Impact of human papillomavirus vaccination on rates of abnormal cervical cytology and histology in young New Zealand women

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ABSTRACT

AIM: Determine the impact of quadrivalent human papillomavirus (HPV) vaccination on abnormal cervical cytology and histology rates in young New Zealand women.

METHODS: Retrospective population-based cohort study of women born 1990–1994, with a cervical cytology or histology recorded when aged 20–24 between 1 January 2010 and 31 December 2015. Data was obtained through linking the National Immunisation Register and National Cervical Screening Programme Register.

RESULTS: N=104,313 women (376,402 person years of follow up) were included. The incidence of high-grade cytology was lower in vaccinated women (at least one dose prior to 18 years) than in unvaccinated women (8.5 vs 11.3 per 1,000 person years [p1000py], incidence rate ratio [IRR 0.75], 95% CI 0.70, 0.80, p<.001). The incidence of high-grade histology was lower in vaccinated women than in unvaccinated women (6.0 vs 8.7 p1000py, IRR 0.69, 95% CI 0.64, 0.75, p<.001). There was no evidence of a difference in the incidence of high-grade histology between European and Māori women overall or after taking vaccination status into account.

CONCLUSIONS: Receiving at least one dose of quadrivalent HPV vaccine prior to 18 years was associated with a 25% lower incidence of high-grade cytology and 31% lower incidence of high-grade histology in women aged 20–24 years.

Cervical cancer is a largely preventable disease. In New Zealand, the commencement of the National Cervical Screening Programme (NCSP) in 1990 initially led to markedly reduced cervical cancer incidence and mortality rates; however, since 2005, rates of cervical cancer have been relatively stable (~6 per 100,000 women).[1] Higher rates of cervical cancer incidence and death among Māori remain a major concern (eg, in 2015 there was an incidence of 9.1 vs 5.4 per 100,000 women and mortality rate of 3.0 vs 1.4 per 100,000 women in Māori compared with European women).[1]

The human papillomavirus (HPV) is the main cause of cervical cell abnormalities and cervical cancer.[2–4] Cervical cancer can be caused by a number of high-risk HPV types but approximately 70% are caused by HPV 16 and 18.[5] The development of cervical cancer is preceded by high-grade intraepithelial cervical abnormalities which are the target of cervical screening programmes. Approximately 50–60% of high-grade cervical abnormalities are caused by HPV 16 and 18.[5,6] A three-dose quadrivalent HPV vaccine (containing HPV virus-like particles of types 6, 11, 16 and 18) was first licensed

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in 2006 and the efficacy of the vaccine for preventing high-grade cervical abnormalities has been demonstrated through large randomised controlled trials.[7]

In order to further reduce the incidence and mortality of cervical cancer and other HPV-related disease, a National HPV vaccination programme was commenced in New Zealand in 2008. When introduced, the quadrivalent HPV vaccine was offered (fully subsidised) to young women born in 1990 and 1991 (ie, women who were 17–18 years old). In 2009, the HPV vaccination programme was extended to girls and young women born from 1992 onwards.

As might be expected following the introduction of HPV vaccination programmes, studies performed in other jurisdictions have demonstrated reductions in HPV 16/18 infection[8–13] and cervical precancer rates.[14–16] The impact of vaccination will depend on a number of factors that vary between different populations; these include the vaccination coverage, the age of vaccination, the age specific prevalence of HPV infection, vaccination type and screening participation. It is therefore important to document and quantify the impact of HPV vaccination in different populations.

Although recent reports from the NCSP have shown a reduction in the rates of cervical abnormalities in young women, there has also been an approximate 5% reduction in screening rates in this age group.[17] The screening register does not have access to vaccination information so limited conclusions can be made regarding the impact of HPV vaccination on disease rates.

