

# Trends in Herpes Simplex Virus Type 1 and Type 2 Seroprevalence in the United States

Fujie Xu, MD, PhD

Maya R. Sternberg, PhD

Benny J. Kottiri, PhD

Geraldine M. McQuillan, PhD

Francis K. Lee, PhD

Andre J. Nahmias, MD

Stuart M. Berman, MD, ScM

Lauri E. Markowitz, MD

**H**ERPES SIMPLEX VIRUS TYPE 2 (HSV-2) is the cause of most genital herpes and is one of the most prevalent sexually transmitted infections worldwide.<sup>1-3</sup> Herpes simplex virus type 1 (HSV-1) is typically transmitted during childhood via nonsexual contact.<sup>4</sup> Most HSV-1 and HSV-2 infections are subclinical. When infection is symptomatic, the clinical manifestations of HSV-2 are typically characterized by recurrent, painful vesicular and ulcerative lesions in the genital and anal areas.<sup>3-5</sup> In contrast, symptomatic HSV-1 infections are usually manifested as recurrent orolabial and facial lesions.<sup>3</sup> However, HSV-1 has emerged as a principle causative agent of genital herpes in some developed countries.<sup>6-9</sup> In the United States, HSV-1 is an important cause of genital herpes and its importance is increasing in college students and other selected populations.<sup>10-13</sup> Both HSV-1 and HSV-2 can also cause infrequent but serious diseases such as blindness, encephalitis, and neonatal infections.<sup>4</sup>

Strong synergy has been found between HSV-2 and human immunodeficiency virus (HIV).<sup>14-17</sup> Infection with HSV-2 can at least double the risk for

**Context** Herpes simplex virus type 1 (HSV-1) and type 2 are common infections worldwide. Herpes simplex virus type 2 (HSV-2) is the cause of most genital herpes and is almost always sexually transmitted. In contrast, HSV-1 is usually transmitted during childhood via nonsexual contacts. Preexisting HSV-1 antibodies can alleviate clinical manifestations of subsequently acquired HSV-2. Furthermore, HSV-1 has become an important cause of genital herpes in some developed countries.

**Objective** To examine trends in HSV-1 and HSV-2 seroprevalence in the United States in 1999-2004 compared with 1988-1994.

**Design, Settings, and Participants** Cross-sectional, nationally representative surveys (US National Health and Nutrition Examination Surveys [NHANES]), were used to compare national seroprevalence estimates from 1999-2004 with those from 1988-1994, and changes in HSV-1 and HSV-2 seroprevalence since 1976-1980 were reviewed. Persons aged 14 to 49 years were included in these analyses.

**Main Outcome Measures** Seroprevalence of HSV-1 and HSV-2 antibodies based on results from type-specific immunodot assays; diagnosis of genital herpes.

**Results** The overall age-adjusted HSV-2 seroprevalence was 17.0% (95% confidence interval [CI], 15.8%-18.3%) in 1999-2004 and 21.0% (95% CI, 19.1%-23.1%) in 1988-1994, a relative decrease of 19.0% between the 2 surveys (95% CI, -28.6% to -9.5%;  $P < .001$ ). Decreases in HSV-2 seroprevalence were especially concentrated in persons aged 14 to 19 years between 1988 and 2004. In adolescents aged 17 to 19 years and young adults, the decreases in HSV-2 seroprevalence were significant even after adjusting for changes in sexual behaviors. Among those infected with HSV-2, the percentage who reported having been diagnosed with genital herpes was statistically different (14.3% in 1999-2004 and 9.9% in 1988-1994;  $P = .02$ ). Seroprevalence of HSV-1 decreased from 62.0% (95% CI, 59.6%-64.6%) in 1988-1994 to 57.7% (95% CI, 55.9%-59.5%) in 1999-2004, a relative decrease of 6.9% between the 2 surveys (95% CI, -11.6% to -2.3%;  $P = .006$ ). Among persons infected with HSV-1 but not with HSV-2, a higher percentage reported having been diagnosed with genital herpes in 1999-2004 compared with 1988-1994 (1.8% vs 0.4%, respectively;  $P < .001$ ).

**Conclusions** These data show declines in HSV-2 seroprevalence, suggesting that the trajectory of increasing HSV-2 seroprevalence in the United States has been reversed. Seroprevalence of HSV-1 decreased but the incidence of genital herpes caused by HSV-1 may be increasing.

JAMA. 2006;296:964-973

www.jama.com

sexually acquired HIV infection because recurrent genital herpes can provide a port of entry for HIV and recruit HIV target cells to the sites of epithelial infection.<sup>18,19</sup> Infection with HSV-2 may accelerate HIV progression and increase the infectiousness of HIV, thus enhancing sexual transmission of HIV.<sup>20-22</sup> Monitoring HSV-2 seroprevalence may help direct HIV pre-

vention efforts to populations at greater risk of acquiring or transmitting HIV infection.

**Author Affiliations:** Centers for Disease Control and Prevention, Atlanta, Ga (Drs Xu, Sternberg, Kottiri, McQuillan, Berman, and Markowitz); and Department of Pediatrics, Emory University School of Medicine, Atlanta, Ga (Drs Lee and Nahmias).

**Corresponding Author:** Fujie Xu, MD, PhD, Mailstop E-02, Centers for Disease Control and Prevention, 1600 Clifton Rd, Atlanta, GA 30333 (fax1@cdc.gov).

Changes in HSV-1 seroprevalence can alter the clinical manifestations of subsequently acquired HSV-2 infection. Compared with persons seropositive for HSV-1, those persons lacking HSV-1 antibodies are almost 3 times more likely to have a symptomatic HSV-2 infection.<sup>13,23</sup> Seroprevalence of HSV-1 may also influence decisions about HSV-2 vaccination strategies because the vaccine that is being clinically tested may be efficacious only in those seronegative for HSV-1.<sup>24</sup>

Serosurveys have been one of the best approaches to study the epidemiology of HSV infections. In the United States, data from National Health and Nutrition Examination Surveys (NHANES) during 1976-1980 (NHANES II) and 1988-1994 (NHANES III) indicated that the overall seroprevalence of HSV-2 increased by 30%,<sup>25</sup> while the overall HSV-1 seroprevalence was unchanged.<sup>26</sup> We examined national trends in HSV-1 and HSV-2 seroprevalence in the 1999-2004 survey compared with the 1988-1994 survey.

## METHODS

### Study Population and Survey Design

The NHANES are a series of cross-sectional national surveys conducted by the National Center for Health Statistics. Details of the survey methods have been published previously.<sup>27</sup> Briefly, during each survey, a random sample of the US civilian, noninstitutionalized population was selected using a complex, stratified, multistage probability sample design. Some populations, such as adolescents, non-Hispanic blacks, and Mexican Americans were oversampled. Persons selected for the surveys were interviewed and underwent a health examination. In 1999, the NHANES was redesigned to become a continuous survey using otherwise similar methods. A nationally representative sample of the US civilian, noninstitutionalized population is selected each year and usually data from 2 or more years are combined to achieve adequate sample sizes for analyses. Seroprevalence of HSV has

been part of NHANES since 1988-1994 but national HSV seroprevalence was first estimated using leftover sera samples from 1976-1980.

For 1999-2004, sex was defined as vaginal, oral, or anal. In contrast, the term *sexual intercourse* was used in 1988-1994. In addition, questionnaires were administered using audio computer-assisted self-interview in 1999-2004 instead of face-to-face interview in 1988-1994. A question about history of diagnosed genital herpes was asked for persons aged 18 years or older ("Has a doctor or other health care professional ever told you that you had genital herpes?").

Our analyses focused on the trends in HSV-1 and HSV-2 seroprevalence between 1988-1994 and 1999-2004. About 10.5 years separates the midpoint between the 2 surveys. The common age groups for the surveys are persons aged 14 to 49 years. Of the persons aged 14 to 49 years who were selected for the NHANES in 1988-1994, 84% were interviewed, 78% were examined, and 61% were tested for HSV-1 and HSV-2. For 1999-2004, the corresponding numbers were 82%, 78%, and 72%, respectively.

