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

Julia M.L. Brotherton [a,c,*], Michael Malloy [a], Alison C. Budd [b], Marion Saville [a], Kelly T. Drennan [a], Dorota M. Gertig [a,c]

[a] Victorian Cytology Service, PO Box 178, Carlton South, Victoria 3053, Australia
[b] Cancer and Screening Unit, Australian Institute of Health and Welfare, Canberra, ACT, Australia
[c] Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, University of Melbourne, Victoria, Australia

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**



* Corresponding author at: Victorian Cytology Service, PO Box 178, Carlton South, Victoria 3053, Australia.
*E-mail address:* jbrother@vcs.org.au (J.M.L. Brotherton).

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).

of diagnosis of the cytological abnormality or, in the case of histology, at the date of the abnormal cytology preceding the histological diagnosis. Where cytology was performed on the day of vaccination, the previous period's vaccination status was assigned (i.e. number of doses – 1). Where women received three doses but those doses were given outside the recommended intervals (too close) and no fourth dose was given (designated as 'not clinically complete'), they were excluded from the analysis.

In this analysis we censored all events occurring during the vaccination course. Using this method, end points assigned to one or two doses are those of women who were only ever partially vaccinated (received one or two doses only) in the study period, reflecting the effectiveness of partial vaccination more accurately than if all cumulative time accruing for women who experience short amounts of time in receipt of one or two doses on the way to three dose vaccination are included. In our primary analysis we did not utilise any further lag periods once the final dose was received before commencing case counting, to reflect what would be observed by women and their clinicians. In a secondary analysis, we censored events occurring during the time period between the woman's final dose and one, six, 12 and 24 months after the woman's final dose to recognise that the abnormalities observed in the early periods following vaccination are likely to be the result of pre-existing HPV infection.

### 2.4. Data analysis

We stratified and/or adjusted all analyses by age, given that age is a strong predictor of the likelihood of sexual activity, diagnosis of a cervical abnormality and, in this cohort, age at vaccination. Together these factors mean that vaccine effectiveness will be higher in women in the cohort who are younger, as previously demonstrated [9].

We used Cox proportional hazard regression, with age as the time axis, to estimate hazard ratios (with 95% CIs) of cervical abnormalities for women in our cohort according to their vaccination status. Using age as the time axis allows the baseline hazard to change as a function of age, which is a better method for controlling the potential confounding due to age [14]. As we only had the month and year of each individual's date of birth, to calculate their age we made the assumption that their date of birth was on the 15th day of each month.

For the regression analysis, women were categorised into the age groups 12–16 years, 17–19 years, 20–23 years and 24–26 years (as at 2007, when the vaccine program commenced), approximately representing women of school age, school leaving age and young and mid-20s. These groups differed broadly in completion rates of the vaccine course, due to differing modes or issues in delivering the vaccine, as well as approximating timing of sexual debut. We also stratified women according to whether they were participating in screening prior to vaccination or afterwards. As cervical screening is only indicated in sexually active women (Australian guidelines state from the age of 18 years or two years after first intercourse (whichever is later)), we used this as a proxy measure for the occurrence of sexual activity prior to vaccination, implying that women vaccinated before they started screening were more likely to be HPV naïve at vaccination. We refer in this manuscript to two groups of women: Those who received their final vaccine dose before screening ("before" group) and those who received their final vaccine dose after they had commenced screening ("after" group).

Where overall estimates are made, these are adjusted for age (categorised or in single years, depending on the outcome and according to best fit for the model). We also adjusted a priori for socioeconomic status and area of remoteness using standard Australian area based measures assigned through postcode of residence [15,16]. The assumption of proportional hazards was not violated for any of the abnormality outcomes.

We also assessed whether there was any difference in vaccine effectiveness of two doses against high-grade histological outcomes according to the number of days between the doses, with the a priori hypothesis that a longer lag time would produce a superior immune response and therefore greater protection. We compared women with spacing between the two doses of less than 6 months with those with a spacing of 6 months or greater (the recommended dose spacing for licensed two dose courses), noting a median difference of 114 days (SD 128 days) between doses in our population.

Analyses of demographic and exposure characteristics of women in the cohort by vaccination status used the Mann–Whitney *U* test for ordinal variables and the Pearson chi-square test for nominal variables. Detection rates were calculated as the number of events per 1000 person–years at risk.

In a non HPV-naïve population, the relative effectiveness of HPV vaccination increases over time from the date of vaccination, as prevalent lesions are detected and treated or cleared and incident lesions occur in the unvaccinated women but not the vaccinated women [17]. Therefore, we also evaluated the observed effectiveness of vaccination by number of doses and screening pre-/post-vaccination over time using Kaplan–Meier failure probability plots. Failure time was calculated as the number of months from the time of their first Pap test or last vaccination dose (which ever was later) until their outcome of interest or time of censoring.

Statistical analyses were performed using Stata/SE 12.1 (StatCorp LP., College Station, TX).

Ethics approval was obtained from the Department of Health and Ageing and the Australian Institute of Health and Welfare's Human Research and Ethics Committees. Approval for use of NHVPR data was given by the Department of Health and Ageing, the data custodian and for the VCCR data by the Victorian Department of Health.

## 3. Results

### 3.1. Cohort characteristics

Results of the linkage process used to create the cohort are shown in Fig. 1. Following exclusion of those who received three doses spaced too close together ($n=426$), 289,478 women (133,055 unvaccinated and 156,423 with at least one dose) were included in the analysis. Characteristics of the cohort are described in Table 1. Maximum follow-up time was 4.75 years with an average follow-up time of 2.89 years (average of 2.73 years for vaccinated and 3.07 years for unvaccinated women). Vaccinated women were younger than unvaccinated women (mean age in 2007, 21.13 vs. 21.98; $p<0.0001$) and had a younger age at cohort entry (22.93 vs. 23.49; $p<0.0001$) and at first screen (20.43 vs. 21.71; $p<0.0001$). Unvaccinated women were more likely to live in a major city (80.53% vs. 75.71%; $p<0.0001$) and reside in areas in the lowest quintile of socioeconomic status (18.05% vs. 15.14%; $p<0.0001$). A greater proportion of vaccinated women were screening prior to April 2007 (vaccine program start date) (42.43% vs. 36.19%; $p<0.0001$). Among vaccinated women, incompletely vaccinated women were more likely to be participating in screening prior to their first vaccine dose than fully vaccinated women (1 dose 66.42%, 2 doses 61.58%, 3 doses 49.89%; $p<0.0001$).

### 3.2. Outcome by vaccination status and vaccination occurrence pre-/post-screening commencement

Overall, vaccinated women (any number of doses) had lower rates of histologically confirmed high-grade cervical abnormalities than

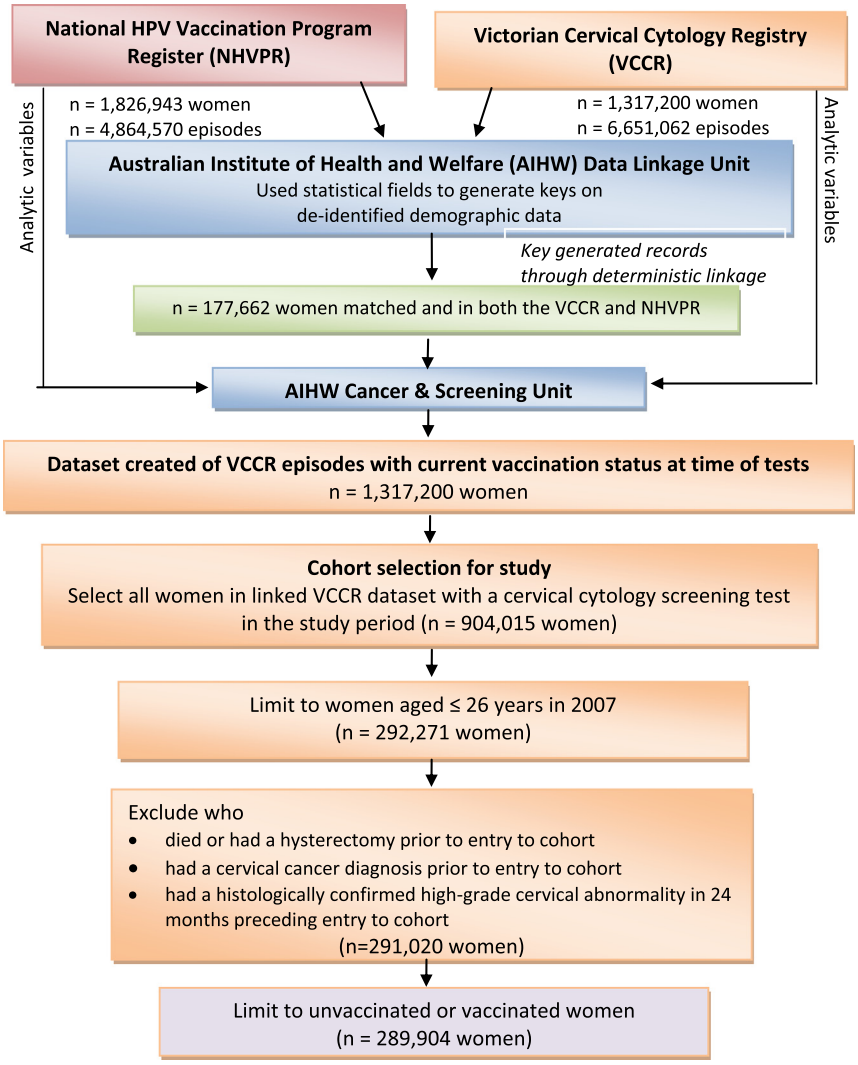


**Fig. 1.** Data linkage process and exclusions for analysis.**Footnote:* Note that the NHVPR data for linkage included all Australian women, whereas the VCCR data only holds records for women resident in Victoria. Approximately 470,000 Victorian females, including those too young to commence screening in the 2007–2011 period (routine age at vaccination in ongoing program is 12–13 years), have records of vaccine doses received in the study period held on the NHVPR.

unvaccinated women as long as they received their final vaccine dose before commencement of screening (6.44 vs. 7.81 per 1000 person years; adjusted hazard ratio 0.86 (95% CI 0.78–0.94)) (Table 2). This was due to the protective effect found among fully vaccinated women, in whom a lower rate was observed whether or not they were vaccinated before (rate 5.37) or after (rate 6.94) their first screen. This effect was greatest for CIN3/AIS (HR for women completing vaccination before screening 0.69 (95% CI 0.58–0.81)) compared with CIN2 (HR for women completing vaccination before screening 0.75 (95% CI 0.65–0.86)). Any number of doses (1, 2 or 3) was found to be associated with lower rates of high grade and low grade cytology diagnoses as long as doses were given prior to 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)) (Table 2). These results were fairly consistent across age groups, although the strongest effects against cytological abnormalities were seen in the oldest age groups in contrast to the histological outcomes, where the youngest women had the strongest evidence of protection. For women aged 16 and under, this protection against high-grade CIN appeared to extend even to partial dose recipients although smaller numbers of women in this group result in less precision in the estimates (see Appendix A Tables A.1–A.4 for age stratified results).

