Vaccine Policy Analyses Can Benefit from Natural History Studies of Human Papillomavirus in Men

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(See the article by Partridge et al., on pages 1128–36.)

With the licensure of the human papillomavirus (HPV) vaccine in the United States and many other countries, an understanding of the natural history of HPV infection is imperative for establishment of appropriate policies and guidelines for its use. Although our knowledge of the natural history of HPV infection in women has increased dramatically over the past decade, the natural history of HPV infection in men is less known. In this issue of the Journal, Partridge et al. present results from a longitudinal study of HPV infection in US men that is reminiscent of their earlier work on a similar cohort of female students from the same university [1]. In light of the imminent (and highly publicized) policy questions surrounding the appropriate vaccine target population, this study is timely in its contribution to the scarce, yet growing, literature on HPV infection in men.

As Partridge et al. note, there have been only a few published longitudinal studies of HPV infection in men [2–5], and none of them report the cumulative incidence of HPV infection. Using samples from 3 genital sites (glans, penile shaft, and scrotum), urine, and under the fingernails, the authors report the prevalence of HPV infection at enrollment and the cumulative incidence of HPV infection among men 18–20 years of age who had multiple clinic visits over 3 years. The 24-month cumulative incidence of HPV infection of any type among Partridge et al.’s male cohort was 62.4%, which is nearly double that among their female counterparts [1]. Compared to the existing literature on HPV infection in men, their findings reinforce previous studies’ common themes regarding both the prevalence and the incidence of HPV infection in men in varied settings: the prevalence of any HPV infection (25.8%) was similar both to that reported for male Danish soldiers of a similar age group [4] and to that reported for males visiting a sexually transmitted disease clinic in The Netherlands [2]. HPV-16 was also found to be the most prevalent HPV type at enrollment and was among those with the highest incidence (although Partridge et al.’s study observed that the highest incidence was for HPV-84, followed by HPV-16). In Partridge et al.’s study, comparisons of HPV detection by use of polymerase chain reaction (PCR) technology revealed minimal difference across genital sites but found decreased sensitivity when urine samples were used, as had been observed in earlier studies [6, 7]. Partridge et al. also explored associations between HPV infection and the usual suspected risk factors and found that the incidence of HPV infection was significantly associated with report of a new sex partner within the past 8 months and with a history of smoking, findings similar to those in the analogous female study [1]. Although other studies of HPV infection in males have reported associations between HPV infection and increased sexual activity, the evidence on HPV infection and smoking in males has been inconsistent [4, 5, 8–10].

Partridge et al. motivate their study by referencing the availability of approaches to the prevention of HPV infection—specifically, the prophylactic vaccine. Simultaneously with the advent of the HPV vaccine—and in reaction to the long-run uncertainties with respect to the vaccine properties—a series of independent mathematical models have made their way to the forefront of the policy arena. These mathematical models allow us to simulate the natural course of disease in populations and to explore what-if scenarios of different interventions, in the absence of empirical data. To evaluate the potential benefits of a prophylactic vaccine against HPV-16– and HPV-18–associated cervical cancer and against HPV-6– and HPV-11–associated genital warts, dynamic models of HPV infection have emerged to reflect...
HPV transmission between sexual partners (to date, only between males and females) and to capture possible indirect effects of the vaccine (i.e., herd immunity) [11–16]. These models rely heavily on epidemiological data, either to estimate direct parameter inputs or, when parameters are uncertain, to serve as data targets for parameter calibration or model validation.

The study by Partridge et al. could contribute to the efforts of model-based policy analyses in at least 3 concrete ways. First and foremost, the reported measures of type-specific cumulative incidence of HPV infection can be used to calculate monthly or annual probabilities of the incidence of HPV infection, which can serve as direct inputs into static (i.e., nondynamic) models of HPV infection in men only. In dynamic models, which can include both women and men, the incidence of HPV infection is a model output, derived as a function of other variables (e.g., the prevalence of HPV infection in the population, the number of sexual contacts, and the per-contact probability that HPV is transmitted given a susceptible-infected partnership). The cumulative incidence of HPV infection that Partridge et al. report therefore would not be used as a direct input per se but could, instead, be used as a calibration target to help infer unobserved parameters, such as the per-contact probability of HPV transmission [17]. This calibration process searches for and identifies parameter values that, when used in the model, produce model-generated outputs of incidence of HPV infection that closely match those observed in Partridge et al.’s study. A second contribution of the study could be to provide estimates of the duration of HPV infection, from which we can calculate HPV clearance rates to use directly in a model. Although in Partridge et al.’s analysis the data were censored after incident HPV infection, their study followed subjects for up to 10 visits at 4-month intervals and therefore can provide type-specific estimates of the duration or persistence of HPV infection; duration of infection is one of the key determinants of HPV transmission in the population and should therefore be considered a priority for future analyses. Third, Partridge et al.’s study reported high compliance in their subjects’ use of biweekly, Web-based diaries that record the sexual activity of study participants; although problems of under- or overreporting may still apply, the frequency may help minimize recall bias. On the basis of these data, we may be able to more closely link the relationship between sexual behavior and incident HPV infection, which may enhance our understanding of HPV transmissibility between partners.

