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BRIEF REPORT

Changes in Cytomegalovirus Seroprevalence Among U.S. Children Aged 1–5 Years: The National Health and Nutrition Examination Surveys

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Data from the cross-sectional National Health and Nutrition Examination Surveys (NHANES) indicate that the seroprevalence of cytomegalovirus immunoglobulin G (IgG) antibodies among US children aged 1–5 years was 20.7% (95% confidence interval [CI]: 14.0, 29.0) in 2011–2012 and 28.2% (95% CI: 23.1–34.0) in 2017–2018 (adjusted prevalence difference, +7.6% [95% CI: −.4, +15.6]).

Keywords. cytomegalovirus; CMV; childhood vaccination; NHANES.

Cytomegalovirus (CMV) is a common virus that can cause a life-long infection. Although primary CMV infection is generally asymptomatic, chronic CMV infection has been associated with inflammation and increased risk of mortality [1]. CMV infection also causes significant morbidity and mortality in immunocompromised populations [2]. Furthermore, congenital CMV due to primary acquisition, reactivation, or reinfection during pregnancy is the most common congenital infection in the United States, often resulting in permanent disability [3].

CMV shedding occurs in saliva, urine, semen, cervicovaginal secretions, and breast milk, leading to a variety of transmission routes [4]. Among CMV-seropositive individuals in the general population, the prevalence of CMV shedding has been shown to be highest in 1–2 years old children, decreasing with older age into adulthood [5]. Contact with young children is considered an important source of infection for adolescents and adults, including pregnant women. Consequently, the seroprevalence of CMV in young children has implications for the risk of CMV infection in adolescents and adults [4]. Young children are also considered a potential target population for CMV vaccination [6].

The National Health and Nutrition Examination Survey (NHANES) has been a primary mode of national surveillance for CMV infection in the United States. In the 2011–2012 NHANES, 20.7% of children aged 1–5 years old had CMV immunoglobulin G (IgG) antibodies—indicative of prior exposure to CMV [6]. Recent estimates of CMV seroprevalence among children in the US population are not available. Using data from NHANES, we describe temporal changes in the seroprevalence of CMV antibodies from 2011 to 2012 to 2017–2018 among US children aged 1–5 years.

METHODS

Data Source

This study uses data from the continuous NHANES, which is conducted by the National Center for Health Statistics (NCHS). NHANES uses a stratified, multistage probability sampling design to create a cross-sectional sample that is nationally representative of the noninstitutionalized, civilian US population. The survey includes in-person household interviews and a follow-up visit to a medical examination center (MEC) where blood samples are collected. Stored serum specimens from children aged 1–5 years in 2011–2012 and in 2017–2018 were assessed for the presence of CMV IgG antibodies. This analysis was conducted among children aged 1–5 years who participated in the medical examination and had valid data on anti-CMV IgG serostatus in 2011–2012 or 2017–2018 [7]. Among children aged 1–5 years, the unconditional response rate for the medical examination was 77.6% in 2011–2012 and 55.2% in 2017–2018 [8].

Laboratory Testing

The presence of IgG antibodies to CMV was assessed using the VIDAS enzyme linked fluorescent immunoassay (Biomerieux, France) [6, 9]. Specimens with indeterminate results were considered invalid and treated as missing data.

Statistical Analysis

Data analysis was conducted using the "survey" package in R statistical software, version 3.6.1 [10]. Unless specified otherwise, analyses incorporated NCHS-derived medical examination survey weights, which account for differential sampling

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probabilities and nonresponse to the medical examination. Taylor series linearization was used to estimate standard errors. Korn and Graubbard 95% confidence intervals (CI) were estimated for prevalence estimates.

