HPV Seroprevalence in the United States: Behavior, Biology, and Prevention

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(See the major article by Liu et al on pages 191–8.)

Keywords: human papillomavirus; sexually transmitted infection; sexual revolution; cohort effect; vaccination.

In this issue of The Journal of Infectious Diseases, Liu and colleagues [1] update their estimates of the cumulative burden of human papillomavirus (HPV) infection in the United States. Using blood samples collected as part of the 2005–2006 National Health and Nutrition Examination Survey (NHANES), the authors report the sex-, age-, and race-specific seroprevalence of the 9 HPV types currently targeted by prophylactic vaccines: HPV16 and 18 targeted by Cervarix (GlaxoSmithKline), Gardasil (Merck & Co, Inc), and Gardasil 9 (Merck & C., Inc); HPV6 and 11 targeted by Gardasil and Gardasil 9; and HPV 31, 33, 45, 52, and 58 targeted by Gardasil 9 (Merck & C., Inc). HPV6 and 11 will develop detectable antibodies (the target analyte for seroprevalence measures), the estimates reported should be viewed as a lower bound of cumulative HPV infection in the United States. These data have several important implications for US HPV-associated cancer prevention.

Even with the likely underestimation of cumulative HPV burden as measured by serology, the data highlight that a substantial proportion of the US female population has been infected by HPV types that are now preventable by prophylactic vaccine. A peak seroprevalence against 1 or more of the 9 types measured occurred in women aged 30–39 years (52.4%). HPV infections appears to be rapidly acquired in the population, with vaccine-preventable seroprevalence more than doubling in the first 5–10 years of sexual activity; from 16.2% in 14–19-year-old females to 44.6% in 20–29-year-old females. These data highlight the importance of completing the prophylactic vaccine series in adolescence to achieve the maximum protection against these common infections. However, the National Immunization Survey-Teen report indicates that in 2013, only 57.3% of adolescent girls (aged 13–17 years) had received at least 1 dose of HPV vaccine, and only 37.6% completed the 3-dose series [2]. Efforts to improve vaccine coverage and a more complete evaluation of the efficacy and duration of protection afforded by <1 dose of vaccine [3] should continue as high-priority public health and research goals, given the high cumulative prevalence of HPV observed by the third decade of life.

Consistent with previous national survey estimates, HPV seroprevalence in US males was significantly lower compared with that in US females (overall 9-type seroprevalence of 19.4% vs 40.5%, respectively). The contrast between significantly lower HPV seroprevalence despite similar HPV DNA prevalence in men compared with women points to potential differences in host-response to genital-tract infection by sex. Of note, a decreased seroconversion to genital-tract viral infections in men is not limited to HPV. For example, seroprevalence of herpes simplex virus type 2 (HSV-2), another sexually transmitted viral infection, also differs significantly in US men and women. In a report from the 2007–2010 NHANES surveys, women had a nearly 2-fold higher HSV-2 seroprevalence (20.3%) compared with men (10.6%) [4]. In contrast, seroprevalence of the nonsexually transmitted herpesvirus, cytomegalovirus (CMV), is similar in women and men (55.5% in women; 45.2% in men) [5]. From a global public health perspective, understanding the sex differences in host response to genital-tract infection is warranted, as the results may provide insights into mechanisms explaining why women continue to bear a disproportionate burden of sexually transmitted infections (including human immunodeficiency virus [HIV] and chlamydia) and their pathologic sequelae.

