MAJOR ARTICLE

Cytomegalovirus Seroprevalence in the United States: The National Health and Nutrition Examination Surveys, 1988–2004

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(See the editorial commentary by Vauloup-Fellous and Picone, on pages 1448–1449.)

Background. Congenital cytomegalovirus (CMV) infection causes permanent disabilities in more than 5500 children each year in the United States. The likelihood of congenital infection and disability is highest for infants whose mothers were CMV seronegative before conception and who acquire infection during pregnancy.

Methods. To provide a current, nationally representative estimate of the seroprevalence of CMV in the United States and to investigate trends in CMV infection, serum samples from the National Health and Nutrition Examination Survey (NHANES) 1999–2004 were tested for CMV-specific immunoglobulin G antibody, and results were compared with those from NHANES III (1988–1994). Individuals aged 6–49 years (21,639 for NHANES III and 15,310 for NHANES 1999–2004) were included.

Results. For NHANES 1999–2004, the overall age-adjusted CMV seroprevalence was 50.4%. CMV seroprevalence was higher among non-Hispanic black and Mexican American children compared with non-Hispanic white children and increased more quickly in subsequent age groups. CMV seropositivity was independently associated with older age, female sex, foreign birthplace, low household income, high household crowding, and low household education. Compared with NHANES 1988–1994, the overall age-adjusted CMV seroprevalence for NHANES 1999–2004 was not significantly different.

Conclusions. Many women of reproductive age in the United States are still at risk of primary CMV infection during pregnancy. There is an urgent need for vaccine development and other interventions to prevent and treat congenital CMV. The substantial disparities in CMV risk among seronegative women suggest that prevention strategies should include an emphasis on reaching racial or ethnic minorities and women of low socioeconomic status.

Cytomegalovirus (CMV), a member of the Herpesviridae family, is endemic throughout the world [1]. Most CMV infections are mild or asymptomatic; however, CMV can cause serious disease in immunocompromised individuals and fetuses. Among newborns, CMV is the leading cause of congenital infection in the developed world [2]. Each year, of an estimated 28,000 children born with congenital CMV infection in the United States, ~150 die, and >5500 have permanent disabilities, such as hearing loss, intellectual disability, psychomotor delay, speech and language disabilities, behavioral disorders, visual impairment, and cerebral palsy [3, 4].

CMV is acquired through contact with CMV-infected body fluids of individuals with symptomatic or asymptomatic CMV infection [1, 5, 6]. Congenital CMV infection is the result of intrauterine transmission of CMV infection from mother to fetus. A fetus is at highest risk of CMV infection when a mother has a primary (ie, first) infection during pregnancy [7, 8]. Compared with a maternal nonprimary infection (ie, reinfection or reactivation), a maternal primary infection is more likely to transmit CMV from mother to fetus (1% vs 32%) and is also more likely to result in severe, long-term sequelae in children born with congenital CMV

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infection [6, 8, 9]. Women who are CMV seropositive before pregnancy are 69% less likely to give birth to a CMV-infected newborn [10].

The best way to assess the prevalence of CMV infection is through seroprevalence studies of CMV-specific immunoglobulin (Ig) G antibody. A previous nationally representative seroprevalence study of CMV infection in the United States, which used data from the National Health and Nutrition Examination Survey (NHANES) III (1988–1994), indicated that large proportions of women of reproductive age are susceptible to primary infection during pregnancy [11].

The purpose of this study was to provide current estimates of CMV seroprevalence in the United States and to investigate trends in CMV infection by comparing seroprevalence data from NHANES III (1988–1994) with data from NHANES 1999–2004. National seroprevalences, particularly among women of reproductive age, are important for establishing accurate estimates of the risk of congenital CMV infection, for quantifying the potential target population for a CMV vaccine, and for identifying risk groups that should be a high priority to receive behavioral interventions and/or vaccine once one becomes available [12, 13]. National trends in CMV infection have not been examined previously and can provide insight into the rate of change in CMV seroprevalence during the past decade as a function of socioeconomic and demographic factors.

METHODS

Survey sample and design. NHANES is a series of cross-sectional surveys conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC) [14]. Data are collected through household interviews, physical examinations, and blood sampling [14]. To select a nationally representative sample, NHANES uses a complex multistage probability cluster sample design, discussed in greater detail elsewhere [15]. This study was approved by the institutional review board of the CDC, and participants provided written informed consent.

NHANES III was conducted from 1988 to 1994. Since 1999, NHANES has been administered as a continuous annual survey released in 2-year increments. The NHANES 1999–2000, 2001–2002, and 2003–2004 data sets were combined to form NHANES 1999–2004. NHANES III and NHANES 1999–2004 oversampled certain population groups to increase the reliability and precision of estimates for each of the groups [14, 16].

