinant CMV envelope glycoprotein B with MF59 adjuvant, as compared with placebo. Three doses of the CMV vaccine or placebo were given at 0, 1, and 6 months to CMV-seronegative women within 1 year after they had given birth. We tested for CMV infection in the women in quarterly tests during a 42-month period, using an assay for IgG antibodies against CMV proteins other than glycoprotein B. Infection was confirmed by virus culture or immunoblotting. The primary end point was the time until the detection of CMV infection.

RESULTS—We randomly assigned 234 subjects to receive the CMV vaccine and 230 subjects to receive placebo. A scheduled interim analysis led to a stopping recommendation because of vaccine efficacy. After a minimum of 1 year of follow-up, there were 49 confirmed infections, 18 in the vaccine group and 31 in the placebo group. Kaplan-Meier analysis showed that the vaccine group was more likely to remain uninfected during a 42-month period than the placebo group (P = 0.02). Vaccine efficacy was 50% (95% confidence interval, 7 to 73) on the basis of infection rates per 100 person-years. One congenital infection among infants of the subjects occurred in the vaccine group, and three infections occurred in the placebo group. There were more local reactions (pain, erythema, induration, and warmth) and systemic reactions (chills, arthralgias, and myalgias) in the vaccine group than in the placebo group.

CONCLUSIONS—CMV glycoprotein B vaccine has the potential to decrease incident cases of maternal and congenital CMV infection. (ClinicalTrials.gov number, NCT00125502.)

Congenital infection with cytomegalovirus (CMV) causes auditory, cognitive, and neurologic impairment in infants. On the basis of a cost-effectiveness analysis, the development of a vaccine for the prevention of congenital CMV infection was listed as a top priority for the United States by a committee of the Institute of Medicine in 2001.[1] Although the first clinical trials of a CMV vaccine took place more than 30 years ago, an effective vaccine for the prevention of CMV infection remains elusive. The Towne CMV vaccine showed efficacy in the prevention of CMV disease in seronegative renal-transplant recipients, but it did not prevent

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infection in these patients or in parents of CMV-infected children.[2,3] Reports indicating that immunity from naturally acquired infection is not completely protective against reinfection or transmission of CMV from mother to fetus suggested that vaccine prevention of infection would be difficult.[4-7]

In the 1990s, a vaccine that was based on CMV envelope glycoprotein B with a new adjuvant, MF59 (a squalene-in-water emulsion), entered clinical trials, which demonstrated that the vaccine was immunogenic and had acceptable profiles of adverse events and side effects.[8-10] In this phase 2, randomized, double-blind, placebo-controlled clinical trial, we enrolled a population of women of childbearing age who had a high rate of incident CMV infection in order to test the efficacy of the CMV glycoprotein B vaccine and to increase knowledge with respect to vaccine safety.

METHODS

STUDY POPULATION

Women were screened on the postpartum wards of hospitals at the University of Alabama at Birmingham and the University of Alabama College of Community Health Sciences in Tuscaloosa. Subjects who were negative for antibody to CMV (seronegative) were invited to participate in the 42-month clinical trial if they were in good health, between the ages of 14 and 40 years, not pregnant, and not nursing and if they met other inclusion and exclusion criteria (see the Supplementary Appendix, available with the full text of this article at NEJM.org).[11]

IMMUNIZATION AND BLINDING

Doses of the study vaccines (either CMV glycoprotein B vaccine with MF59 adjuvant or placebo) were dispensed according to a randomization schedule provided to the study pharmacist in sealed envelopes by the project statistician. Randomization, which was based on permuted blocks of two and four, was performed at each study site and was stratified according to the study site. All study subjects and staff (with the exception of the statistician and the pharmacist dispensing vaccines) were unaware of study-group assignments after the data set was closed and until the analysis was completed.

The CMV vaccine was composed of 0.02 mg of glycoprotein B and 13.25 mg of MF59 (squalene, sorbitan trioleate, and polysorbate 80) with citrate buffer in 1 ml of normal saline. The placebo was 0.9% sodium chloride for injection. Study vaccines were transported from the pharmacy to the study site in covered containers and were given by intramuscular injection in the left deltoid by a nurse not otherwise involved in the study. A urine pregnancy test was performed before each injection; subjects with a positive pregnancy test were not immunized.