The New Zealand National Immunisation register (NIR) holds information from the HPV Immunisation Programme on dispensed doses of vaccine per person. HPV vaccination coverage in New Zealand has increased from 39% (for all three HPV doses) for the cohort born in 1990 to 67% (for all three HPV doses) for the cohort born in 2003.[18]

All cervical cytology, histology and HPV test results for New Zealand women are held in the NCSP Register unless a woman opts off. Opt off rates are very low (eg, 1–4 in 100,000 women withdrew from the NCSP register 2010–2015).[17] In 2010, the rate of high-grade histologies (cervical intraepithelial neoplasia [CIN] grade 2 or 3) in the overall population was 21.2 per 1,000 women screened (ages 20–24 years).[19] The primary objective of this audit was to determine the incidence of high-grade cytology and high-grade histology diagnoses reported in young women (aged 20–24 years) vaccinated with the quadrivalent HPV vaccine compared with HPV-unvaccinated young women. In addition, we investigated the impact of other factors such as ethnicity and number of vaccine doses on incidence of high-grade cytology and histology. Secondary objectives were to determine the incidence of low-grade cytology and low-grade histology diagnoses reported in young HPV-vaccinated women (aged 20–24 years) compared with HPV-unvaccinated young women.

Methods

The data included all women who (a) were born in 1990–1994 and (b) had had a cervical cytology or histology and associated data recorded in the NCSP Register (when aged 20–24 years) between 1 January 2010 and 31 December 2015 ('audit period').

Data from the NCSP Register during the audit period for women aged 20–24 years and HPV vaccination data from the NIR were linked using a unique national health identifier and de-identified data were provided to the research team. Prioritised ethnicity was obtained from the NCSP register and was coded using Health Information Standards Organisation (HISO) standards for output of ethnicity data.[20]

The women were split into three groups:

- Vaccinated prior to 18 years (ie, at least one dose of the HPV vaccine prior to 18 years)
- Late vaccinated (ie, all doses of the HPV vaccine at 18 years or older)
- Unvaccinated (ie, no HPV vaccination at any age)

Low-grade cytology was defined as atypical squamous cells of undetermined significance (ASCUS) or low-grade squamous intraepithelial lesion (LSIL). High-grade cytology was defined as atypical squamous cells—cannot exclude high-grade (ASC-H) or worse.

Low-grade histology was defined as HPV effect, atypia, CIN not otherwise specified or CIN1. High-grade histology was defined as CIN2 or worse or glandular lesion.

Incidence of high- and low-grade cytology or histology per 1,000 person years was calculated for each group. The time that women were considered at risk of an event is from age 20 years until the earliest of the following:

- First occurrence of the outcome being assessed (eg, CIN2 histology), or
- age 25 years,
- end of audit period (31 December 2015).

Power analyses

Previous research has reported a wide range for HPV vaccine effectiveness depending on the study population with studies reporting a decrease in high-grade cervical abnormalities of between 26–80% in women who have had at least one dose of the HPV vaccine.[14,21]

In 2011, 150 per 1,000 cervical cytology samples showed low-grade abnormalities and 27 per 1,000 showed high-grade abnormalities in women aged 20–24 years.[19] Taking the lowest estimated rate reduction of 26%, sample sizes of 10,063 in each group would provide 90% power for observing a change in the rate of high-grade cervical cell abnormalities of at least 26% (p=.05).

In 2011, 38.3 per 1,000 women screened were diagnosed with histologically-confirmed CIN in women ages 20–24 years (14.7 per 1,000 for CIN1 and 23.6 per 1,000 for CIN2 or worse).[19] Sample sizes of 6,962 in each group would provide 90% power for observing a change in the rate of CIN of at least 26% (p=.05). If considering only high-grade CIN (CIN2 or worse), sample sizes of 11,547 in each group would provide 90% power for observing a change in the rate of CIN2 or worse of at least 26% (p=.05).

Primary hypotheses

Compared with unvaccinated women, women vaccinated prior to 18 years will have lower rates of (a) high-grade cytology and (b) high-grade histology.

The effectiveness of vaccination for lowering high-grade cytology and histology incidence rates will be dose dependent.

The effectiveness of vaccination for lowering high-grade cytology and histology incidence rates will be impacted by the age at which the first dose of the HPV vaccine was received (ie, prior to 18 vs after 18 years).

High-grade cytology and histology incidence rates will be impacted by ethnicity.

Secondary hypotheses

Compared with unvaccinated women, women vaccinated prior to 18 years will have lower rates of (a) low-grade cytology and (b) low-grade histology.

Statistical analysis

A two-sample test of proportions was used to compare proportions using STATA (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP). To compare group differences in rates of high-grade cytology and histology, incidence rate ratio (IRR) analyses were implemented in R version 3.5.2 (R Core Team. 2013. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/). Significance level was set at alpha =.05. Ninety-five percent confidence intervals are reported.

