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Age-Appropriate Use of Human Papillomavirus Vaccines in the U.S.*

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Abstract

Cervical infections by approximately 15 cancer-associated (carcinogenic) human papillomavirus (HPV) genotypes cause virtually all cervical cancer and its immediate precursor lesions worldwide. Prophylactic vaccines against human papillomavirus (HPV) types HPV16 and HPV18, which cause 70% of cervical cancer worldwide, hold great promise for reducing the burden of cervical cancer worldwide. However, current HPV vaccines prevent future infections and related cervical abnormalities and do not treat pre-existing HPV infections. In the U.S., HPV vaccine introduction should be considered in the context of a very successful cervical cancer screening program that has reduced the rates of cervical cancer by 75% or more. Thus, HPV vaccines will only prevent an incremental number of additional cervical cancers in the U.S. The introduction of HPV vaccines can also prevent other HPV-related sequelae, most importantly cervical intraepithelial neoplasia grade 2 or 3 (CIN2/3), which precede the development of cervical cancer and require clinical follow-up and treatment. Examining data from 7 clinical centers in the U.S., the median age of CIN2/3 is

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typically between 25-30 years of age in 2007; if screen-detected CIN2/3 develops on average 5-10 years after the causal infection is acquired, HPV vaccination will only prevent a significant proportion of CIN2/3 if it is given to women before the age of 26 and more so if given to women 18 and younger. It is increasingly evident that prophylactic HPV vaccines will provide the greatest public health or population benefit only when delivered to adolescent women.

I. Introduction

Persistent infections of the uterine cervix by 15-20 cancer-associated (“carcinogenic”) human papillomavirus (HPV) genotypes cause virtually all cervical cancer (1;2), and its immediate precursor lesions (3), worldwide. Based on this nearly absolute etiologic link between carcinogenic HPV and cervical cancer, new approaches for the prevention of cervical cancer have emerged, including vaccination for primary HPV prevention in younger women and improved screening including HPV tests in older women (4). Two HPV vaccines are based on the self-assembly of the recombinant L1 protein into non-infectious capsids (virus-like particles or VLPs) that contain no genetic material. Gardasil™ (Merck and Co, USA) has gained regulatory approval in several countries including the U.S. Cervarix™ (GlaxoSmithKline, Belgium) has been approved in Australia and in the European Union, and applications for approval have been submitted to regulatory agencies in the USA and other countries. Both vaccines target HPV16 and HPV18 genotypes, which cause approximately 70% of cervical cancer worldwide (5); Gardasil also targets HPV6 and HPV11, the two HPV genotypes that cause 90% of genital warts.

When all 3 doses are administered at the correct times, both HPV vaccines have shown better than 90% efficacy for preventing persistent HPV infections and precancerous lesions (cervical intraepithelial neoplasia grade 2 [CIN2], CIN3, and adenocarcinoma *in situ*) from the targeted types for up to 5 years in women not already infected with these HPV genotypes (6-8). It is noteworthy that although highly efficacious in the ideal population, the efficacy of these vaccines for prevention of precancerous lesions in the subsequent few years from the targeted types was less than 50% (when reported) in the general study (intention-to-treat) populations (9), which was selected based on sexual and Pap smear history to be at lowered risk of prior HPV infection. The wide gap in efficacy between the ideal target sub-group and whole study population, and the expected greater gap between the ideal sub-group and the general population, is primarily because neither vaccine treats common pre-existing HPV infections and related cervical abnormalities (6;7;10).

HPV testing should not be done as a screen prior to administering the HPV vaccine. Even with a FDA-approved test for HPV16 and HPV18 (<http://www.fda.gov/cdrh/mda/docs/P080015.html>), many women would need to be screened to find a few that currently HPV16 and/or HPV18 DNA positive (11). Additionally, there is no commercially-available serologic test that would reliably identify past exposure to HPV vaccine genotypes. The cost of pre-vaccination screening of all sexually active women would escalate the cost of vaccine administration.

The implication from these trial results is that rational integration of HPV vaccination and cervical screening will need to consider the health benefit per public health dollar invested to the whole vaccinated population rather than efficacy in a virus-naïve subgroup (12). Consideration of cost effectiveness of vaccination will be highly dependent on age, and will require understanding of HPV natural history and the stages of cervical cancer development. Young, HPV-naïve women are the most likely to get new HPV infections within a few years of sexual debut and therefore need protection against acquiring the riskiest HPV infections. Conversely, with increasing age, women are less likely to acquire new HPV infections; but if

already infected, are more likely to have cervical precancer or cancer. They are best served by cervical screening, diagnosis of the screen positives, and treatment of those diagnosed with precancer or cancer.

