Research Highlights

Highlights from the latest articles in human papillomavirus vaccination and cervical cancer research

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Sexual risk assessment is not helpful for recommendations on human papillomavirus vaccination

Evaluation of: Dempsey AF, Gebremariam A, Koutsky LA, Manhart L: Using risk factors to predict human papillomavirus infection: implications for targeted vaccination strategies in young adult women. *Vaccine* 26(8), 1111–1117 (2008).

The Advisory Committee on Immunization Practices (ACIP) in the USA recommends that the quadrivalent human papillomavirus (HPV) vaccine be given to all 11–12-year-old girls [1], as well as older adolescent females and young adult women up to 26 years of age. While this latter strategy would not prevent all vaccine-type HPV infections, acquisition of genital HPV infection continues at a relatively high rate throughout early adulthood [2]. Modeling supports the cost–effectiveness of catch-up vaccination of older adolescent and young adult women and predicts an accelerated reduction in HPV circulation in a population [3,4]. Many countries have made this recommendation; however, few have backed the recommendation with comprehensive funding (Australia was the first country to roll out a fully funded vaccination program from 2007). Young adult women may therefore need to pay for the vaccine. It is likely that clinicians will be asked about the health benefit of this vaccine by young women, or they may wish to advise young women regarding whether the vaccine is likely to provide a high level of benefit for their individual situation.

This study uses the dataset from the National Longitudinal Study of Adolescent Health in the USA [101]. It aimed to identify risk factors for HPV infection in a cross-sectional analysis of data, which was collected when participants were aged 18–26 years (in 2001–2002). Sexual behavior data was collected, as was HPV type-specific DNA, which was analyzed using PCR on self-collected urine samples. The authors examined the relationship between six behavioral risk factors that have been identified to be associated with HPV infection and which could be easily assessed in the clinical setting. These were: history of an older male partner, having had more than three sexual partners, a new sexual partner in the past 12 months, illegal drug use, sexual intercourse while intoxicated, and never-married status. In multivariate analyses, only age of sexual partner, number of sexual partners and recent sexual partner change were predictive of prevalent vaccine-type HPV infection. Sociodemographic characteristics were not associated with infection.

The authors examined whether a 'threshold' of risk factors exists for prediction of vaccine-type HPV infection. While the odds of infection increased significantly with the number of risk factors, this was not especially predictive of infection. This is because the prevalence of these sexual behavior risk factors was high in the population (72% of women had had an older partner), and the prevalence of vaccine-type HPV infection in the sample was comparatively low (fewer than 10% of women infected with vaccine types). Put another way, while women with multiple risk factors were

more likely to have an HPV infection than those without (10–16% versus 2%), the majority of women with risk factors did not have a prevalent infection. The authors concluded that targeting women with risk factors for vaccination would leave a sizeable proportion of susceptible women unvaccinated, as would the targeting of women without risk factors.

The value of this study is that it helps to illustrate the limitations of targeted HPV vaccination strategies in the clinical or population setting, as sexual risk factors are not discriminatory in predicting prevalent HPV infection. However, as the authors also point out, past HPV exposure and risk of future exposure also influence vaccine benefit. While serology is not currently available in the clinical setting, and only a proportion of women seroconvert after cervical HPV infection, serology provides some information about past exposure. It is possible that prospective studies with frequent collection of sexual behavior data, as well as frequent cervical sampling for HPV DNA and serology, would be informative for targeted HPV vaccine approaches. While very few published studies have collected this type of data in large samples, the placebo group of the Phase III HPV vaccine clinical trials could provide this data. This analysis is not a priority for vaccine companies, but it could still be very informative for vaccination strategies.

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Website

101. The National Longitudinal Study of Adolescent Health website. www.nichd.nih.gov/health/topics/add_health_study.cfm

Expecting the unexpected: human papillomavirus vaccination and coincident adverse events

Evaluation of: Siegrist C-A, Lewis EM, Eskola J, Evans SJW, Black SB: Human papilloma virus immunization in adolescent and young adults. A cohort study to illustrate what events might be mistaken for adverse reactions. *Pediatr. Infect. Dis. J.* 26, 979–984 (2007).

Within population birth cohorts, every year individuals experience new and often serious illnesses. Thus superimposing new vaccines, at a population level, inevitably leads to chance associations between vaccination and the onset of disease or acute heath events. As vaccine trials can not reliably identify rare adverse events following immunization (<1 in 10,000), adverse events surveillance systems are important components of vaccination programs. 'Safety signals', in the form of reports of particular illnesses following vaccination, can be investigated to assess causality by further epidemiological and scientific assessment, including careful analysis of expected rates of the disease in the vaccinated population. Examples of previous 'signals', and their subsequent investigation and determination of chance associations, include hepatitis B vaccines and multiple sclerosis [1], and pertussis vaccination and sudden infant death syndrome [2]. In this paper, in anticipation of large-scale HPV vaccine delivery in adolescent and young adult women, the authors identify the frequency of emergency care, hospitalizations and outpatient visits for autoimmune-related conditions in such a population.