LABORATORY METHODS

Subjects were screened for CMV antibody with the use of CMV IgG (Axsym, Abbott Laboratories). After randomization, we tested all subjects for CMV infection every 3 months, using an assay to test for IgG antibodies against CMV proteins other than glycoprotein B.[12,13] Within 1 month after detection of infection, samples of blood and urine and swabs of the mouth and vagina were collected for confirmatory virus culture and polymerase-chainreaction (PCR) assay.[14,15] Real-time PCR was performed at the University of Washington Virology Laboratory for detection of CMV; a result of 50 or more genome equivalents (ge) per milliliter of sample was considered positive. If neither culture nor PCR was positive, infection was assessed by immunoblotting (recomBlot CMV IgG, Mikrogen).

VACCINE REACTOGENICITY AND SAFETY

Subjects were given a digital thermometer, a metric ruler, and detailed instructions on how to complete a diary card listing possible adverse events. Daily entries were made on the diary card for 7 days after each injection. Erythema and induration at the injection site were graded on the basis of the size of the reaction (<10 mm, mild; 10 to 50 mm, moderate; >50 mm, severe). Other injection-site reactions (pain and warmth) and systemic reactions (fever, chills, headache, nausea, myalgia, fatigue, rash, and arthralgia) that were listed on the diary card were considered mild if signs or symptoms did not require medication or the interruption of the subject's daily routine; moderate reactions were those that required medication to relieve symptoms or interfered with the daily routine, and severe reactions were those that made the subject unable to perform her daily routine or that required medical attention.

At each study visit, subjects were asked about adverse events not listed on the diary card. Serious adverse events were defined according to Food and Drug Administration guidelines.[16] Included in the analyses of reactogenicity and adverse events were all subjects who received at least one dose of a study vaccine, including those who were seropositive on the day of enrollment and thus were not included in the efficacy analysis.

SPONSORSHIP AND SAFETY MONITORING

The study was conducted under an investigational-new-drug application, with support from the National Institute of Allergy and Infectious Diseases and Sanofi Pasteur, which provided the vaccine. The MF59 adjuvant was provided by Chiron (now Novartis). A data and safety monitoring board consisting of scientists with expertise in vaccine clinical trials, clinical virology, statistics, neonatology, and maternal and fetal medicine reviewed the progress and safety data on an annual basis and reviewed serious adverse events as they were reported; board members are listed in the Appendix. The study was approved by the institutional review board at each university and each participating hospital, and all subjects provided written informed consent.

STATISTICAL ANALYSIS

The sample size of 400 was calculated on the basis of a hypothesis of 50% efficacy, an estimated infection rate of 20% in the placebo group, and an attrition rate of 20%, with the use of a two-sided type I error of 5%. The estimated rate of infection in the placebo group was based on a previous observational study in the same population.[17] The primary end point, the time from enrollment (initial immunization) to the detection of CMV infection, was estimated by the Kaplan-Meier method, and groups were compared with the use of the log-rank test.[18] Interim efficacy analyses, with the adoption of early-stopping rules according to the Lan-DeMets use function corresponding to the O'Brien-Fleming boundaries, were scheduled when 50% and 75% of expected end points had occurred, with boundaries of 0.0031 and 0.0197, respectively.[19,20] Vaccine efficacy was calculated on the basis of infection rates per 100 person-years of follow-up; 95% confidence intervals were based on the Poisson exact method.[21] The chi-square test or Fisher's exact test was used to compare rates. The Kruskal-Wallis test was used to compare ordinal factors. Cox proportional-hazards modeling was used to assess the relative risk of acquiring CMV infection, after adjustment for potential confounders. Factors with a univariate probability of 0.25 or less were used in a multivariate model.[22] All reported P values are two-sided and have not been adjusted for multiple testing.

RESULTS

STUDY POPULATION AND STOPPING RECOMMENDATION

Enrollment took place from August 1999 through April 2006. A total of 464 seronegative subjects underwent randomization. Of these subjects, 23 (9 in the vaccine group and 14 in the placebo group) were excluded because they did not meet inclusion criteria on the day of enrollment. Among the remaining 441 subjects, some subjects did not receive all three planned injections for a variety of reasons (Fig. 1). For a 14-month interval after Sanofi Pasteur acquired the rights to the study vaccine from Chiron (now Novartis), the study vaccine was unavailable while the manufacturer established procedures for monitoring vaccine stability. There were no significant differences between the two groups in any of the baseline characteristics (Table 1).