The NHANES survey for 1999-2004 was approved by the institutional review board of the US Centers for Disease Control and Prevention. Informed consent was obtained from survey participants or their legal guardians.

### Laboratory Methods

Purified glycoproteins specific for HSV-1 (gG-1) or HSV-2 (gG-2) were used as antigens to detect type-specific antibodies using solid-phase enzymatic immunodot assays.<sup>28,29</sup> The performance of the immunodot assays is high with respect to sensitivity and ability to discriminate between HSV-1 and HSV-2.<sup>28-30</sup> In 1999-2004, the same immunodot assays and the same laboratory were used as for previous NHANES.<sup>25,26</sup>

### Statistical Analyses

SUDAAN software version 9.0 (Research Triangle Institute, Cary, NC) was used for statistical analyses to

account for the complex survey design. We estimated HSV-1 and HSV-2 seroprevalence by age, sex, and race/ethnicity according to NHANES design domains. Confidence intervals (CIs) for the seroprevalence estimates were calculated based on a log transformation with the SE calculated using the  $\Delta$  method.<sup>31</sup> Differences in seroprevalence between the surveys were considered to be statistically significant if the 2-sampled *t* test had a *P* value of less than .05.<sup>32</sup>

Race/ethnicity categories were nearly identical between 1988-1994 and 1999-2004<sup>33</sup> and were defined by self-report as non-Hispanic black, non-Hispanic white, and Mexican American. Persons who did not fit into these categories were classified as *other* and were included in the total population. The race categories used for 1976-1980 were white, black, and other. To permit comparisons between the 3 surveys, participants who reported Hispanic ancestry in the 1976-1980 survey were excluded from the white and black race categories.

All seroprevalence estimates were weighted to represent the US civilian, noninstitutionalized population and to account for oversampling and nonresponse to the interview and the medical examination.<sup>34</sup> Among participants aged 14 to 49 years who were interviewed and examined during 1999-2004, 8.6% did not have HSV serological results. The reasons for missing results may include refusal or unsuccessful venipuncture or the need to use serum for other tests. We investigated the impact of the missing serological results on HSV-1 and HSV-2 seroprevalence estimates by identifying significant demographic predictors of missing results through a weighted logistic regression model and used the model to further adjust the weights. The estimates using further adjusted weights changed slightly (changes in point estimates ranging from -1.3% to 0.6% for HSV-1 and -0.1 to 0.9% for HSV-2) but were within 95% CIs of seroprevalence estimates based on weights published by the National

Center for Health Statistics. Similar results were found from investigations into the missing HSV serological results in 1988-1994. These results convinced us to use weights from the National Center for Health Statistics in our analyses.

Logistic regression methods described by Korn and Barry<sup>35</sup> were used to examine whether differences in sociodemographic or sexual behavior between the survey participants might explain the observed changes in HSV-2 seroprevalence between 1988-1994 and

1999-2004. The survey indicator variable was forced into the model, and other variables were added in order of statistical significance. The criteria for inclusion and remaining in the model was based on the Satterthwaite-adjusted F-test *P* value of .10 or less. Once all variables that met the criteria had been included in the model, pairwise interactions were evaluated. Several significant interactions with sex led us to develop models separately for males and females. Variables that met the entry criteria in either model were included in the final models for both sexes. To facilitate interpretations, adjusted seroprevalence was calculated from the sex-specific logistic regression model using the PREDMARG statement in SUDAAN. The adjusted seroprevalence, also known as predictive margin, was generated using the logistic regression model to estimate the probability of being HSV-2 positive for every individual, averaging over the distribution of the covariates among the entire weighted sample.

**Table 1.** Weighted Herpes Simplex Virus 2 Seroprevalence for NHANES in 1999-2004

	Sample Size	HSV-2 Seroprevalence (95% CI)	<i>P</i> Value*
Overall	11 508	17.2 (15.9-18.7)	
Sex			
Male	5511	11.2 (9.9-12.8)	]<.001
Female	5997	23.1 (21.5-24.9)	
Race/ethnicity			
Non-Hispanic white	4311	13.7 (12.5-15.0)	]<.001
Non-Hispanic black	2926	40.3 (37.3-43.5)	
Mexican American	3406	11.9 (10.4-13.5)	
Other†	865	17.7 (14.2-22.1)	
Age group, y			
14-19	4650	1.6 (1.3-2.0)	]<.001
20-29	2412	10.6 (8.9-12.5)	
30-39	2251	22.1 (20.1-24.3)	
40-49	2195	26.3 (24.2-28.7)	
Marital status			
Never married	6154	10.3 (8.8-12.0)	]<.001
Living with partner	682	24.9 (20.9-29.6)	
Married	3595	16.8 (15.1-18.7)	
Divorced	486	35.9 (29.8-43.2)	
Separated	274	34.5 (28.5-41.9)	
Widowed	48	47.4 (27.1-83.0)	
Poverty index			
<Poverty level	2732	21.5 (18.7-24.7)	]<.001
≥Poverty level	7909	16.5 (15.2-17.9)	
Education			
<High school	5614	15.8 (14.0-17.7)	]<.14
High school	2211	17.7 (15.0-20.8)	
>High school	3675	17.8 (16.1-19.6)	
Ever used cocaine‡			
Yes	1052	28.6 (25.4-32.3)	]<.001
No	5911	14.7 (13.1-16.5)	
Age at first sex, y§			
≤17	5788	21.1 (19.5-22.9)	]<.001
≥18	2405	14.3 (12.6-16.3)	
Lifetime No. of sex partners			
0	2342	2.6 (1.4-5.0)	]<.001
1	1568	3.8 (2.6-5.7)	
2-4	2432	13.3 (11.4-15.6)	
5-9	1843	20.8 (18.5-23.5)	
10-49	1847	27.2 (25.0-29.6)	
≥50	284	39.9 (33.7-47.3)	

Abbreviations: CI, confidence interval; HSV-2, herpes simplex virus type 2; NHANES, National Health and Nutrition Examination Survey.

\*Calculated using  $\chi^2$  test.

†Includes all participants who do not belong to the 3 main racial/ethnic groups, such as those whose race/ethnicity was missing and persons who reported "multiracial."

‡Estimates from NHANES for 1999-2002 only. Drug use data have not been released from NHANES for 2003-2004.

§Defined as vaginal, oral, or anal.

||Estimates may be unreliable because the relative SE is large (SE/seroprevalence >30%).

## RESULTS

### Seroprevalence of HSV-2 in 1999-2004

In 1999-2004, the seroprevalence of HSV-2 among participants aged 14 to 49 years was 17.2% (95% CI, 15.9%-18.7%; TABLE 1). The seroprevalence was higher among females than among males (23.1% vs 11.2%;  $P<.001$ ). Seroprevalence of HSV-2 was 13.7% among non-Hispanic whites, 40.3% among non-Hispanic blacks, and 11.9% among Mexican Americans.

The overall HSV-2 seroprevalence increased rapidly with increasing age from 1.6% in participants aged 14 to 19 years to 26.3% in participants aged 40 to 49 years.

As reported in previous NHANES,<sup>25</sup> HSV-2 seroprevalence also varied significantly by a number of demographic and behavioral factors (Table 1). Seroprevalence of HSV-2 was higher among persons who were divorced, separated, or widowed; those living below the poverty level; who had ever used cocaine; and who had sex for the

first time at the age of 17 years or younger. Seroprevalence of HSV-2 was 3.8% in those who reported 1 lifetime sex partner. This prevalence increased to 39.9% in those who reported 50 or more lifetime partners. Seroprevalence of HSV-2 was higher in those who had a larger number of lifetime sexual partners (FIGURE 1). In non-Hispanic black women, however, the seroprevalence of HSV-2 was significantly higher compared with others who reported the same number of lifetime partners.