Individuals included in this study were those aged 6–49 years who were interviewed and examined, consented to be a part of additional testing, had serum samples available for testing, and had a nonequivocal CMV test result. The final study sample included 21,639 individuals for NHANES III and 15,310 individuals for NHANES 1999–2004. Serum sample availability was fairly uniform across variable categories except for the 6- to 11-year-old age group, in which greater percentages of persons were without available serum specimens. To address the impact of missing CMV data on the generalizability of the study results, we created adjusted weights by multiplying the original NCHS weights by the weighted proportion of available serum samples for that participant's sex, age, and race/ethnicity [11]. Seroprevalence analyses using the adjusted weights produced only slightly different point estimates that were within 95% confidence intervals (CIs) of estimates computed with the original NCHS weights; therefore, NCHS weights were used for all subsequent analyses.

Serologic testing. Laboratory methods for detecting CMV IgG antibody in serum from NHANES 1999–2004 followed the same procedures used previously for testing NHANES III samples [11]. To maximize testing sensitivity, specificity, and throughput, serum samples were screened for CMV-specific IgG antibody with the SeraQuest enzyme immunoassay (Quest International) and the Triturus enzyme-linked immunosorbent assay robot (Grifols USA). Then serum samples with reactivities within a narrow range of the SeraQuest assay cutoff were tested using the VIDAS test (bioMérieux Vitek). Discrepant results between the SeraQuest and VIDAS tests were resolved with an immunofluorescence assay (Bion Enterprises). All testing was conducted by laboratory personnel at the CDC.

Measures. Variables of interest included sex, age (6–11, 12–19, 20–29, 30–39, and 40–49 years), race or ethnicity (non-Hispanic white, non-Hispanic black, Mexican American), birthplace (born in the 50 states, born in Mexico, born elsewhere), household income level (ratio of household income to the family's appropriate poverty threshold: low [$\leq$1.300], middle [1.301–3.500], or high [$\geq$3.501]), insurance status (covered or not covered by health insurance), household education level (less than high school, high school diploma including Graduate Educational Development diploma, or more than high school), and household crowding index (low [<0.5 person per room], average [0.5–1 person per room], or high [>1 person per room]). Individuals not fitting into 1 of the 3 race/ethnicity groups were classified as "other" in 1999–2004 univariate results but were excluded from 1999–2004 multivariate analyses and comparisons between results from 1988–1994 and 1999–2004. Household income level was based on the poverty income ratio variable, which is the ratio of household income to the family's appropriate poverty threshold [17]. For the 1999–2004 analyses, household education level represented the highest education level of the household reference person or the reference person's spouse, if applicable. For comparison with 1988–1994 data, only the reference person's education level was used to be consistent with the NHANES III household education variable definition.

Statistical analysis. SUDAAN software, version 10.0 (RTI International), was used for statistical analyses. All prevalence estimates were weighted to represent the civilian, noninstitu-

tionalized US population and to account for the unequal probability of sampling and nonresponse to the household interview and physical examination. To reduce potential confounding by age, age-adjusted estimates were computed using the direct method to the 2000 US Census population [18].

For analyses of the 1999–2004 data, demographic factors were first evaluated with adjustment for age using a general linear contrast procedure. Next, logistic regression models were used to assess the association between CMV seropositivity and the demographic factors while adjusting for multiple covariates. The final logistic model included age, sex, race/ethnicity, household income level, birthplace (country of origin), household education, crowding index, and an age by sex interaction, age by race/ethnicity interaction, and race/ethnicity by sex interaction. The Satterthwaite adjusted *F* test was used to assess the statistical significance of variables and interactions in the model. Model fit was evaluated using the Hosmer-Lemeshow goodness-of-fit Satterthwaite-adjusted *F* test. Individuals with missing data on the variables in the multivariate models were excluded.

Table 1. Differences in Age-Adjusted Cytomegalovirus (CMV) Seroprevalence in Individuals Aged 6–49 Years, by Selected Demographic Factors between National Health and Nutrition Examination Survey (NHANES) 1988–1994 and 1999–2004