After the second scheduled interim review of efficacy results, the data and safety monitoring board reported that the vaccine was superior to placebo and had crossed the preset boundary ($P = 0.0197$) for statistical significance. The board recommended that the study continue under blinded conditions until all subjects had been followed for at least 6 months after the final dose of a study vaccine. When that milestone was met in April 2007, 99 subjects in each group had completed all study visits; 75 in the vaccine group and 64 in the placebo group were still in follow-up. A total of 51 of 225 vaccine recipients (23%) dropped out of the study before completion of the trial, as did 53 of 216 placebo recipients (25%). There were no significant differences between the two groups in the rate of early termination ($P = 0.64$) or in the time to early termination ($P = 0.65$ by Kaplan-Meier analysis and the log-rank test). Reasons for early termination in the vaccine group were loss to follow-up (28 subjects), adverse events (3 subjects), withdrawal (9 subjects), and noncompliance (11 subjects). In the placebo group, the reasons were loss to follow-up (39 subjects), withdrawal (7 subjects), and noncompliance (7 subjects). At the time of the review by the data and safety monitoring board, 49 end points had been detected; by the time the data set was closed in June 2007, 1 additional CMV infection had occurred in each group.

VACCINE EFFICACY

A total of 19 CMV infections occurred in the vaccine group and 32 in the placebo group. None of the infections were diagnosed medically, and no subjects had symptoms that were suggestive of a mononucleosis-like illness during the interval of seroconversion. Infection was confirmed by the detection of CMV in body fluids by culture, PCR, or both in all but two subjects. In these two subjects (both in the vaccine group), immunoblots showed the presence of antibody against two or more non-glycoprotein B proteins, confirming infection. Two CMV infections (one in each group) occurred after subjects had completed the 42-month follow-up schedule. These subjects were pregnant at their termination visit and were followed, per protocol, to determine the outcome of the pregnancy. Because only pregnant subjects were followed beyond 42 months, efficacy calculations were censored at 42 months, so 49 subjects were included in the efficacy analysis, 18 in the vaccine group and 31 in the placebo group.

Vaccine recipients were more likely to remain uninfected than placebo recipients ($P = 0.02$) (Fig. 2). CMV infection occurred in 18 of 225 subjects in the vaccine group (8%) and in 31 of 216 subjects in the placebo group (14%). Rates of infection per 100 person-years were 3.3 in the vaccine group and 6.6 in the placebo group, for an overall vaccine efficacy of 50% (95% confidence interval [CI], 7 to 73). In addition to the characteristics listed in Table 1, the following variables were assessed with the use of Cox proportional-hazards regression: the type of regimen (vaccine or placebo), the number of days between screening and enrollment, the occurrence of pregnancy during the study, height, the number of doses of vaccine received, and the presence in the home of children under 13 months of age, from 13 to 36 months of age, and between 37 and 72 months of age. The regimen was the only covariate that had a P value

of less than 0.05 in the univariate model. Age, race, height, and the presence in the home of children from 13 to 36 months of age had P values of 0.25 or less and were included in a multivariate proportional-hazards model. The type of regimen was the only variable that was significant in this model (P = 0.02), with a hazard ratio in the vaccine group of 0.51 (95% CI, 0.29 to 0.92).

OUTCOME OF PREGNANCIES

A greater proportion of subjects in the placebo group than in the vaccine group became pregnant during the trial (P = 0.04) (Table 2). There were no significant differences between the two groups in the time to pregnancy (according to Kaplan-Meier analysis) or in any of the pregnancy outcome variables shown in Table 2. The mean (±SD) birth weights of infants were similar in the two study groups (3193±65 g in the vaccine group and 3178±68 g in the placebo group). Congenital CMV infection was detected in 1 of 81 infants born to mothers in the vaccine group (1%) and in 3 of 97 infants born to mothers in the placebo group (3%, P = 0.41). All congenital infections were the result of maternal infection during pregnancy. One infected newborn in the placebo group had severe symptomatic congenital CMV infection with microcephaly, intracranial calcifications, and thrombocytopenia; follow-up revealed delayed psychomotor development. The other three infants with congenital CMV infection were asymptomatic at birth and were free of sequelae 3 to 5 years later. The congenitally infected newborn of a mother in the vaccine group was born 8 months after the subject had completed her study termination visit and 50 months after the first dose of vaccine.