The population consisted of young females (aged 9–30 years) registered with the Northern Californian Kaiser Permanente Medical Care Program health maintenance organization (HMO) during 2005 (n = 436,368). The first instance of inpatient and outpatient diagnoses with ICD-9 codes of interest were identified, and rates calculated from the enrolled population. A hypothetical HPV immunization schedule of three doses, at 0, 1 and 6 months (80% coverage for adolescents, 40% for young adults), was superimposed upon the distribution of the medical events to estimate at what rate apparent temporal associations between vaccination and the medical event would occur.

In the adolescent population studied, the most common reasons for emergency room attendance were infections, psychiatric conditions, and immune-mediated conditions (10.3%). Atopic/allergic conditions, most commonly asthma, occurred at a rate of 325 per 100,000 consultations. Non-allergic immune-mediated conditions, such as diabetes, were also common (86 per 100,000). Results for young adult women were similar (attendance with immune-mediated disease 837 per 100,000). Hospitalization rates with autoimmune diseases, of which thyroiditis was the most frequent, occurred at rates of 53 and 389 per 100,000 for adolescents and young women, respectively. Multiple sclerosis and optic neuritis were more frequent in young women than adolescents (12 vs 3.7 per 100,000 hospitalizations). When theoretical instances of vaccination were superimposed, three per 100,000

adolescents would have presented with asthma or allergy within 24 h of a vaccination and ten per 100,000 would have been hospitalized with an autoimmune disease within 6 weeks. Among young women, 28 per 100,000 would have been hospitalized with thyroiditis within 6 weeks.

A major strength of this study is the complete capture of medical presentations for care within this population, as well as a defined denominator population. However, it is subject to the usual limitations of disease classification and coding systems, as well as being limited to 1 year, which may not account for fluctuations in incidence. The purpose of the study was not to estimate baseline rates of disease in young women generally, as the population under study may not be representative of the wider population by demographics or patterns of healthcare-seeking behavior. Rather, the study exemplifies a method for identifying common relevant disease presentations, and thus anticipating possible vaccine safety signals within a population. While other countries may not have such HMO databases, similar analyses could be derived from emergency data presentations, hospitalization data, general practice databases and so on.

This is an extremely useful paper for explaining the difficulties in attributing causality to vaccination from incident health events at a population level. This will have a great deal of relevance, as millions of young women receive HPV vaccines globally.

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High risk of human papillomavirus infection with a young woman's first sexual partner reinforces the importance of vaccinating early

Evaluation of: Winer RL, Feng Q, Hughes JP, O'Reilly S, Kiviat NB, Koutsky LA: Risk of female human papillomavirus acquisition associated with first male sex partner. *J. Infect. Dis.* 197(2), 279–282 (2008).

Detailed understanding of the natural history of HPV infection is critically important to appropriate guidelines for prophylactic vaccination strategies, for governments developing population-based initiatives and for the clinician's practice. Published clinical trials indicate that the vaccine must be administered prior to first exposure and infection with vaccine-type-specific HPV. Women with evidence of previous or current exposure to a vaccine-type HPV do not appear to derive benefit from vaccination against this type (up to 3 years follow-up) [1]. It has been recognized for some time that cervical HPV infection is acquired almost exclusively through vaginal sexual intercourse, and so, intuitively, vaccinating young girls prior to sexual debut makes sense.

However, for several reasons this is not straightforward. Firstly, vaccination should occur prior to the median age of sexual debut based on population data, at a time well before the majority have initiated sexual activity. This has provoked concern that vaccination will accelerate girls' sexual debut. For parents and young adults, the knowledge that HPV is a sexually transmitted disease may be a source of concern owing to the stigma associated with these diseases. In some developing countries with conservative cultures, acceptance of vaccination against a sexually transmitted disease is likely to be more challenging, as women in these cultures are generally virgins at marriage [2]. For the general practitioner, confusion exists regarding the appropriate timing of vaccination for adolescent and young adult women who are attending their practice and inquiring about this vaccine.

This paper [3] describes a study that examines the acquisition of HPV in young women with their first sexual partner. It is notable for the frequent (4-monthly) sampling for HPV DNA using physician and self-collected vaginal and cervical samples, and the 2-weekly collection of sexual behavior data, via a web-based confidential diary. Women were University of Washington undergraduate students, aged 18–22 years (median: 19.4 years) at recruitment. Included in this analysis were 130 women who experienced first sexual intercourse with a male partner within 3 months of recruitment or during the follow-up, and who had had at least one clinic visit after first intercourse. The mean follow-up was 28.2 months, with censoring at the first report of intercourse with a second partner. The 12-month cumulative incidence of HPV infection was 28.5% (95% CI: 20.6–38.6%); at 24 months was 39.2% (95% CI: 28.6–52%); and at 36 months was 49.1% (95% CI: 35.8–64.2%). Of note, most infections were acquired during the first 12 months of the sexual relationship. The sexual experience of the woman's partner was significantly associated with higher risk of HPV infection after adjustment for other factors, such as age of woman at first intercourse, age of partner and years since menarche.