	NHANES 1988–1994		NHANES 1999–2004		
Demographic factor	Sample size	CMV seroprevalence, % (95% CI)	Sample size	CMV seroprevalence, % (95% CI)	Difference, % (95% CI)
Total	14,538	50.8 (48.7–52.9)	15,310	50.4 (48.0–52.7)	−0.4 (−3.6 to 2.8)
Sex					
Female (reference)	7695	56.1 (53.5–58.7)	7882	55.5 (53.3–57.7)	−0.6 (−4.0 to 2.8)
Male	6843	45.5[a] (43.1–47.8)	7428	45.2[a] (42.4–48.0)	−0.3 (−3.9 to 3.3)
Race/ethnicity					
Non-Hispanic white (reference)	4209	41.7 (39.3–44.2)	5284	39.5 (36.9–42.2)	−2.2 (−5.8 to 1.4)
Non-Hispanic black	4759	70.9[a] (69.6–72.1)	4227	70.6[a] (68.5–72.8)	−0.2 (−2.6 to 2.2)
Mexican American	4921	77.6[a] (75.8–79.4)	4679	76.9[a] (74.1–79.6)	−0.7 (−3.9 to 2.5)
Age, years					
6–11 (reference)	2679	36.3 (32.7–39.9)	2384	37.5 (34.2–40.8)	1.2 (−3.6 to 6)
12–19	2918	41.7[a] (38.2–45.2)	6066	42.7[a] (39.6–45.9)	1.1 (−3.5 to 5.7)
20–29	3302	49.0[a] (45.5–52.5)	2391	49.5[a] (46.1–52.8)	0.5 (−4.3 to 5.3)
30–39	3156	54.0[a] (50.2–57.9)	2251	56.7[a] (53.2–60.1)	2.6 (−2.6 to 7.8)
40–49	2483	64.3[a] (60.4–68.1)	2218	58.0[a] (54.8–61.1)	−6.3 (−11.3 to −1.3)[b]
Birthplace					
United States (reference)	11,573	46.1 (44.0–48.3)	12,387	45.1 (42.7–47.6)	−1 (−4.2 to 2.2)
Mexico	2054	90.7[a] (88.4–93.0)	1880	89.4[a] (87.6–91.2)	−1.3 (−4.1 to 1.5)
Other	869	78.8[a] (74.3–83.4)	1042	76.0[a] (71.4–80.6)	−2.9 (−9.3 to 3.5)
Household income level[c]					
Low (≤1.300)	5388	66.3[a] (63.2–69.5)	5380	66.0[a] (62.4–69.6)	−0.3 (−5.1 to 4.5)
Middle (1.301–3.500)	5676	52.2[a] (48.5–55.9)	5209	50.9[a] (47.9–53.8)	−1.3 (−5.9 to 3.3)
High (≥3.501; reference)	2282	37.7 (34.4–41.1)	3624	38.9 (36.5–41.4)	1.2 (−3.0 to 5.4)
Insurance					
Insured (reference)	10,493	48.4 (46.0–50.8)	11,423	47.0 (44.6–49.4)	−1.4 (−4.8 to 2.0)
Not insured	3215	60.9[a] (57.1–64.8)	3694	62.8[a] (58.7–66.9)	1.9 (−3.7 to 7.5)
Household education level					
Less than high school	5557	67.6[a] (64.4–70.8)	4909	69.2[a] (66.0–72.4)	1.6 (−2.8 to 6.0)
High school graduate or GED diploma	4496	52.0[a] (48.6–55.3)	3620	51.2[a] (47.7–54.8)	−0.8 (−5.6 to 4.0)
More than high school (reference)	4381	42.5 (39.6–45.4)	6216	42.8 (40.0–45.6)	0.3 (−3.7 to 4.3)
Crowding index					
Low (<0.5 person per room) (reference)	3684	42.2 (39.8–44.6)	4405	41.4 (38.9–44.0)	−0.8 (−4.4 to 2.8)
Average (0.5–1 person per room)	7617	53.1[a] (50.3–56.0)	8047	54.2[a] (51.5–56.9)	1.0 (−2.8 to 4.8)
High (>1 person per room)	3195	73.8[a] (70.2–77.3)	2673	75.8[a] (72.1–79.6)	2.1 (−2.9 to 7.1)

NOTE. Ages were adjusted to the year 2000 US Census Bureau by the direct method to the age groups 6–11, 12–19, 20–29, 30–39, and 40–49 years. CI, confidence interval; GED, General Educational Development.

[a] $P \leq .05$ (associated with the Student *t* test evaluating pairwise comparisons).

[b] $P < .05$ (associated with the Student *t* test comparing pairwise differences between prevalence percentages).

[c] Household income level was based on the poverty income ratio variable, which is the ratio of household income to the family's appropriate poverty threshold.

Table 2. Factors Associated with Cytomegalovirus (CMV) Seroprevalence in the United States: Predictive Margins (Multivariate Adjusted CMV Seroprevalences), by Sex and Race or Ethnicity, National Health and Nutrition Examination Survey 1999–2004