### 3.3. *Effects of dose spacing and censorship periods on outcome measures*

There was no discernible attenuation of effect for high grade histology outcomes seen when women who received two doses were stratified into those with 6 months or more separation between doses and less than 6 months (Appendix A Table A.5). However, applying censorship periods before counting end points for high grade histology and CIN3/AIS indicated that increasing lag times resulted in evidence of vaccine effectiveness over time for those who received one or two doses prior to commencing screening (Appendix A Table A.6). This is consistent with the Kaplan–Meier failure probability plots, which indicate, most notably for CIN3/AIS histology, that the effect of partial vaccination becomes apparent over time within the cohort (Fig. 2). By 48 months the incidence of CIN3/AIS among each of the vaccine dose groups vaccinated prior to screening is below that of the unvaccinated group (Fig. 3; see Appendix B for other outcome plots).

## 4. Discussion

Australia's large scale HPV vaccination catch up program, and relatively intensive cytology based cervical screening program,

**Table 1**
Summary of descriptive characteristics of entire cohort eligible for vaccine (aged 26 years or less in 2007).

| | Unvaccinated[a] | Vaccinated, any dose | Vaccinated, 1 dose | Vaccinated, 2 doses | Completely vaccinated[a], 3 doses |
|---|---|---|---|---|---|
| **Number of observations** | 133,055 | 156,423 | 20,659 | 27,500 | 108,264 |
| **Mean age in 2007** | 21.98 (±3.16) | 21.13 (±3.23) | 21.86 (±2.82) | 21.72 (±2.88) | 20.84 (±3.34) |
| **Mean age at first screen** | 21.71 (±3.42) | 20.43 (±2.74) | 20.77 (±2.96) | 20.69 (±2.90) | 20.30 (±2.64) |
| **Mean age at entry to cohort** | 23.49 (±2.96) | 22.93 (±2.86) | 23.40 (±2.65) | 23.39 (±2.69) | 22.72 (±2.92) |
| **Age in 2007 (years)** | | | | | |
| ≤16 | 8005 (6.02%) | 14,453 (9.24%) | 797 (3.86%) | 1372 (4.99%) | 12,284 (11.35%) |
| 17–19 | 23,066 (17.34%) | 36,236 (23.17%) | 3688 (17.85%) | 4944 (17.98%) | 27,604 (25.50%) |
| 20–23 | 50,255 (37.77%) | 60,992 (38.99%) | 9351 (45.26%) | 12,466 (45.33%) | 39,175 (36.18%) |
| 24–26 | 51,729 (38.88%) | 44,742 (28.60%) | 6823 (33.03%) | 8718 (31.70%) | 29,201 (26.97%) |
| **Remoteness area[b]** | | | | | |
| Major cities | 106,738 (80.53%) | 118,381 (75.71%) | 15,845 (76.72%) | 20,915 (76.09%) | 81,621 (75.42%) |
| Inner regional | 21,496 (16.22%) | 31,987 (20.46%) | 3970 (19.22%) | 5421 (19.72%) | 22,596 (20.88%) |
| Outer regional | 4261 (3.21%) | 5944 (3.80%) | 831 (4.02%) | 1141 (4.15%) | 3972 (3.67%) |
| Remote | 55 (0.04%) | 43 (0.03%) | 7 (0.03%) | 10 (0.04%) | 26 (0.02%) |
| **Socioeconomic status[c]** | | | | | |
| 1 (lowest) | 23,809 (18.05%) | 23,595 (15.14%) | 3383 (16.43%) | 4368 (15.94%) | 15,844 (14.69%) |
| 2 | 23,224 (17.60%) | 26,669 (17.11%) | 3917 (19.02%) | 4834 (17.64%) | 17,918 (16.61%) |
| 3 | 26,097 (19.78%) | 29,552 (18.96%) | 4140 (20.10%) | 5319 (19.41%) | 20,093 (18.62%) |
| 4 | 32,438 (24.59%) | 40,474 (25.96%) | 5062 (24.58%) | 7031 (25.66%) | 28,381 (26.31%) |
| 5 (highest) | 26,365 (19.98%) | 35,591 (22.83%) | 4091 (19.87%) | 5853 (21.36%) | 25,647 (23.77%) |
| **Age at first screen (years)** | | | | | |
| ≤16 | 4666 (3.51%) | 6359 (4.07%) | 962 (4.66%) | 1277 (4.64%) | 4120 (3.81%) |
| 17–19 | 36,585 (27.50%) | 60,236 (38.51%) | 6942 (33.60%) | 9522 (34.63%) | 43,772 (40.43%) |
| 20–23 | 51,137 (38.43%) | 66,950 (42.80%) | 8839 (42.79%) | 11,787 (42.86%) | 46,324 (42.79%) |
| 24+ | 40,667 (30.56%) | 22,878 (14.63%) | 3916 (18.96%) | 4914 (17.87%) | 14,048 (12.98%) |
| **Mean number of Pap tests** | 2.41 (±1.92) | 2.75 (±2.03) | 2.78 (±2.02) | 2.82 (±2.02) | 2.73 (±2.04) |
| **Mean number of Pap tests by abnormality status** | | | | | |
| No abnormalities | 1.95 (±1.31) | 2.19 (±1.37) | 2.19 (±1.34) | 2.22 (±1.34) | 2.18 (±1.38) |
| 1 or more abnormalities | 4.22 (±2.71) | 4.62 (±2.66) | 4.51 (±2.60) | 4.62 (±2.56) | 4.65 (±2.70) |
| **Screening history** | | | | | |
| Screening before 1 April 2007 | 48,157 (36.19%) | 66,367 (42.43%) | 9576 (46.35%) | 12,839 (46.69%) | 43,952 (40.60%) |
| First screen after 1 April 2007 | 84,898 (63.81%) | 90,056 (57.57%) | 11,083 (53.65%) | 14,661 (53.31%) | 64,312 (59.40%) |
| **Screening history (first dose)** | | | | | |
| First dose received prior to year of first screen | | 71,756 (45.87%) | 6938 (33.58%) | 10,565 (38.42%) | 54,253 (50.11%) |
| First dose received after year of first screen | | 84,667 (54.13%) | 13,720 (66.42%) | 16,936 (61.58%) | 54,011 (49.89%) |
| **Screening history (Final dose)** | | | | | |
| Final dose received prior to year of first screen | | 60,934 (38.95%) | 6938 (33.59%) | 8638 (31.41%) | 45,358 (41.90%) |
| Final dose received after year of first screen | | 95,489 (61.05%) | 13,720 (66.41%) | 18,863 (68.59%) | 62,906 (58.10%) |
| **Age commenced vaccination (years)** | | | | | |
| ≤16 | | 19,353 (12.37%) | 668 (3.23%) | 1541 (5.60%) | 17,144 (15.84%) |
| 17–19 | | 30,055 (19.21%) | 2790 (13.51%) | 4158 (15.12%) | 23,107 (21.34%) |
| 20–23 | | 59,377 (37.96%) | 8941 (43.28%) | 11,987 (43.59%) | 38,449 (35.51%) |
| 24+ | | 47,638 (30.45%) | 8260 (39.98%) | 9814 (35.69%) | 29,564 (27.31%) |
| **Year entered cohort** | | | | | |
| 2007 | 58,834 (44.22%) | 8949 (5.72%) | 3802 (18.40%) | 2933 (10.67%) | 2214 (2.05%) |
| 2008 | 13,992 (10.52%) | 69,914 (44.70%) | 7349 (35.57%) | 10,905 (39.65%) | 51,660 (47.72%) |
| 2009 | 17,267 (12.98%) | 39,390 (25.53%) | 5627 (27.24%) | 8339 (30.32%) | 25,964 (23.98%) |
| 2010 | 19,923 (14.97%) | 19,146 (12.24%) | 2226 (10.77%) | 2895 (10.53%) | 14,025 (12.95%) |
| 2011 | 23,039 (17.32%) | 18,484 (11.82%) | 1655 (8.01%) | 2428 (8.83%) | 14,401 (13.30%) |
| **Cytological abnormalities diagnosed on entry into cohort** | | | | | |
| **Negative** | 73,016 (88.49%) | 52,555 (88.78%) | 5869 (87.49%) | 7382 (88.23%) | 39,304 (89.08%) |
| **Low-grade** | 7846 (9.51%) | 5727 (9.67%) | 697 (10.39%) | 824 (9.85%) | 4206 (9.53%) |
| **High-grade** | | | | | |
| Possible | 795 (0.96%) | 499 (0.84%) | 79 (1.18%) | 81 (0.97%) | 339 (0.77%) |
| Definite | 824 (1.00%) | 406 (0.69%) | 63 (0.94%) | 78 (0.93%) | 265 (0.60%) |
| **Endocervical** | 34 (0.04%) | 10 (0.02%) | 0 (0%) | 2 (0.02%) | 8 (0.02%) |

*Note*: 426 observations categorised as 'Not Clinically Complete' are excluded. Entry into the cohort was at first Pap test, or 1 April 2007 if screened before this date. Missing data on 2079 women excluded.

[a] Count is of women; "unvaccinated" refers to women screened who did not receive any dose of HPV vaccine; "completely vaccinated" refers to women who were clinically completely vaccinated with three doses of HPV vaccine.

[b] Women were allocated to a remoteness area based on their postcode of usual residence, according to the Australian Standard Geographic Classification (ASGC) for 2006. Missing data on 140 women excluded.

[c] Women were allocated to a socioeconomic status (SES) groups based on their postcode of usual residence, according to the Australian Bureau of Statistics Socio-Economic Indexes for Areas (SEIFA) Index of Relative Socio-Economic Disadvantage [17]. Missing data on 320 women excluded.

have provided the opportunity to undertake early assessments of vaccination impact. We have taken advantage of the relatively large numbers of women in the population who did not complete their vaccine courses to assess whether there is any evidence, five years after the commencement of the program, that less than three doses of vaccine provide any protection against cervical disease. We found that for women who were vaccinated before commencing screening (an indicator that they were less likely to be sexually active and therefore not already exposed to HPV prior to vaccination), that one or two doses were associated with lower

**Table 2**
Number and rate of cervical abnormalities for completely vaccinated, partially vaccinated and unvaccinated women relative to their vaccination status at first screen (final dose of vaccine before, final dose of vaccine after or unvaccinated).