This audit protocol was approved by the New Zealand Health and Disability Ethics Committee (Ethics ref: 14/STH/141, 29 September 2014. 14/STH/141/AM02 Amendment to Protocol approved 22 February 2016) and had site authorisation.

Results

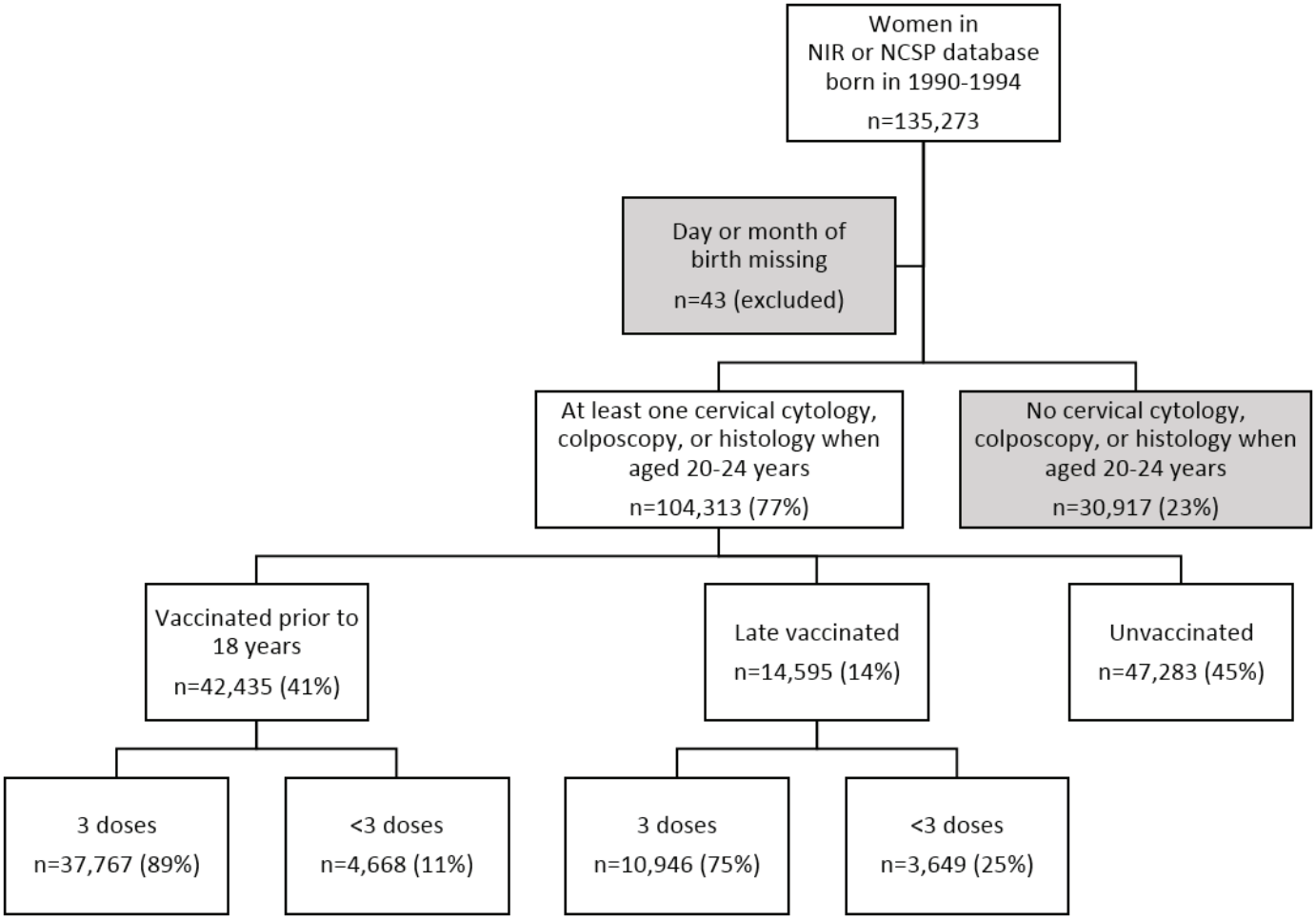
The combined NIR and NCSP dataset contained data for n=135,273 women born 1990–1994. Day or month of birth was missing in the dataset for n=43 women and these women were excluded. Of the remaining women, n=104,313 (77%) women had at least one cervical cytology sample, colposcopy or histology recorded when aged 20–24 years (see Figure 1).