	Non-Hispanic white females		Non-Hispanic black females		Mexican American females		Non-Hispanic white males		Non-Hispanic black males		Mexican American males	
Characteristic	Sample size	Predictive margin (95% CI)	Sample size	Predictive margin (95% CI)	Sample size	Predictive margin (95% CI)	Sample size	Predictive margin (95% CI)	Sample size	Predictive margin (95% CI)	Sample size	Predictive margin (95% CI)
Subpopulation total	2760	45.2 (42.9–47.6)	2125	77.2 (74.7–79.6)	2394	78.2 (74.6–81.8)	2522	35.1 (31.9–38.3)	2102	61.9 (58.7–65.2)	2272	73.1 (70.2–76.0)
Age, years												
6–11	302	29.6 (24.2–34.9)	394	45.6 (40.5–50.7)	401	61.3 (53.9–68.7)	319	28.3 (21.3–35.3)	405	46.4 (40.5–52.3)	415	62.3 (55.9–68.7)
12–19	785	33.8 (29.5–38.1)	943	56.5 (51.6–61.3)	1064	70.4 (64.4–76.3)	792	29.6 (24.4–34.8)	1020	52.8 (48.2–57.3)	1053	65.8 (60.7–70.8)
20–29	599	35.7 (31.4–40.0)	261	76.6 (70.0–83.2)	378	81.3 (75.4–87.2)	438	32.6 (26.6–38.7)	214	62.4 (54.9–69.9)	287	72.9 (67.1–78.6)
30–39	602	52.1 (47.3–57.0)	256	94.6 (91.8–97.4)	266	87.8 (82.4–93.2)	464	36.2 (30.7–41.7)	206	74.5 (66.9–82.1)	236	78.6 (70.6–86.5)
40–49	472	57.5 (52.2–62.9)	271	90.3 (86.9–93.6)	285	90.1 (84.4–95.8)	509	42.0 (36.9–47.1)	257	70.2 (61.7–78.7)	281	86.2 (82.7–89.7)
Birthplace												
United States	2635	44.2 (41.7–46.7)	1991	76.5 (74.0–79.0)	1482	72.8 (67.8–77.8)	2397	33.8 (30.5–37.2)	1938	59.3 (55.9–62.7)	1310	62.8 (58.5–67.1)
Mexico	…[a]	…	0	…	912	89.7 (86.1–93.3)	…[a]	…	0	…	962	85.2 (82.4–88.0)
Other	125	68.4 (54.9–81.9)	133	87.5 (79.0–96.0)	…[b]	…	125	60.1 (48.4–71.9)	164	90.5 (82.8–98.2)	…[b]	…
Household income level[c]												
Low (⩽1.300)	613	51.6 (45.6–57.6)	944	81.3 (77.9–84.7)	1086	81.2 (76.4–86.1)	495	45.4 (39.6–51.2)	846	63.7 (57.8–69.6)	953	77.4 (73.2–81.7)
Middle (1.301–3.500)	885	44.2 (39.4–49.0)	693	76.5 (72.0–81.0)	835	77.7 (73.4–82.1)	807	35.0 (30.3–39.7)	716	62.0 (57.5–66.4)	887	73.0 (69.4–76.6)
High (⩾3.501)	1129	43.1 (39.5–46.7)	309	67.4 (58.4–76.5)	288	72.5 (64.4–80.5)	1082	31.6 (28.1–35.1)	356	58.9 (51.9–65.9)	235	62.9 (54.4–71.5)
Insurance												
Insured	2382	44.2 (41.9–46.5)	1765	76.6 (74.0–79.2)	1474	78.5 (75.0–82.1)	2059	34.2 (31.1–37.4)	1624	59.6 (55.8–63.4)	1277	73.2 (70.2–76.1)
Not insured	361	51.4 (43.7–59.1)	339	80.2 (75.1–85.3)	896	77.5 (71.4–83.6)	427	39.3 (31.0–47.5)	433	68.8 (64.6–73.1)	965	73.1 (68.1–78.0)
Household education level												
Less than high school	268	57.8 (52.2–63.5)	645	81.5 (76.8–86.3)	1157	83.4 (79.7–87.1)	236	36.6 (29.5–43.7)	608	66.3 (60.7–71.8)	1146	75.8 (72.4–79.3)
High school graduate or GED diploma	612	50.0 (45.4–54.5)	553	80.8 (76.7–84.8)	520	76.7 (72.3–81.2)	561	35.2 (30.4–40.1)	506	64.2 (58.8–69.6)	484	74.3 (69.8–78.8)
More than high school	1837	42.3 (39.4–45.2)	886	72.7 (69.6–75.9)	641	73.9 (67.6–80.1)	1691	34.9 (31.6–38.3)	916	58.6 (54.7–62.5)	569	69.2 (63.2–75.3)
Crowding index												
Low	1313	42.1 (39.1–45.2)	564	74.7 (70.4–78.9)	252	69.4 (61.2–77.5)	1196	34.2 (30.5–37.9)	554	60.6 (54.1–67.1)	257	69.7 (61.3–78.1)
Average	1337	48.3 (45.0–51.6)	1238	78.0 (75.4–80.6)	1303	78.6 (75.0–82.2)	1196	36.1 (32.2–39.9)	1187	61.5 (57.2–65.9)	1132	72.8 (69.2–76.4)
High	90	53.0 (40.8–65.2)	301	80.6 (75.3–85.9)	817	83.6 (79.0–88.3)	96	38.1 (28.6–47.6)	320	67.4 (61.3–73.6)	860	76.1 (71.8–80.5)

NOTE. The models for sex by race/ethnicity were adjusted for age, birthplace, household income level, insurance, household education, and crowding index. CI, confidence interval; GED, General Educational Development.

[a] The logistic models for non-Hispanic whites excluded 1 female born in Mexico and 1 male born in Mexico.

[b] The logistic model for Mexican Americans excluded 6 females born in "other" country and 7 males born in "other" country.