VACCINE REACTOGENICITY

There were no significant differences between the vaccine group and the placebo group in the frequency of fever, headache, nausea, fatigue, or rash after the first, second, or third doses of a study vaccine. Arthralgias occurred significantly more frequently in the vaccine group but only after the third dose (10 of 176 subjects in the vaccine group [6%] vs. 1 of 159 subjects in the placebo group [1%], P = 0.03). Similarly, chills occurred significantly more often in vaccine recipients than in placebo recipients but only after the third dose (14 of 176 subjects in the vaccine group [8%] vs. 2 of 159 subjects in the placebo group [1%], P = 0.01). The rate of myalgias was greater in the vaccine group than in the placebo group after the first dose (36 of 228 subjects [16%] vs. 13 of 225 subjects [6%], P = 0.007) and after the third dose (28 of 176 subjects [16%] vs. 5 of 159 subjects [3%], P = 0.001). The majority of all systemic reactions were mild. The only systemic reaction for which there was a significant difference in the duration of symptoms was headache, which was of longer duration in the placebo group than in the vaccine group after the second dose. The median duration for most reactions was less than 1 day.

Local reactions at the site of injection within 7 days after immunization occurred more often in the vaccine group (Table 3). After the third dose of vaccine, 3% of subjects in the vaccine group reported severe pain, and 2% reported severe erythema; for all other injection-site reactions, the proportion of subjects in the vaccine group who reported having severe symptoms was 1% or less. In the placebo group, only one subject reported severe pain after the first dose, and there were no other severe local reactions. The majority of all local reactions lasted less than 1 day, and there was no significant between-group difference in the duration of symptoms, with the exception of pain at the injection site (for all three doses) and warmth and erythema (for the third dose only).

ADVERSE EVENTS

There were no significant differences between the vaccine group and the placebo group in overall rates of adverse events, in adverse events that were at least moderate in severity, or in serious adverse events in the subjects or their infants born during the study (Table 4). Adverse

events that were considered to be possibly related to a study vaccine occurred in 16 of 231 subjects in the vaccine group (7%) and in 4 of 226 subjects in the placebo group (2%, P=0.01). The nonspecific character of the possibly related adverse events (which are listed in the footnote to Table 4) suggests that CMV glycoprotein B vaccine with MF59 adjuvant has systemic reactogenicity in a small percentage of subjects that was not captured by the systemic reactions listed on diary cards.

Two serious adverse events were considered possibly related to a study drug. One subject in the vaccine group had fever, myalgia, weakness (unable to walk), and rash 8 days after the second dose of vaccine; she recovered fully over a period of 6 to 7 months. One subject in the placebo group had peripheral neuropathy characterized by numbness and paresthesia affecting her feet and hands 10 weeks after the second dose of vaccine. An extensive neurologic evaluation was not able to identify a cause. Her symptoms improved substantially but had not completely cleared at the end of the study. Serious adverse events were noted in seven newborns (eight events) of mothers in the vaccine group and in eight newborns (eight events) of mothers in the placebo group. The affected babies were conceived 3 to 40 months after the last dose of a study vaccine was administered.

DISCUSSION

CMV infection typically induces a serum antibody response to glycoprotein B.[23] This protein is an important target of neutralizing antibody, and key epitopes for virus neutralization are contained within conserved regions of glycoprotein B.[24] It is likely that antibodies play a role in the protective effect of this vaccine. Antibody data from previous studies showed that healthy adults who received three doses of vaccine (at 0, 1, and 6 months) achieved peak levels of antibody to CMV glycoprotein B that were several times higher than those in adults with past CMV infection. The data also showed that the peak level of neutralizing antibody was similar to that observed in persons with naturally acquired infection.[8,9] In our study, the duration of protection that was conferred by CMV glycoprotein B vaccine and the correlation between antibody level and protection remain to be determined.