Most women identified as New Zealand European or other European (64%). The remaining women identified as Māori (18%), Pacific (7%), Asian (7%) or other/not stated (4%).

N=42,435 (41%) women were vaccinated prior to 18 years, n=14,595 (14%) women were late vaccinated and n=47,283 (45%) women were unvaccinated.

A higher proportion of the women vaccinated prior to 18 years received all three HPV vaccine doses compared with the late vaccinated women (89% vs 75%, two-sample test of proportions z=41.3, p<.001, 95% CI 13, 15% difference).

Figure 1: Study analysis flow chart.



The mean age of vaccination decreased across birth cohorts (including both women vaccinated prior to 18 years and late vaccinated women) as most vaccinated women in these birth cohorts were vaccinated in 2008 or 2009 (Figure 2). Figure 2 includes the proportion of women who were not vaccinated and thus had no age of vaccination.

Incidence rate ratio (IRR) analyses included 376,402 person years of follow up.

The incidence of high-grade cytology was lower in women vaccinated prior to 18 years than in unvaccinated women (8.5 vs 11.3 per 1,000 person years [p1000py], IRR 0.75, 95% CI 0.70, 0.80, p<.001). The incidence of high-grade cytology was also lower in late vaccinated women than in unvaccinated women (9.7 vs 11.3 p1000py, IRR 0.86, 95% CI 0.79, 0.94, p<.001).

The incidence of high-grade histology was lower in women vaccinated prior to 18 years than in unvaccinated women (6.0 vs 8.7 p1000py, IRR 0.69, 95% CI 0.64, 0.75, p<.001). However, there was no difference in the incidence of high-grade histology in late vaccinated vs unvaccinated women (8.1 vs 8.7 p1000py, IRR 0.93, 95% CI 0.84, 1.02, p=.122) (see Figure 3).

When taking into account the number of HPV vaccine doses, the incidence of high-grade histology was lower in women who had all three doses (with at least one dose prior to 18 years) than in unvaccinated women (5.8 vs 8.7 p1000py, IRR 0.66, 95% CI 0.60, 0.72, p<.001). There was weak evidence for a lower incidence of high-grade histology in women who had had two vaccine doses (with at least one dose prior

Figure 2: Distribution of age of first dose of the vaccine (including both women vaccinated prior to 18 years and late vaccinated women) by birth cohort. The proportion of women born each year but not vaccinated and thus having no age of vaccination is shown by the bars labelled 'Not vaccinated'.