[c] Household income level was based on the poverty income ratio variable, which is the ratio of household income to the family's appropriate poverty threshold.

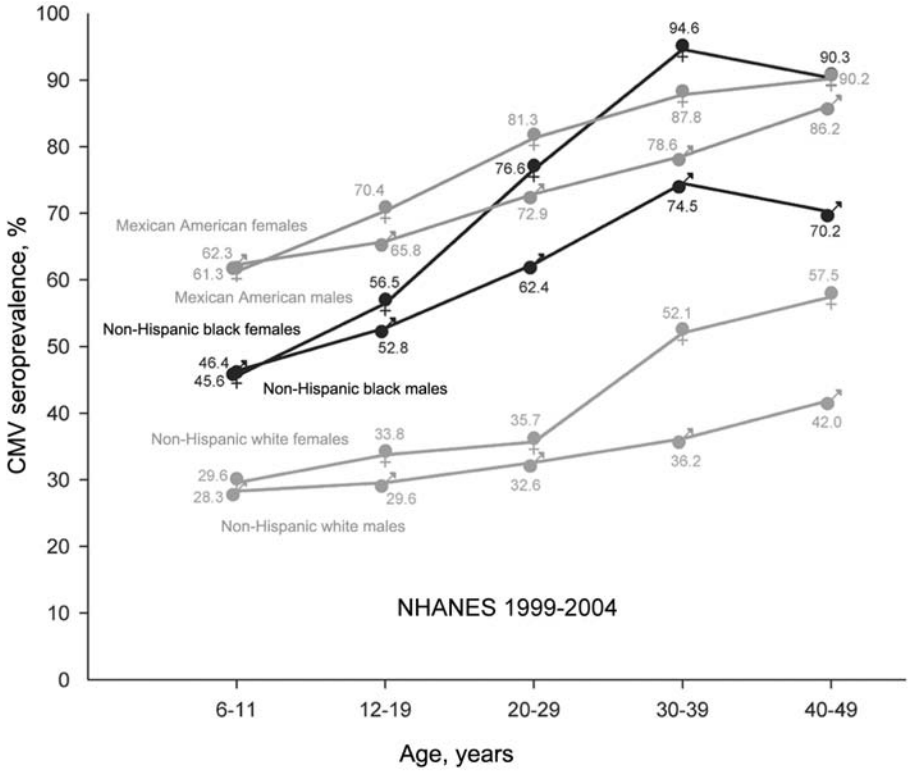

Figure 1. Predictive margins (multivariate adjusted cytomegalovirus [CMV] seroprevalences) in the United States, National Health and Nutrition Examination Survey (NHANES) 1999–2004, stratified by age, sex, and race/ethnicity. The circles representing the female and male prevalences are distinguished by the female (♀) and male (♂) icons. To better distinguish between females and males, the circles representing the prevalences in the 6–11-year-old age groups are plotted slightly above and below their true values; true prevalences are shown in the text next to the circles.

Because of interactions, logistic models were created for each age, sex, and racial/ethnic subgroup, as well as for combined subgroups for sex and race/ethnicity (eg, non-Hispanic white females) and sex and age (eg, 6- to 11-year-old girls). To aid the interpretation of odds ratios (ORs), predictive margins were computed using the PREDMARG statement in SUDAAN. Predictive margins are akin to adjusted seroprevalences; the predictive margin for a group represents the average predicted response if all individuals in the sample had been in that group, while controlling for all other covariates [19, 20]. The 95% CIs of predictive margins were based on the actual degrees of freedom for each level of each variable.

Methods to compare the 1988–1994 and 1999–2004 data were similar to those used for analyses of the 1999–2004 data, except that a variable representing survey year (1 for NHANES 1998–1994 and 2 for NHANES 1999–2004) was forced into the model. The final logistic model included age, sex, race/ethnicity, household income level, birthplace, household education, crowding index, and an age by sex, age by race/ethnicity, age by household income level, race/ethnicity by sex, and age by race/ethnicity by sex interaction. Because of numerous interactions with age, logistic models were performed for each age group. Additional stratifications were performed because of a significant 3-way interaction among age, race/ethnicity, and sex.

RESULTS

NHANES 1999–2004. The overall age-adjusted seroprevalence of CMV infection for individuals 6–49 years old was 50.4% (Table 1). In age-adjusted analyses, CMV seropositivity was significantly associated with female sex, non-Hispanic black race and Mexican American ethnicity, older age, foreign birthplace, low household income level, lack of insurance, low household education, and high crowding index (Table 1).