The prevention of congenital CMV infection and its sequelae is the ultimate goal of a CMV vaccine. Although the sample size for this study was not large enough to test a hypothesis concerning congenital infection, newborns of subjects were tested for CMV infection. One congenital CMV infection occurred in an infant whose mother was in the vaccine group; that baby was born 50 months after maternal enrollment and has had no sequelae from infection. Three congenital CMV infections occurred among infants whose mothers were in the placebo group; one of these infants was symptomatic at birth and has central nervous system sequelae. Although these numbers are too small to support any conclusions, they are similar to results from a previous observational study that showed that infants whose mothers had antibody to CMV from past infection had a 67% reduction in the rate of congenital infection, as compared with infants of women who were initially seronegative.[25]

The general pessimism about vaccine prevention of CMV infection is at least partly the result of studies that show that repeated infections with new strains of CMV occur in previously infected persons.[6,7,26,27] In addition, CMV is a large and complex virus with a number of immunogenic proteins and many genes that encode products with the potential to interfere with host immune responses.[28] Prevention of infection by immunization with a single envelope glycoprotein has seemed unlikely to many experts in this field. Furthermore, congenital infection may be due to either primary maternal infection during pregnancy or infections in women with preconception immunity to CMV.[4,25,29-31] If future studies, such as a phase 3 clinical trial, continue to demonstrate reasonable efficacy, safety, and an acceptable level of

reactogenicity, then this vaccine may be useful in preventing CMV infection in young women and congenital CMV in their infants.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Dr. Pass reports receiving consulting fees from Vical, Alpha-Vax, Merck, and MedImmune and having a partial interest in relevant patents; Drs. Pass and Zhang and Ms. Hill, receiving research grants from Sanofi Pasteur; Dr. Evans and Ms. Davis, receiving research support from Novartis; Dr. Simpson, receiving research support from GlaxoSmithKline; Dr. Corey, receiving grant support from GlaxoSmithKline, Novartis, and Bristol-Myers Squibb; and Ms. Cloud, receiving consulting fees from Pfizer and having a partial interest in relevant patents.

Appendix

APPENDIX

The following persons have been members of the data and safety monitoring board since 1999, unless otherwise indicated: John W. Gnann (chair), Waldemar A. Carlo, and Dwight J. Rouse, University of Alabama at Birmingham, Birmingham; Jeanette Lee, University of Arkansas for Medical Sciences, Little Rock; Thomas Heineman, Saint Louis University, St. Louis (2004-2006); Wendy Keitel, Baylor College of Medicine, Houston (2004-present); and Lisa Frenkel, University of Washington, Seattle (2006-present).