| Outcome | | Vaccination relative to first screen | Number of women /women-doses | Number of abnormalities | Rate[a] | Hazard ratio[b] |
|---|---|---|---|---|---|---|
| **Histological abnormalities** | | | | | | |
| Any high grade[c] | Unvaccinated | | 133,055 | 3140 | 7.81 | 1 |
| | Vaccinated (unadjusted) | Before | | | | 0.82 (0.75–0.89) |
| | | After | | | | 0.96 (0.91–1.02) |
| | Vaccinated (adjusted) | Before | 60,934 | 678 | 6.44 | 0.86 (0.78–0.94) |
| | | After | 95,489 | 2402 | 7.60 | 0.95 (0.90–1.00) |
| | 1 Dose | Before | 6938 | 124 | 9.28 | 1.19 (0.99–1.43) |
| | | After | 13,720 | 408 | 8.78 | 1.10 (0.99–1.22) |
| | 2 Doses | Before | 8638 | 142 | 9.30 | 1.21 (1.02–1.44) |
| | | After | 18,863 | 548 | 8.96 | 1.12 (1.02–1.23) |
| | 1 or 2 Doses | Before | 15,576 | 266 | 9.29 | 1.20 (1.06–1.37) |
| | | After | 32,583 | 956 | 8.88 | 1.11 (1.03–1.20) |
| | Complete | Before | 45,358 | 412 | 5.37 | 0.71 (0.64–0.80) |
| | | After | 62,906 | 1446 | 6.94 | 0.87 (0.82–0.93) |
| CIN3/AIS[c] | Unvaccinated | | 133,055 | 1726 | 4.26 | 1 |
| | Vaccinated (unadjusted) | Before | | | | 0.85 (0.75–0.96) |
| | | After | | | | 0.96 (0.89–1.03) |
| | Vaccinated (adjusted) | Before | 60,934 | 343 | 3.24 | 0.87 (0.77–0.99) |
| | | After | 95,489 | 1327 | 4.17 | 0.95 (0.88–1.02) |
| | 1 Dose | Before | 6938 | 78 | 5.81 | 1.41 (1.12–1.77) |
| | | After | 13,720 | 216 | 4.60 | 1.04 (0.91–1.20) |
| | 2 Doses | Before | 8638 | 72 | 4.68 | 1.17 (0.92–1.48) |
| | | After | 18,863 | 305 | 4.95 | 1.12 (0.99–1.27) |
| | 1 or 2 Doses | Before | 15,576 | 150 | 5.21 | 1.28 (1.08–1.52) |
| | | After | 32,583 | 521 | 4.80 | 1.09 (0.99–1.20) |
| | Complete | Before | 45,358 | 193 | 2.51 | 0.69 (0.58–0.81) |
| | | After | 62,906 | 806 | 3.85 | 0.87 (0.80–0.95) |
| CIN2[c] | Unvaccinated | | 133,055 | 1607 | 3.97 | 1 |
| | Vaccinated (unadjusted) | Before | | | | 0.79 (0.71–0.89) |
| | | After | | | | 0.99 (0.92–1.06) |
| | Vaccinated (adjusted) | Before | 60,934 | 377 | 3.56 | 0.85 (0.75–0.96) |
| | | After | 95,489 | 1241 | 3.90 | 0.97 (0.90–1.05) |
| | 1 Dose | Before | 6938 | 54 | 4.01 | 0.98 (0.75–1.29) |
| | | After | 13,720 | 220 | 4.70 | 1.17 (1.02–1.35) |
| | 2 Doses | Before | 8638 | 77 | 5.01 | 1.22 (0.97–1.54) |
| | | After | 18,863 | 283 | 4.59 | 1.14 (1.01–1.30) |
| | 1 or 2 Doses | Before | 15,576 | 131 | 4.54 | 1.11 (0.92–1.33) |
| | | After | 32,583 | 503 | 4.64 | 1.16 (1.05–1.28) |
| | Complete | Before | 45,358 | 246 | 3.20 | 0.75 (0.65–0.86) |
| | | After | 62,906 | 738 | 3.52 | 0.88 (0.81–0.96) |
| **Cytological abnormalities** | | | | | | |
| High-grade cytology[d] | Unvaccinated | | 133,055 | 3000 | 7.46 | 1 |
| | Vaccinated (unadjusted) | Before | | | | 0.54 (0.48–0.60) |
| | | After | | | | 1.18 (1.13–1.25) |
| | Vaccinated (adjusted) | Before | 60,934 | 404 | 3.81 | 0.53 (0.48–0.60) |
| | | After | 95,489 | 2834 | 8.98 | 1.17 (1.11–1.23) |
| | 1 Dose | Before | 6938 | 44 | 3.25 | 0.44 (0.32–0.59) |
| | | After | 13,720 | 390 | 8.36 | 1.09 (0.98–1.21) |
| | 2 Doses | Before | 8638 | 72 | 4.67 | 0.63 (0.50–0.80) |
| | | After | 18,863 | 565 | 9.22 | 1.20 (1.09–1.31) |
| | 1 or 2 Doses | Before | 15,576 | 116 | 4.01 | 0.54 (0.45–0.65) |
| | | After | 32,583 | 955 | 8.85 | 1.15 (1.07–1.24) |
| | Complete | Before | 45,358 | 288 | 3.74 | 0.53 (0.47–0.60) |
| | | After | 62,906 | 1879 | 9.05 | 1.17 (1.11–1.25) |
| Low-grade cytology[c] | Unvaccinated | | 133,055 | 6499 | 16.48 | 1 |
| | Vaccinated (unadjusted) | Before | | | | 0.68 (0.64–0.72) |
| | | After | | | | 1.25 (1.21–1.30) |
| | Vaccinated (adjusted) | Before | 60,934 | 1298 | 12.35 | 0.66 (0.62–0.71) |
| | | After | 95,489 | 6367 | 20.58 | 1.25 (1.20–1.29) |
| | 1 Dose | Before | 6938 | 114 | 8.48 | 0.48 (0.40–0.58) |
| | | After | 13,720 | 851 | 18.56 | 1.13 (1.05–1.21) |
| | 2 Doses | Before | 8638 | 143 | 9.32 | 0.52 (0.44–0.61) |
| | | After | 18,863 | 1196 | 19.88 | 1.21 (1.13–1.28) |

**Table 2** (*continued*)

| Outcome | | Vaccination relative to first screen | Number of women /women-doses | Number of abnormalities | Rate[a] | Hazard ratio[b] |
|---|---|---|---|---|---|---|
| | 1 or 2 Doses | Before | 15,576 | 257 | 8.93 | 0.50 (0.44–0.57) |
| | | After | 32,583 | 2047 | 19.31 | 1.17 (1.11–1.23) |
| | Complete | Before | 45,358 | 1041 | 13.64 | 0.73 (0.68–0.78) |
| | | After | 62,906 | 4320 | 21.25 | 1.28 (1.23–1.33) |

*Note:* 426 observations listed as 'Not Clinically Complete' are not included.
All high-grade histology defined as CIN2, CIN3, AIS and mixed CIN3/AIS.
High-grade cytology defined as possible high-grade squamous intraepithelial lesion (HSIL), HSIL, HSIL with possible microinvasion/invasion, squamous cell carcinoma, possible high-grade endocervical glandular lesion, AIS, AIS with possible microinvasion/invasion and adenocarcinoma.
Low-grade cytology defined as possible low-grade squamous intraepithelial lesions (LSIL), LSIL and atypical endocervical cells of uncertain significance.
Unvaccinated refers to women screened who did not receive any dose of HPV vaccine; completely vaccinated refers to women who were clinically completely vaccinated with three doses of HPV vaccine.

[a] Rate per 1000 person-years.
[b] Hazard ratio adjusted for age in 2007, remoteness and socioeconomic status.
[c] Age in 2007 fitted as a categorical variable (i.e. $<=16$, 17–19, 20–23 and 24+).
[d] Age in 2007 fitted as a continuous variable.

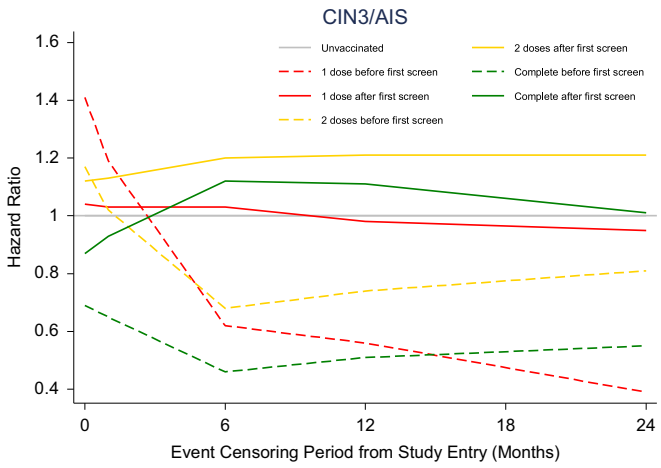


**Fig. 2.** CIN3/AIS adjusted* hazard ratio (unvaccinated=1) by vaccination status & first screen status) by censorship period to event counting. *Adjusted for Age in 2007 (Categorized), 'Remoteness' and 'SES'.

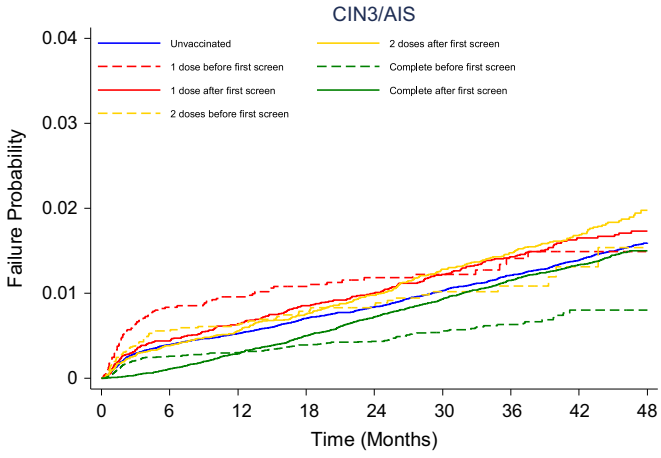


**Fig. 3.** Failure probability plot for CIN3/AIS by vaccination status & first screen status.

rates of high grade and low grade cytology outcomes. By prolonging the interval until outcomes were counted (allowing prevalent disease to resolve or be treated), we also found evidence that partial vaccination courses provide protection against high grade histological disease.

Our data add to the current evidence by noting that, even when given to a sexually active population using a conventional dosing schedule, some evidence of vaccine effect on cervical abnormalities can be observed from partial vaccination. It is consistent with findings from another Australian study, in which Crowe et al. estimated vaccine effectiveness of 21% against high-grade cervical disease in Queensland women vaccinated with two doses attending for their first Pap test [18]. A study of females vaccinated in the school program in British Columbia found significant reduction in high-grade disease in vaccine eligible cohorts but individual dose data was not utilised so no assessment of the relative impact of partial versus complete vaccination courses was made [19]. Swedish data suggest considerable effectiveness against genital warts from less than three doses of a conventional three-dose schedule [20]. Studies from Denmark have also demonstrated effectiveness of quadrivalent HPV vaccine against cervical lesions [21,22] but, in the case of genital warts, suggest that each dose provides an additional (and therefore necessary) degree of protection when using a standard three-dose schedule [23]. In contrast, data from the Costa Rica trial of the more immunogenic bivalent HPV vaccine suggested that less than three doses of that vaccine may be as effective as three, finding equally high levels of efficacy against disease despite lower but sustained antibody titres induced by partial vaccination [24,25]. Interestingly early data from Scotland did not detect a significant effect of partial bivalent vaccination on high grade CIN in young women attending for their first screens [26].

