RE: Population-Level Impact of the Bivalent, Quadrivalent, and Candidate Nonavalent Human Papillomavirus Vaccines: A Comparative Model-Based Analysis

Suba et al. (1) raise concerns that prophylactic human papillomavirus (HPV) vaccines may increase the risk of high-grade cervical disease despite the overwhelming evidence to the contrary. The natural history of HPV (2) predicts the rise of early high-grade cervical disease in a cohort of women aged 20 to 29 years, as many have been previously infected with HPV, some several years before and now have persistent HPV infection, which is a strong predictor of high-grade cervical disease (3). A cohort of HPV-positive younger women is therefore expected to accumulate high-grade cervical disease over time. The median age of screen-detected high-grade cervical disease is typically in the late 20s and early 30s (4), 10 to 15 years after HPV infections are acquired. Notably, cervical cancer rates rise sharply with age until the mid-40s in the United States (5) (http://seer.cancer.gov/) despite widespread cervical cancer screening primarily by Pap testing. By the same arguments presented by Suba et al. (1) against the use of HPV vaccines, one could conclude erroneously that Pap smears cause cervical cancer rather than prevent it, as is widely accepted based on ecological data.

Even if the duration of prophylactic HPV vaccines protection is only 15 to 20 years, in the worst case scenario, these vaccines will protect women at least until their mid-20s and thereby protect women from a large proportion of HPV infections that are acquired over a lifetime are acquired before that age. If one considers the age-specific HPV prevalence as a simple proxy of when women get exposed (which does not account for the fact that most prevalent HPV infections detected in older women are due to long-term persistent infections rather than new infections), most causal HPV infections, those that eventually go on to cancer if not prevented, probabilistically must be acquired within the first few years after population median age of sexual initiation.

The continued advocacy for Pap-only approach to cervical cancer prevention ignores the fact that after more than 60 years since its introduction Pap has failed to prevent cervical cancer in most places in the world, including Vietnam, which has much less than 10% Pap coverage in the population. Although Pap testing may reduce cervical cancer rates by 60% within 3 years, a program of Pap screening over 30 to 50 years is necessary to reduce the risk of cancer by 60% over a lifetime, which is not achievable in most parts of the world. HPV vaccination may reduce the lifetime risk of cervical cancer by up to 70% with the bivalent or quadrivalent vaccines and nearly 90% with a nonavalent vaccine. Unlike a cervical Pap test, HPV vaccination will also prevent a large proportion of penile, vulvar, vaginal, anal, and oropharyngeal cancers over a lifetime. Importantly, the Global Alliance for Vaccination and Immunization (http://www.gaviorganisation org/support/nvs/human-papillomavirus-vaccine-support/) has made HPV vaccines available at a greatly reduced price to the countries with the least resources.

Although prophylactic HPV vaccines may be the ultimate cervical cancer prevention strategy, there are two to three generations of women who will not benefit from HPV vaccination, and the benefits of HPV vaccination will not be experienced for 20 to 30 years after introduction, so screening programs are needed to prevent cancer now (6). Nevertheless, alternative strategies to Pap testing for cervical cancer screening are needed to complement current efforts to avoid the predictable millions of preventable cervical cancer–related deaths over the next 50 years (7).

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References

Notes
P. Castle has served as a paid consultant for BD, Roche, Cepheid, GE Healthcare, and Gen-Probe/ Hologic; has received HPV tests and reagents for research at a reduced or no cost from Qiagen, Roche, Norchip, and mtm; and is a paid member of a data and safety monitoring board for clinical trials of HPV vaccines for Merck.

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Response
Castle observes that a cohort of women in their 20s will demonstrate greater high-grade cervical disease rates than the same cohort during their teenage years. These observations do not explain why a cohort of Australian women in their 20s, after the introduction of human papillomavirus (HPV) vaccination, demonstrated greater high-grade cervical disease rates than a cohort of Australian women in their 20s before the introduction of HPV