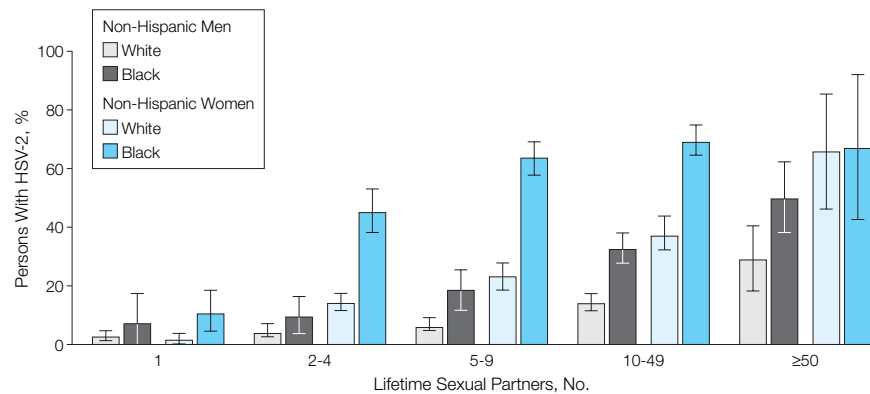
### Trends in HSV-2 Seroprevalence Between 1988-1994 and 1999-2004

The analyses included 9165 persons from the 1988-1994 survey and 11 508 persons from the 1999-2004 survey who were aged 14 to 49 years and had serum samples tested for HSV-2 (TABLE 2). Using the 2000 US Census civilian, noninstitutionalized population aged 14 to 49 years as the standard, the overall age-adjusted HSV-2 seroprevalence was 21.0% (95% CI, 19.1%-23.1%) in 1988-1994 and 17.0% (95% CI, 15.8%-18.3%) in 1999-2004, a relative decrease of 19.0% (95% CI, -28.6% to -9.5%) between the 2 surveys ( $P < .001$ ). Seroprevalence of HSV-2 decreased significantly in males, non-Hispanic whites, and Mexican Americans. The overall decreases in females and non-Hispanic blacks were not statistically significant.

The decrease in HSV-2 seroprevalence was concentrated in the younger age groups. The decreases were significant in all age groups except in participants aged 40 to 49 years (Table 2). Statistically significant decreases occurred in adolescents aged 14 to 19 years in both males and females and in all race/ethnicity groups. Based on the civilian, noninstitutionalized population counts from the 2000 US Census, there were 24 million adolescents aged 14 to 19 years in the United States; the decrease in HSV-2 seroprevalence from 5.8% to 1.6% corresponds to 1 million fewer infections in this age group alone.

Selected sexual behaviors between 1988-1994 and 1999-2004 were com-

**Figure 1.** Age-Adjusted Herpes Simplex Virus Type 2 Seroprevalence According to the Lifetime Number of Sex Partners, by Race/Ethnicity and Sex on NHANES in 1999-2004



Error bars indicate 95% confidence intervals; HSV-2, herpes simplex virus type 2; NHANES, National Health and Nutrition Examination Survey.

pared. Due to different ages at which sexual behavior questions were asked in the 2 surveys, the percentage who ever had sex were compared only in those aged 15 years or older and the number of lifetime sex partners were compared only in those aged 17 years or older. The percentage of participants aged 15 to 19 years who reported having had sex decreased from 59.6% in 1988-1994 to 54.8% in 1999-2004, a relative decrease of 8% ( $P = .05$ ); among participants aged 20 to 29 years, the decrease was 4% from 95.5% to 91.6% ( $P = .002$ ). Among those who had sex, the mean number of lifetime sex partners did not differ in participants aged 17 to 19 years but increased in those aged 20 to 49 years ( $P < .001$ ). Further analyses showed that this increase occurred only in females and was statistically significant in all 3 age groups from 20 through 49 years. The geometric mean number of sex partners in females aged 20 to 49 years increased from 3.3 (95% CI, 3.1-3.6) in 1988-1994 to 4.5 (95% CI, 4.2-4.7) ( $P < .001$ ).

The adjusted HSV-2 seroprevalence in males and females after controlling for differences in sociodemographics and/or sexual behaviors between the 2 surveys are presented in TABLE 3. The decrease in HSV-2 seroprevalence became significant in females but the overall decreases were still greater in males

(31.9%) than in females (19.4%) (Table 3). Adjusted HSV-2 seroprevalence significantly decreased in males younger than 40 years and in all female age groups with the exception of those aged 30 to 39 years. In males, the adjusted decreases were significant in non-Hispanic whites and Mexican Americans. In females, the adjusted decreases were significant among all 3 racial/ethnic groups.

### Trends in HSV-1 Seroprevalence Between 1988-1994 and 1999-2004

In 1999-2004, HSV-1 seroprevalence varied by age and race/ethnicity, similar to the previous report.<sup>26</sup> The overall age-adjusted seroprevalence of HSV-1 was 62.0% (95% CI, 59.6%-64.6%) in 1988-1994 and 57.7% (95% CI, 55.9%-59.5%) in 1999-2004, a relative decrease of 6.9% (95% CI, -11.6% to -2.3%;  $P = .006$ ; TABLE 4). When HSV-1 seroprevalence was compared by key demographic variables, changes ranging from -21.6% to 2.6% were observed (Table 4). Although the decreases were statistically significant in many groups, there was no concentration in any subpopulation defined by age, sex, or race/ethnicity.

Further analyses limited only to persons born in any of the 50 states in the United States or in Washington, DC,

were performed because birthplace can be an important determinant for HSV-1 acquisition during childhood. The corresponding age-adjusted seroprevalence was generally lower in persons born in the United States but the trend was similar to that in the total population. In US-born persons, HSV-1 sero-

prevalence decreased by 10% from 59.4% (95% CI, 56.8%-62.0%) in 1988-1994 to 53.3% (95% CI, 51.3%-55.4%) in 1999-2004 ( $P<.001$ ). As in the total US population, the decreases in HSV-1 seroprevalence in those born in the United States did not show a concentration in any subpopulations.

### Trends in HSV-1 and HSV-2 Coinfection Between 1988-1994 and 1999-2004

The seroprevalence of coinfection with HSV-1 and HSV-2 decreased from 14.6% in 1988-1994 to 10.5% in 1999-2004 ( $P<.001$ ). In contrast, the seroprevalence of HSV-2 only did not

**Table 2.** Changes in Weighted Herpes Simplex Virus 2 Seroprevalence in Persons Aged 14 to 49 Years Between NHANES in 1988-1994 and 1999-2004