For both females and males, multivariate-adjusted CMV seroprevalences were higher for non-Hispanic blacks and Mexican Americans compared with non-Hispanic whites (Table 2 and Figure 1). Overall CMV seroprevalences were higher for non-Hispanic black and Mexican American 6–11-year-olds (45.7% and 61.7%, respectively) compared with non-Hispanic white children of the same age group (29.0%). Compared with the 6–11-year age group, CMV seroprevalences for the 12–19-year and 20–29-year age groups were significantly higher for non-Hispanic blacks (OR, 1.6 [95% CI, 1.2–2.1] and 4.1 [95%

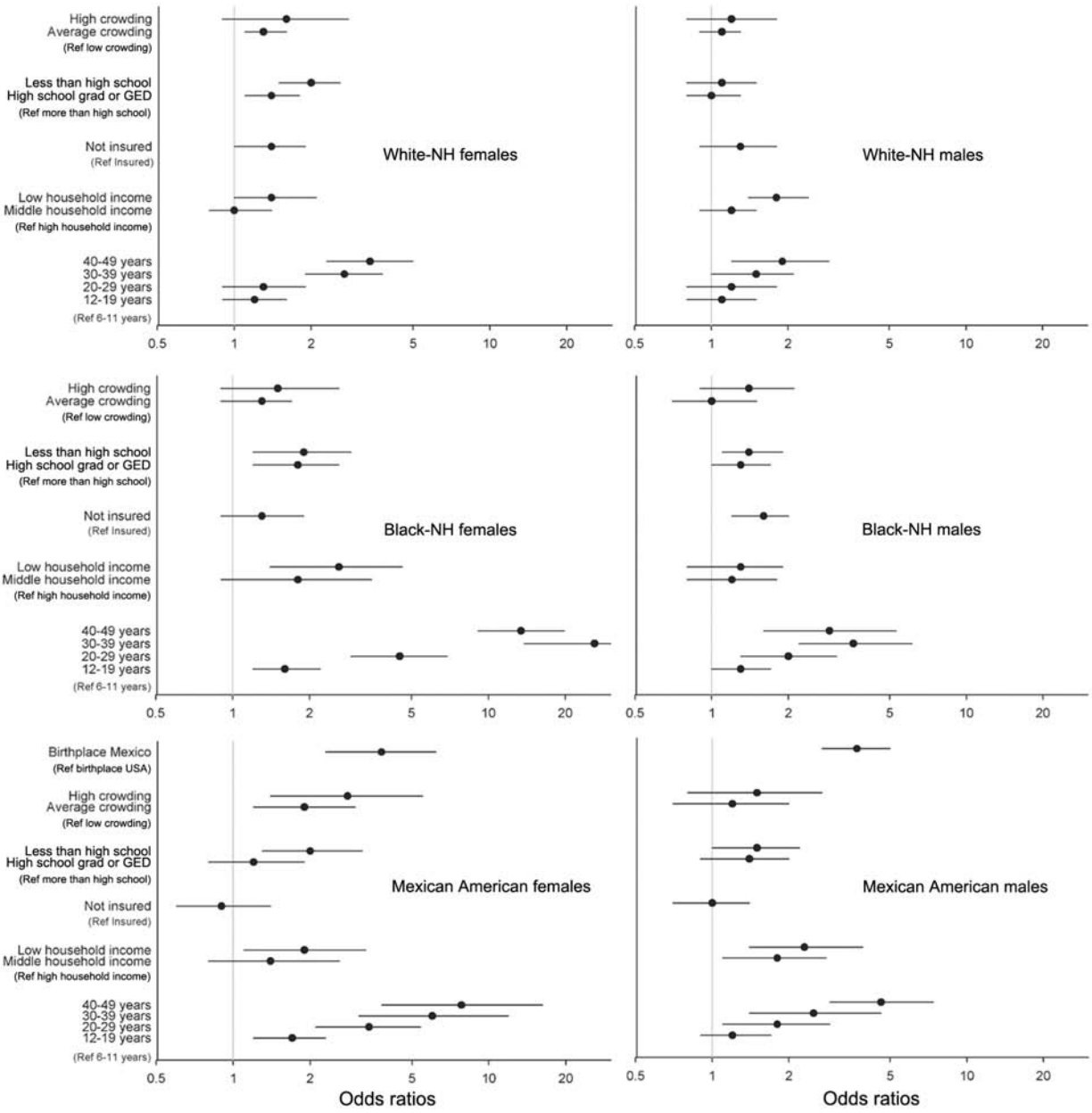

Figure 2. Factors associated with cytomegalovirus (CMV) seroprevalence in the United States: adjusted odds ratios and 95% confidence intervals (error bars) by sex and race/ethnicity, Health and Nutrition Examination Survey (NHANES) 1999–2004. Upper confidence limit for non-Hispanic (NH) black women aged 30–39 years was 49.2 but was truncated because of space constraints.

