

Trends in Genital Warts in the Era of Human Papillomavirus Vaccination

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Chronic infection with human papillomavirus (HPV) causes more than 300,000 cases of genital warts and nearly 26,000 new cancers in the United States each year, incurring costs of around \$8 billion annually.^{1,2} Preventing most of these cases of disease through widespread HPV vaccination is a singular opportunity that the United States is largely missing.³ Human papillomavirus vaccination is low in the United States, despite multiple national guidelines that call for adolescents to routinely receive the vaccine at ages 11 or 12 years.⁴ Only 40% of girls aged 13 to 17 years in the United States and 22% of boys of the same ages had completed the 3-dose HPV vaccine series by 2014.⁵ These coverage rates fall far short of the Healthy People 2020 goal of 80% for HPV vaccine coverage.⁶ They are well below coverage for other adolescent vaccines. They are dramatically lower than HPV vaccination coverage in other countries such as Canada, Australia, and the United Kingdom.^{7,8} The United States has reasonable HPV vaccination goals that it has not met and is not anywhere close to meeting.

Even with these large missed opportunities, HPV vaccination is having an impact in the United States, as reported by Perkins et al.⁹ in this issue of the journal. Perkins and colleagues examined rates of genital wart diagnoses from 2004 to 2013 among low-income and minority US adolescents and young adults. They then mapped the rates of genital warts onto 3 periods that correspond to policy changes: pre-HPV vaccination from 2004 to 2006, primarily female HPV vaccination from 2007 to 2010, and sex-neutral HPV vaccination from 2011 to 2013. Perkins and colleagues found that genital wart diagnoses declined markedly among both females and males aged 16 to 26 years in the later periods that correspond to increases in quadrivalent HPV vaccination coverage. Previous research in Australia similarly shows that rates of genital warts for men younger than 30 years began to decrease after introduction of quadrivalent HPV vaccination for young women in 2007.¹⁰ Other studies in the United States also show that the prevalence of genital warts decreased among primarily white and insured females in the age groups most likely to have been affected by the introduction of HPV vaccine in 2006.^{11,12} A novel contribution of the study by Perkins and colleagues is showing that declines in genital warts were similar for males and females of different races and ethnicities. No other US study has assessed the effects of HPV vaccination on genital warts in such a racially and ethnically diverse sample. The finding of Perkins et al. that low-income and minority populations are benefitting from HPV vaccination is especially important because minority populations in the United States are disproportionately affected by HPV infection and HPV-related cancers.¹³

At the same time, the promising findings of the study by Perkins and colleagues highlight an important lost opportunity. Australia quickly reached high HPV vaccination coverage in the first year and, as a result, has reduced genital warts at a greater rate than the United States.¹⁰ Some areas of Australia now report no cases of genital warts at all for some periods.¹⁴ The United States has seen more modest reductions in genital warts,^{11,12} and hopes of a period with no genital warts reported remain a hypothetical. Similar patterns of attenuated impact in the United States relative to other countries with higher HPV vaccination rates may well play out in HPV-associated cancers.

It is important to keep in mind the potential limitations present in this and other similar studies. First, the authors' ecological analysis precludes inferences about causal association and allows for ecological fallacies in inferences about benefit to individuals who receive HPV vaccine. Second, the data source of medical record databases allows for the possibility of misclassifications of genital warts or changes in coding practice across medical settings. However, we do not see this concern as offering a meaningful explanation for the results observed. Finally, it is not possible to determine from these data whether the observed increase in genital wart diagnoses from 2004 to 2006 reflects true changes in prevalence or whether these additional cases resulted from better genital warts screening practices or higher clinician awareness as industry prepared to introduce HPV vaccine commercially. Despite these

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limitations and others discussed in the article, this study remains a valuable addition to the literature because these data provide additional evidence about the short-term impact of HPV vaccination.

Monitoring trends of HPV-attributable diseases is critical to evaluate progress of national and state HPV vaccination programs and policies.¹⁵ Although large clinical trials have demonstrated the prophylactic efficacy of HPV vaccines, less is known about the population effectiveness of HPV vaccination and its potential to reduce HPV-related health disparities.^{11,16} Precancerous lesions and cancers develop over decades, which complicates current efforts to monitor the population impact of HPV vaccine. In contrast, because genital warts often develop within months of HPV infection, reductions in genital warts can assist early evaluations of the impact of HPV vaccine effectiveness. Studies like this one by Perkins and colleagues are valuable because they can help us estimate the real-world impact of HPV vaccination is having on genital warts and more accurately forecast the impact it will have on cancer.

Allow us to speculate on an unpleasant future for the United States as we look back on the present time as a lost opportunity for a generation of young people. We will know that HPV vaccine was having an impact, and we will regret that we did not do more. Physicians will retire wondering why they were unable to more successfully vaccinate their patients. Mothers and fathers who will by then be grandparents will watch in dismay as cancers that we could have prevented stalk their now adult sons and daughters as they age. The genital warts data show early success, spotlight a large missed opportunity, and provide a potent call to action. The United States can and must raise its HPV vaccination coverage to prevent HPV-attributable diseases.

We believe, as others do, that concerted action by multiple stakeholders can increase HPV vaccination coverage. The President's Cancer Panel has provided specific, evidence-based, and practical recommendations for addressing low HPV vaccination coverage in the United States.³ First, the panel recommended reducing missed opportunities for vaccination, for example, by providing communication trainings for clinicians^{17,18} and quality improvement visits to clinics.^{19,20} Second, the panel recommended increasing acceptability of the vaccine, for example, by better understanding parental hesitancy and concerns and intervening to address these issues.^{21,22} Third, the panel recommended maximizing access, for example, by increasing the viability of alternative vaccination settings such as schools and pharmacies.^{23–25} It is time to begin vigorous implementation of these recommendations for supporting widespread HPV vaccination throughout the United States. National groups such as the National HPV Vaccination Roundtable and regional groups such as state physician organizations can offer leadership and coordination for quick action.

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