	NHANES				
	1988-1994		1999-2004		Change, % (95% CI)
	Sample Size	HSV-2 Seroprevalence, % (95% CI)	Sample Size	HSV-2 Seroprevalence, % (95% CI)	
Overall*	9165	21.0 (19.1 to 23.1)	11 508	17.0 (15.8 to 18.3)	-19.0 (-28.6 to -9.5)†
Age group, y					
14-19	1787	5.8 (4.4 to 7.5)	4650	1.6 (1.3 to 2.0)	-72.4 (-81.5 to -63.3)†
20-29	2750	17.2 (14.9 to 19.8)	2412	10.6 (8.9 to 12.5)	-38.4 (-51.6 to -25.2)†
30-39	2567	27.8 (24.6 to 31.4)	2251	22.1 (20.1 to 24.3)	-20.5 (-32.4 to -8.6)†
40-49	2061	26.3 (23.1 to 30.1)	2195	26.4 (24.3 to 28.7)	0 (-15.3 to 15.3)
Sex by age group, y					
Male					
All ages*	4422	17.0 (14.6 to 19.7)	5511	11.2 (9.9 to 12.6)	-34.1 (-46.4 to -21.9)†
14-19	847	5.6 (3.9 to 8.0)	2368	0.9 (0.5 to 1.5)	-83.9 (-93.7 to -74.2)†
20-29	1332	12.1 (9.0 to 16.1)	1044	5.6 (4.0 to 7.9)	-53.7 (-73.9 to -33.5)†
30-39	1203	24.4 (20.5 to 29.1)	1005	14.5 (12.6 to 16.7)	-40.6 (-53.6 to -27.6)†
40-49	1040	20.2 (16.1 to 25.4)	1094	18.6 (15.7 to 21.9)	-7.9 (-33.3 to 17.4)
Female					
All ages*	4743	25.2 (23.2 to 27.3)	5997	22.8 (21.2 to 24.4)	-9.9 (-19.3 to 0)
14-19	940	5.9 (4.5 to 7.9)	2282	2.3 (1.7 to 3.2)	-61.0 (-77.4 to -44.6)†
20-29	1418	22.3 (19.5 to 25.5)	1368	15.6 (13.1 to 18.5)	-30.0 (-44.9 to -15.2)†
30-39	1364	31.2 (27.8 to 35.0)	1246	29.5 (26.6 to 32.7)	-5.4 (-19.7 to 8.8)
40-49	1021	32.6 (28.1 to 37.8)	1101	33.9 (31.1 to 37.1)	3.7 (-13.8 to 21.2)
Race/ethnicity by age group, y†					
Non-Hispanic white					
All ages*	2652	16.5 (14.4 to 18.9)	4311	13.0 (12.0 to 14.1)	-21.2 (-33.2 to -9.2)§
14-19	461	4.0 (2.6 to 6.4)	1220	1.0 (0.6 to 1.7)	-75.0 (-91.5 to -58.5)†
20-29	675	14.7 (11.8 to 18.2)	1042	6.4 (4.8 to 8.5)	-56.5 (-71.5 to -41.5)†
30-39	792	21.8 (18.5 to 25.8)	1070	18.0 (15.5 to 20.7)	-17.4 (-35.0 to 0.1)
40-49	724	19.6 (16.0 to 24.0)	979	20.7 (18.9 to 22.8)	5.6 (-17.1 to 28.3)
Non-Hispanic black					
All ages*	3007	43.2 (41.2 to 45.3)	2926	41.7 (38.5 to 45.1)	-3.9 (-12.5 to 4.7)
14-19	598	11.2 (8.0 to 15.5)	1470	5.0 (3.8 to 6.6)	-55.4 (-73.5 to -37.2)†
20-29	891	33.3 (29.9 to 37.1)	476	35.3 (29.9 to 41.8)	6.0 (-14.3 to 26.3)
30-39	884	54.2 (50.2 to 58.6)	460	53.5 (48.8 to 58.6)	-1.5 (-12.8 to 9.9)
40-49	634	59.0 (55.2 to 63.1)	520	56.2 (50.8 to 62.1)	-5.4 (-16.6 to 5.8)
Mexican American					
All ages*	3113	22.6 (20.4 to 25.0)	3406	13.6 (12.1 to 15.3)	-39.8 (-48.8 to -30.8)†
14-19	636	5.7 (3.9 to 8.4)	1658	0.9 (0.5 to 1.5)	-84.2 (-93.7 to -74.7)†
20-29	1072	14.8 (12.5 to 17.6)	678	7.9 (5.3 to 11.7)	-46.6 (-68.6 to -24.7)†
30-39	793	28.8 (26.2 to 31.8)	505	14.2 (11.2 to 18.0)	-51.0 (-63.0 to -39.1)†
40-49	612	32.8 (27.9 to 38.5)	565	25.2 (20.9 to 30.4)	-23.2 (-41.2 to -5.1)§

Abbreviations: CI, confidence interval; HSV-2, herpes simplex virus type 2; NHANES, National Health and Nutrition Examination Survey.

\*Age-adjusted using the 2000 US Census civilian, noninstitutionalized population aged 14 to 49 years as the standard.

† $P<.005$ .

‡For the 1988-1994 survey, 393 persons in the "other" race/ethnicity category were excluded; for the 1999-2004 survey, 865 persons in the "other" race/ethnicity category were excluded.

§ $P<.05$ .

change (6.4% in 1988-1994 and 6.7% in 1999-2004). As a result, the percentage of HSV-2 infected persons who lacked HSV-1 antibodies increased from 30.4% in 1988-1994 to 38.9% in 1999-2004 ( $P=.002$ ). There were no changes in the overall seroprevalence of HSV-1 only. However, the percentage of participants seronegative for both HSV-1 and HSV-2 increased from 32.0% in 1988-1994 to 35.4% in 1999-2004 ( $P=.02$ ). Among adolescents aged 14 to 19 years, the percentage of participants seronegative for both HSV-1 and HSV-2 increased from 52.8% in 1988-1994 to 60.2% in 1999-2004 ( $P=.002$ ).

### Trends in the Diagnosis of Genital Herpes

The overall percentage of survey participants who reported having been diagnosed with genital herpes did not change significantly between 1988-1994 and 1999-2004 (3.3% and 3.8%, respectively). However, among those who were HSV-2 seropositive, the percentage reporting a diagnosis of genital herpes increased from 9.9% in 1988-1994 to 14.3% in 1999-2004 ( $P=.02$ ). The percentage of persons having been diagnosed with genital herpes increased among those infected with HSV-2 only

and among those with both HSV-1 and HSV-2 but the differences between the 2 surveys did not reach statistical significance (FIGURE 2). In both 1988-1994 and 1999-2004, persons infected with HSV-2 only were significantly more likely to report having been diagnosed with genital herpes than those infected with both HSV-1 and HSV-2. In 1988-1994, 6.6% of those infected with both HSV-1 and HSV-2 had been diagnosed with genital herpes compared with 17.2% in those infected with HSV-2 only ( $P=.001$ ; Figure 2). Similarly, in 1999-2004, 11.0% of those infected with both HSV-1 and HSV-2 had been diagnosed with genital herpes compared with 19.3% in those infected with HSV-2 only ( $P<.001$ ).

A higher percentage of persons infected with HSV-1 only reported having been diagnosed with genital herpes in 1999-2004 than in 1988-1994 (1.8% vs 0.4%;  $P<.001$ ) (Figure 2). Furthermore, in 1999-2004, a person infected with HSV-1 only was more likely to have been diagnosed with genital herpes compared with those seronegative for HSV-1 (adjusted odds ratio, 2.9; 95% CI, 1.7-5.0), while there was no difference in 1988-1994. The mean age for persons infected with HSV-1 only who had been diagnosed with

genital herpes was similar between 1988-1994 and 1999-2004.

### Review of HSV-1 and HSV-2 Seroprevalence from 3 NHANES

In FIGURE 3, HSV-2 seroprevalence from the 3 NHANES are presented for non-Hispanic whites and non-Hispanic blacks by age. No data were available for Mexican Americans in 1976-1980. In non-Hispanic whites, HSV-2 seroprevalence from the 1999-2004 survey was not significantly different from that observed in 1976-1980 for any of the age groups. This indicates that the significant increases among participants aged 14 to 19 years, 20 to 29 years, and 30 to 39 years<sup>25</sup> between 1976-1980 and 1988-1994 had all been reversed (Figure 3). There were no statistically significant differences in HSV-2 seroprevalence in non-Hispanic blacks between the 3 surveys (Figure 3).