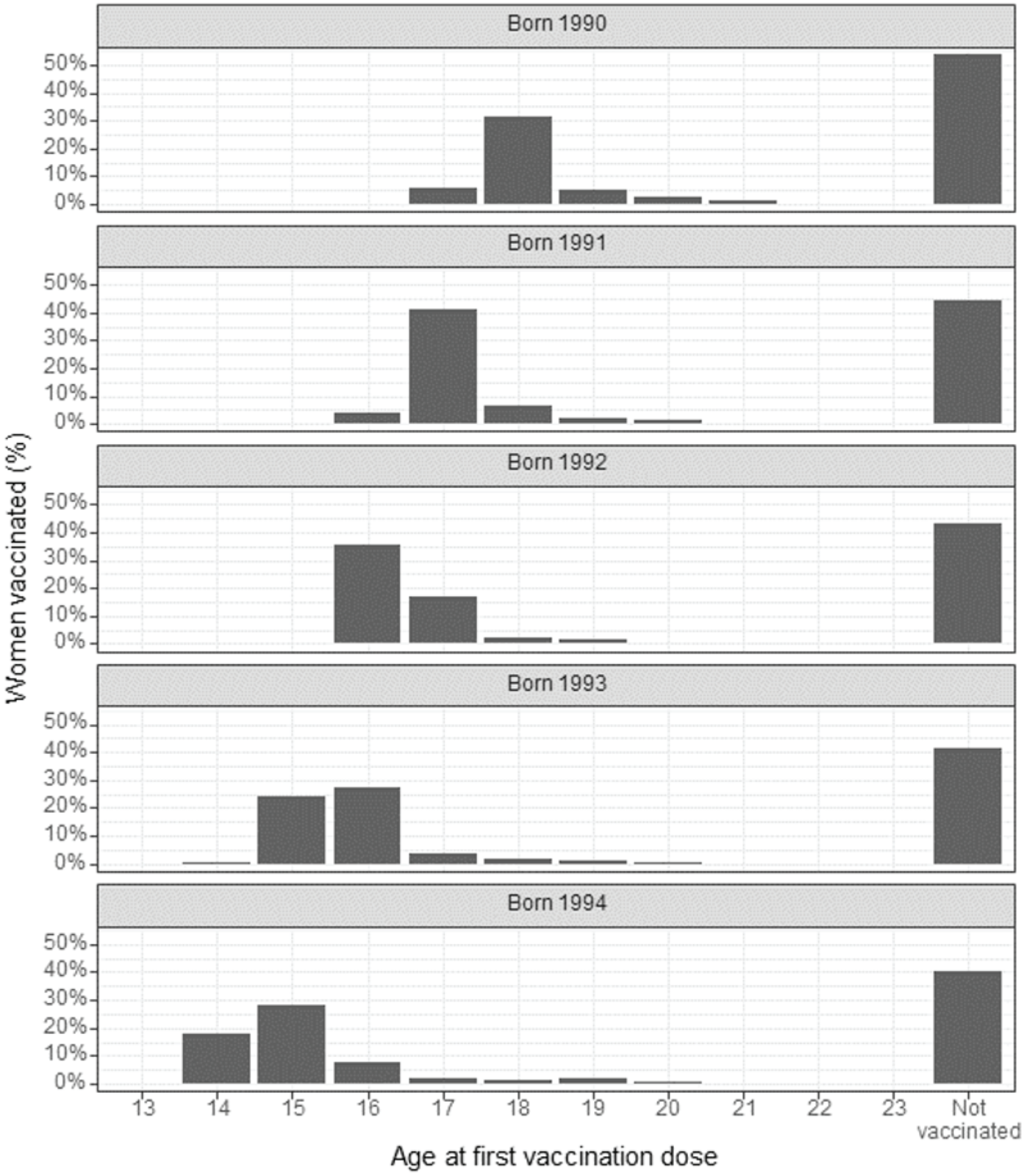


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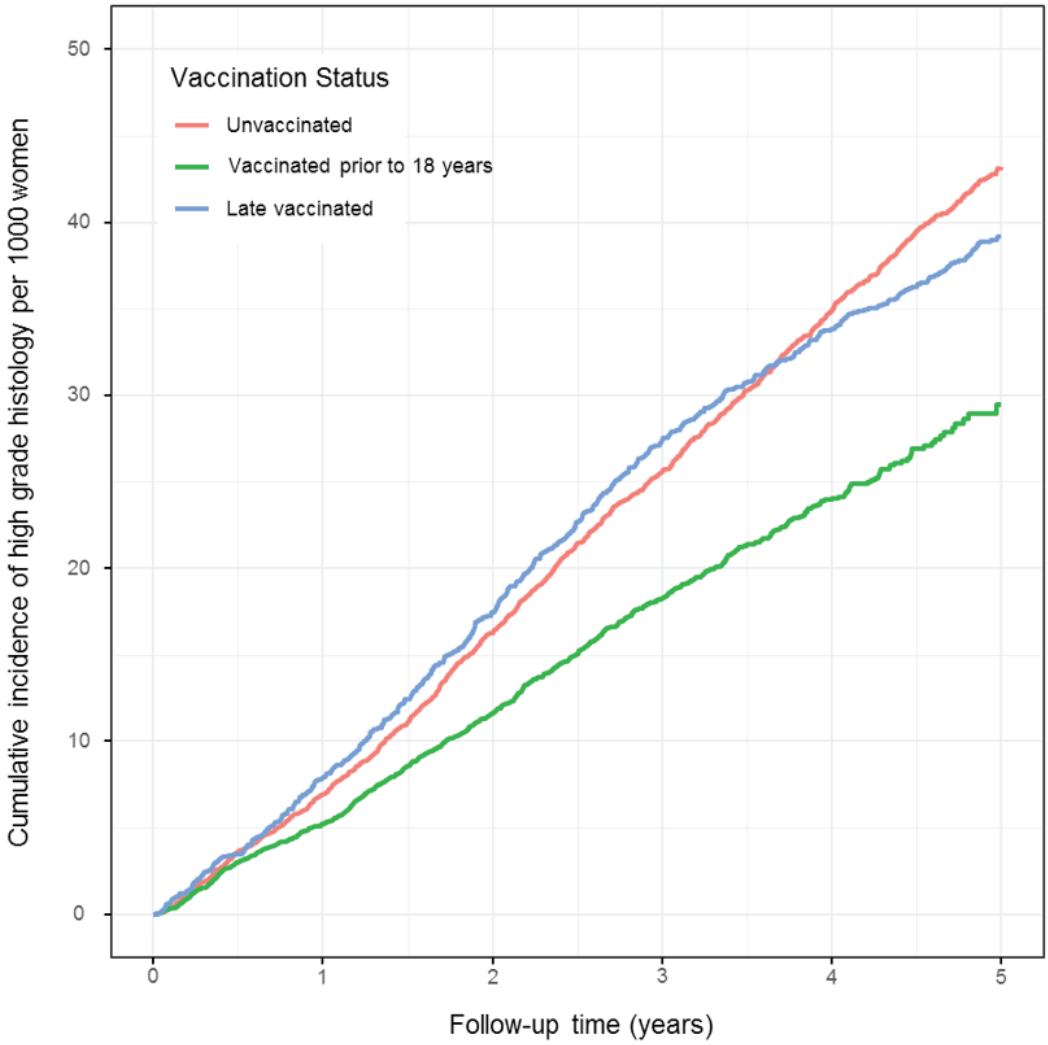
Figure 3: Cumulative incidence of high-grade histology in women aged 20–24 years by HPV vaccination status.