CI, 2.7–6.2], respectively) and Mexican Americans (OR, 1.6 [95% CI, 1.2–2.2] and 3.2 [95% CI, 2.1–4.9], respectively), whereas CMV prevalences were not significantly higher by age group among non-Hispanic whites until the 30–39-year age group (OR, 2.7; 95% CI, 1.9–3.7). Among non-Hispanic blacks, a strong association with CMV seropositivity (OR, 21.3; 95% CI, 11.7–38.9) occurred in the 30–39-year age category (compared with 6–11-year-olds). Examination of estimates by sex and race indicated that this was due to a strong association for women (OR, 26.0; 95% CI, 13.8–49.2) rather than men (OR, 3.6; 95% CI, 2.2–6.1) (Figure 2); CMV seroprevalences were 76.6% and 94.6% for non-Hispanic black women aged 20–29 years and 30–39 years, respectively, whereas seroprevalences were 62.4% and 74.5% for non-Hispanic black men of the corresponding age groups (Figure 1).

Household education level was significantly associated with CMV seropositivity for females of all 3 race/ethnicities and non-Hispanic black males (Figure 2). Those with an education level

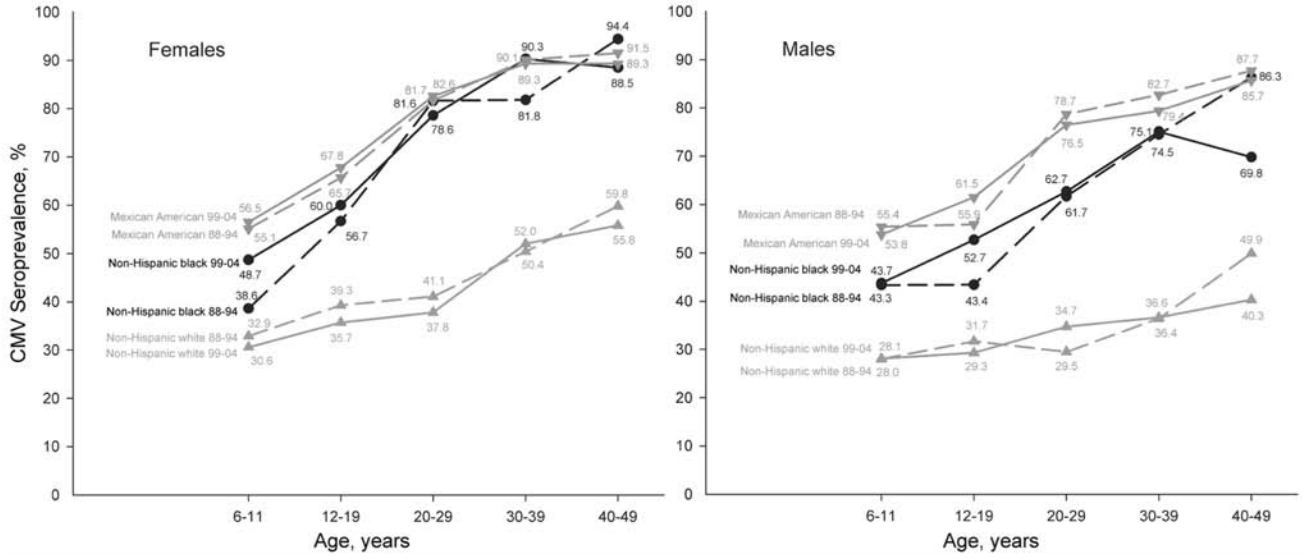

Figure 3. Differences in predictive margins (multivariate adjusted cytomegalovirus [CMV] seroprevalences) in the United States between Health and Nutrition Examination Survey (NHANES) 1988–1994 (*dashed lines*) and NHANES 1999–2004 (*solid lines*), stratified by age, sex, and race/ethnicity. GED, Graduate Educational Development diploma; NH, non-Hispanic; Ref, reference.

of less than high school had higher CMV prevalences than those with an education level of more than high school (57.8% vs 42.3% for non-Hispanic white females, 81.5% vs 72.7% for non-Hispanic black females, 83.4% vs 73.9% for Mexican American females, and 66.3% vs 58.6% for non-Hispanic black males). Household crowding was significantly associated with CMV seropositivity only for Mexican American females (69.4% for the low crowding group, 78.6% for the average crowding group, and 83.6% for the high crowding group) and for 1 of the group comparisons for non-Hispanic white females (48.3% for the average crowding group and 42.1% for the low crowding group). Nevertheless, for all sex and racial or ethnic groups, the ORs were greater than 1 and increased as the level of crowding increased (Figure 2). Low household income level was significantly associated with CMV seropositivity for all race and sex groups except non-Hispanic black males (Figure 2). Conversely, non-Hispanic black males were the only race-sex group for which not having insurance was a significant risk factor for CMV seropositivity (Figure 2). Mexican Americans born in Mexico had higher CMV prevalences compared with those born in the United States (OR for females, 3.8; 95% CI, 2.3–6.2; OR for males, 3.7; 95% CI, 2.7–5.0). For non-Hispanic whites and non-Hispanic blacks, sample sizes for the "other" birthplace category were too small to make any inferences about an association with CMV seropositivity.