II. HPV Vaccination in the U.S

Due to the introduction of the Pap smear for cervical cytology screening over 50 years ago, the U.S. rates of cervical cancer incidence and related deaths have dropped by more than 75% to approximately 11,000 incident cases and 4,000 related-deaths per year.(13) It is therefore unlikely that widespread vaccination will greatly reduce the burden of cervical cancer in the U.S. The primary arguments for widespread HPV vaccination in the U.S. are: 1) prevention of HPV-related sequelae that require clinical management; and 2) cancer prevention in underserved, unscreened populations, in whom more than 60% of all cervical cancers occur in the U.S. (<http://www.cdc.gov/cancer/cervical/>), 3) prevention of rarer, non-cervical HPV-related cancers, for which there is currently no other preventive techniques. It is also possible that HPV vaccination might improve the cost-effectiveness of the current cervical cancer prevention program, provided that HPV vaccination and screening are thoughtfully integrated (12).

The HPV-related sequelae relevant to cervical cancer prevention are CIN3, which is certainly precancer, and CIN2, which is equivocal precancer (14;15) that is treated for safety. Cervical cancer presumably arises from a subset of women who develop CIN2/3, especially CIN3 (16), although there is heterogeneity in progression of untreated CIN3 to invasion (17) Widespread and effective vaccination prior to infection could potentially alleviate the need to manage approximately 55% of CIN2/3, or 70% if the reports regarding the cross-protection of vaccination against additional HPV types are accurate (6-8), under the unproven assumption of lifetime immunity. Elimination of approximately 70% of CIN2/3 could significant reduce treatment costs, estimated to be \$3,221 per case for direct medical and non-medical costs (office visit, procedures, follow-up) of treatment of CIN2/3 (18), provided that screening and management algorithms are adjusted to lower population risk (12).

If, in addition to reducing further the burden of cervical cancer, one of the primary benefits of HPV vaccination is the prevention of CIN2/3 as the precursors to cervical cancer, it makes sense to ask the relevant questions: 1) at what ages is CIN2/3 diagnosed?, and 2) at what ages should vaccination be given in order to greatly reduced the need for treatment of CIN2/3?

III. Age Distribution of CIN2/3

To answer the first question, we elected not to use published data from epidemiologic studies or clinical trials, which can introduce potential biases by the subject selection criteria as well as differences in screening and diagnostic procedures compared to current standard-of-care practice. Instead we collected data on the age of CIN2/3 diagnosed (N = 3,596) in 2007 from 7 large clinical centers throughout the U.S. to assess “real-world” patient outcomes (Figure 1). These diagnoses represent those from the general population in these regions as these large clinical centers serve central urban areas and their surrounding regions.

Shown in Figure 1A is the cumulative percentage of CIN2/3 by age group for each institution. There are several key points: First, there is a rapidly increasing cumulative diagnosis by age in all locales. Second, the median age of CIN2/3, the age at which 50% of cases happen below and above that age, varies significantly between the different clinical sites. More than 50% cases occurred in women aged 24 or younger from Mississippi (60%) and Alabama (55%), aged 29 and younger from Oklahoma (66%), Pittsburgh (60%), Detroit (54%), and Kaiser Permanente Northwest (51%), and aged 34 and younger from Kaiser Permanente Northern California (53%). Third, the age distribution of CIN2/3 was shifted to the younger ages in

women from the poorest states, like Mississippi and Alabama, which have higher rates of cervical cancer (13;19). The reasons for the variability in the median age of CIN2/3 diagnoses are uncertain.

To achieve maximum effectiveness of HPV vaccination, women must be vaccinated at an age in which the majority of women are protected against the causal infections. In order to estimate the fraction of prevented CIN2/3 by vaccination with age, the median time between the causal infections and CIN2/3 must be estimated. Although CIN2/3 can arise [as a miniscule lesion] within a couple of years after acquisition of carcinogenic HPV infections, the general consensus is that it takes 5-10 years from the time of causal HPV acquisition for the CIN2/3 lesion to grow sufficiently large to be screen-detected (n.b., If the median age of CIN2/3 mid to late 20s, and sexual debut is 17, then approximately 10 years is the longest interval. However, most new infections will occur within the first 5 years after debut and therefore, stochastically, it seems likely that most causal infection would be acquired 5-10 years prior to CIN2/3 diagnosis).

To examine the estimated fraction of CIN2/3 prevented by HPV vaccination per protocol, one conservatively assumed a **median** interval time between acquisition and diagnosis of 5 years and assumed that the vaccine could prevent 70% CIN2/3 from incident carcinogenic HPV infections (Figure 1B) if vaccination were to take place at least 5 years or more before average age of diagnosis (n.b. we note that there is likely to be significant variation in the time between acquisition of causal HPV and diagnosis of CIN2/3. We are using an estimated median time i.e. half of the CIN2/3 develops in a shorter time interval and half in a longer time interval based on the fact that it is about 10 years from the median time of sexual debut to the median age of screen-detected CIN2/3 but most exposures to HPV happen within 5 year of sexual debut, or 5-10 years before diagnosis). HPV vaccination of a cohort of women aged 10-14 would prevent approximately 50% of CIN2/3 in Mississippi and 70% at Kaiser Permanente Northern California.