The main strengths of our analysis lie in the use of comprehensive high quality population based data sources. The greatest limitation to our analyses is an inability to completely control for confounding between the groups of women. This is not a randomised study and the available demographic data indicate that women differed significantly according to their vaccination status. Most notably those who only ever completed one or two doses of vaccine were screening participants at an earlier age (suggesting earlier onset of sexual activity) than vaccine completers or unvaccinated women, suggesting that they may have a higher underlying risk of HPV infection. This is supported by our finding that these groups had significantly higher rates of high grade histology diagnoses in the summary estimates, and of cytological abnormalities when vaccine was given after screening commencement, than unvaccinated women (Table 2). Notably however in the two youngest age strata (16 and under and 17–19 years (Tables A.1 and A.2, Appendix A)), hazard ratios for histological outcomes in partially vaccinated women were one or below one, suggesting

these demographic differences in risk profile can be overcome when vaccine is given at a young age. Our finding that a greater impact on cytology of partial doses was seen in older women rather than in the youngest may be due to less stable estimates of vaccine impact in younger women due to small numbers. Conversely the finding that suggestion of protection against high grade histology in the youngest women may be because young women are more likely to have HPV16 as the cause of high grade disease [27,28] and because young women produce higher antibody responses which may mean they can derive a greater benefit from partial vaccination than older women.

The greater relative impact on cytological outcomes, than on high-grade histologically confirmed disease, may partly be due to our greater power to detect differences in rates of cytological abnormalities because of their much higher frequency. In the Australian screening program, only a small subset of women proceed to colposcopy and, if required, biopsy. An additional and important factor that may explain the differences is the expected time course between vaccine impacts on infection related outcomes compared to high-grade disease outcomes which take longer after initial infection to develop. Low-grade cytology is a manifestation of acute HPV infection, so differences in incidence would be expected to occur rapidly after vaccination. Whilst most high-grade cytology does predict the presence of underlying high-grade pathology, it is imperfect with a positive predictive value of 79% in Victoria [29]. If 21% of high-grade cytology is in fact misclassified then this may be why an impact of partial vaccination was observed overall for high-grade cytology but not histology amongst $<3$ dose vaccine recipients. Additionally there is a lag time between high-grade cytology diagnosis and eventual diagnosis at biopsy, meaning that women diagnosed with high-grade cytology in the last months of the study may not have had their biopsies by the end of the study period. As shown in the study, the longer the interval between vaccination and outcome measurement, the stronger the effect of vaccination, meaning that the last period of the study is in fact when the highest vaccination impact would be expected. This is consistent with the findings of Hariri et al., who used the indirect cohort method to estimate vaccine effectiveness against HPV16/18 attributed high grade CIN among women in sentinel populations in the USA [30]. They found a clear relationship between vaccine effectiveness and time since vaccination, with effectiveness increasing over time. There was no significant effectiveness on CIN3/AIS lesions of 1 or more doses of HPV vaccine until 3 years post vaccination (after 2 years for CIN2+) in this similar population of young women. However the study lacked power to explore effectiveness by number of doses received.

It is interesting to note that Pollock et al. in Scotland also obtained odds ratios of high grade disease above 1.0 for partially vaccinated women, supporting our hypothesis that partially vaccinated young women may be at a somewhat higher underlying risk of HPV, possibly relating to demographic or behavioural characteristics which are also correlated with not completing the vaccine course [26]. Hariri et al. also noted prevalence ratios greater than one in young women in the first year post vaccination, again indicating the high rates of prevalent infection in young women [30]. We were not able to control for age at first intercourse or number of sexual partners in this population based data set, although we used age and stratification by vaccination relative to screening commencement (as screening should only commence at least two years after first intercourse) to partially control for likelihood of sexual activity/number of partners. Analysis of national HPV vaccine register data has previously found an association between socioeconomic status and course completion, with first dose uptake equal across socioeconomic strata but dose 2 and 3 completion rates lower in the lowest socioeconomic groups [31]. We adjusted for socioeconomic status in our analysis. A study of 1139 young women in NSW, Australia, recruited to a cohort following a negative Pap test, found that HPV vaccinated women were more likely to be single, nulliparous, alcohol drinkers, had fewer lifetime sexual partners but were more likely to have a history of non-HPV STI, and were more likely to be using oral contraceptives [32]. There was no association with educational attainment. These factors can thus said to be associated with decision making to receive HPV vaccination in young adult women in the context of the national catch up program – it is less likely that these factors relate to vaccination within the school cohorts. Unfortunately, as these data were collected whilst the catch up program was still ongoing, factors associated with course completion could not be examined.

As partially vaccinated women were earlier screeners, they also had more opportunity for detection of lesions. During the catch up vaccination program there was a significant amount of coincident screening and vaccination, with 11% of vaccinated women having their first screen during the vaccination course [10]. There is thus a possible detection bias, with vaccinated women more likely to have abnormalities detected. In the present analysis, outcomes diagnosed during the vaccination course were censored from the analysis and the average number of screening tests did not vary greatly between the groups of women in the study (Table 1). During this period in Australia, the incidence of high grade abnormalities peaked in women aged 20–24 years [33]. Because the median age of first intercourse in Australia is 16 years, most of the vaccinated women in our cohort of screening women are likely to have been sexually active prior to vaccination. As the HPV vaccine works by preventing infection and does not treat existing infection, discerning the effect of the vaccine in this population is difficult. It is encouraging that, similar to the increasing vaccine effectiveness over time observed in the ITT analyses of the original vaccine trials, we were able to discern some evidence of increasing effectiveness over time. By 2012 the overall rates of high grade disease in young Australian women had fallen in both the $<20$ and the 20–24 year old age group to such an extent that peak rates are now in the 25–29 year old age group for the first time ever [11]. A repeated analysis using data from 2012 onwards would be useful to monitor rates by vaccination status in upcoming cohorts of young women.

Other limitations include some underreporting to the register of vaccine doses, meaning that some women with incomplete courses may actually have received further doses. This would lead to an overestimate of the effect of partial vaccination. A national mobile phone survey suggested that nationally the degree of under reporting to the register is by about 5%/10%/15% for doses 1/2/3, respectively, in adult women (aged 18–26 during the catch up program) [5]. Under notification is much less for younger females as school reporting is virtually complete and Victorian school vaccinees incomplete on the register are sent reminders asking them to either complete the course or notify the register if they have received further doses (for example from their general practitioner) [34]. The data linkage undertaken was deterministic as no unique identifier was available for use and we were not permitted to use identified data for linkage under existing legislation. Hopefully in the future the use of the unique healthcare identifier on national health data sets in Australia, as well as revised legislation for the cervical screening registers to allow data to be used for data linkage, will result in datasets being linked with better certainty that records are correctly matched.

## 5. Conclusions

In summary we have observed an impact of both complete vaccination courses and incomplete vaccination courses on

cervical disease in Victorian women, despite many being sexually active prior to vaccination. At this stage our data support an effect of partial vaccination, although protection does not appear to be equivalent to that provided by three doses. We anticipate, as our analysis of the first 5 years of screening data following the start of the vaccination program suggests, that the effects of vaccination will increase over time. Females vaccinated prior to sexual debut will commence screening and women already infected prior to vaccination will clear those infections or have them removed through treatment, increasing the differential incident rate of vaccine-preventable HPV infection and disease to be observed between vaccinated and unvaccinated women in future.

## Role of the funding source

This study was funded by VCS Inc., a health promotion charity whose activities centre on the provision of laboratory testing and registry services for the Australian National Cervical Screening Program and the National HPV Vaccination Program. VCS is the employer of authors JMLB, MM, DMG, KTD and MS.

## Acknowledgements

We thank Genevieve Chappell, Cathryn May, Karen Winch and the information technology team at the Victorian Cytology Service (VCS Inc) for assisting with data extraction and testing, and staff at the Data Linkage Unit at the AIHW for conducting the data linkage. The VCCR is fully funded by the Victorian Department of Health and operated by the VCS. The NHVPR is owned by the Australian Government Department of Health and operated by the VCS.

## Appendix A

Appendix A Tables A1-A.6

**Table A.1**
Number and rate of cervical abnormalities for completely vaccinated, partially vaccinated and unvaccinated women (16 years of age or younger) relative to their first screen.

| Outcome | | Vaccination relative to first screen | Number of women/women-doses | No. of abnormalities | Rate[a] | Hazard ratio[b] |
|---|---|---|---|---|---|---|
| **Histological abnormalities** | | | | | | |
| Any high grade[c] | Unvaccinated | | 8005 | 65 | 6.51 | 1 |
| | Vaccinated (unadjusted) | Before | | | | 0.62 (0.44–0.88) |
| | | After | | | | 0.39 (0.16–0.97) |
| | Vaccinated (adjusted) | Before | 13,756 | 65 | 4.14 | 0.61 (0.43–0.87) |
| | | After | 697 | 5 | 2.51 | 0.38 (0.15–0.94) |
| | 1 Dose | Before | 681 | 5 | 5.63 | 0.83 (0.33–2.05) |
| | | After | 116 | 1 | 3.13 | 0.47 (0.06–3.38) |
| | 2 Doses | Before | 1215 | 7 | 4.72 | 0.70 (0.32–1.53) |
| | | After | 157 | 2 | 4.71 | 0.72 (0.17–2.94) |
| | 1 or 2 Doses | Before | 1896 | 12 | 5.06 | 0.75 (0.40–1.39) |
| | | After | 273 | 3 | 4.03 | 0.61 (0.19–1.95) |
| | Complete | Before | 11,860 | 53 | 3.98 | 0.59 (0.41–0.85) |
| | | After | 424 | 2 | 1.60 | 0.24 (0.06–0.99) |
| CIN3/AIS[c] | Unvaccinated | | 8005 | 27 | 2.70 | 1 |
| | Vaccinated (unadjusted) | Before | | | | 0.50 (0.28–0.88) |
| | | After | | | | 0.39 (0.09–1.65) |
| | Vaccinated (adjusted) | Before | 13,756 | 22 | 1.40 | 0.48 (0.27–0.84) |
| | | After | 697 | 2 | 1.00 | 0.38 (0.09–1.61) |
| | 1 Dose | Before | 681 | 3 | 3.37 | 1.20 (0.37–3.92) |
| | | After | 116 | 1 | 3.13 | 1.16 (0.16–8.67) |
| | 2 Doses | Before | 1215 | 2 | 1.34 | 0.48 (0.11–2.03) |
| | | After | 157 | 1 | 2.34 | 0.89 (0.12–6.72) |
| | 1 or 2 Doses | Before | 1896 | 5 | 2.10 | 0.75 (0.29–1.96) |
| | | After | 273 | 2 | 2.67 | 1.01 (0.24–4.34) |
| | Complete | Before | 11,860 | 17 | 1.27 | 0.43 (0.23–0.79) |
| | | After | 424 | 0 | 0.00 | – |
| CIN2[c] | Unvaccinated | | 8005 | 39 | 3.90 | 1 |
| | Vaccinated (unadjusted) | Before | | | | 0.75 (0.49–1.14) |
| | | After | | | | 0.52 (0.19–1.45) |
| | Vaccinated (adjusted) | Before | 13,756 | 47 | 2.99 | 0.76 (0.49–1.16) |
| | | After | 697 | 4 | 2.01 | 0.50 (0.18–1.41) |
| | 1 Dose | Before | 681 | 2 | 2.24 | 0.55 (0.13–2.27) |
| | | After | 116 | 0 | 0.00 | - |
| | 2 Doses | Before | 1215 | 6 | 4.04 | 1.00 (0.42–2.38) |
| | | After | 157 | 2 | 4.71 | 1.18 (0.28–4.94) |
| | 1 or 2 Doses | Before | 1896 | 8 | 3.37 | 0.83 (0.39–1.78) |
| | | After | 273 | 2 | 2.68 | 0.67 (0.16–2.78) |
| | Complete | Before | 11,860 | 39 | 2.93 | 0.74 (0.48–1.16) |
| | | After | 424 | 2 | 1.60 | 0.40 (0.10–1.67) |
| **Cytological abnormalities** | | | | | | |
| High-grade cytology[d] | Unvaccinated | | 8005 | 47 | 4.69 | 1 |
| | Vaccinated (unadjusted) | Before | | | | 0.64 (0.43–0.95) |
| | | After | | | | 0.98 (0.47–2.05) |
| | Vaccinated (adjusted) | Before | 13,756 | 49 | 3.12 | 0.64 (0.43–0.96) |
| | | After | 697 | 8 | 4.03 | 0.92 (0.43–1.94) |
| | 1 Dose | Before | 681 | 4 | 4.49 | 0.97 (0.35–2.70) |
| | | After | 116 | 2 | 6.32 | 1.41 (0.34–5.87) |
| | 2 Doses | Before | 1215 | 9 | 6.05 | 1.27 (0.62–2.58) |
| | | After | 157 | 5 | 11.88 | 2.80 (1.10–7.08) |