For each time period (2011–2012 and 2017–2018), seroprevalence of anti-CMV IgG was estimated overall and within subgroups described by age, sex, race/ethnicity, the presence of other children 5 years or younger in the household, poverty status, household reference person's education level, and exposure to breast milk. Logistic regression was used to calculate crude and adjusted predicted margins of anti-CMV IgG seroprevalence in 2011–2012 and 2017–2018; the absolute difference in the predicted margins is presented as a prevalence difference (average marginal effect). To obtain subgroup prevalence difference estimates, separate models were used that included interaction terms between time period and each covariate to obtain the strata-specific average marginal probability. The average marginal effects are the average change in predicted probability of CMV over time for each characteristic, treating all observations as if they had that particular characteristic of interest. Adjusted prevalence differences between time periods were estimated controlling for all sociodemographic and behavioral factors previously described. A secondary analysis was conducted to examine factors associated with seroprevalence of anti-CMV IgG in 2017–2018. For this analysis, crude and adjusted prevalence ratios (PR) were calculated from the predicted margins estimated by logistic regression [11].

Sensitivity Analyses. Because place of birth is a known predictor of CMV infection, but the sample size of foreign-born children was too small to examine, we replicated the analysis restricted to US-born children. Additionally, because there were missing data for several variables including anti-CMV IgG serostatus (Table S1), a sensitivity analysis was performed using multiple imputation by chained equations to handle missing data (Supplemental Material).

Ethics Statement

Data collection was approved by the NCHS Research Ethics Board, and parental consent was obtained. The analysis was conducted using de-identified publicly available data and was waived from review by Johns Hopkins University School of Medicine Institutional Review Board.

RESULTS

Of 1135 children aged 1–5 years examined in 2011–2012, 699 had a serum sample available to be tested for anti-CMV IgG and 698 had a valid result. In 2017–2018, there were 931 age-eligible examinees, of which 607 had a serum sample available to be tested for anti-CMV IgG and 606 had a valid result. Characteristics of the study population are shown in Table S1. In both survey periods, excluded participants due to missing data on anti-CMV IgG were more likely to be of younger age. For instance, in 2017–2018, 15.6% of included participants were 1-year-olds, whereas 26.3% of participants excluded due to missing anti-CMV IgG data were 1-year-olds.

Between 2011–2012 and 2017–2018, the overall anti-CMV IgG seroprevalence among children aged 1–5 years increased from 20.7% (95% CI = 14.0–29.0) to 28.2% (95% CI = 23.1–34.0) (Table 1). The adjusted prevalence difference in anti-CMV IgG seroprevalence by survey period was +7.6% (95% CI = −.4%, +15.6%). There were notable increases in anti-CMV IgG seroprevalence over time among various subgroups, including 1-year-olds, non-Hispanic Whites, children living above the poverty level, and being the only child <5 years in the household. Similar estimates were obtained in sensitivity analyses restricted to US-born children (Table S2) and following multiple imputation (Table S3). The overall adjusted prevalence difference by survey period was +8.2% (95% CI = +.4%, +16.1%) when using multiply imputed data.

In 2017–2018, anti-CMV IgG seroprevalence was associated with previous exposure to breast milk (vs. never; crude-PR = 2.2 [95% CI = 1.2, 4.0]) (Table 1). Compared to non-Hispanic White children, anti-CMV IgG seroprevalence was higher among Hispanic children (crude-PR = 1.5 [95% CI = 1.2–1.9]). Statistically significant associations with anti-CMV IgG seroprevalence were not observed in multivariable analysis. However, in the sensitivity analysis of multiply imputed data, children in the non-Hispanic other/multiracial group were independently associated with anti-CMV IgG seroprevalence (adjusted-PR = 1.7 [95% CI = 1.1, 2.2]) (Table S3).

DISCUSSION

This study reports updated nationally representative estimates of anti-CMV IgG seroprevalence among young children in the United States. A increase in anti-CMV IgG seroprevalence was observed between 2011–2012 and 2017–2018 among 1-year-olds and non-Hispanic White children. To our knowledge, this observed increase in CMV seroprevalence among US children in recent years has not been previously documented. Additional surveillance is needed to validate these findings given the public health consequences of CMV infection.

Factors associated with anti-CMV IgG seroprevalence in 2017–2018 were generally consistent with the literature in that ethnic/racial minority groups had a higher seroprevalence of CMV, as well as exposure to breast milk and other children <5 years old [4]. However, because CMV seroprevalence increased over time among children at or above the poverty level although remaining consistent among those below poverty, there was no longer an association between poverty and CMV seroprevalence in 2017–2018. Future studies will need to examine more refined measures of socioeconomic status and

Table 1. Seroprevalence of Anti-Cytomegalovirus Immunoglobulin G (IgG) Among Children Aged 1–5 Years in the United States by Survey Period, the National Health and Nutrition Examination Surveys, 2011–2012 and 2017–2018.

