Papillomavirus Research 1 (2015) 59–73

Contents lists available at ScienceDirect

Papillomavirus Research

journal homepage: www.elsevier.com/locate/pvr

Effectiveness of less than three doses of quadrivalent human papillomavirus vaccine against cervical intraepithelial neoplasia when administered using a standard dose spacing schedule: Observational cohort of young women in Australia

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ARTICLE INFO

Article history:
Received 9 April 2015
Received in revised form
18 May 2015
Accepted 21 May 2015
Available online 15 June 2015

Keywords:
Human papillomavirus
Vaccination
Vaccine effectiveness

ABSTRACT

Background: Optimised two-dose human papillomavirus (HPV) vaccine schedules are now endorsed for young adolescents by the World Health Organization. Limited data are available about effectiveness of <3 doses using a standard dose schedule.

Methods: Deterministic data linkage was undertaken between the Victorian Cervical Cytology Registry and National HPV Vaccination Program Register to determine quadrivalent HPV vaccination status and incidence of cervical pathology among vaccine eligible women (aged 26 years or younger in 2007) screened in Victoria, Australia between April 2007 and December 2011. Proportional hazards regression was used to estimate hazard ratios (HR) adjusted for age, socioeconomic status and area of residence. Women were stratified into those vaccinated before or after first screen.

Results: Any number of doses (1, 2 or 3) were associated with lower rates of high grade and low grade cytology diagnoses as long as doses were given before screening commencement (one dose HR high grade 0.44 (95% CI 0.32–0.59), one dose low grade 0.48 (95% CI 0.40–0.58); two doses HR high grade 0.63 (95% CI 0.50–0.80), HR low grade 0.52 (95% CI 0.44–0.61); three doses HR high grade 0.53 (95% CI 0.47–0.60), HR low grade 0.73 (95% CI 0.68–0.78)). Three doses of vaccine, but not fewer, were associated with reduced risk of high grade histologically confirmed abnormality in this cohort, regardless of whether vaccination occurred before or after screening (HR before 0.71 (95% CI 0.64–0.80), HR after 0.87 (95% CI 0.82–0.93)). Secondary analyses censoring end points occurring within 1, 6, 12, or 24 months of final vaccine dose suggested an increasing effect of partial vaccination courses over time.

Conclusion: Our data suggest that less than three doses of quadrivalent HPV vaccine provides some protection against cervical intraepithelial neoplasia, even when measured within 5 years in a population including those who were sexually active at the time of vaccination.

Contents

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http://dx.doi.org/10.1016/j.pvr.2015.05.005

1. Introduction

Between 2007 and 2009, Australia vaccinated over half of its young women aged 12–26 years against human papillomavirus (HPV) types 6, 11, 16 and 18 using the quadrivalent HPV vaccine [1]. These HPV types cause over 90% of genital warts, 35% of low-grade cervical intraepithelial neoplasia (CIN), 50–60% of high-grade CIN (higher in younger women) and 70–80% of cervical cancers [2,3]. The vaccine was provided through both school-based programs and community providers, who were predominantly general practitioners. It remains the world's most broadly targeted funded HPV vaccination catch up program. The three-dose course was generally offered at the recommended spacing of 0, 2 and 6 months, with an accelerated schedule of 0, 1 and 4 months also used in the first year of the program in order to facilitate course completion within the school year. However, not all women completed the course, with dose 1 coverage in the population at least 15% higher than dose 3 coverage across the age range [1,4]. Reasons for this apparent failure to complete the course include school absence, lack of awareness of the need to complete three doses, interruption by pregnancy or travel, simply forgetting and under reporting of the final dose(s) to the register [1,5–7].

On the basis of immunogenicity[1] data from randomised trials, optimised two dose schedules (using a prime-boost spacing of at least 6 months between doses) have now been endorsed by the World Health Organisation for use in females < 15 years of age for both HPV vaccines. It is possible that even one dose of vaccine may be protective, with the recent hypothesis from Schiller and Lowy that the repetitive antigen display on the virus like particles stimulates an immune response that is more similar to that induced by a viral infection or attenuated live virus vaccine than a sub-unit vaccine [8].

Given that Australia has a considerable population of women who have only received one or two doses of the vaccine, we aimed to estimate the effectiveness of one or two doses of HPV vaccine against cervical abnormalities when administered as the first dose/s in a standard HPV vaccination schedule.

2. Methods

2.1. Data linkage and cohort assembly

As described previously, we undertook a deterministic data linkage between the Victorian Cervical Cytology Registry (VCCR) and the National HPV Vaccination Program Register (NHVPR) for vaccine age-eligible women resident in Victoria, Australia [9,10]. These registers, operating under opt-off consent, hold records of cervical screening tests and HPV vaccination doses for individual women. Briefly, identifying data was extracted and de-identified from each register in a similar manner and the Australian Institute of Health and Welfare's (AIHW's) data linkage unit generated varying combinations of perturbed details (such as selected letters from given name and surname, perturbed date of birth, postcode, parts of the Medicare number) and ascertained the best linkage pair combinations to achieve correct matching of unique individuals. For linked records, an identifying key was provided to each record set to allow analytical data fields from each register to be matched to the fields from the other register. Women who had a record identified in each register were thus identified as being both vaccinated and screened, whereas other women had either a screening or vaccination record only. In this analysis we only consider records for women with a screening history, creating a cohort of screened women, who may or may not be vaccinated. A retrospective cohort was constructed of women aged 26 or younger in 2007 (funded vaccine eligible) who had a Pap test recorded on the VCCR during the study period, 1 April 2007 (the date the HPV vaccination program commenced) to 31 December 2011. Women were counted as at risk of a diagnosis of a cervical abnormality from the time they commenced cervical screening, and were entered into the cohort at their first Pap test (or on 1 April 2007 if their first Pap test was prior to that time). Women were followed until the outcome of interest, date of death, hysterectomy or the end of the study period.

2.2. Outcome measures

The primary outcome was histologically confirmed high-grade (HG) cervical disease (CIN2+/AIS), defined as CIN2, CIN3 and adenocarcinoma in situ or mixed CIN3/AIS. We also considered histologically confirmed CIN3 and CIN2. We also examined the cytologically predicted abnormalities grouped as low-grade (possible LSIL, LSIL according to the Australian Modified Bethesda Classification) and high-grade (possible HSIL, HSIL, HGIL, possible HGIL). Histological and cytological outcomes were assigned according to categorisation used by the AIHW [11] and Australian Standardised Modified Bethesda System, respectively [12]. For all outcomes, a woman's first relevant abnormality or her first in two years with at least two negative cytology tests in between was counted.

2.3. Vaccination status and censorship before vaccine course completion

Vaccination status was defined as the number of doses received in accordance with the Chief Medical Officer of Australia's guidelines [13] (0, 1, 2, 3) with vaccination status defined as at the date

[1] **Abbreviations:** Victorian Cervical Cytology Registry (VCCR); National HPV Vaccination Program Register (NHVPR); Australian Institute of Health and Welfare (AIHW).