By contrast, HPV vaccination of women 20-24, an age group within ACIP age recommendations for vaccination (20) but not included in the ACS age recommendations (21), would prevent only about 10% of CIN2/3 in Mississippi and, at very most, 45% at Kaiser Permanente Northern California. Vaccination at age 40-44 would prevent virtually no CIN2/3 in Mississippi and 10% at Kaiser Northern California. If the median interval between infection and CIN2/3 diagnosis (n.b., not development of the initial lesion but average diagnosis) is assumed to be 10 years, the absolute reduction in CIN2/3 by vaccinated age group is diminished even further, especially in higher-risk populations like those in Mississippi: HPV vaccination of women 20-24 would prevent only about 5% of CIN2/3 in Mississippi and 30% at Kaiser Permanente Northern California. Vaccination at age 40-45 would prevent virtually no CIN2/3 in Mississippi and 5% at Kaiser Northern California. These benefits may be expected to be reduced further by imperfect compliance with number of vaccine doses and dose intervals.

IV. Genital Warts

Another potential benefit afforded by Gardasil is protection against genital warts. There are no good studies of the cumulative incidence or proportions by age of genital warts in the U.S. The most definitive study was conducted on the general population of 70,000 women from 4 Nordic countries, with a median age of sexual debut of approximately 17 years (22)(as it is in the U.S. (23)). In that study, half or more the population diagnosed with genital warts had their primary occurrence before the age of 26. Even if genital warts manifest in a short interval after HPV6/11 infections, the majority of genital warts will only be prevented with HPV vaccination (with Gardasil) in women under 26.

V. Infections in Older Women

As part of the ongoing effort to maximize uptake of the current vaccine, much emphasis will no doubt be placed on the risk of new acquisition of HPV infection by older women. Health care providers and policy makers sifting through these messages in search of clinical relevance need to understand that with increasing age an increasing percentage of HPV detected is prevalent infection rather than newly acquired infection (24) (and increasingly likely to persist because these are most likely long-standing infections). Importantly, HPV vaccination protects against new infections and does not treat these pre-existing (prevalent) infections or significantly alter their natural history. In addition, the risk of CIN2/3 associated with the presence of HPV in older women is low, as Figure 1 clearly depicts, despite the fact that screening is recommended and conducted through age 65 at minimum (25). *In toto*, these observations make it clear that few infections ultimately leading to CIN2/3 and then cancer, which occurs on average approximately 20 years following the development of precancer (From 2001-2005, the median age at diagnosis for cancer of the cervix uteri was 48 years of age; www.seer.cancer.gov), will be prevented with HPV vaccination of women in their late 20's, 30's, and 40's.

Importantly, newly detected or incident infections do not pose a greater risk of persistence or developing into CIN2/3 in older women versus younger women (26), the predominant outcome of which is to clear within a year or two (26-28). Thus, it seems less and less likely with age that HPV vaccination will prevent risky HPV infections given two additional factors: 1) The prevalence of HPV declines sharply with age in most populations, including in U.S. populations (29;30); and 2) a greater proportion of prevalent HPV infection detected in older women is due to long-term persisting infections (24) that the HPV vaccines cannot impact.

VI. Vaccination and Participation in Screening Programs

While the development of prophylactic HPV vaccines is a great technological advance, it is important to consider its role vis-à-vis screening and treatment of precancerous lesions and cancer in cervical cancer prevention programs. It remains a concern that some vaccinated women, including some who already harbor undiagnosed CIN2/3, will choose not to participate in cervical cancer screening programs because of a false sense of security, despite messages which clearly articulate the need to continue screening. Recent data from health economic models provides evidence that a small decrement in participation in cervical cancer screening programs can completely offset the benefits of vaccination (18). Thus, widespread promotion of vaccination at older ages has the potential to negatively impact health outcomes as well as driving the costs of the current prevention program even higher with almost no anticipated reduction in CIN2/3 and cancer.

Conversely, if women are screened starting at later ages and at more reasonable intervals with more selective follow-up and treatment, in the setting of vaccination, than the cost-effectiveness of the cervical cancer control program could improve. If the opportunity costs of an inefficient program are recouped, then these resources could be invested in ensuring disadvantaged women not receiving appropriate screening are screened.

Current guidelines (25;31;32) recommend that cervical cancer screening by cervical cytology is initiated at age 21 or 3 years past the age of sexual debut. In populations whose overall risk of cervical cancer is significantly lowered by HPV vaccination i.e. ≤ 18 years old, it is rational to consider initiating screening at later age such as 25 years (12). Conversely, screening guidelines should remain unchanged in those populations vaccinated at older ages (19 years old and older) because these women will have had only a minimal reduction in their cancer risk.