Comparison of 1988–1994 and 1999–2004 data. The overall age-adjusted seroprevalence of CMV did not change significantly from 1988–1994 to 1999–2004 (50.8% and 50.4%, respectively) (Table 1). After stratifying by sex and race/ethnicity, there were a handful of statistically significant changes in CMV seroprevalence among certain levels of age and household income, but no consistent patterns were observed. For non-Hispanic whites, no significant differences were observed for females; for males, the multivariate-adjusted CMV seroprevalences among 40–49-year-olds decreased between 1988–1994 and 1999–2004 (from 49.9% to 40.3%). For non-Hispanic black females, statistically significant increases occurred among 6–11-year-olds (from 38.6% to 48.7%) and 30–39-year-olds (from 81.8% to 90.3%), and a decrease occurred among 40–49-year-olds (from 94.4% to 88.5%) (Figure 3). For non-Hispanic black males, an increase in multivariate-adjusted CMV seroprevalence was observed among 12–19-year-olds (from 43.4% to 52.7%); also, as with non-Hispanic black females, a decrease occurred at the 40–49-year age level (from 86.3% to 69.8%) (Figure 3). For Mexican Americans, the only significant difference between 1988–1994 and 1999–2004 was an increase in age-adjusted CMV seroprevalence among males and females within the middle household income level (from 70.9% to 75.2%).

DISCUSSION

CMV seroprevalence across most age, sex, and racial/ethnic groups in the United States showed few changes between 1988–1994 and 1999–2004. Given this relative lack of temporal trends, differences in CMV seroprevalence by age approximate seroconversion rates among persons moving from one age group to the next. Thus, we can conclude that among the substantial proportion of US women who are CMV seronegative as they enter their reproductive years, many experience

seroconversion. For example, of the ~45% of non-Hispanic black women who are CMV seronegative during their teen years, nearly all (~8 of 9) seroconvert by the time they are in their 30s. Approximately one-half of CMV-seronegative Mexican American women and one-fourth of CMV-seronegative non-Hispanic white women also seroconvert during the same period. This means that many women are at risk of experiencing a primary CMV infection during pregnancy, which is associated with a higher risk of congenital infection [8] and permanent damage to the child [21].

Such risk highlights the urgent need for interventions, such as a vaccine, which can reduce the likelihood of adverse outcomes, such as maternal infection, congenital infection, or childhood disability. Although no licensed vaccines are currently available, a number are in various stages of development, including a gB subunit vaccine that showed efficacy in a recent phase 2 trial [22]. Several target populations have been proposed for future vaccines, including women of reproductive age [22], preadolescents [23], and children [24]. Our study shows that all of these groups contain large proportions of CMV-seronegative individuals who could be protected from CMV infection by vaccination.

Sex, race or ethnicity, country of origin, and factors associated with low socioeconomic status, such as crowding and low household income, were all independently associated with and substantially affected CMV seropositivity. These multiple associations are not surprising, given the multiple ways that CMV can be transmitted. The main transmission routes for CMV infection are breast-feeding [5, 25], close contact with young children [26–31], and intimate contact with adults (ie, kissing or sexual intercourse) [27, 32, 33]. The chance of becoming infected depends primarily on 2 factors: the frequency of these contacts and the likelihood that any given contact will be with a person who is shedding CMV in their bodily fluids. These factors differ for each of the main transmission routes and change during a lifetime, making it difficult to precisely explain what drives CMV seroprevalence results and what accounts for racial or ethnic differences. For instance, possible explanations include breast-feeding rates, household demographic factors and child care arrangements, and sexual behaviors and networks, all of which differ substantially by race or ethnicity [34–39]. However, there is no clear correlation between these racial/ethnic variations in exposure to prominent CMV transmission modes and the likelihood of being CMV seropositive. Thus, although this study is useful for identifying at-risk populations, it is less able to assess the relative importance of different modes of CMV transmission.

The major strengths of this study are that it was nationally representative, reported a current estimate of CMV seroprevalence in the United States, and assessed time trends in the US population as a whole. The major limitation was its cross-sectional design (both NHANES III and NHANES 1999–2004 were cross-sectional samples), which does not allow for the definitive detection of a birth cohort effect. However, comparison of data between 1988–1994 and 1999–2004 indicated that with the exception of some minor changes in CMV seroprevalences in the oldest age group, CMV seroprevalences were relatively constant between individuals of the same age who were born ~10 years apart, suggesting that any birth cohort effect was minimal and that incidence has not changed substantially in the recent past. Also, a cross-sectional design does not reveal when seropositive individuals became infected with CMV. Furthermore, the time-dependent variables, such as crowding or household income level, were measured at only one point in time (ie, the time of the NHANES survey). Thus, it was impossible to determine whether the exposures of interest occurred at a time that was relevant to the CMV infection.

In summary, many women of reproductive age in the United States are still at risk of primary CMV infection during pregnancy. As a result, there is an urgent need for vaccine development and other clinical and public health interventions that can benefit children and their families. The substantial disparities in CMV risk among seronegative women suggest that prevention strategies should include an emphasis on reaching racial or ethnic minorities and women of low socioeconomic status.

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