Characteristic	2011–2012[a]	2017–2018[a]	2017–2018 vs 2011–2012		2017–2018	
	Prevalence, % (95% CI)	Prevalence, % (95% CI)	PD (95% CI)[b]	aPD (95% CI)[c]	PR (95% CI)[d]	aPR (95% CI)[e]
Overall	20.7 (14.0, 29.0)	28.2 (23.1, 34.0)	7.5 (−1.0, 16.0)	7.6 (−0.4, 15.6)	…	…
Age, y						
1	12.3 (6.4, 20.6)	23.3 (16.4, 31.5)	**11.1 (1.6, 20.5)**	**12.7 (2.5, 23.0)**	1	1
2–3	20.0 (11.7, 30.7)	24.5 (16.2, 34.4)	4.4 (−7.5, 16.4)	6.4 (−5.3, 18.1)	1.0 (.6, 1.5)	1.0 (.6, 1.5)
4–5	24.2 (16.6, 33.2)	33.9 (24.0, 44.9)	9.7 (−2.6, 22.0)	6.9 (−5.6, 19.4)	1.5 (.8, 2.1)	1.3 (.7, 1.9)
Sex						
Male	19.9 (12.8, 28.7)	26.5 (19.2, 34.8)	6.6 (−3.7, 16.9)	7.2 (−2.1, 16.5)	1	1
Female	21.7 (14.2, 30.9)	30.0 (23.4, 37.4)	8.4 (−1.7, 18.4)	8.0 (−2.4, 18.4)	1.1 (.8, 1.5)	1.1 (.6, 1.5)
Race/ethnicity						
Non-Hispanic White	10.6 (2.5, 26.7)[f]	24.2 (19.0, 30.1)	**13.7 (2.8, 24.5)**	**15.1 (5.3, 24.8)**	1	1
Non-Hispanic Black	24.6 (19.6, 30.2)	15.9 (9.0, 25.1)	**−8.8 (−17.0, −.6)**	−11.9 (−23.8, .1)	0.7 (.3, 1.0)	0.7 (.3, 1.1)
All Hispanic	31.0 (25.9, 36.5)	36.7 (24.8, 49.9)	5.7 (−6.4, 17.8)	3.0 (−8.9, 14.9)	**1.5 (1.2, 1.9)**	1.3 (1.0, 1.7)
Non-Hispanic other/multiracial	37.0 (22.6, 53.2)[g]	40.0 (26.4, 54.9)	3.1 (−15.9, 22.0)	3.0 (−14.8, 20.9)	1.7 (.9, 2.4)	1.5 (.8, 2.3)
Family income to poverty ratio						
Below poverty level (<1.0)	31.1 (23.8, 39.2)	26.4 (16.3, 38.6)	−4.8 (−17.2, 7.7)	−3.7 (−14.7, 7.3)	1	1
At or above poverty level (≥1.0)	14.9 (8.2, 24.1)	27.6 (22.9, 32.6)	**12.6 (4.1, 21.1)**	**13.1 (4.0, 22.2)**	1.0 (.7, 1.4)	1.1 (.7, 1.6)
Household reference person's education						
Less than HS diploma	31.3 (24.4, 38.8)	37.2 (24.7, 51.1)	5.9 (−7.7, 19.6)	5.5 (−7.2, 18.2)	1	1
GED, HS diploma, associate degree, some college	16.7 (11.0, 23.9)	22.6 (17.0, 29.0)	5.9 (−2.2, 14.0)	5.0 (−3.5, 13.4)	0.6 (.4, .8)	0.6 (.3, .9)
College degree or more	17.8 (6.1, 36.7)[f,g]	34.7 (24.7, 45.7)	**16.8 (.2, 33.4)**	14.6 (−3.4, 32.7)	0.9 (.5, 1.4)	0.8 (.3, 1.3)
Other children 5 years old or under in household						
No	15.4 (10.7, 21.2)	24.7 (18.9, 31.3)	**9.3 (1.8, 16.8)**	**11.3 (4.0, 18.5)**	1	1
Yes	25.7 (16.1, 37.4)	31.5 (23.5, 40.4)	5.8 (−6.8, 18.3)	4.2 (−7.9, 16.4)	1.3 (.8, 1.7)	1.1 (.7, 1.5)
Breast milk exposure						
Never fed breast milk	16.5 (11.4, 22.8)	16.6 (9.1, 26.7)	0.0 (−9.3, 9.3)	2.5 (−7.5, 12.6)	1	1
Ever fed breast milk	22.0 (13.7, 32.3)	30.7 (25.1, 36.8)	8.7 (−1.4, 18.8)	8.9 (−.3, 18.0)	1.9 (1.0, 2.7)	1.7 (.9, 2.5)