Between 1976-1980 and 1999-2004, HSV-1 seroprevalence has been decreasing in both non-Hispanic whites and non-Hispanic blacks. When all age groups were combined, the test for trend was significant for non-Hispanic whites ( $P<.001$ ) and non-Hispanic blacks ( $P<.001$ ; FIGURE 4); the gaps in HSV-1 seroprevalence be-

**Table 3.** Changes in Weighted Herpes Simplex Virus 2 Seroprevalence Between NHANES in 1988-1994 and 1999-2004 in Persons Aged 17 to 49 Years After Adjustment\*

	Adjusted HSV-2 Seroprevalence, %					
	Males			Females		
	NHANES		Change (95% CI)	NHANES		Change (95% CI)
	1988-1994 (n = 3597)	1999-2004 (n = 3478)		1988-1994 (n = 3932)	1999-2004 (n = 3838)	
Overall	16.6	11.3	-31.9 (-44.4 to -19.4)†	28.3	22.8	-19.4 (-27.1 to -11.8)†
Age group, y						
17-19	6.0	1.0	-83.3 (-96.5 to -70.1)†	12.4	4.9	-60.5 (-81.9 to -39.1)†
20-29	12.8	6.1	-52.3 (-74.1 to -30.5)†	23.4	15.4	-34.2 (-48.0 to -20.4)†
30-39	22.0	13.2	-40.0 (-54.4 to -25.6)†	29.6	26.4	-10.8 (-23.8 to 2.2)
40-49	16.5	15.9	-3.6 (-31.2 to 23.9)	35.3	30.0	-15.0 (-27.5 to -2.6)‡
Race/ethnicity						
Non-Hispanic white	14.6	9.2	-37.0 (-52.5 to -21.5)†	23.4	18.6	-20.5 (-31.5 to -9.5)†
Non-Hispanic black	27.5	24.2	-12.0 (-29.2 to 5.2)	51.3	46.1	-10.1 (-19.5 to -0.8)‡
Mexican American	18.6	11.0	-40.9 (-57.6 to -24.2)†	32.5	18.9	-41.8 (-52.9 to -30.8)†

Abbreviations: CI, confidence interval; HSV-2, herpes simplex virus type 2; NHANES, National Health and Nutrition Examination Survey.

\*Adjusted for age, race/ethnicity, poverty level, number of lifetime partners, marital status, and education level.

† $P<.005$ .

‡ $P<.05$ .

tween non-Hispanic whites and non-Hispanic blacks were about 18 percentage points in all 3 surveys.

## COMMENT

The seroprevalence of HSV-2 in the United States decreased by 19% in persons aged 14 to 49 years over an aver-

age interval of 10.5 years. The change in HSV-2 seroprevalence contrasts sharply with data from a previous report, which found that HSV-2 seroprevalence increased 30% between the 2 NHANES conducted in 1976-1980 and 1988-1994.<sup>25</sup> Our study suggests that the trajectory of increasing HSV-2

seroprevalence in the United States has been reversed.

Because HSV-2 is a lifetime infection, any increases or decreases in HSV-2 seroprevalence are expected to be first seen in younger persons. In adolescents and younger adults, HSV-2 seroprevalence is a cumulative measure of re-

**Table 4.** Changes in Weighted Herpes Simplex Virus 1 Seroprevalence in Persons Aged 14 to 49 Years Between NHANES in 1988-1994 and 1999-2004

	NHANES				
	1988-1994		1999-2004		Change, % (95% CI)
	Sample Size	HSV-1 Seroprevalence, % (95% CI)	Sample Size	HSV-1 Seroprevalence, % (95% CI)	
Overall*	9167	62.0 (59.6 to 64.6)	11 508	57.7 (55.9 to 59.5)	-6.9 (-11.6 to -2.3)†
Age group, y					
14-19	1788	45.7 (42.0 to 49.7)	4650	39.0 (36.8 to 41.3)	-14.7 (-23.1 to -6.2)‡
20-29	2750	56.2 (52.5 to 60.2)	2412	54.4 (51.8 to 57.1)	-3.2 (-11.1 to 4.7)
30-39	2567	65.7 (62.0 to 69.7)	2251	63.5 (60.8 to 66.5)	-3.3 (-10.3 to 3.6)
40-49	2062	72.6 (69.0 to 76.5)	2195	65.3 (62.6 to 68.0)	-10.1 (-15.8 to -4.3)‡
Sex by age group, y					
Male					
All ages*	4423	59.0 (55.9 to 62.3)	5511	55.9 (53.8 to 58.2)	-5.3 (-11.4 to 0.9)
14-19	848	43.3 (38.3 to 48.9)	2368	36.8 (34.3 to 39.4)	-15.2 (-26.8 to -3.7)†
20-29	1332	50.8 (46.1 to 56.0)	1044	51.7 (48.6 to 55.1)	1.8 (-9.6 to 13.2)
30-39	1203	61.9 (56.8 to 67.6)	1005	63.5 (59.6 to 67.6)	2.6 (-8.1 to 13.2)
40-49	1040	72.3 (68.6 to 76.2)	1094	62.9 (58.8 to 67.3)	-13.0 (-20.2 to -5.8)‡
Female					
All ages*	4744	65.0 (61.9 to 68.3)	5997	59.5 (57.6 to 61.4)	-8.5 (-13.7 to -3.2)‡
14-19	940	48.1 (42.6 to 54.3)	2282	41.4 (38.3 to 44.7)	-13.9 (-26.0 to -1.9)†
20-29	1418	61.7 (57.3 to 66.4)	1368	57.1 (53.6 to 60.9)	-7.5 (-16.2 to 1.3)
30-39	1364	69.6 (65.6 to 73.8)	1246	63.7 (60.6 to 67.0)	-8.6 (-15.5 to -1.7)†
40-49	1022	73.0 (68.0 to 78.3)	1101	67.5 (64.6 to 70.6)	-7.5 (-15.0 to 0)
Race/ethnicity by age group, y*§					
Non-Hispanic white					
All ages*	2652	56.6 (53.8 to 59.5)	4311	50.1 (47.8 to 52.6)	-11.5 (-17.5 to -5.5)‡
14-19	461	38.1 (33.9 to 42.8)	1220	30.7 (27.6 to 34.1)	-19.7 (-32.0 to -7.4)†
20-29	675	49.4 (44.6 to 54.7)	1042	46.1 (42.2 to 50.3)	-6.7 (-18.7 to 5.4)
30-39	792	61.2 (56.6 to 66.3)	1070	56.4 (52.7 to 60.4)	-8.0 (-17.2 to 1.2)
40-49	724	68.8 (64.3 to 73.7)	979	58.5 (55.0 to 62.1)	-15.0 (-22.4 to -7.5)‡
Non-Hispanic black					
All ages*	3009	74.0 (71.3 to 76.8)	2926	68.3 (65.1 to 71.7)	-7.7 (-13.2 to -2.2)†
14-19	599	57.2 (52.3 to 62.6)	1470	55.7 (51.9 to 59.7)	-2.6 (-13.3 to 8.0)
20-29	891	70.8 (66.3 to 75.7)	476	55.5 (49.9 to 61.8)	-21.6 (-31.1 to -12.1)‡
30-39	884	76.4 (72.5 to 80.5)	460	75.2 (70.4 to 80.3)	-1.6 (-9.5 to 6.4)
40-49	635	84.0 (80.8 to 87.4)	520	79.8 (75.0 to 85.0)	-5.0 (-11.7 to 1.7)
Mexican American					
All ages*	3113	86.0 (83.6 to 88.4)	3406	80.8 (78.7 to 83.0)	-6.0 (-9.6 to -2.5)‡
14-19	636	71.4 (66.2 to 76.9)	1658	57.6 (54.8 to 60.5)	-19.5 (-26.4 to -12.6)‡
20-29	1072	84.1 (81.7 to 86.6)	678	80.0 (75.4 to 84.9)	-4.9 (-10.9 to 1.1)
30-39	793	89.4 (86.7 to 92.0)	505	86.3 (82.6 to 90.3)	-3.5 (-8.4 to 1.4)
40-49	612	92.5 (88.6 to 96.6)	565	89.2 (86.5 to 92.1)	-3.6 (-8.4 to 1.3)

Abbreviations: CI, confidence interval; HSV-1, herpes simplex virus type 1; NHANES, National Health and Nutrition Examination Survey.

\*Age-adjusted using the 2000 US census civilian, noninstitutionalized population aged 14 to 49 years as the standard.

† $P < .05$ .

‡ $P < .005$ .