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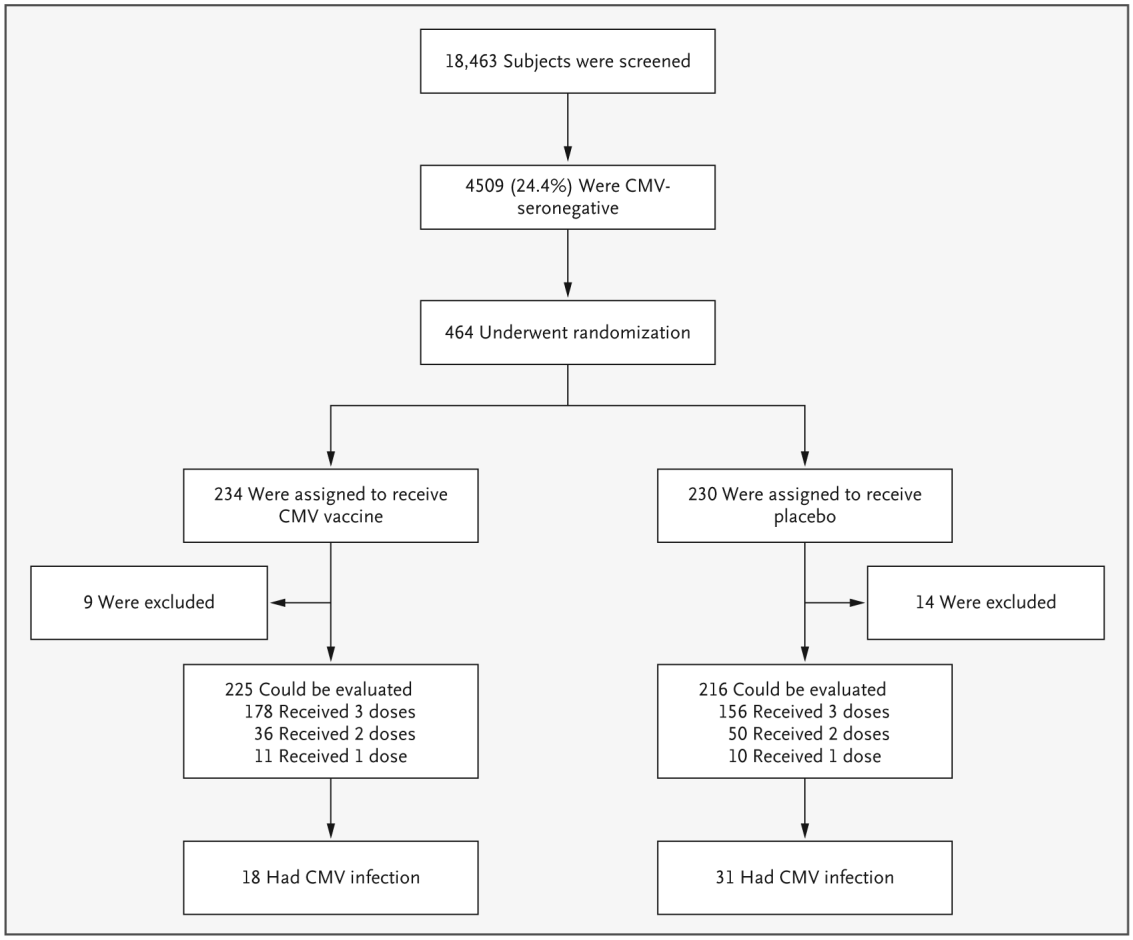

Figure 1. Enrollment and Outcomes

In the vaccine group, 47 subjects did not receive the full three doses of vaccine because 4 were lost to follow-up, 5 had an adverse event, 7 had a compliance issue, 5 withdrew from the study, 2 were found to have CMV infection, 6 became pregnant, and 18 were unable to receive the vaccine owing to its unavailability. In the placebo group, 60 subjects did not receive three doses of placebo because 16 were lost to follow-up, 2 had an adverse event, 4 had a compliance issue, 4 withdrew from the study, 4 were found to have CMV infection, 13 became pregnant, and 17 were unable to receive placebo owing to its unavailability.