To date, there have been no published clinical-trial data on vaccine efficacy in men, and, as a result, mathematical models have been used to explore the potential benefits and cost-effectiveness of vaccination of boys, in addition to girls, under various hypothetical scenarios. Even under the most generous assumptions about the vaccine properties in both females and males, cost-effectiveness analyses have found contradictory results in the context of the US population: in one study, Taira et al. [11] estimated that, compared with vaccination of girls only, inclusion of boys in a vaccination program would cost nearly $450,000 per quality-adjusted life-year (QALY), whereas another study, by Elbashia et al. [15], found that vaccination of both girls and boys (and inclusion of a catch-up program up to the age of 24 years, for both sexes) was <$50,000/QALY. Both of these modeling studies used limited data on HPV infection in men; undoubtedly, epidemiological studies such as that by Partridge et al. can contribute to the refinement or validation of mathematical models that are currently being used to inform policy decisions.

In light of Partridge et al. study’s strength and potential contribution to future modeling efforts, a few caveats should be underscored. Because the study’s eligibility criteria included history of vaginal intercourse, it is possible that subjects had prior HPV infections. Because individuals with prior exposure may develop an immune response against future type-specific infections, the study’s findings could represent an underestimate of the incidence of HPV infection, compared with that in a sexually naive population. Although Partridge et al. allude to the female-cohort study, which did not find a significant difference between the cumulative incidence of HPV infection in a subset of virgins and that in a subset of nonvirgins [1], an analogy between the male and female cohorts may not be plausible, in light of the different sexual behaviors of women, which may lead to different exposure (e.g., the number of lifetime sex partners for men was higher than that for women of the same age group). Serological testing of the blood samples collected from the men may provide hints of prior HPV infection, but serology has been found to be a poor marker of both present and past HPV infection [18]. Partridge et al. also suggest that HPV infection may have a shorter duration in men than in women, because the incidence in men was found to be higher but the prevalence was found to be similar. Although they propose that the difference in incidence “may be due, in part, to differences in sexual behaviors, ease of sampling external versus internal genital sites, or an increased sensitivity of the HPV PCR-based testing procedures,” it is also worth noting that fewer HPV samples were taken in the female-cohort study [1], which may have led to an underestimation of the prevalence and/or incidence of HPV infection; with many possible confounders, it is unclear whether any inferences can be drawn regarding the natural history of HPV infection in men versus that in women. Finally, we should remember that Partridge et al.’s study was limited to a select group of US college-based heterosexual men 18–20 years of age and therefore that the findings are not necessarily generalizable to other populations with different demographic characteristics and sexual behaviors.

The authors conclude by stating that “the high rates of HPV infection in men...
should be considered when strategies for the prevention of HPV infection in female adolescents and young women are being developed. Indeed, because HPV is sexually transmitted, HPV infection in men will impact HPV incidence in women. However, it is imperative that we gain a stronger knowledge base of HPV infection among men, not only for the indirect benefits that such knowledge may confer to females but also for the direct benefits that may accrue to men themselves (e.g., reduction in penile cancers and genital warts). It may be the case that the HPV vaccine has far less efficacy in men than in women (as is the case for the herpes simplex virus type 2 vaccine), but as we await more data on the impact of the HPV vaccine, we will have to rely on the projections of mathematical models to help inform policy. Studies of HPV infection in men, such as the current study by Partridge et al., will not only further our understanding of the natural history of HPV infection in men but also enable us to enhance the analytic tools used to project long-term outcomes, in the absence of empirical data.

References