§For the 1988-1994 survey, 393 persons in the "other" race/ethnicity category were excluded; for the 1999-2004 survey, 865 persons in the "other" race/ethnicity category were excluded.

cent exposures. The decrease in HSV-2 seroprevalence in adolescents and young adults provides biological evidence supporting findings from behavioral surveys that sexual risk behaviors decreased in adolescents.<sup>36</sup> Seroprevalence of HSV-2 is not subject to self-reporting biases, and is a more direct measure of risk for sexually acquired HIV infection. Because audio computer-assisted self-interviewing increases the reporting of sexual behaviors in adolescents,<sup>37</sup> the change in methods likely made the reporting of sexual activities more complete in 1999-2004. As a result, the observed decreases in sexual behaviors in adolescents between the 2 surveys are likely to be underestimates.

The reasons that HSV-2 seroprevalence significantly decreased even after accounting for changes in measured sexual behaviors may include a combination of unmeasured factors, such as careful partner selection, condom use, and/or choosing oral sex over vaginal sex<sup>36,38-41</sup>; additionally, adjusting for individual-level behavioral changes may not fully adjust for their population effects. Recent research into the structure of sexual networks indicates that in adolescents, relative low levels of behavioral change can radically limit the spread of sexually transmitted infections.<sup>42</sup> The finding that the mean number of lifetime sex partners

increased in adult females but did not change in adult males may have contributed to the greater decreases in HSV-2 seroprevalence in males relative to females between the 2 surveys.

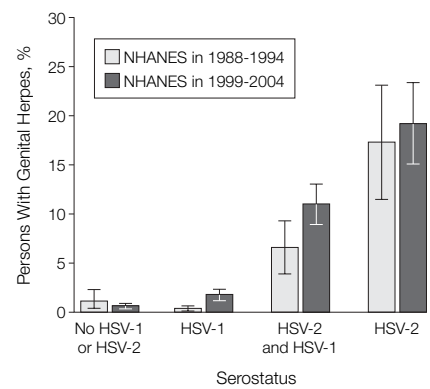
The overall seroprevalence of HSV-1 decreased by 7% between 1988-1994 and 1999-2004. During the same interval, there was an increase in persons infected with HSV-1 only who had been diagnosed with genital herpes. Our findings are consistent with previous reports that genital herpes caused by HSV-1 may be increasing in the United States, as in other developed countries.<sup>6-13</sup>

A decrease in HSV-1 seroprevalence in the United States is not unexpected due to improvements in living and hygiene conditions and experiences in other developed countries. In European countries, HSV-1 seroprevalence was inversely correlated with the national gross domestic product.<sup>43</sup> In the United Kingdom and in the Netherlands, the seroprevalence of HSV-1 has decreased since the late 1980s.<sup>44,45</sup> In Japan, changes in socioeconomic status and family size were associated with decreases in HSV-1 seroprevalence.<sup>46</sup> The overall seroprevalence of HSV-1 was unchanged between 1976-1980 and 1988-1994, probably because immigrants from countries with high HSV-1 seroprevalence offset the decrease in HSV-1 seroprevalence in those born in the United States.<sup>26</sup> Our

finding that HSV-1 seroprevalence decreased overall by 7% but by 10% in those born in the United States supports this hypothesis.

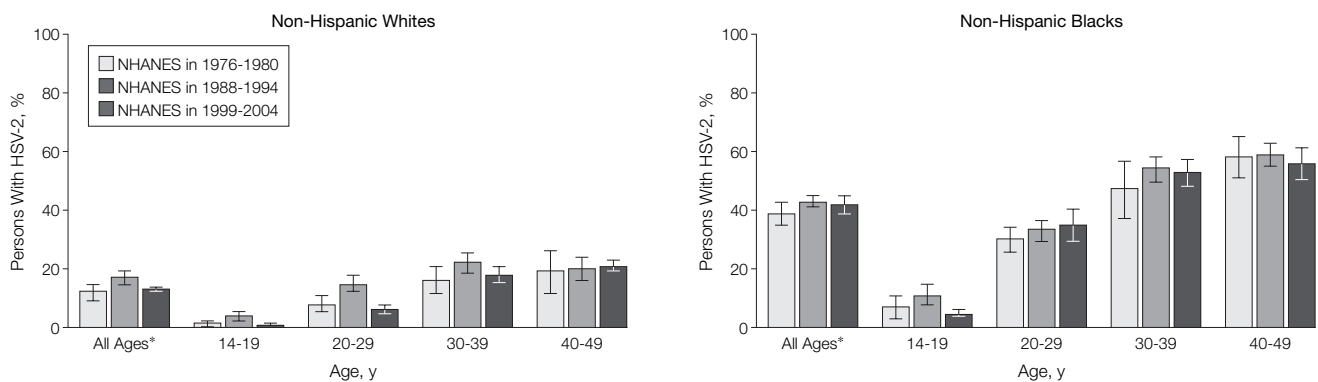
The changing HSV-1 seroprevalence may have an impact on genital herpes for several reasons. First, declines in HSV-1 acquisition before onset of sexual activity will leave more individuals susceptible to genitally acquired HSV-1 infection when they become sexually active. Second, more individuals would acquire HSV-2 infection with-

**Figure 2.** Persons Aged 18 to 49 Years Who Had Been Diagnosed With Genital Herpes, by Herpes Simplex Virus Serostatus on NHANES in 1988-1994 and 1999-2004



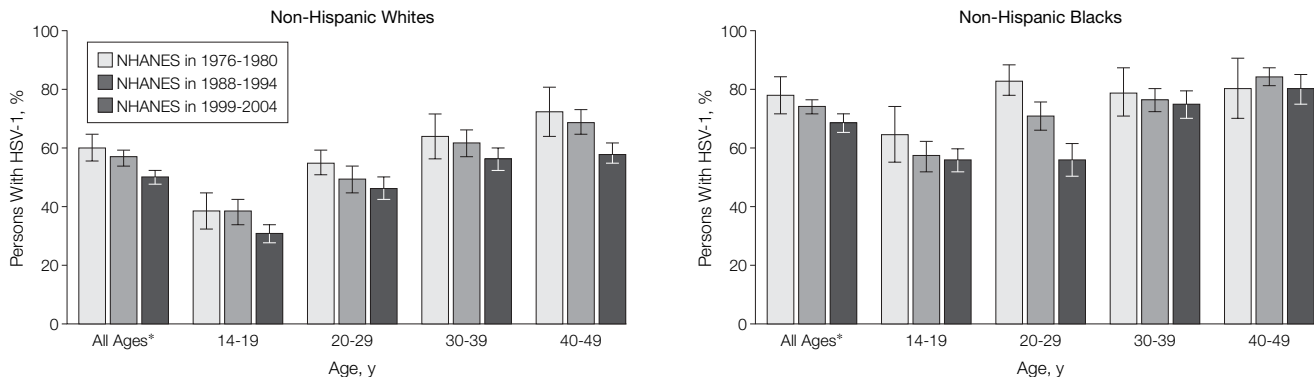
Error bars indicate 95% confidence intervals; HSV-1, herpes simplex virus type 1; HSV-2, herpes simplex virus type 2; NHANES, National Health and Nutrition Examination Survey.

**Figure 3.** Herpes Simplex Virus Type 2 Seroprevalence in Non-Hispanic Whites and Non-Hispanic Blacks by Age, on NHANES in 1976-1980, 1988-1994, and 1999-2004



The percentage of persons is weighted. Error bars indicate 95% confidence intervals; HSV-2, herpes simplex virus type 2; NHANES, National Health and Nutrition Examination Survey.

\*Age-adjusted using the 2000 US Census civilian, noninstitutionalized population aged 14 to 49 years as the standard.

**Figure 4.** Herpes Simplex Virus Type 1 Seroprevalence in Non-Hispanic Whites and Non-Hispanic Blacks by Age, on NHANES in 1976-1980, 1988-1994, and 1999-2004

The percentage of persons is weighted. Error bars indicate 95% confidence intervals; HSV-1, herpes simplex virus type 1; NHANES, National Health and Nutrition Examination Survey.