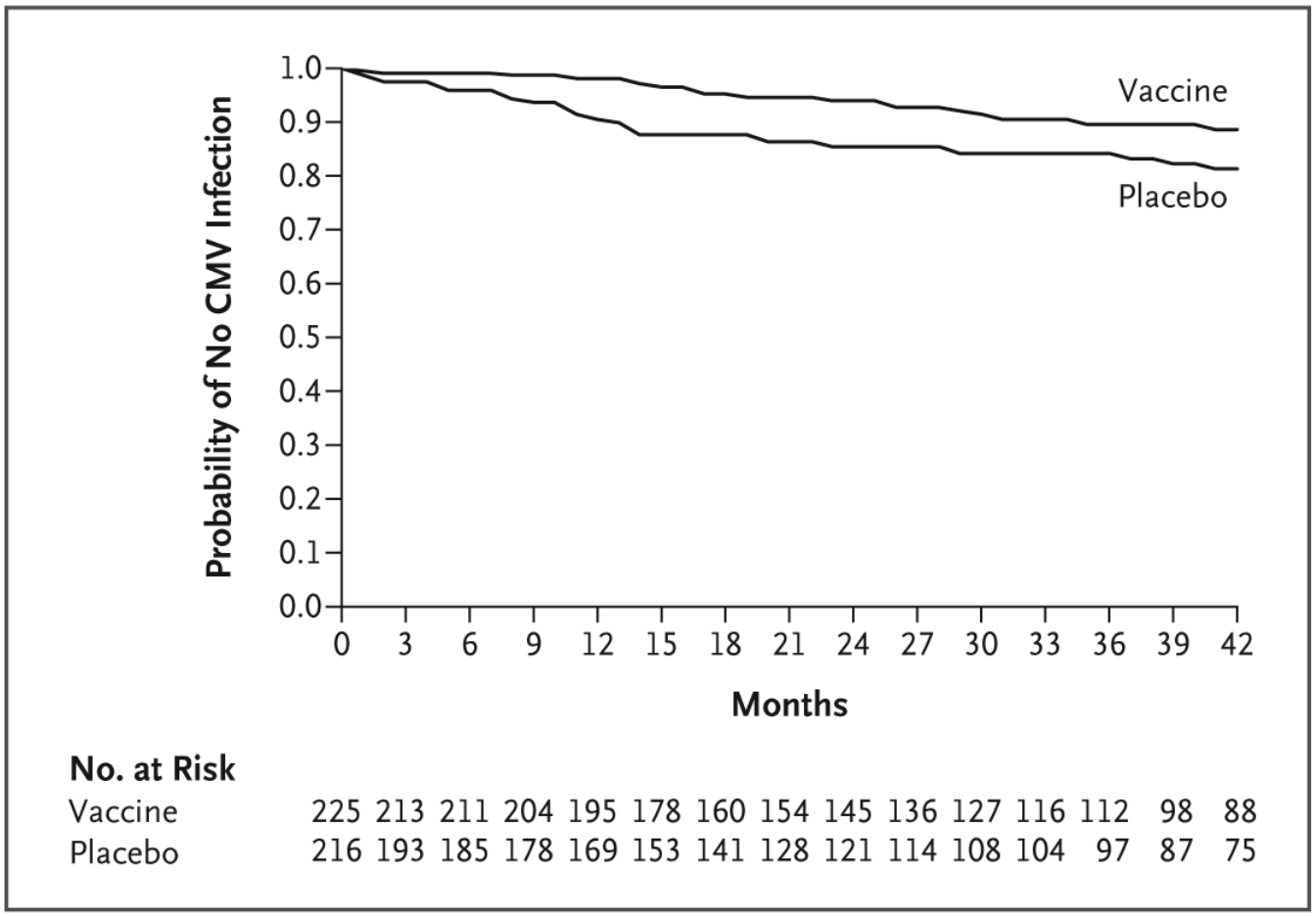

Figure 2. Kaplan-Meier Estimates of Probability of Remaining Free of CMV Infection

Up to 42 months after study enrollment, subjects in the vaccine group were more likely to remain free of CMV infection than were subjects in the placebo group (P = 0.02). In the vaccine group, 18 subjects were found to have CMV infection, as compared with 31 in the placebo group.

Table 1
Baseline Characteristics of the Subjects

Variable	Vaccine	Placebo
Age — yr		
Median	20	20
Range	15-40	14-38
Black race — no./total no. (%)*	158/225 (70)	162/216 (75)
Time since last birth — mo		
Median	2.2	2.2
Range	0.8-11.5	1.3-15.4
Study site — no./total no. (%)		
Birmingham	204/225 (91)	197/216 (91)
Tuscaloosa	21/225 (9)	19/216 (9)
Weight — kg		
Median	75	73
Range	43-171	37-153
Body-mass index†		
Median	28	27
Range	16-61	17-55
Not married — no./total no. (%)	172/225 (76)	171/215 (80)
High-school graduate — no./total no. (%)	135/222 (61)	138/216 (64)
Employed — no./total no. (%)	74/195 (38)	70/192 (36)
Child ranging in age from 13 to 36 mo at home — no./total no. (%)	46/224 (21)	47/214 (22)

*Race was self-reported.

†The body-mass index is the weight in kilograms divided by the square of the height in meters.

Table 2

Outcome of Pregnancy during the Study Period*

Outcome	Vaccine	Placebo	P Value
Subjects who became pregnant — no./total no. (%)	80/225 (36)	97/216 (45)	0.04
Total pregnancies	97	118	
Delivery of live-born infants — no./total no. (%)	79/97 (81)	95/118 (81)	0.80
Spontaneous abortion — no./total no. (%)	14/97 (14)	12/118 (10)	0.34
Ectopic pregnancy — no./total no. (%)	1/97 (1)	3/118 (3)	0.41
Induced abortion — no./total no. (%)	3/97 (3)	8/118 (7)	0.21
Premature infant (gestational age <37 wk) — no./total no. (%)†	12/81 (15)	15/97 (15)	0.88
Congenital CMV infection — no./total no. (%)†	1/81 (1)	3/97 (3)	0.41

*Plus-minus values are means ±SD.