**Table A.1** (*continued*)

| Outcome | | Vaccination relative to first screen | Number of women/women-doses | No. of abnormalities | Rate[a] | Hazard ratio[b] |
|---|---|---|---|---|---|---|
| | 1 or 2 Doses | Before | 1896 | 13 | 5.46 | 1.16 (0.63–2.14) |
| | | After | 273 | 7 | 9.50 | 2.18 (0.98–4.85) |
| | Complete | Before | 11,860 | 36 | 2.70 | 0.55 (0.35–0.86) |
| | | After | 424 | 1 | 0.80 | 0.18 (0.03–1.32) |
| Low-grade cytology[c] | Unvaccinated | | 8005 | 140 | 14.13 | 1 |
| | Vaccinated (unadjusted) | Before | | | | 0.83 (0.67–1.03) |
| | | After | | | | 1.79 (1.27–2.52) |
| | Vaccinated (adjusted) | Before | 13,756 | 189 | 12.10 | 0.81 (0.66–1.01) |
| | | After | 697 | 44 | 22.86 | 1.79 (1.27–2.51) |
| | 1 Dose | Before | 681 | 10 | 11.26 | 0.82 (0.43–1.55) |
| | | After | 116 | 6 | 19.45 | 1.49 (0.65–3.38) |
| | 2 Doses | Before | 1215 | 10 | 6.74 | 0.48 (0.25–0.90) |
| | | After | 157 | 12 | 29.65 | 2.39 (1.31–4.34) |
| | 1 or 2 Doses | Before | 1896 | 20 | 8.43 | 0.60 (0.38–0.96) |
| | | After | 273 | 18 | 25.24 | 1.99 (1.21–3.25) |
| | Complete | Before | 11,860 | 169 | 12.76 | 0.85 (0.68–1.06) |
| | | After | 424 | 26 | 21.47 | 1.67 (1.10–2.55) |

*Note:* 426 observations listed as 'Not Clinically Complete' are not included. All high grade histology defined as CIN2, CIN3, AIS and mixed CIN3/AIS. High-grade cytology defined as possible high-grade squamous intraepithelial lesion (HSIL), HSIL, HSIL with possible microinvasion/invasion, squamous cell carcinoma, possible high-grade endocervical glandular lesion, AIS, AIS with possible microinvasion/invasion and adenocarcinoma. Low-grade cytology defined as possible low-grade squamous intraepithelial lesions (LSIL), LSIL and atypical endocervical cells of uncertain significance. Unvaccinated refers to women screened who did not receive any dose of HPV vaccine; completely vaccinated refers to women who were clinically completely vaccinated with three doses of HPV vaccine.

[a] Rate per 1000 person-years.
[b] Hazard ratio adjusted for age in 2007, remoteness and SES.
[c] Age in 2007 fitted as a categorical variable (i.e. $<=16$, 17–19, 20–23 and 24+).
[d] Age in 2007 fitted as a continuous variable.

**Table A.2**
Number and rate of cervical abnormalities for completely vaccinated, partially vaccinated and unvaccinated women (17–19 years of age) relative to their first screen.

| Outcome | | Vaccination relative to first screen | Number of women/women-doses | No. of abnormalities | Rate[a] | Hazard ratio[b] |
|---|---|---|---|---|---|---|
| **Histological abnormalities** | | | | | | |
| Any high grade[c] | Unvaccinated | | 23,066 | 435 | 8.22 | 1 |
| | Vaccinated (unadjusted) | Before | | | | 0.71 (0.61–0.82) |
| | | After | | | | 0.88 (0.76–1.03) |
| | Vaccinated (adjusted) | Before | 25,014 | 270 | 5.78 | 0.69 (0.59–0.80) |
| | | After | 11,222 | 264 | 7.25 | 0.85 (0.73–0.99) |
| | 1 Dose | Before | 2078 | 34 | 8.58 | 1.02 (0.72–1.45) |
| | | After | 1610 | 35 | 6.74 | 0.78 (0.55–1.10) |
| | 2 Doses | Before | 2797 | 45 | 8.67 | 1.01 (0.74–1.37) |
| | | After | 2147 | 67 | 10.08 | 1.18 (0.91–1.53) |
| | 1 or 2 Doses | Before | 4875 | 79 | 8.63 | 1.01 (0.79–1.29) |
| | | After | 3757 | 102 | 8.62 | 1.00 (0.81–1.25) |
| | Complete | Before | 20,139 | 191 | 5.08 | 0.61 (0.51–0.72) |
| | | After | 7465 | 162 | 6.60 | 0.78 (0.65–0.93) |
| CIN3/AIS[c] | Unvaccinated | | 23,066 | 202 | 3.78 | 1 |
| | Vaccinated (unadjusted) | Before | | | | 0.73 (0.58–0.91) |
| | | After | | | | 0.89 (0.71–1.11) |
| | Vaccinated (adjusted) | Before | 25,014 | 129 | 2.75 | 0.70 (0.56–0.88) |
| | | After | 11,222 | 126 | 3.44 | 0.86 (0.69–1.08) |
| | 1 Dose | Before | 2078 | 22 | 5.53 | 1.38 (0.89–2.15) |
| | | After | 1610 | 15 | 2.87 | 0.68 (0.39–1.16) |
| | 2 Doses | Before | 2797 | 24 | 4.60 | 1.11 (0.72–1.70) |
| | | After | 2147 | 34 | 5.07 | 1.25 (0.87–1.80) |
| | 1 or 2 Doses | Before | 4875 | 46 | 5.00 | 1.23 (0.89–1.70) |
| | | After | 3757 | 49 | 4.11 | 1.00 (0.73–1.38) |
| | Complete | Before | 20,139 | 83 | 2.20 | 0.56 (0.44–0.73) |
| | | After | 7465 | 77 | 3.12 | 0.80 (0.61–1.04) |
| CIN2[c] | Unvaccinated | | 23,066 | 263 | 4.94 | 1 |
| | Vaccinated (unadjusted) | Before | | | | 0.70 (0.57–0.85) |
| | | After | | | | 0.89 (0.73–1.08) |
| | Vaccinated (adjusted) | Before | 25,014 | 161 | 3.43 | 0.69 (0.56–0.84) |
| | | After | 11,222 | 159 | 4.35 | 0.86 (0.70–1.05) |
| | 1 Dose | Before | 2078 | 13 | 3.26 | 0.66 (0.38–1.15) |
| | | After | 1610 | 22 | 4.22 | 0.84 (0.54–1.30) |
| | 2 Doses | Before | 2797 | 24 | 4.60 | 0.92 (0.61–1.41) |
| | | After | 2147 | 40 | 5.99 | 1.18 (0.84–1.65) |
| | 1 or 2 Doses | Before | 4875 | 37 | 4.02 | 0.81 (0.57–1.14) |
| | | After | 3757 | 62 | 5.21 | 1.03 (0.78–1.36) |

**Table A.2** (*continued*)

| Outcome | | Vaccination relative to first screen | Number of women/women-doses | No. of abnormalities | Rate[a] | Hazard ratio[b] |
|---|---|---|---|---|---|---|
| | Complete | Before | 20,139 | 124 | 3.29 | 0.66 (0.53–0.81) |
| | | After | 7465 | 97 | 3.93 | 0.78 (0.61–0.98) |
| **Cytological abnormalities** | | | | | | |
| High-grade cytology[d] | Unvaccinated | | 23,066 | 358 | 6.73 | 1 |
| | Vaccinated (unadjusted) | Before | | | | 0.59 (0.50–0.71) |
| | | After | | | | 1.36 (1.17–1.58) |
| | Vaccinated (adjusted) | Before | 25,014 | 190 | 4.05 | 0.59 (0.50–0.71) |
| | | After | 11,222 | 343 | 9.45 | 1.33 (1.14–1.54) |
| | 1 Dose | Before | 2078 | 14 | 3.50 | 0.48 (0.28–0.82) |
| | | After | 1610 | 39 | 7.50 | 1.03 (0.74–1.44) |
| | 2 Doses | Before | 2797 | 23 | 4.40 | 0.61 (0.40–0.93) |
| | | After | 2147 | 72 | 10.83 | 1.50 (1.16–1.93) |
| | 1 or 2 Doses | Before | 4875 | 37 | 4.01 | 0.56 (0.40–0.78) |
| | | After | 3757 | 111 | 9.37 | 1.29 (1.04–1.60) |
| | Complete | Before | 20,139 | 153 | 4.06 | 0.60 (0.50–0.73) |
| | | After | 7465 | 232 | 9.49 | 1.35 (1.14–1.59) |
| Low-grade cytology[c] | Unvaccinated | | 23,066 | 977 | 18.74 | 1 |
| | Vaccinated (unadjusted) | Before | | | | 0.83 (0.75–0.91) |
| | | After | | | | 1.40 (1.28–1.53) |
| | Vaccinated (adjusted) | Before | 25,014 | 738 | 15.91 | 0.81 (0.74–0.90) |
| | | After | 11,222 | 940 | 26.65 | 1.39 (1.27–1.52) |
| | 1 Dose | Before | 2078 | 47 | 11.87 | 0.61 (0.46–0.82) |
| | | After | 1610 | 107 | 21.01 | 1.10 (0.90–1.34) |
| | 2 Doses | Before | 2797 | 71 | 13.71 | 0.70 (0.55–0.89) |
| | | After | 2147 | 144 | 22.05 | 1.15 (0.96–1.37) |
| | 1 or 2 Doses | Before | 4875 | 118 | 12.91 | 0.66 (0.55–0.80) |
| | | After | 3757 | 251 | 21.59 | 1.13 (0.98–1.29) |
| | Complete | Before | 20,139 | 620 | 16.64 | 0.85 (0.77–0.94) |
| | | After | 7465 | 689 | 29.14 | 1.51 (1.37–1.67) |

Note: 426 observations listed as 'Not Clinically Complete' are not included. All high grade histology defined as CIN2, CIN3, AIS and mixed CIN3/AIS. High-grade cytology defined as possible high-grade squamous intraepithelial lesion (HSIL), HSIL, HSIL with possible microinvasion/invasion, squamous cell carcinoma, possible high-grade endocervical glandular lesion, AIS, AIS with possible microinvasion/invasion and adenocarcinoma. Low-grade cytology defined as possible low-grade squamous intraepithelial lesions (LSIL), LSIL and atypical endocervical cells of uncertain significance. Unvaccinated refers to women screened who did not receive any dose of HPV vaccine; completely vaccinated refers to women who were clinically completely vaccinated with three doses of HPV vaccine.