\*Age-adjusted using the 2000 US Census civilian, noninstitutionalized population aged 14 to 49 years as the standard.

out HSV-1 antibodies. Despite the overall decrease in HSV-2 seroprevalence between 1988-1994 and 1999-2004, the seroprevalence of HSV-2 only (the group of persons with the highest medical burden of genital herpes) did not change. Finally, because genital HSV-1 recurs relatively infrequently, confirmation of HSV type may contribute to optimal management of patients with symptomatic genital herpes.<sup>47,48</sup>

One limitation of our study is the small number of questions about sexual behaviors in NHANES. We cannot compare rates of condom use because such data were not collected in the surveys. Another limitation is that the interpretation of national trends can be problematic for Mexican Americans due to the recent arrival of a large number of immigrants in the United States.<sup>49</sup>

While our data show declines in HSV-2 seroprevalence, HSV-2 is still prevalent in the United States. Furthermore, the gaps in HSV-2 seroprevalence between the sexes are widening and the disparity between racial groups persists despite the recent decrease in HSV-2 seroprevalence. There are several additions to the armamentarium for control of HSV-2 infection. A candidate vaccine that is partially protective in women has been reported.<sup>24</sup> Once-daily HSV-2 suppressive therapy can cut the risk of HSV-2 transmis-

sion in discordant couples by half,<sup>50</sup> and condoms use can also reduce the risk of transmission.<sup>39,40</sup>

Type-specific serological tests for HSV have become available<sup>51</sup> and can be used to identify populations in need of intensified interventions. Trials are ongoing to assess the impact of HSV-2 suppressive therapy on HIV acquisition.<sup>52</sup> If effective, HSV-2 suppressive therapy may become a new biomedical intervention limiting the spread of HIV as well as HSV-2 infection. The percentage of HSV-2 seropositive persons who had been diagnosed with genital herpes was higher in 1999-2004 compared with 1988-1994. However, the vast majority of persons seropositive for HSV-2 did not know that they were infected. These data are consistent with the lack of widespread testing in the general population.

NHANES provide a measure of population burdens of both HSV-1 and HSV-2 infections. In populations in which childhood acquisition of HSV-1 is common, such as in non-Hispanic blacks and Mexican Americans, sexual transmission of HSV-1 would be minimal. However, in populations whose acquisition of HSV-1 during childhood is relatively low and who have relatively low HSV-2 seroprevalence, such as non-Hispanic whites, sexual transmission of HSV-1 could become an increasingly impor-

tant cause of genital herpes in the future. Recent changes in adolescent sexual behavior (particularly the practice of oral-genital sex) and the possible evolution of HSV-1 may accelerate this shift.<sup>41,42,53</sup> The ability to monitor HSV-1 seroprevalence along with HSV-2 seroprevalence in NHANES is important for the development of HSV-2 prevention strategies, such as those related to vaccination.<sup>24</sup> The changes in HSV-1 and HSV-2 seroprevalence will also directly affect the cause of neonatal herpes.<sup>54</sup> Future studies are needed to monitor the changing HSV-1 and HSV-2 trends and to develop effective strategies to prevent HSV infection.

**Author Contributions:** Dr Xu had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Xu, Kottiri, McQuillan, Nahmias, Markowitz.

**Acquisition of data:** Xu, Kottiri, McQuillan, Lee.

**Analysis and interpretation of data:** Xu, Sternberg, Kottiri, McQuillan, Lee, Nahmias, Berman, Markowitz.

**Drafting of the manuscript:** Xu, Sternberg, Kottiri, Nahmias.

**Critical revision of the manuscript for important intellectual content:** Xu, Sternberg, Kottiri, McQuillan, Lee, Nahmias, Berman, Markowitz.

**Statistical analysis:** Xu, Sternberg, Kottiri, McQuillan. **Administrative, technical, or material support:** Kottiri, McQuillan, Lee, Berman.

**Study supervision:** Nahmias, Berman, Markowitz.

**Financial Disclosures:** None reported.

**Funding/Support:** This study was funded exclusively by the US Centers for Disease Control and Prevention.

**Role of the Sponsor:** The Division of STD Prevention at the US Centers for Disease Control and Prevention proposed to have the data on both herpes simplex vi-

rus 1 and herpes simplex virus 2 serology collected through the National Health and Nutrition Examination Surveys (NHANES). After the data became available, the Epidemiology and Surveillance Branch analyzed the data and developed the manuscript. The manuscript was reviewed and approved by the Division of STD Prevention, the Centers for Disease Control and Prevention, and then cross-clearance and approval was granted by the National Center for Health Statistics, Centers for Disease Control and Prevention.

**Disclaimer:** The findings and conclusions reported in this article are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