†This category refers only to live-born infants. Two subjects in each study group gave birth to twins.

Table 3

Rates of Injection-Site Reactions of Any Severity, According to the Number of Doses Administered*

Reaction and Dose No.	Vaccine	Placebo	P Value
	no./total no. (%)		
Pain			
1	135/228 (59)	54/225 (24)	<0.001
2	103/214 (48)	32/206 (16)	<0.001
3	99/176 (56)	25/159 (16)	<0.001
Warmth			
1	34/228 (15)	20/225 (9)	0.13
2	27/214 (13)	11/206 (5)	0.004
3	30/176 (17)	13/159 (8)	0.04
Erythema			
1	23/228 (10)	14/225 (6)	0.28
2	15/214 (7)	11/206 (5)	0.78
3	24/176 (14)	7/159 (4)	0.03
Induration			
1	11/228 (5)	7/223 (3)	0.47
2	18/214 (8)	4/206 (2)	0.003
3	31/176 (18)	4/159 (3)	0.001

* The data are based on diary cards completed by subjects. The denominators are the numbers of subjects who received the designated dose of a study vaccine and provided the required data on the diary card.

Table 4

Rates of Adverse Events and Serious Adverse Events*

Event	Vaccine (N = 231)	Placebo (N = 226)	P Value
	no. (%)		
Adverse event			
Any	184 (80)	174 (77)	0.49
Moderate severity	166 (72)	160 (71)	0.80
Possibly related to study drug†	16 (7)	4 (2)	0.01
Serious adverse event			
Any‡	32 (14)	19 (8)	0.07
Possibly related to study drug	1 (<1)	1 (<1)	0.99
In infant born during study§	7/81 (9)	8/97 (8)	0.89

*Included in the analysis of adverse events were all subjects who received at least one dose of a study vaccine, including those who were found to be CMV-seropositive on the day of enrollment and were not included in the efficacy analysis.

†Unless otherwise noted, the severity of the following adverse events was mild and each event occurred in only one subject. Events in the vaccine group were pruritus, leg cramps (moderate), fever (with myalgia, rash, and weakness) (severe), abdominal pain (in two patients), accidental injury (moderate), flushing, pharyngitis, pharyngitis (moderate), upper respiratory infection, increased cough, gastroenteritis, gastroenteritis (moderate), dizziness, flulike illness, metrorrhagia, back pain, and odontalgia. Events in the placebo group were peripheral neuropathy (severe), headache (in two patients), urticaria (moderate), and rhinitis.

‡Unless otherwise noted, each of the following serious adverse events occurred in only one subject. Serious adverse events in the vaccine group were metrorrhagia, fever (with myalgia, rash, and weakness), tonsillitis with dehydration, pelvic abscess, cyst removal, surgical wound with skin graft, depression (two), spontaneous abortion (three), abdominal pain from ovarian cyst, endometritis, macromastia (four), goiter, asthma, cholelithiasis (two), staphylococcal skin infection, accidental injury (two), postoperative bleeding, elective bilateral mastectomy, preeclampsia, acute cholecystitis (two), dyspnea (two), premature labor, peritonsillar abscess, pulmonary embolus, renal calculus, urinary tract infection, inguinal hernia, tubal ligation, and pulmonary tuberculosis. In the placebo group, serious adverse events were ectopic pregnancy, premature labor (seven), syncope, aseptic meningitis, tonsillar abscess, spontaneous abortion, accidental injury (three), endometritis (two), peripheral neuropathy, toxemia, urinary tract infection, macromastia, and wound hematoma.

§This category refers only to live-born infants. Unless otherwise noted, each of the following serious adverse events occurred in only one infant. In the vaccine group, eight serious adverse events involving seven infants were trisomy 21 with arteriovenous canal, imperforate anus and urethral atresia (two events in one infant), myelomeningocele, death from sepsis, prematurity, respiratory distress, and abdominal distention. In the placebo group, eight serious adverse events involving eight infants were symptomatic congenital CMV infection, transposition of great vessels, persistent urachus, death from extreme prematurity (two), and prolonged hospitalization because of prematurity (three).