[a] Rate per 1000 person-years.
[b] Hazard ratio adjusted for age in 2007, remoteness and SES.
[c] Age in 2007 fitted as a categorical variable (i.e. $<=16$, 17–19, 20–23 and 24+).
[d] Age in 2007 fitted as a continuous variable.

**Table A.3**
Number and rate of cervical abnormalities for completely vaccinated, partially vaccinated and unvaccinated women (20–23 years of age) relative to their first screen.

| Outcome | | Vaccination relative to first screen | Number of women/women-doses | No. of abnormalities | Rate[a] | Hazard ratio[b] |
|---|---|---|---|---|---|---|
| **Histological abnormalities** | | | | | | |
| Any high grade[c] | Unvaccinated | | 50,255 | 1321 | 8.43 | 1 |
| | Vaccinated (unadjusted) | Before | | | | 0.95 (0.82–1.09) |
| | | After | | | | 1.01 (0.94–1.10) |
| | Vaccinated (adjusted) | Before | 15,303 | 230 | 7.82 | 0.95 (0.82–1.09) |
| | | After | 45,689 | 1248 | 8.39 | 1.00 (0.92–1.08) |
| | 1 Dose | Before | 2820 | 55 | 9.75 | 1.16 (0.88–1.53) |
| | | After | 6531 | 227 | 10.49 | 1.25 (1.09–1.44) |
| | 2 Doses | Before | 3182 | 64 | 10.88 | 1.33 (1.03–1.71) |
| | | After | 9284 | 279 | 9.42 | 1.12 (0.98–1.28) |
| | 1 or 2 Doses | Before | 6002 | 119 | 10.32 | 1.25 (1.03–1.51) |
| | | After | 15,815 | 506 | 9.87 | 1.18 (1.06–1.30) |
| | Complete | Before | 9301 | 111 | 6.21 | 0.75 (0.62–0.91) |
| | | After | 29,874 | 742 | 7.62 | 0.91 (0.83–0.99) |
| CIN3/AIS[c] | Unvaccinated | | 50,255 | 707 | 4.47 | 1 |
| | Vaccinated (unadjusted) | Before | | | | 0.91 (0.75–1.11) |
| | | After | | | | 0.99 (0.89–1.10) |
| | Vaccinated (adjusted) | Before | 15,303 | 121 | 4.09 | 0.92 (0.76–1.12) |
| | | After | 45,689 | 665 | 4.44 | 0.98 (0.88–1.09) |
| | 1 Dose | Before | 2820 | 34 | 5.99 | 1.30 (0.91–1.85) |
| | | After | 6531 | 121 | 5.53 | 1.22 (1.00–1.48) |
| | 2 Doses | Before | 3182 | 31 | 5.22 | 1.18 (0.82–1.69) |
| | | After | 9284 | 147 | 4.92 | 1.09 (0.91–1.30) |
| | 1 or 2 Doses | Before | 6002 | 65 | 5.60 | 1.24 (0.96–1.60) |
| | | After | 15,815 | 268 | 5.18 | 1.14 (0.99–1.32) |
| | Complete | Before | 9301 | 56 | 3.12 | 0.71 (0.54–0.93) |
| | | After | 29,874 | 397 | 4.05 | 0.90 (0.79–1.01) |
| CIN2[c] | Unvaccinated | | 50,255 | 699 | 4.42 | 1 |

**Table A.3** (*continued*)

| Outcome | | Vaccination relative to first screen | Number of women/women-doses | No. of abnormalities | Rate[a] | Hazard ratio[b] |
|---|---|---|---|---|---|---|
| | Vaccinated (unadjusted) | Before | | | | 0.98 (0.81–1.19) |
| | | After | | | | 1.04 (0.93–1.16) |
| | Vaccinated (adjusted) | Before | 15,303 | 123 | 4.16 | 0.98 (0.80–1.19) |
| | | After | 45,689 | 663 | 4.43 | 1.02 (0.92–1.13) |
| | 1 Dose | Before | 2820 | 25 | 4.39 | 1.03 (0.69–1.54) |
| | | After | 6531 | 121 | 5.54 | 1.28 (1.06–1.55) |
| | 2 Doses | Before | 3182 | 36 | 6.06 | 1.45 (1.03–2.02) |
| | | After | 9284 | 149 | 4.99 | 1.14 (0.96–1.37) |
| | 1 or 2 Doses | Before | 6002 | 61 | 5.24 | 1.24 (0.95–1.62) |
| | | After | 15,815 | 270 | 5.22 | 1.20 (1.04–1.39) |
| | Complete | Before | 9301 | 62 | 3.45 | 0.80 (0.62–1.04) |
| | | After | 29,874 | 393 | 4.01 | 0.92 (0.81–1.04) |
| **Cytological abnormalities** | | | | | | |
| High-grade cytology[d] | Unvaccinated | | 50,255 | 1223 | 7.79 | 1 |
| | Vaccinated (unadjusted) | Before | | | | 0.51 (0.43–0.62) |
| | | After | | | | 1.22 (1.13–1.32) |
| | Vaccinated (adjusted) | Before | 15,303 | 119 | 4.01 | 0.52 (0.43–0.62) |
| | | After | 45,689 | 1413 | 9.51 | 1.20 (1.11–1.30) |
| | 1 Dose | Before | 2820 | 20 | 3.49 | 0.45 (0.29–0.70) |
| | | After | 6531 | 199 | 9.14 | 1.16 (1.00–1.35) |
| | 2 Doses | Before | 3182 | 30 | 5.04 | 0.65 (0.45–0.93) |
| | | After | 9284 | 280 | 9.43 | 1.19 (1.05–1.36) |
| | 1 or 2 Doses | Before | 6002 | 50 | 4.28 | 0.55 (0.41–0.73) |
| | | After | 15,815 | 479 | 9.31 | 1.18 (1.06–1.31) |
| | Complete | Before | 9301 | 69 | 3.83 | 0.49 (0.39–0.63) |
| | | After | 29,874 | 934 | 9.62 | 1.22 (1.12–1.32) |
| Low-grade cytology[c] | Unvaccinated | | 50,255 | 2744 | 17.87 | 1 |
| | Vaccinated (unadjusted) | Before | | | | 0.53 (0.47–0.60) |
| | | After | | | | 1.26 (1.20–1.32) |
| | Vaccinated (adjusted) | Before | 15,303 | 277 | 9.39 | 0.53 (0.47–0.60) |
| | | After | 45,689 | 3224 | 22.19 | 1.25 (1.18–1.31) |
| | 1 Dose | Before | 2820 | 43 | 7.55 | 0.43 (0.32–0.58) |
| | | After | 6531 | 432 | 20.21 | 1.14 (1.03–1.26) |
| | 2 Doses | Before | 3182 | 49 | 8.25 | 0.47 (0.36–0.62) |
| | | After | 9284 | 643 | 22.13 | 1.25 (1.15–1.37) |
| | 1 or 2 Doses | Before | 6002 | 92 | 7.91 | 0.45 (0.37–0.56) |
| | | After | 15,815 | 1075 | 21.32 | 1.21 (1.12–1.29) |
| | Complete | Before | 9301 | 185 | 10.35 | 0.58 (0.50–0.67) |
| | | After | 29,874 | 2149 | 22.65 | 1.27 (1.20–1.34) |

*Note:* 426 observations listed as 'Not Clinically Complete' are not included.
All high grade histology defined as CIN2, CIN3, AIS and mixed CIN3/AIS. High-grade cytology defined as possible high-grade squamous intraepithelial lesion (HSIL), HSIL, HSIL with possible microinvasion/invasion, squamous cell carcinoma, possible high-grade endocervical glandular lesion, AIS, AIS with possible microinvasion/invasion and adenocarcinoma. Low-grade cytology defined as possible low-grade squamous intraepithelial lesions (LSIL), LSIL and atypical endocervical cells of uncertain significance. Unvaccinated refers to women screened who did not receive any dose of HPV vaccine; completely vaccinated refers to women who were clinically completely vaccinated with three doses of HPV vaccine.

[a] Rate per 1000 person-years.
[b] Hazard ratio adjusted for age in 2007, remoteness and SES.
[c] Age in 2007 fitted as a categorical variable (i.e. $<=16$, 17–19, 20–23 and 24+).
[d] Age in 2007 fitted as a continuous variable.

**Table A.4**
Number and rate of cervical abnormalities for completely vaccinated, partially vaccinated and unvaccinated women (24–26 years of age) relative to their first screen.

| Outcome | | Vaccination relative to first screen | Number of women/women-doses | No. of abnormalities | Rate[a] | Hazard ratio[b] |
|---|---|---|---|---|---|---|
| **Histological abnormalities** | | | | | | |
| Any high grade[c] | Unvaccinated | | 51,729 | 1319 | 7.24 | 1 |
| | Vaccinated (unadjusted) | Before | | | | 1.22 (1.01–1.49) |
| | | After | | | | 0.97 (0.89–1.06) |
| | Vaccinated (adjusted) | Before | 6861 | 113 | 8.37 | 1.24 (1.02–1.50) |
| | | After | 37,881 | 885 | 6.86 | 0.96 (0.88–1.04) |
| | 1 Dose | Before | 1359 | 30 | 10.48 | 1.53 (1.06–2.21) |
| | | After | 5464 | 145 | 7.50 | 1.04 (0.88–1.24) |
| | 2 Doses | Before | 1444 | 26 | 9.58 | 1.41 (0.95–2.08) |
| | | After | 7274 | 200 | 8.17 | 1.15 (0.99–1.33) |
| | 1 or 2 Doses | Before | 2803 | 56 | 10.04 | 1.47 (1.12–1.93) |
| | | After | 12,738 | 345 | 7.88 | 1.10 (0.97–1.24) |
| | Complete | Before | 4058 | 57 | 7.20 | 1.07 (0.82–1.40) |
| | | After | 25,143 | 540 | 6.34 | 0.88 (0.80–0.98) |
| CIN3/AIS[c] | Unvaccinated | | 51,729 | 790 | 4.31 | 1 |
| | Vaccinated (unadjusted) | Before | | | | 1.26 (0.98–1.61) |
| | | After | | | | 0.97 (0.87–1.08) |

**Table A.5**
Adjusted hazard ratios[a] for high grade histology and CIN3/AIS histology for women receiving two doses, stratified by dose spacing > =6 months[b] and whether vaccination was before or after screening commencement. Censorship time refers to lag times until counting of outcomes commences.