Looking at HPV across the lifespan, HPV seroprevalence peaked in women aged 30–39 years, followed by subsequent decline with age. A similar decline in seroprevalence was observed in men, but peak prevalence was observed a decade later at age 40–49 years. As stated by the authors, the lower HPV seroprevalence with increasing age might be explained by waning immunity over time, or birth-cohort specific differences in cumulative HPV exposure. Nationally representative surveys of sexual behavior in the US male and female populations provide clear evidence of increasing number of lifetime sex partners in both men and women over time; from a median of 2.6 and 6.7 in women and men, respectively, in the 1940–1949 birth cohort (age 56–65 years at the time of...
the current seroprevalence survey) to a median of 5.3 and 8.8 in women and men, respectively, in the 1970–1979 birth cohort (age 26–35 in the current seroprevalence survey) [6]. Importantly, the peak in median lifetime sex partners in men overall occurred a decade earlier (median 8.9 lifetime partners in the 1960–1969 birth cohort) compared with women (median 5.3 lifetime partners in the 1970–1979 birth cohort). This change in the sexual behavior by birth cohort parallels the age-specific differences in peak HPV seroprevalence in men and women observed in the report in this issue by Liu and colleagues [1], and strongly supports a profound effect of birth-cohort sexual behavior differences as a likely explanation for the lower HPV seroprevalence at older ages. Given the birth cohort differences in cumulative HPV exposure and increasing evidence to support recrudescence of undetectable HPV infection during periods of immune suppression such as aging [7], trends in HPV-associated precancer and cancer incidence in men and women in the United States over the next two decades should be closely monitored.

A key feature of the NHANES survey is the oversampling of the non-Hispanic black and Mexican American populations, which allows for stratified comparisons of HPV seroprevalence by race/ethnicity. The 1.6- and 1.4-fold higher HPV9 seroprevalence observed in non-Hispanic black compared with non-Hispanic white women and men, respectively, generally parallels the higher number of lifetime sex partners reported by non-Hispanic black women and men [6]. Compared to non-Hispanic whites, Mexican American women reported a lower average number of lifetime sex partners, while Mexican American men reported a similar lifetime number of sex partners. These sexual behavior patterns mirrored similar HPV seroprevalence for HPV6, 11, 16, and 18 in Mexican Americans and white individuals; however, Mexican American women and men had a significantly higher seroprevalence for HPV31, 33, 45, 52, and 58 (23.6% and 9.3%, respectively) compared with non-Hispanic white women and men (15.9% and 5.4%, respectively). The prevalence of these HPV genotypes is also increased relative to HPV16 in HIV-positive women, with and without cytological abnormalities, compared with the general population [8], suggesting that compromised immune responses may contribute to higher non-HPV16 prevalence. As suggested by Liu et al [1], it will be important to determine whether there are biological factors specific to Hispanic ethnicity that contribute to disparities in HPV infection. To support this possibility, it is noted that despite similar sexual behaviors reported in non-Hispanic whites and Mexican Americans, HSV-2 seroprevalence is also higher in Mexican American men (13.0%) and women (22.5%) compared to white men (7.2%) and women (15.3%) [4]. The authors correctly emphasize that these differences may not translate to difference in cervical cancer rates, as the majority of cervical cancers in all race/ethnicity groups are attributable to HPV16/18. However, in a recent population-based analysis from New Mexico, the HPV type-specific attributable fraction of high-grade cervical intraepithelial neoplasia grade 3 (CIN3) preventable by Gardasil is 58.4%, which increases to 83.7% when including all 9 types prevented by the Gardasil 9 vaccine [9]. Thus, the increased seroprevalence of HPV31/33/45/52/58 in Mexican Americans may result in a disproportionately higher number of excisional treatments and ethnic disparities in the harms of screening.

Taken together, the broad similarities in age-, sex-, and race-specific patterns of HPV seroprevalence illuminate the huge potential afforded by early prophylactic HPV vaccination in the prevention of HPV-associated cancers in the US population. The general correlation between observed HPV seroprevalence patterns and birth cohort and race/ethnicity-specific sexual behaviors supports sexual transmission as the primary driving force of HPV infection. However, the observed differences, including lower seroprevalence in men versus women despite similar HPV DNA prevalence and higher sexual risk profiles, lower seroprevalence at older ages/birth cohorts in both men and women, and genotype-specific differences in seroprevalence in Mexican Americans compared with non-Hispanic whites raise important questions about differences in sexual behavior by age and birth cohort and biological differences in the immune response to HPV infection. Similar disparities by sex and race in HPV genotype-specific and HSV-2 seroprevalence suggest a need for more intensive evaluation of the variability in immune responses to viral infections in the genital tract.

Notes

Financial support. P. E. G. is supported by research grants from the US National Institute of Allergy and Infectious Diseases (U19 AI113187 and R21 AI107224).

Potential conflict of interest. Author certifies no potential conflicts of interest. The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References


