Real-world HPV Vaccine Effectiveness Studies: Guideposts for Interpretation of Current and Future Studies

Nicole G. Campos PhD[1], Anil K. Chaturvedi PhD[2], Aimée R. Kreimer PhD[2]

[1]Department of Health Policy and Management, Harvard T.H. Chan School of Public Health, Boston, MA 02115, USA

[2]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD 20892, USA

Corresponding author

Aimée R. Kreimer, PhD

Senior Investigator, Infections & Immunoepidemiology Branch

Division of Cancer Epidemiology and Genetics, NCI

9609 Medical Center Drive, RM 6-E104

Bethesda, MD 20892

Telephone: 240.276.7102

Email: kreimera@mail.nih.gov

Registry-based effectiveness studies provide evidence for the real-world impact of the Human papillomavirus (HPV) vaccine. Given the length of time between acquisition of a "causal" HPV infection and cancer incidence, initial studies focused on the reduction of surrogate endpoints such as genital warts and cervical precancer.[1] Now, studies from Denmark[2] and Sweden[3] document the profound impact that HPV vaccination can have on reducing incidence of cervical cancer— a leading cause of cancer death in women, particularly in low- and middle-income countries.

Kjaer et al[2] report results from a nation-wide cohort study in Denmark showing that, 12 years after implementation of HPV vaccination, there was an 86% decrease in cervical cancer among the youngest vaccinees (aged ≤16 years) and a 68% decrease among older teens (aged 17-19 years) who were HPV-vaccinated. These findings are consistent with a recent Swedish study,[3] and offer proof-of-principle that there is great utility in vaccinating adolescent girls and young women.[2] Whereas the Swedish study found a 62% decrease in cervical cancer among women vaccinated between 20 and 30 years of age, the Denmark study observed a non-statistically significant increase in cervical cancer among women vaccinated between the ages of 20 and 30 years compared to unvaccinated women.

Collectively, the two studies reaffirm the benefits of vaccination of young women prior to sexual debut. However, the impact of vaccinating women past sexual debut into the late teens and 20s remains uncertain. Anticipating an abundance of future studies on HPV vaccine effectiveness against cervical cancer, we propose a few key guideposts for analysis and interpretation of results from these early studies to guard against premature conclusions regarding the impact of HPV vaccination at older ages.

Early results from registry-based observational studies with short durations of follow-up are expected to differ from health decision model projections that adopt a lifetime perspective

When cervical cancer is the endpoint, short-term observational studies (particularly those that compare the benefits of young versus older ages at vaccination) need to incorporate: 1) adequate follow-up time such that causal HPV infections acquired prior to vaccination can be observed through progression to cervical cancer; and 2) adequate follow-up time post-vaccination such that prevention of HPV infections could manifest as reductions in cervical cancer incidence (relative to unvaccinated individuals). In contrast to short-term observational studies, health decision models can simulate follow-up time over the full life-course to more completely address these two temporal aspects.

The Denmark study[2] is only able to ascertain vaccine impact on cancers up to age 31 years, over an average follow-up time for study participants of 6.4 years (5.3 years for vaccinated; 7.9 years for unvaccinated) and a maximum follow-up time of ~13 years. The early-onset cervical cancers through age 31 years (which account for <10% of all cervical cancers in Denmark)[4] are primarily caused by HPV infections acquired at young ages. We would thus expect vaccine administration prior to age 20 years to reduce these early-onset cancers. By contrast, the duration of follow-up time is too short in the Denmark study to evaluate the true utility (or futility) of vaccination at ages 20 to 30 years. In that, the follow-up time is not sufficient to observe the accrual of benefits from prevention of causal infections post-vaccination. Therefore, the most appropriate conclusion from the study by Kjaer and colleagues

is that for prevention of cervical cancers that occur prior to age 30 years, vaccination prior to age 17 years is most efficacious.

Recent modeling analyses suggest that in the United States, the range of the median age at causal infection is most likely in the early to mid-20s.[5] If the model projections are accurate and can be reasonably applied to Denmark, we would expect HPV vaccination between the ages of 20 and 30 years to prevent a substantial proportion (~50%) of cervical cancers that would otherwise occur in the 40s and beyond. Thus, follow-up time for women vaccinated at older ages will likely need to extend to middle age when cervical cancer is the endpoint of interest.

Registry-based studies of the effectiveness of HPV vaccination against cervical cancer need to carefully account for potential biases inherent in observational studies

These biases include: 1) estimation of follow-up time pre-vaccination and post-vaccination (accounted for by Kjaer et al.[2] through the use of vaccination as a time-varying intervention); 2) comparability of study follow-up time across groups defined by ages at vaccination (accounted for by Kjaer et al., in part, through adjustment for attained age); 3) consideration of prevalent disease from infections acquired pre-vaccination (evaluated by Kjaer et al. through the use of buffer periods post-vaccination); and 4) self-selection bias if early adopters of HPV vaccination at older ages represent individuals with an elevated risk of HPV acquisition prior to vaccination (as appropriately discussed by Kjaer et al.).