VII. Final Comments

Although vaccine manufacturers have sought regulatory approval for vaccination of women through age 45 in the U.S. and have received it in Australia (33), there is virtually no evidence that vaccination above age 26 will have a large impact on clinically-relevant outcomes -- CIN2/3 and cancer. The cost effectiveness between ages 18 and 26 is debated (20;21). Delivery of HPV vaccine to adolescents will prevent the largest proportion of CIN2/3, and vaccination of adolescents in underserved populations will have the greatest impact on cervical cancer incidence and mortality and possibly overcome cancer health disparities. Importantly, these facts will not fundamentally change as the result of partial protection against a few of the most genetically-related, weaker carcinogenic HPV genotypes (8;34;35) or even the introduction of the next generation of HPV vaccines, which will target 8 HPV genotypes (4), which will have only an incremental greater capacity (~15%) to prevent CIN2/3 and cancer. Based on epidemiologic and natural history data, most causal infections occur within a few years of sexual debut during the peak exposure to HPV infections. While older individuals may on rare occasions benefit from HPV vaccination, they might well glean no more benefit than routine screening would provide, which all older women will need regardless of whether they were HPV vaccinated.

We acknowledge that we did not conduct a formal cost-effective analysis to assess the relative utility of vaccination with age, although the aforementioned health economic models have demonstrated that the marginal benefit of HPV vaccination for 21-24 year olds is half the benefit as for 12 year olds (18). Even under the assumptions of lifetime, 100% effective immunity against all HPV16/18-related disease outcomes (cervical cancer, genital warts, juvenile onset recurrent respiratory papillomatosis, and other cancers), the incremental cost-effectiveness of HPV vaccination quadruples when comparing the vaccination of 12 year olds vs. 12-26 year olds, from approximately \$20,000 to \$90,000 per quality-adjusted life-year, respectively (36). Policies and decisions around any medical intervention are best made when taking into account the balance between benefit and cost. In order to help clarify the benefit portion of this equation, we sought to describe the relationship of age to CIN2/3 diagnoses and cancer in the U.S. As shown, the population effectiveness of vaccination in the U.S. must decline precipitously with age even as the costs of expanding "catch-up vaccination" to older women remain large (\$360 wholesale costs for vaccination plus the pharmacy mark-up and administration costs) and constant. While women in their late 20's, 30's and 40's may consider being vaccinated "out-of-pocket", they should be first educated by clinicians about the limited benefit and their continuing need to be screened.

At least for the public sector, health resources are limited and competitive, and any large expenditure must be considered in relation to other competing health care needs, especially for the poor and uninsured. Cervical cancer prevention in the U.S. already costs billions of dollars and is largely effective; age-appropriate application of HPV vaccination, as well as screening, will maximize the health benefit per health care dollar (37). More importantly, targeting medically-underserved populations suffering an excess burden of cervical cancer (19), such as women living in the Mississippi Delta, Appalachia, Washington D.C., and along the U.S.-Mexico Border, for age-appropriate HPV vaccination and screening will have the greatest impact on reducing the burden of cervical cancer in the U.S.

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Figure 1.

examines the relationship of diagnosis of CIN2/3 at 7 clinical centers (Kaiser Permanente Northern California (KPNC) (Oakland, CA), Kaiser Permanente Northwest (KPNW) (Portland, Oregon), Wayne State University (WSU) (Detroit, MI), University of Mississippi (Jackson, MI), University of Alabama Birmingham (U. AL) (Birmingham, AL), and University of Oklahoma (U. OK) (Oklahoma City, OK), and Pittsburgh (University of Pittsburgh, PA) in the U.S. in 2007 (n.b., the data from KPNC are from June 2006 to June 2007). Data from Pittsburgh were based on biopsies only. Age was categorized into 5-year age groups, and in some cases 5-year age groups combined, to avoid age categories with <5 cases that might violated HIPAA regulations. For each site, the oldest age group represents that age group and

older (to ensure that there no less than 5 cases per age group). The use of the data was approved or exempted by the institutional review boards of the clinical sites, and was deemed not applicable to human subjects research review by the NCI institutional review board. Figure 1A shows cumulative percentage of CIN2/3 diagnoses with 5-year age groups. Figure 1B shows the projected number of CIN2/3 prevented with age-group of vaccination for the clinical sites with youngest and oldest median age of CIN2/3 for a 5-year or 10-year median interval between acquisition of the causal HPV infection and screen-detected diagnosis. It was assumed that the vaccine prevents 70% of the CIN2/3 arising from incident carcinogenic HPV infections after vaccination.