REFERENCES

HPV vaccination: More evidence of benefit


SUMMARY
This study aimed at evaluating cancer and low- and high-grade cervical abnormalities after the introduction of the national human papilloma virus (HPV) vaccination programme with the quadrivalent vaccine (Gardasil) in Victoria, Australia for all women 12–26 years of age during 2007–2009.

The vaccination programme consisted of a continuing component that targets 12–13-year-old girls in schools and two catch-up programmes, one for 13–17-year-old school girls and the other for 18–26-year-old women through general practice and community settings delivered between July 2007 and December 2009. A telephone-based survey indicated that the programme achieved a coverage of 74% for one dose, 69% for two doses and 56% for three doses. The programme includes one of the broadest funded catch-up range in the world. This vaccination programme overlaps with the national cervical cancer screening programme of Australia established in 1991. It recommends one cervical cytology test every 2 years, beginning at the age of 18 years (or 2 years after the onset of sexual activity, whichever is later) until the age of 69 years.

There is a rapid effect on infection with vaccine-targeted HPV types after the implementation of the population-based HPV vaccination programme. However, because of the long lead time between infection and its malignant transformation, the programme’s effect on cancer will need decades to assess. This study reported cervical abnormality rates in young women in the first 3 years after the national HPV vaccination programme as these cervical abnormalities are more proximal.

The data were extracted from the Victorian Cervical Cytology Registry (VCCR) for all screening-related episodes between 1 January 2001 and 31 December 2009. Data were analysed to determine whether the incidence of cervical abnormalities changed after the introduction of the HPV vaccination programme in April 2007 compared with 4 years before its introduction. Cytopathologically defined high-grade abnormality (HGA) was the primary outcome measure and low-grade abnormality (LGA) was the secondary outcome measure. An LGA or HGA outcome was regarded as incident if it was a woman’s first LGA or HGA diagnosis, or a woman’s first abnormality that occurred at least 2 years (730 days) after a previous abnormality, with at least two negative tests in the intervening period. Incidence rates were defined as the number of incident events per 100 women tested within 3 months. Incidence rates were estimated for 3-month periods and stratified by five age groups which had different exposure to vaccination: women of age ≤17 years, 18–20 years, 21–25 years, 26–30 years and ≥31 years) and two periods: before vaccination (1 January 2003 to 31 March 2007) and after vaccination (1 April 2007 to 31 December 2009). Comparisons between the two periods for each age group were done with Fisher exact test.

Lowess smoothing (bandwidth 0.5) was used to show incidence trends over time. A quantitative comparison of HGA temporal trends before and after vaccination was done with piece-wise Poisson regression analysis. In the context of a constant trend, the incidence rate ratio (IRR) was used as a measure of proportional change in incidence rate within a 3-month period. IRR was used to estimate the ratios of slopes for temporal trends before and after vaccination. Stata SE (version 10) was used to do all statistical analyses.

A decrease in LGA incidence was recorded in age groups 21–25 years, 26–30 years and ≥31 years. There was no decrease in LGA incidence in those younger than 18 years of age or those 18–20 years of age after the introduction of the HPV vaccination programme.

There was a significant decrease of 0.38% (95% CI –0.61 to 0.16; p=0.003) in the incidence of HGA in women ≤17 years of age, beginning shortly after the introduction of the HPV vaccination programme, with a reduction from 0.85% in 2006 (the year before vaccination) to 0.22% in 2009 (p=0.003). There was no significant change in the incidence of HGA in women 18–20 years of age. Small increases in incidence were seen in women 21–30 years of age (0.17%–0.18%, 95% CI 0.10–0.26; p=0.0001) and in those ≥31 years of age (0.02%, 95% CI 0.01–0.04; p=0.002). There was a significant progressive linear decrease in the incidence of HGA after the introduction of the vaccination programme in girls ≤17 years of age but in those 18–20 years of age, the HGA incidence trend after the introduction of vaccination was non-linear, and the decline was smaller and delayed.

COMMENT
The discovery that persistent infection with oncogenic HPV is the cause of cervical cancer and the long precancerous phase has
made cervical cancer largely preventable through Pap smear/HPV screening programmes, and more recently by HPV vaccination. This article represents an important public health success story.

HPV vaccination was approved by the US Food and Drug Administration (FDA) for prevention of cervical and vaginal cancers and their precursor lesions in 2006. Several countries have included HPV vaccination in their national immunization schedule. Australia was the first country to roll out an extensive, funded national HPV vaccination programme with the quadrivalent vaccine Gardasil™. This study is the first to report the effect of a national HPV vaccination programme on cervical abnormalities at a population level, using the Victorian Cervical Cytology Registry, which is one of the eight Pap test registries in Australia and promotes regular participation of women in the National Cervical Screening Programme by sending reminder letters and enables the follow-up of women with abnormal Pap tests. On the basis of the Registry, the authors could report almost complete population-based data about outcomes related to cervical-screening. The results have important implications for India which is the second most populous country in the world and bears one-quarter of the world’s cervical cancer burden. In India, both vaccines have been licensed for use in women since October 2008 (Gardasil) and February 2009 (Cervarix).

Testing efficacy of HPV vaccination in the elimination of HPV infection and HPV-related disease is an important issue since there is a considerable burden of HPV infection worldwide. In the present study, the temporal trend analysis from the population cohort is remarkable, illustrating the changing trends of disease with immunization. The study reported a decrease in incidence of high-grade cervical lesions in girls ≤17 years of age, 3 years after the start of the HPV vaccination programme. The decrease in the incidence of HGA occurred in the youngest vaccination cohort before it occurred in older catch-up cohorts who may have already acquired HPV infection. This reinforces the appropriateness of targeting the vaccines at pre-adolescent girls. The authors had used national standard classification for coding histopathological abnormalities and an appropriate 6-month period was allowed for reporting of histology to the register and checking of data. The definition of incident abnormalities used in the study was conservative, requiring both an extended time interval and two negative tests after a previous abnormality for new lesions to be defined as incident. Prevalence trends reported in this study were similar to incidence trends supporting the robustness of findings. The definition of the period after vaccination was also conservative because this phase was defined as starting at the introduction of the vaccination programme, rather than after the first date (4 months after its introduction) when women could have completed the three-dose course. This takes into account the biological plausibility that some vaccine efficacy starts after one to two doses of prophylactic vaccine.

The limitation of the present analysis is that it is epidemiological in nature, and therefore a causal link between the recorded decrease in incidence and the vaccination programme cannot necessarily be ascribed. To substantiate these findings, cervical cytology data should be linked to the HPV vaccination register data to enable analysis of cervical abnormality rates and participation rates by vaccination status. A great proportion of countries that have made a recommendation had completed a mathematical modelling project or had undertaken an economic assessment. However, the authors report strong biological plausibility and that the specific temporal association, differential by age (which is related to both coverage and likelihood of sexual activity and therefore HPV exposure before vaccination), suggests that the vaccination programme caused the decrease. HPV vaccination programmes may play an even more important role in settings like India that do not have an effective cervical cancer screening strategy.

REFERENCES


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