All data are weighted using Medical Examination Center (MEC) survey weights provided by the National Center for Health Statistics.

Abbreviations: aPD, adjusted prevalence difference; aPR, adjusted prevalence ratio; CI, confidence interval; GED, general education development (high school equivalency certificate); HS, high school; IgG, immunoglobin G; PD, prevalence difference; PR, prevalence ratio.

[a]Data are weighted prevalence estimates of anti-CMV IgG seroprevalence (%) with corresponding Korn and Graubard 95% CIs.

[b]Crude prevalence differences (average marginal effect of each category) and corresponding 95% CIs were estimated from survey-weighted multivaraiate logistic regression models which included a term for the interaction of time and the variable of interest, the main effect of time and the variable of interest. Crude prevalence difference (average marginal effect of each category) and corresponding 95% CIs for time were estimated from a univariable model with a term for time.

[c]Adjusted prevalence differences (average marginal effect of each category) and corresponding 95% CIs in CMV prevalence were estimated by survey-weighted multivariable logistic regression models, which included a term for the interaction of time and the variable of interest, the main effect of time and the variable of interest, and adjustment for all other variables shown.

[d]Crude prevalence ratios (average marginal effect of each category) and corresponding 95% CIs were estimated from survey-weighted univariable logistic regression.

[e]Adjusted prevalence ratios (average marginal effect of each category) and corresponding 95% CIs in CMV prevalence were estimated by survey-weighted multivariable logistic regression models adjusting for all other variables shown.

[f]Relative CI width >130%. Estimate is considered unstable and should be interpreted with caution.

[g]Absolute CI width >30%. Estimate is considered unstable and should be interpreted with caution.

assess its impact on CMV risk, given that socioeconomic status has historically been associated with CMV infection in the United States [4]. Other factors believed to be determinants of CMV transmission that were not examined in this study, such as day care attendance, also warrant further investigation.

NHANES is a well-established survey that allows the calculation of nationally representative estimates. However, this study may be subject to selection bias. The unit nonresponse rate for participation in NHANES has been decreasing over time [12]. NCHS investigated the potential effects of increasing nonresponse in NHANES and found that nonresponse did not substantially bias prevalence estimates. However, their analysis only looked at overall age subpopulations, and therefore nonresponse bias among other subgroups, such as by race/ethnicity and income, cannot be ruled out. Although weights were incorporated to correct for differential sampling probabilities, oversampling procedures changed between 2011–2012 and 2017–2018 [7]. Non-Hispanic White and other/multiracial participants that were ≤130% of the federal poverty level were oversampled in 2011–2012, whereas non-Hispanic White and other/multiracial participants who were ≤185% of the federal poverty level were oversampled in 2017–2018. Finally, this study had a significant

degree of missing data on anti-CMV serostatus, although estimates were consistent following multiple imputation.

In the United States, congenital CMV infection occurs in approximately 1 out of every 150 live births and annually causes >5000 children to be born with disability [3]. Previous research has highlighted the extensive potential benefits of vaccination, deeming CMV vaccine development a high priority [2]. The updated CMV prevalence estimates as well as the evidence of a possible increase in seroprevalence among young children may help inform the implementation of interventions aimed at prevention as well as informing epidemiological models.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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