| | Vaccine status | Vaccination relative to first screen | Time between doses | Hazard ratio | Censoring time | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | 1 Month | 6 Months | 12 Months | 24 Months |
| | | | | | Hazard ratio | Hazard ratio | Hazard ratio | Hazard ratio |
| **Any high grade histology** | Unvaccinated | | | 1 | 1 | 1 | 1 | 1 |
| | 2 doses | Before | < 6 Months | 1.25 (1.03–1.51) | 1.13 (0.92–1.39) | 0.81 (0.60–1.09) | 0.88 (0.63–1.22) | 0.92 (0.57–1.49) |
| | | After | < 6 Months | 1.18 (1.06–1.30) | 1.19 (1.07–1.32) | 1.15 (1.01–1.30) | 1.18 (1.03–1.35) | 1.13 (0.95–1.34) |
| | | Before | > =6 Months | 1.05 (0.72–1.55) | 0.94 (0.61–1.45) | 0.81 (0.46–1.42) | 0.96 (0.52–1.79) | 1.38 (0.57–3.32) |
| | | After | > =6 Months | 0.96 (0.80–1.16) | 1.01 (0.84–1.22) | 1.12 (0.92–1.38) | 1.15 (0.92–1.44) | 1.04 (0.75–1.43) |
| **CIN3/AIS** | Unvaccinated | | | 1 | 1 | 1 | 1 | 1 |
| | 2 doses | Before | < 6 Months | 1.19 (0.91–1.56) | 1.02 (0.76–1.38) | 0.62 (0.40–0.98) | 0.61 (0.36–1.04) | 0.58 (0.26–1.29) |
| | | After | < 6 Months | 1.17 (1.02–1.34) | 1.17 (1.02–1.35) | 1.21 (1.03–1.42) | 1.22 (1.03–1.44) | 1.23 (0.99–1.52) |
| | | Before | > =6 Months | 1.08 (0.64–1.82) | 1.01 (0.57–1.78) | 0.87 (0.41–1.82) | 1.23 (0.58–2.58) | 1.97 (0.74–5.26) |
| | | After | > =6 Months | 0.99 (0.78–1.26) | 1.01 (0.78–1.29) | 1.17 (0.89–1.52) | 1.18 (0.88–1.57) | 1.13 (0.75–1.68) |

[a] Adjusted for Age in 2007 (Categorized), 'Remoteness' and 'SES'.
[b] 20,297 (73.8%) women with a final dose status of two doses had dose two given within 6 months. 7204 (26.2%) women had the second dose administered 6 months or more after dose one.

**Table A.6**
Impact of censoring time until end point assessment for high grade histology and CIN3/AIS. For partially vaccinated women who were vaccinated before commencing screening, hazard ratios decrease over time.

| | | Vaccination relative to first screen | Hazard ratio | Censoring time | | | |
|---|---|---|---|---|---|---|---|
| | | | | 1 Month | 6 Months | 12 Months | 24 Months |
| | | | | Hazard ratio | Hazard ratio | Hazard ratio | Hazard ratio |
| **Any high-grade** | Unvaccinated | | 1 | 1 | 1 | 1 | 1 |
| | Vaccinated (unadjusted) | Before | 0.82 (0.75–0.89) | 0.74 (0.67–0.82) | 0.58 (0.51–0.66) | 0.64 (0.56–0.74) | 0.72 (0.59–0.88) |
| | | After | 0.96 (0.91–1.02) | 1.01 (0.96–1.07) | 1.12 (1.06–1.19) | 1.10 (1.03–1.18) | 1.01 (0.93–1.10) |
| | Vaccinated (adjusted) | Before | 0.86 (0.78–0.94) | 0.77 (0.70–0.85) | 0.59 (0.52–0.67) | 0.66 (0.57–0.76) | 0.72 (0.58–0.88) |
| | | After | 0.95 (0.90–1.00) | 0.99 (0.94–1.05) | 1.10 (1.04–1.17) | 1.09 (1.02–1.16) | 0.99 (0.91–1.08) |
| | 1 Dose | Before | 1.19 (0.99–1.43) | 1.03 (0.84–1.27) | 0.66 (0.49–0.89) | 0.65 (0.46–0.93) | 0.54 (0.30–0.95) |
| | | After | 1.10 (0.99–1.22) | 1.07 (0.96–1.20) | 1.02 (0.90–1.16) | 1.00 (0.87–1.15) | 0.89 (0.74–1.08) |
| | 2 Doses | Before | 1.21 (1.02–1.44) | 1.09 (0.90–1.32) | 0.81 (0.62–1.05) | 0.89 (0.67–1.20) | 1.00 (0.65–1.52) |
| | | After | 1.12 (1.02–1.23) | 1.14 (1.04–1.25) | 1.14 (1.02–1.27) | 1.17 (1.04–1.32) | 1.11 (0.95–1.29) |
| | 1 or 2 Doses | Before | 1.20 (1.06–1.37) | 1.06 (0.92–1.23) | 0.74 (0.60–0.90) | 0.78 (0.62–0.98) | 0.76 (0.54–0.89) |
| | | After | 1.11 (1.03–1.20) | 1.11 (1.03–1.20) | 1.09 (1.00–1.19) | 1.10 (1.00–1.20) | 1.01 (0.89–1.15) |
| | Complete | Before | 0.71 (0.64–0.80) | 0.65 (0.57–0.73) | 0.53 (0.45–0.62) | 0.61 (0.51–0.72) | 0.70 (0.55–0.89) |
| | | After | 0.87 (0.82–0.93) | 0.94 (0.88–1.00) | 1.11 (1.04–1.19) | 1.09 (1.01–1.17) | 0.98 (0.89–1.09) |
| **CIN3/AIS** | Unvaccinated | | 1 | 1 | 1 | 1 | 1 |
| | Vaccinated (unadjusted) | Before | 0.85 (0.75–0.96) | 0.83 (0.67–1.03) | 0.49 (0.36–0.68) | 0.55 (0.45–0.68) | 0.57 (0.42–0.77) |
| | | After | 0.96 (0.89–1.03) | 1.05 (0.94–1.17) | 1.21 (1.07–1.36) | 1.13 (1.03–1.23) | 1.06 (0.95–1.19) |
| | Vaccinated (adjusted) | Before | 0.87 (0.77–0.99) | 0.79 (0.69–0.91) | 0.52 (0.43–0.63) | 0.55 (0.45–0.68) | 0.56 (0.42–0.76) |
| | | After | 0.95 (0.88–1.02) | 0.98 (0.91–1.06) | 1.12 (1.03–1.22) | 1.11 (1.01–1.21) | 1.04 (0.93–1.16) |
| | 1 Dose | Before | 1.41 (1.12–1.77) | 1.19 (0.92–1.54) | 0.62 (0.41–0.95) | 0.56 (0.33–0.93) | 0.39 (0.16–0.95) |
| | | After | 1.04 (0.91–1.20) | 1.03 (0.89–1.19) | 1.03 (0.87–1.22) | 0.98 (0.82–1.18) | 0.95 (0.75–1.20) |
| | 2 Doses | Before | 1.17 (0.92–1.48) | 1.02 (0.78–1.33) | 0.68 (0.46–1.00) | 0.74 (0.48–1.14) | 0.81 (0.43–1.51) |
| | | After | 1.12 (0.99–1.27) | 1.13 (1.00–1.28) | 1.20 (1.04–1.38) | 1.21 (1.04–1.41) | 1.21 (0.99–1.46) |
| | 1 or 2 Doses | Before | 1.28 (1.08–1.52) | 1.10 (0.91–1.33) | 0.65 (0.49–0.87) | 0.65 (0.46–0.91) | 0.60 (0.36–1.00) |
| | | After | 1.09 (0.99–1.20) | 1.09 (0.98–1.20) | 1.13 (1.00–1.26) | 1.11 (0.98–1.26) | 1.09 (0.93–1.27) |
| | Complete | Before | 0.69 (0.58–0.81) | 0.65 (0.55–0.77) | 0.46 (0.36–0.58) | 0.51 (0.39–0.66) | 0.55 (0.38–0.79) |
| | | After | 0.87 (0.80–0.95) | 0.93 (0.86–1.02) | 1.12 (1.02–1.23) | 1.11 (1.00–1.22) | 1.01 (0.89–1.15) |

## Appendix B

Appendix B Figs. B1–B5.

