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Control of HPV-associated cancers with HPV vaccination

***Mark Schiffman** and **Mona Saraiya**

Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA (MSc); Division of Cancer Prevention and Control, Centers for Disease Control and Prevention, Atlanta, GA, USA (MSa) schiffmm@mail.nih.gov

In the *Lancet Infectious Diseases*, Eric Chow and colleagues[1] present evidence of remarkable population effectiveness against human papillomavirus (HPV), with virtual eradication of targeted types, among heterosexual men within a few years after vaccination of the young Australian female population with the quadrivalent HPV vaccine (4vHPV). Their study is notable because of its inventive observational methods and compelling implications.

To study the effectiveness of the vaccine in this population, they tracked trends in the prevalence of specified HPV genotypes in mainly urine specimens from 1466 heterosexual men aged 25 years or younger who had tested positive for *Chlamydia trachomatis* at the Melbourne Sexual Health Centre from 2004 to 2015. By studying men with chlamydia, which is also transmitted by sexual contact, the investigators had a population with high exposure to HPV, including to the 13 high-risk genotypes that cause almost all cases of cervical cancer and many oropharyngeal, anal, penile, vaginal, and vulvar cancers (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68; Chow and colleagues also included genotype 66 in their analysis although there is limited evidence that it causes cervical cancer).[2]

The Centre routinely stores frozen urine from men who test positive for chlamydia. Although urine testing for HPV DNA in men is an indirect and seldom-used measure of vaccine efficacy in women, in this study it proved to be an acceptable and appropriate measure of population effect;[3] the findings from Chow and colleagues study showed reductions in the prevalence of the genotypes targeted by the vaccine between 2004 and 2015: genotypes 6 and 11 (from 12% [95% CI 6–21%] to 3% [1–7%], p_{trend}=0·008), 16 and 18 (from 13% [95% CI 7–22%] to 3% [1–6%], p_{trend}<0·0001), and all 4vHPV-targeted genotypes together (from 22% [95% CI 14–33%] to 6% [3–10%], p_{trend}<0·0001). To strengthen their point using a natural comparison, Chow and colleagues[1] showed that the prevalence of the remaining oncogenic HPV types not targeted by the vaccine did not decrease over the study period. The untargeted HPV types served as ideal controls for the four targeted genotypes,[4] and provided convincing evidence of population effectiveness without a clinical trial.

Finally, a substantial proportion of the men in the clinic had recently arrived in Australia (within 2 years) from England, Scotland, Wales, Cook Islands, Northern Ireland, or the

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Netherlands, all of which at that time were offering women HPV vaccination with the bivalent vaccine (2vHPV) against genotypes 16 and 18.[5] Among these men, the prevalence of genotypes 16 and 18 decreased in the postvaccination period compared with the prevaccination period (adjusted prevalence ratio [PR] 0·32, 95% CI 0·14–0·74; p=0·008) but types 6 and 11 did not (adjusted PR 0·50, 0·16–1·56; p=0·234). The investigators made excellent scientific use of country-of-birth data, a risk stratifier, and by doing so they were able to further strengthen their ability to attribute decreases in HPV prevalence by type to the specific vaccine offered to girls in the men's country of birth. Country-of-birth data are not routinely collected in many countries, and obtaining them can be sensitive because they are sometimes related to immigration status. Nonetheless, in countries with a large immigrant population, strategies such as screening among vaccinated populations might need to consider differential risks by country-of-birth.

These encouraging data regarding herd immunity and interruption of HPV transmission are thought-provoking. The 4vHPV-vaccine programme started among Australian girls aged 12–13 years in April, 2007, and quickly achieved high population coverage.[6] Eradication of targeted HPV types took only a few years after high coverage was achieved. Although the programme in Australia used a three-dose schedule, two doses of HPV vaccine are now considered sufficient by WHO and could conceivably produce similar herd immunity.[7] In fact, data from a study[8] show that one dose of the bivalent vaccine protects against HPV for at least several years, if not longer, prompting a new clinical trial of one-dose efficacy. The results will show whether a one-dose campaign might produce substantial population immunity, such as that noted with the Australian three-dose programme.

In framing prevention strategies, it is important to remember that HPV typically causes cancer in three broad, necessary steps: acquisition, persistence linked to development of precancer, and invasion,[9] and that sexual transmission of HPV peaks in young adults. Precancer begins to appear within a few years of the usual age of HPV acquisition, whereas invasion usually follows decades of slow, initially intraepithelial lateral spread of precancerous lesions.

Because of this causal pathway, interruption of HPV acquisition in adolescents and young adults almost completely ensures the subsequent elimination of the second peak of precancer and eventually the control of cancer;[10] therefore, vaccine efficacy might not need to last a lifetime. Moreover, if the new nonavalent vaccine can prevent 90% of oncogenic-type infections,[11] and duration of protection is just as long as for the original vaccines, we have the methods needed for a major public health victory.

In terms of efficacy, giving two or three doses of vaccine before these women become sexually active is the reference standard and goal. However, if prevention of cancer as soon as possible is also our goal, the focus might need to be shifted from vaccine efficacy to population effectiveness. The clearest route to elimination of HPV transmission is to vaccinate as many young women as possible. In view of the high coverage, protection against HPV that lasts past a decade would do a large amount of good, even if the protection is not lifelong. Expansion of the target age range for vaccination, and a reduction in the number of vaccine doses might be the best public health approach where resources are

scarce and cervical cancer or other HPV-related cancer burden is high and where setting up a resource-intensive screening programme might not be feasible (ie, in many low-income and some middle-income countries).[12]

Some strategies have been proposed[12] that combine a global vaccination campaign with HPV testing and treatment of women who are HPV-positive expanded throughout the ages of greatest HPV transmission, but further assessments of these strategies are warranted. If herd protection is as powerful as suggested by the findings from Chow and colleagues' study, the ultimate goal of controlling HPV-associated cancers could be achieved decades faster than with current approaches.

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