Re: Impact of Human Papillomavirus (HPV)-6/11/16/18 Vaccine on All HPV-Associated Genital Diseases in Young Women

As we contemplate the astonishing successes of human papillomavirus (HPV) vaccines, it is worthwhile to consider whether randomized controlled trials of the sort recently published in the Journal can ever show reductions in cervical cancer rates (1). In their excellent article, Muñoz et al. (1) reported nearly complete efficacy of quadrivalent HPV vaccine against vulvar and cervical intraepithelial neoplasia, adenocarcinoma in situ, and genital warts that contained viral types in the vaccine. Of course, this study did not show differences in cervical cancer because that was never its intent. However, the hope that one day randomized controlled trials like these will finally show that HPV vaccines prevent cervical cancer is nicely summarized by the conclusion of a recent systematic review (2) of HPV vaccine trials, "To evaluate cervical cancer incidence and mortality, a longer follow-up is necessary."

But is this really true? Assessing clinical trial outcomes related to cervical disease typically requires regular Papanicolaou test screenings, and ethics require that women with abnormal screening results receive follow-up and treatment, as appropriate. This combination of screening and treatment should prevent all but the most aggressive interval cervical cancers (3). Indeed, one of the most interesting findings reported by Muñoz et al. was that none of the women in the trial developed cervical cancer during the approximately 63 000 women-years reported. Because their study participants had at least annual screening for cervical abnormalities to assess the main outcomes, clinicians treated abnormalities identified during the tests with procedures known to be effective in preventing cervical cancer and thus vastly reduced the chances the women would get cervical cancer. We can think of this risk reduction as reflecting a "cervical cancer Heisenberg principle," according to which studying intermediate outcomes obliterates more severe ones.

One way that researchers have devised to get around this Heisenbergian challenge is to design studies that continue past the duration of most efficacy trials (ie, beyond 4–6 years) (3). Women remain randomly assigned to condition, but they no longer receive regular testing as part of the trial. Instead, the researchers follow the women over the next decades by linking their identities to national cancer registries. The ethical justification is that routine screening and medical treatment outside the trial are the standard of care. In contrast, HPV vaccine provision to older women is not the standard of care, and the majority of HPV infections will have already occurred during the ages in which women were enrolled in the trial.

The other alternative to get around this Heisenbergian challenge is to evaluate HPV vaccine impact at the population level by use of one of the many alternatives that we have previously reviewed elsewhere (4). These evaluations have to rely on prospective cohort studies and other nonexperimental study designs that yield weaker evidence than randomized controlled trials. One such study (5) recently reported decreases in the incidence of genital warts after implementation of a national HPV vaccination program in Australia. It is highly likely that additional studies, many of which are under way, will provide similar correlational evidence for the population-level impact of HPV vaccine on cervical cancer. While we wait for further evidence to accumulate, it is important to remember that most randomized controlled trials cannot and will not tell us whether HPV vaccines prevent cervical cancer.

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