## REFERENCES

- Nahmias AJ, Lee FK, Beckman-Nahmias S. Seroepidemiological and -sociological patterns of herpes simplex virus infection in the world. *Scand J Infect Dis Suppl.* 1990;69:19-36.
- Smith JS, Robinson NJ. Age-specific prevalence of infection with herpes simplex virus types 2 and 1: a global review. *J Infect Dis.* 2002;186:53-528.
- Corey L, Wald A. Genital herpes. In: Holmes KK, Sparling FP, Mardh PA, et al, eds. *Sexually Transmitted Diseases*. 3rd ed. New York, NY: McGraw-Hill; 1999:285-312.
- Stanberry LR, Jorgensen DM, Nahmias AJ. Herpes simplex viruses 1 and 2. In: Evans AS, Kaslow R, eds. *Viral Infections of Humans: Epidemiology and Control*. 4th ed. New York, NY: Plenum Publishers; 1997:419-454.
- Kimberlin DW, Rouse DJ. Clinical practice: genital herpes. *N Engl J Med.* 2004;350:1970-1977.
- Lowhagen GB, Tunback P, Andersson K, Bergstrom T, Johannisson G. First episodes of genital herpes in a Swedish STD population: a study of epidemiology and transmission by the use of herpes simplex virus (HSV) typing and specific serology. *Sex Transm Infect.* 2000;76:179-182.
- Nilsen A, Myremel H. Changing trends in genital herpes simplex virus infection in Bergen, Norway. *Acta Obstet Gynecol Scand.* 2000;79:693-696.
- Tran T, Druce JD, Catton MC, Kelly H, Birch CJ. Changing epidemiology of genital herpes simplex virus infection in Melbourne, Australia, between 1980 and 2003. *Sex Transm Infect.* 2004;80:277-279.
- Scoular A, Norrie J, Gillespie G, et al. Longitudinal study of genital infection by herpes simplex virus type 1 in Western Scotland over 15 years. *BMJ.* 2002;324:1366-1367.
- Lafferty WE, Downey L, Celum C, Wald A. Herpes simplex virus type 1 as a cause of genital herpes: impact on surveillance and prevention. *J Infect Dis.* 2000;181:1454-1457.
- Ribes JA, Steele AD, Seabolt JP, Baker DJ. Six-year study of the incidence of herpes in genital and nongenital cultures in a central Kentucky medical center patient population. *J Clin Microbiol.* 2001;39:3321-3325.
- Roberts CM, Pfister JR, Spear SJ. Increasing proportion of herpes simplex virus type 1 as a cause of genital herpes infection in college students. *Sex Transm Dis.* 2003;30:797-800.
- Langenberg AG, Corey L, Ashley RL, Leong WP, Straus SE; Chiron HSV Vaccine Study Group. A prospective study of new infections with herpes simplex virus type 1 and type 2. *N Engl J Med.* 1999;341:1432-1438.
- Holmberg SD, Stewart JA, Gerber AR, et al. Prior herpes simplex virus type 2 infection as a risk factor for HIV infection. *JAMA.* 1988;259:1048-1050.
- Serwadda D, Gray RH, Sewankambo NK, et al. Human immunodeficiency virus acquisition associated with genital ulcer disease and herpes simplex virus type 2 infection: a nested case-control study in Rakai, Uganda. *J Infect Dis.* 2003;188:1492-1497.
- Renzi C, Douglas JM Jr, Foster M, et al. Herpes simplex virus type 2 infection as a risk factor for human immunodeficiency virus acquisition in men who have sex with men. *J Infect Dis.* 2003;187:19-25.
- Reynolds SJ, Risbud AR, Shepherd ME, et al. Recent herpes simplex virus type 2 infection and the risk of human immunodeficiency virus type 1 acquisition in India. *J Infect Dis.* 2003;187:1513-1521.
- Wald A, Link K. Risk of human immunodeficiency virus infection in herpes simplex virus type 2-seropositive persons: a meta-analysis. *J Infect Dis.* 2002;185:45-52.
- Freeman EE, Weiss HA, Glynn JR, Cross PL, Whitworth JA, Hayes RJ. Herpes simplex virus type 2 increases HIV acquisition in men and women: systematic review and meta-analysis of longitudinal studies. *AIDS.* 2006;20:73-83.
- Schacker T, Ryncarz AJ, Goddard J, Diem K, Shaughnessy M, Corey L. Frequent recovery of HIV-1 from genital herpes simplex virus lesions in HIV-1-infected men. *JAMA.* 1998;280:61-66.
- McClelland RS, Wang CC, Overbaugh J, et al. Association between cervical shedding of herpes simplex virus and HIV-1. *AIDS.* 2002;16:2425-2430.
- Schacker T, Zeh J, Hu H, Shaughnessy M, Corey L. Changes in plasma human immunodeficiency virus type 1 RNA associated with herpes simplex virus reactivation and suppression. *J Infect Dis.* 2002;186:1718-1725.
- Xu F, Schillinger JA, Sternberg MR, et al. Sero-prevalence and coinfection with herpes simplex virus type 1 and type 2 in the United States, 1988-1994. *J Infect Dis.* 2002;185:1019-1024.
- Stanberry LR, Spruance SL, Cunningham AL, et al; GlaxoSmithKline Herpes Vaccine Efficacy Study Group. Glycoprotein-D-adjunct vaccine to prevent genital herpes. *N Engl J Med.* 2002;347:1652-1661.
- Fleming DT, McQuillan GM, Johnson RE, et al. Herpes simplex virus type 2 in the United States, 1976-1994. *N Engl J Med.* 1997;337:1105-1111.
- Schillinger JA, Xu F, Sternberg MR, et al. National seroprevalence and trends in herpes simplex virus type 1 in the United States, 1976-1994. *Sex Transm Dis.* 2004;31:753-760.
- Plan and operation of the Third National Health and Nutrition Examination Survey: 1988-94. *Vital Health Stat 1.* 1994;(32):20-34.
- Lee FK, Coleman RM, Pereira L, Griffin C, Reid E, Nahmias A. Detection of herpes simplex virus type-2-specific antibody with glycoprotein G. *J Clin Microbiol.* 1985;22:641-644.
- Lee FK, Pereira L, Griffin C, Reid E, Nahmias A. A novel glycoprotein (gG-1) for detection of herpes simplex virus specific antibodies. *J Virol Methods.* 1986;14:111-118.
- Ashley RL, Militoni J, Lee F, Nahmias A, Corey L. Comparison of western blot (immunoblot) and glycoprotein G-specific immunodot enzyme assay for detecting antibodies to herpes simplex virus type 1 and type 2 in human sera. *J Clin Microbiol.* 1988;26:662-667.
- Elandt-Johnson RC, Johnson NL. *Survival Models and Data Analyses*. New York, NY: John Wiley; 1980:69-71.
- Schenker N, Gentleman JF. On judging the significance of differences by examining the overlap between confidence intervals. *Am Stat.* 2001;55:182-186.
- National Center for Health Statistics. NHANES Analytic Guidelines: June 2004. [http://www.cdc.gov/nchs/data/nhanes/nhanes\\_general\\_guidelines\\_june\\_04.pdf](http://www.cdc.gov/nchs/data/nhanes/nhanes_general_guidelines_june_04.pdf). Accessibility verified July 21, 2006.
- Modadjer L, Montaquila J, Waksberg J, et al. *National Health and Nutrition Examination Survey III: Weighting and Estimation Methodology*. Hyattsville, Md: National Center for Health Statistics; 1996.
- Korn EL, Barry GL. *Analysis of Health Surveys*. New York, NY: Wiley; 1999.
- Centers for Disease Control and Prevention. Trends in sexual risk behaviors among high school students—United States, 1991-2001. *MMWR Morb Mortal Wkly Rep.* 2002;51:856-859.
- Turner CF, Ku L, Rogers SM, Lindberg LD, Pleck JH, Sonenstein FL. Adolescent sexual behavior, drug use, and violence: increased reporting with computer survey technology. *Science.* 1998;280:867-873.
- Santelli JS, Abma J, Ventura S, et al. Can changes in sexual behaviors among high school students explain the decline in teen pregnancy rates in the 1990s. *J Adolesc Health.* 2004;35:80-90.
- Wald A, Langenberg AG, Link K, et al. Effect of condoms on reducing the transmission of herpes simplex virus type 2 from men to women. *JAMA.* 2001;285:3100-3106.
- Wald A, Langenberg AG, Krantz E, et al. The relationship between condom use and herpes simplex virus acquisition. *Ann Intern Med.* 2005;143:707-713.
- Mosher WD, Chandra A, Jones J. Sexual behavior and selected health measures: men and women 15-44 years of age, United States, 2002. *Adv Data.* 2005;(362):10-27.
- Halpern-Felsher BL, Cornell JL, Kropp RY, Tschann JM. Oral versus vaginal sex among adolescents: perceptions, attitudes, and behavior. *Pediatrics.* 2005;115:845-851.
- Cowan FM. Commentary: developing preventative strategies in Europe. *Int J Epidemiol.* 2001;30:588-589.
- Vyse AJ, Gay NJ, Slomka MJ, et al. The burden of infection with HSV1 and HSV-2 in England and Wales: implications for the changing epidemiology of genital herpes. *Sex Transm Infect.* 2000;76:183-187.
- Pebody RG, Andrews N, Brown D, et al. The seroepidemiology of herpes simplex virus type 1 and 2 in Europe. *Sex Transm Infect.* 2004;80:185-191.
- Hashido M, Kawana T, Matsunaga Y, Inouye S. Changes in prevalence of herpes simplex virus type 1 and 2 antibodies from 1973 to 1993 in the rural districts of Japan. *Microbiol Immunol.* 1999;43:177-180.
- Lafferty WE, Coombs RW, Benedetti J, Critchlow C, Corey L. Recurrences after oral and genital herpes simplex virus infection: influence of site of infection and viral type. *N Engl J Med.* 1987;316:1444-1449.
- Engelberg R, Carrell D, Krantz E, Corey L, Wald A. Natural history of genital herpes virus type 1 infection. *Sex Transm Dis.* 2003;30:174-177.
- Schmidley DA. *Profile of the Foreign-Born Population in the United States: 2000*. Washington, DC: US Government Printing Office; 2001.
- Corey L, Wald A, Patel R, et al. Once-daily valacyclovir to reduce the risk of transmission of genital herpes. *N Engl J Med.* 2004;350:11-20.
- Wald A, Ashley-Morrow R. Serological testing for herpes simplex virus (HSV)-1 and HSV-2 infection. *Clin Infect Dis.* 2002;35:S173-S182.
- Celum CL, Robinson NJ, Cohen MS. Potential effect of HIV type 1 antiretroviral and herpes simplex virus type 2 antiviral therapy on transmission and acquisition of HIV type 1 infection. *J Infect Dis.* 2005;191(suppl 1):S107-S114.
- Nahmias AJ, Lee FK, Beckman-Nahmias S. The natural history and epidemiology of herpes simplex viruses. In: Studahl M, Cinque P, Bergström T, eds. *Herpes Simplex Viruses*. New York, NY: Publisher; 2006:55-97.
- Brown ZA, Wald A, Morrow RA, Selke S, Zeh J, Corey L. Effect of serologic status and Cesarean delivery on transmission rates of herpes simplex virus from mother to infant. *JAMA.* 2003;289:203-209.