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Letter to the Editor of Lancet

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The evidence is clear. HPV virus like particle (VLP) vaccines are highly effective in preventing persistent HPV infection and related cervical disease in girls and women naïve to the relevant HPV type(s). However, what remains unclear is the public health benefit (PHB) to be derived from vaccination of mid adult women 24-45: the age cohort considered in the study by Munoz et al[1]. Here's why:

In the trial, the vaccine efficacy (VE) in the per-protocol population was 90% for disease or infection related to HPV 6, 11, 16, and 18. VE is the appropriate metric to answer the focused question of whether the vaccine is able to prevent infection and disease in women naïve to the relevant HPV type. However this is not the best metric to evaluate the PHB of vaccination. To assess PHB, a different cohort, disease endpoint and metric may be considered.

1. Cohort: Analysis of PHB should use the intention-to-treat population rather than the per-protocol cohort that excludes women with pre-existing infections and women who do not complete the full course of vaccination. (VE in the intention to treat population was only 31% in the Munoz study). It also should evaluate the generalizability of results from the cohort to the target population.
2. Endpoint: Newly-detected infections that persist for 6 months may be a reasonable surrogate endpoint for evaluating VE, however PHB should be based on the reduction in an endpoint close to the disease targeted for prevention (i.e. CIN2+, or better yet CIN3+, as surrogates for cancer risk). In the Munoz study, virtually all the endpoints were either persistent infection or CIN1 (which the authors admit is considered a manifestation of productive HPV infection). The number of cases of CIN2+ is not reported.
3. Metric: A relative ratio of disease reduction as measured by VE, does not account for the incidence of disease (attack rate) in the unvaccinated population in contrast to an absolute rate reduction of disease (e.g. how many cases averted per 1,000 women vaccinated). To illustrate the importance of attack rate in assessing PHB, consider these examples: a vaccine with only 50% VE against a disease that would affect 20% of the population will prevent 100 events per 1,000 vaccinated, while a vaccine with 90% VE against a disease that would strike 1.0% of the population will prevent only 9 events per 1,000 vaccinated.

Recent data provide evidence that new HPV infections in older, sexually-experienced women carry only a low risk of developing into CIN2+. [2] In the Munoz study, 25 “cases” of persistent

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HPV-16 and/or HPV-18 persistent infection or disease (largely CIN1) were averted in almost 4000 person-years of follow-up. If 10% of these infections would have been expected to develop into CIN2 or worse, then the extrapolated PHB of vaccinating women 24-45 would be prevention of 1.33 cases of CIN2+/1000 women over two years.

HPV vaccination is expensive. It is clear that targeting young women prior to sexual debut will provide the greatest benefit from HPV vaccination for a given cost. The peak of CIN2/3 occurs in women in their late-20's and early 30's---HPV vaccination must precede the acquisition of those causal HPV infections that occurred 5-10 years earlier.[3] PHB and cost-effectiveness, not just VE, should be considered before establishing vaccination recommendations.

References

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