As the number of vaccinated women increases, herd immunity will reduce intermediate outcomes and cervical cancer in unvaccinated women, thus "apparently" diminishing the observed effectiveness of HPV vaccination

While it is probably too early to observe indirect benefits of HPV vaccination on cervical cancer in Denmark, it will be important to analyze time trends in the prevalence of HPV infection,[6] precancer, and cervical cancer among both vaccinated and unvaccinated women to evaluate the potential contribution of herd immunity to estimates of vaccine effectiveness. By anticipating an apparent attenuation in vaccine effect due to herd immunity, we can ensure data are available to avoid underestimating the benefits of HPV vaccination.

HPV vaccine effectiveness by age at vaccination is anticipated to differ across settings

While modeling studies from high-resource settings are informative, model projections of the age at causal infection cannot necessarily be extrapolated across settings with different HPV prevalence patterns,[7] the reasons for such differences notwithstanding (e.g., differences in HPV natural history, sexual behavior, screening uptake/adherence, and vaccine uptake).[8] Of note, there is an urgent need for HPV natural history data and vaccine efficacy/effectiveness data from low-resource settings, particularly in sub-Saharan Africa, a region with very high cervical cancer incidence.

In summary, registry-based studies from Sweden and now Denmark provide the valuable insight that HPV vaccination is effective at reducing early-onset cervical cancer among

girls vaccinated during adolescence. For the methodologic reasons outlined above, early results on the apparently limited impact of vaccination after adolescence must be interpreted with caution. Determining a reasonable upper age limit for effective HPV vaccination will require extended follow-up for women vaccinated after adolescence; evaluation of time trends in HPV, precancer, and cancer in both vaccinated and unvaccinated women for evidence of herd immunity; and additional data on HPV natural history and vaccine effectiveness from settings with the greatest risk of cervical cancer.

Funding

None.

Notes

Role of the funder: Not applicable.

Disclosures: The authors have no disclosures.

Acknowledgements: We thank Jane J. Kim, John T. Schiller and Douglas R. Lowy for their feedback and insights included in this editorial.

Author contributions: Writing, original draft— NGC, AKC, ARK. Writing, editing and revision— NGC, AKC, ARK.

Data Availability

Not applicable.

References

1. Drolet M, Benard E, Perez N, Brisson M. Population-level impact and herd effects following the introduction of human papillomavirus vaccination programmes: updated systematic review and meta-analysis. Lancet 2019;394:497-509.

2. Kjaer SK, Dehlendorff, C., Belmonte, F., Baandrup, L. Real-world effectiveness of Human Papillomavirus vaccination against cervical cancer. *Journal of the National Cancer Institute* 2021.

3. Lei J, Ploner A, Elfstrom KM, Wang J, Roth A, Fang F, Sundstrom K, Dillner J, Sparen P. HPV Vaccination and the Risk of Invasive Cervical Cancer. N Engl J Med 2020;383:1340-1348.

4. Bray F, Colombet, M., Mery, L., Lineros, M., Anzaor, A., Zanetti, R., and Ferlay, J. Cancer Incidence in Five Continents, Vol. XI. In. Lyon: International Agency for Research on Cancer; 2017.

5. Burger EA, de Kok I, Groene E, Killen J, Canfell K, Kulasingam S, Kuntz KM, Matthijsse S, Regan C, Simms KT, Smith MA, Sy S, Alarid-Escudero F, Vaidyanathan V, van Ballegooijen M, Kim JJ. Estimating the Natural History of Cervical Carcinogenesis Using Simulation Models: A CISNET Comparative Analysis. J Natl Cancer Inst 2020;112:955-963.

6. McClung NM, Lewis RM, Gargano JW, Querec T, Unger ER, Markowitz LE. Declines in Vaccine-Type Human Papillomavirus Prevalence in Females Across Racial/Ethnic Groups: Data From a National Survey. J Adolesc Health 2019;65:715-722.

7. Bruni L, Diaz M, Castellsague X, Ferrer E, Bosch FX, de Sanjose S. Cervical human papillomavirus prevalence in 5 continents: meta-analysis of 1 million women with normal cytological findings. J Infect Dis 2010;202:1789-99.

8. Campos NG, Demarco M, Bruni L, Desai KT, Gage JC, Adebamowo SN, de Sanjose S, Kim JJ, Schiffman M. A proposed new generation of evidence-based microsimulation models to inform global control of cervical cancer. Prev Med 2021;144:106438.