These results indicate that women are at high risk of HPV, even with one sexual partner. In addition, the risk appears to be highest early in the relationship. This is consistent with several other studies that have examined HPV infection from the onset of sexual activity [4–6]. In one study, the median time from first intercourse to first detection of HPV was only 2.6 months [6]. A woman's past history of sexual partners was a less important risk factor for HPV acquisition than her partner's sexual experience, in a similar study by the same authors [4].

These findings highlight the importance of starting the three-dose course of HPV vaccine well before a woman has sexual intercourse, for maximal benefit. It provides a strong case for vaccinating all adolescents at a young age, in order to ensure protection for the great majority. It also suggests that even women with a history of one partner, and who are monogamous in that relationship, may still have a high risk of HPV infection. Clinicians should therefore not wait until their female patients are sexually active to offer the HPV vaccine; they should offer it as soon as any young woman or adolescent presents to their clinic.

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Surveillance of human papillomavirus infections and disease in the vaccine era

Evaluation of: Antonishyn NA, Horsman GB, Kelln RA, Saggar J, Severini A: The impact of the distribution of human papillomavirus types and associated high-risk lesions in a colposcopy population for monitoring vaccine efficacy. *Arch. Pathol. Lab. Med.* 132, 54–60 (2008).

As roll-out of HPV vaccines occurs, attention is turning to methods for the evaluation of the population-level impact of these vaccines. The type specificity of the vaccines poses particular challenges for evaluation, with only a percentage of all cervical lesions and cancers prevented, and this varying somewhat by region [1]. As HPV typing of cervical specimens is not routine, the ideal method for monitoring of vaccine effectiveness, and ascertaining whether any type replacement of HPV 16 and 18 occurs, is yet to be determined. An attractive option will be sentinel surveillance from an appropriate site within the population, monitoring HPV types using standardized and reproducible methods over time. This study reports on baseline results from such a site in Saskatchewan, Canada.

The study population comprised women referred to the colposcopy clinic at the Women's Health Centre, Regina General Hospital, Saskatchewan, between 1998 and 2005. Women were referred if they had two abnormal Pap smears in 6 months or a single Pap smear showing cervical intraepithelial neoplasia (CIN) 3. Cervical cells for DNA testing were collected immediately following the Pap smear specimen using a brush. HPV DNA detection was performed using standardized (redundant) methods over time, consisting of an L1 PCR as a primary screen, with negative specimens tested with a second PCR targeting an E1 open reading frame. Automated sequencing was performed, with indeterminate genotypes further analyzed and amplified. Real-time PCR was used, in addition, to identify mixed infections with HPV 16 and 31, the most common genotypes detected.

Overall, 1355 DNA samples were matched to 1166 patients. In total, 56% of the samples were positive for HPV DNA, reflecting that this was a selected 'high-risk' clinical population for HPV positivity (of specimens with matched histology, 19% were CIN3, 14% were CIN2, 37% were CIN1 and 30% had no CIN at the time of biopsy). The three most common HPV types detected in the clinic population were HPV 16 (18%), HPV 31 (6.1%) and HPV 18 (3.6%). Among those with high-grade cervical lesions (CIN2+), 47% had HPV 16, 15% had HPV 31 and 3.9% had HPV 18. Type 31 was significantly more likely to be associated with severe cytologic abnormalities than HPV 18 ($p = 0.004$). In all years but one, HPV 16 was the most prevalent type detected.

The identification of HPV 31 as the second most common type causing high-grade disease in this population is consistent with a worldwide meta-analysis [2], suggesting that these lesions are more likely to regress than high-grade lesions caused by HPV 18, given that HPV 18 is the second most common type found in cervical cancers [1]. The study also confirmed that traditional typing methods miss mixed infections. Additional mixed infections were detected in those specimens assessed further in the presence of HPV 16 or 31. The significance of mixed infections, underdiagnosed in the past, may become more apparent post-vaccination if the incidence of high-grade disease does not fall as much as anticipated. This study supports the need for the use of multiple primer sets in screening specimens.

Strengths of the study are the large population monitored over time, although a robust sentinel surveillance system is likely to need an even larger pool of specimens within each histological classification in order to have sufficient power to measure significant changes in HPV type causing disease over time. The present data are also useful for determining what this sample size is likely to be. The major limitation of the study is the selection bias inherent in selecting a clinic-based population, limiting the generalizability of the findings. However, if the selection criteria for attendance at the clinic and the source population remain stable over time, such a sample can perform a useful function as a sentinel surveillance system, particularly if combined with results from other sites that include women from various demographic groups representative of the total population.

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