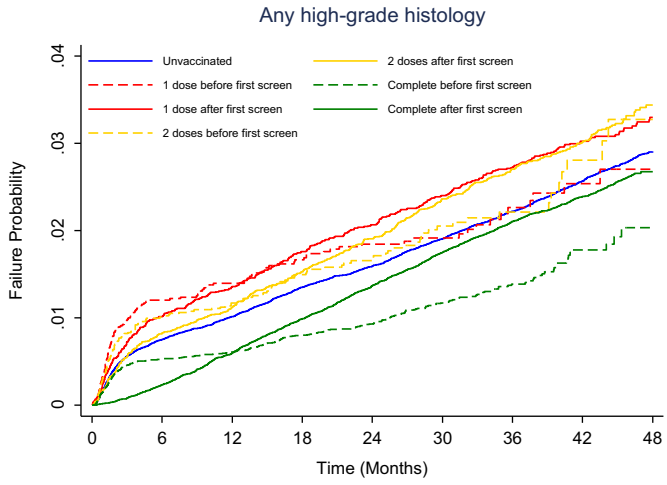


**Fig. B1**

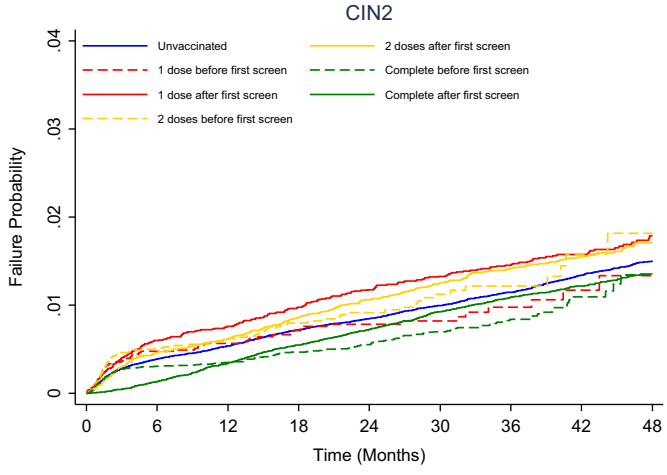


**Fig. B2**

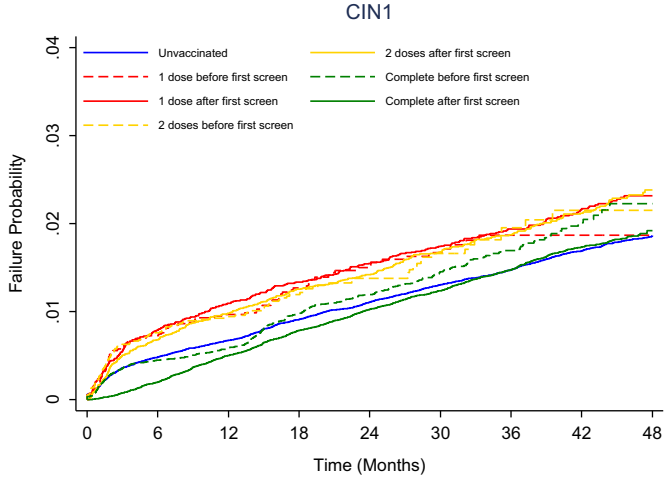


**Fig. B3**

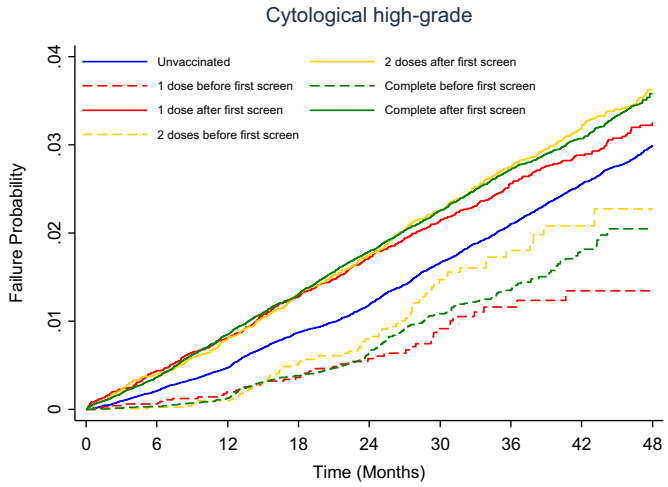


**Fig. B4**

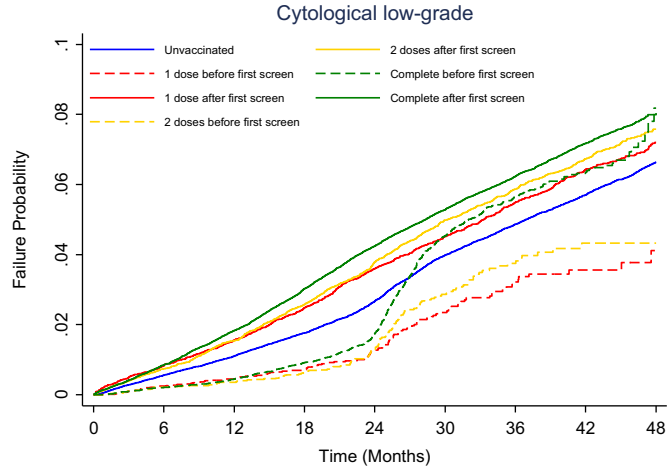


**Fig. B5**

## References

[1] J.M. Brotherton, S.L. Murray, M.A. Hall, L.K. Andrewartha, C.A. Banks, D. Meijer, et al., Human papillomavirus vaccine coverage among female Australian adolescents: success of the school-based approach, Med. J. Aust. 199 (2013) 614–617.
[2] P. Guan, R. Howell-Jones, N. Li, L. Bruni, S. de Sanjose, S. Franceschi, et al., Human papillomavirus types in 115,789 HPV-positive women: a meta-analysis from cervical infection to cancer, Int. J. Cancer 131 (2012) 2349–2359.
[3] D. Forman, C. de Martel, C.J. Lacey, I. Soerjomataram, J. Lortet-Tieulent, L. Bruni, et al., Global burden of human papillomavirus and related diseases, Vaccine 30 (Suppl. 5) (2012) F12–F23.
[4] J.M.L. Brotherton, D.M. Gertig, G.A. Chappell, L. Rowlands, M. Saville, Catching up with the catch-up: HPV vaccination coverage data for Australian women aged 18-26 year from the National HPV Vaccination Program Register, Commun. Dis. Intell. 35 (2011) 197–201.
[5] J.M. Brotherton, B. Liu, B. Donovan, J.M. Kaldor, M. Saville, Human papillomavirus (HPV) vaccination coverage in young Australian women is higher than previously estimated: Independent estimates from a nationally representative mobile phone survey, Vaccine 32 (2014) 592–597.
[6] M. Watson, J. Lynch, K. D'Onise, J. Brotherton, Barriers to better three-dose coverage with HPV vaccination in school-based programs, Aust. N. Z. J. Public Health 38 (2014) 91–92.

[7] J.M. Brotherton, R.M. Mullins, Will vaccinated women attend cervical screening? A population based survey of human papillomavirus vaccination and cervical screening among young women in Victoria, Australia, Cancer Epidemiol. 36 (2012) 298–302.
[8] J.T. Schiller, D.R. Lowy, Raising expectations for subunit vaccine, J. Infect. Dis. 211 (9) (2014) 1373–1375.
[9] D.M. Gertig, J.M. Brotherton, A.C. Budd, K. Drennan, G. Chappell, A.M. Saville, Impact of a population-based HPV vaccination program on cervical abnormalities: a data linkage study, BMC Med. 11 (2013) 227.
[10] A.C. Budd, J.M. Brotherton, D.M. Gertig, T. Chau, K.T. Drennan, M. Saville, Cervical screening rates for women vaccinated against human papillomavirus, Med. J. Aust. 201 (2014) 279–282.
[11] AIHW, Cervical Screening in Australia 2011–2012, Cancer Series No. 82, AIHW Canberra Cat. No. CAN 79.
[12] NHMRC Guidelines for the Management of Asymptomatic Women with Screen Detected Abnormalities, ⟨https://www.nhmrc.gov.au/guidelines-publications/wh39⟩ (accessed 07.04.15).
[13] Chief Medical Officer, Guidelines, ⟨http://www.health.gov.au/internet/immunise/publishing.nsf/Content/cmo-full-advice-hpv-cnt/$File/CMO-full-advice-hpv.pdf⟩ (accessed 07.04.15).
[14] E.L. Korn, B.I. Graubard, D. Midthune, Time-to-event analysis of longitudinal follow-up of a survey: choice of the time-scale, Am. J. Epidemiol. 145 (1997) 72–80.
[15] Australian Bureau of Statistics, 1216.0 – Australian Standard Geographical Classification (ASGC), 2006 Canberra (AUST), ABS, 2006.
[16] Australian Bureau of Statistics, 2039.0 – An Introduction to Socio-Economic Indexes for Areas (SEIFA) 2006 [Internet], Canberra (AUST), ABS, 2008 [cited 2011 Jun 8], ⟨http://www.abs.gov.au/ausstats/abs@.nsf/mf/2039.0⟩.
[17] J.T. Schiller, X. Castellsague, S.M. Garland, A review of clinical trials of human papillomavirus prophylactic vaccines, Vaccine 30 (Suppl. 5) (2012) F123–F138.
[18] E. Crowe, N. Pandeya, J.M. Brotherton, A.J. Dobson, S. Kisely, S.B. Lambert et al., Effectiveness of quadrivalent human papillomavirus vaccine for the prevention of cervical abnormalities: case-control study nested within a population based screening programme in Australia, BMJ (Clin. Res. Ed.) 348 (2014) 1458.
[19] L.M. Smith, E.C. Strumpf, J.S. Kaufman, A. Lofters, M. Schwandt, LE. Lévesque, The early benefits of human papillomavirus vaccination on cervical dysplasia and anogenital warts, 135 (5) (2014) e1131–e1140.
[20] E. Herweijer, A. Leval, A. Ploner, S. Eloranta, J.F. Simard, J. Dillner, et al., Association of varying number of doses of quadrivalent human papillomavirus vaccine with incidence of condyloma, JAMA 311 (2014) 597–603.
[21] B. Baldur-Felskov, C. Dehlendorff, J. Junge, C. Munk, S.K. Kjaer, Incidence of cervical lesions in Danish women before and after implementation of a national HPV vaccination program, Cancer Causes Control 25 (2014) 915–922. http://dx.doi.org/10.1007/s10552-014-0392-4, Epub 2014 May 6.
[22] B. Baldur-Felskov, C. Dehlendorff, C. Munk, S.K. Kjaer, Early impact of human papillomavirus vaccination on cervical neoplasia—nationwide follow-up of young Danish women, J. Natl. Cancer Inst. (2014), http://dx.doi.org/10.1093/jnci/djt460, Epub 2014 Feb 19.
[23] M. Blomberg, C. Dehlendorff, C. Sand, S.K. Kjaer, Dose-related differences in effectiveness of HPV vaccination against genital warts: a nationwide study of 550,000 young girls, Clin. Infect. Dis. (2015), May 5. pii: civ364. [Epub ahead of print].
[24] A.R. Kreimer, A.C. Rodriguez, A. Hildesheim, R. Herrero, C. Porras, M. Schiffman, et al., Proof-of-principle evaluation of the efficacy of fewer than three doses of a bivalent HPV16/18 vaccine, J. Natl. Cancer Inst. 103 (2011) 1444–1451.
[25] M. Safaeian, C. Porras, Y. Pan, A. Kreimer, J.T. Schiller, P. Gonzalez, et al., Durable antibody responses following one dose of the bivalent human papillomavirus L1 virus-like particle vaccine in the Costa Rica Vaccine Trial, Cancer Prev. Res. 6 (2013) 1242–1250.
[26] K.G. Pollock, K. Kavanagh, A. Potts, J. Love, K. Cuschieri, H. Cubie, C. Robertson, M. Cruickshank, T.J. Palmer, S. Nicoll, M. Donaghy, Reduction of low- and high-grade cervical abnormalities associated with high uptake of the HPV bivalent vaccine in Scotland, Br. J. Cancer 111 (2014) 1824–1830. http://dx.doi.org/10.1038/bjc.2014.479, Epub 2014 Sep 2.
[27] J.M.L. Brotherton, S.N. Tabrizi, S.M. Garland, Does human papillomavirus type 16 or 18 prevalence in CIN3 lesions vary by age? An important issue for post vaccination surveillance, Future Microbiol. 7 (2012) 193–199.
[28] P.E. Castle, R. Shaber, B.J. LaMere, W. Kinney, B. Fetterman, N. Poitras, et al., Human papillomavirus (HPV) genotypes in women with cervical precancer and cancer at Kaiser Permanente Northern California, Cancer Epidemiol. Biomark. Prev. 20 (2011) 946–953.
[29] Victorian Cervical Cytology Registry, Statistical Report 2013, VCS Inc., Melbourne, Australia, 2014, Available from: ⟨http://www.vccr.org/data-research/statistical-reports/annual-statistical-reports⟩ (accessed 18.05.15).
[30] S. Hariri, N.M. Bennett, L.M. Niccolai, S. Schafer, I.U. Park, K.C. Bloch, E.R. Unger, E. Whitney, P. Julian, M.W. Scahill, N. Abdullah, D. Levine, M.L. Johnson, M. Steinau, L.E. Markowitz, HPV-IMPACT Working Group, Reduction in HPV 16/18-associated high grade cervical lesions following HPV vaccine introduction in the United States – 2008–2012, Vaccine 33 (2015) 1608–1613. http://dx.doi.org/10.1016/j.vaccine.2015.01.084, Epub 2015 Feb 11.
[31] B. Barbaro, J.M.L. Brotherton, Assessing HPV vaccine coverage in Australia by geography and socioeconomic status: are we protecting those most at risk? Aust. N. Z. J. Public Health 38 (5) (2014) 419–423.
[32] K. Canfell, S. Egger, L.S. Velentzis, J.D. Brown, D.L. O'Connell, E. Banks, F. Sitas, Factors related to vaccine uptake by young adult women in the catch-up phase of the National HPV Vaccination Program in Australia: results from an observational study, Vaccine 33 (2015) 2387–2394. http://dx.doi.org/10.1016/j.vaccine.2015.01.024, Epub 2015 Apr 3.
[33] AIHW, Cervical Screening in Australia 2008–2009, Cancer Series No 61, AIHW Canberra Cat. No. CAN 57.
[34] J.M.L. Brotherton, M. Batchelor, K. Winch, Utility of reports and routine correspondence from the National HPV Vaccination Program Register, Med. J. Aust. 199 (2013) 463.