to 18 years) compared with unvaccinated women (7.0 vs 8.7 p1000py, IRR 0.81, 95% CI 0.63, 1.03, p=.07). However, compared to unvaccinated women, there was no evidence of a difference in the incidence of high-grade histology in women who had had only one dose (prior to 18 years) (9.7 vs 8.7 p1000py, IRR 1.1, 95% CI 0.85, 1.45, p=.43) (see Figure 4).

Proportions of women who were vaccinated prior to 18 years, late vaccinated or unvaccinated by ethnicity are given in Table 1. In screened women, Māori and Asian women were less likely to be vaccinated prior to 18 years than European women (Māori women 38% vs 42%, two-sample test of proportions z=9.67, p<.001, 95% CI 3, 5% difference; Asian women 33% vs 42%, two-sample test of proportions z=14.57, p<.001, 95% CI 8, 10% difference).

There was no evidence of a difference in the incidence of high-grade histology between screened European and Māori women overall (Cox proportional hazard ratio 0.96, 95% CI 0.85, 1.06, p=.40) or after taking vaccination status into account (Cox proportional hazard ratio 0.93, 95% CI 0.83, 1.03, p=.17). However, all other ethnicities had lower rates of high-grade histology (Cox proportional hazard ratio [range] 0.27–0.39, p<.001).

Figure 5 shows the incidence of high-grade histology over five years in women grouped by ethnicity.

Table 1: Proportions of screened women who were vaccinated prior to 18 years, late vaccinated, or unvaccinated by ethnicity.

Ethnicity	Vaccinated prior to 18 years	Late vaccinated	Unvaccinated	Total
European	28,309 (42%)	9,749 (15%)	29,102 (43%)	67,160
Māori	7,082 (38%)	2,435 (13%)	9,021 (48%)	18,538
Pacific	2,952 (41%)	957 (13%)	3,243(45%)	7,152
Asian	2,302 (33%)	859 (12%)	3,791 (55%)	6,952
Other or not stated	1,790 (40%)	595 (13%)	2,126 (47%)	4,511
Total	42,435 (41%)	14,595 (14%)	47,283 (45%)	104,313

There was no difference in the incidence of low-grade cytology in women vaccinated prior to 18 years compared with unvaccinated women (66.6 vs 65.0 p1000py, IRR 1.03, 95% CI 0.99, 1.06, p=.10) (Table 2). However, the incidence of low-grade cytology was lower in late vaccinated women than in unvaccinated women (61.2 vs 65.0 p1000py, IRR 0.94, 95% CI 0.91, 0.98, p=.002).

The incidence of low-grade histology was lower in women vaccinated prior to 18 years than in unvaccinated women (13.3 vs 15.7 p1000py, IRR 0.85, 95% CI 0.80, 0.90, p<.001). However, there was only limited evidence of any difference in the incidence of low-grade histology in late vaccinated vs unvaccinated women (16.7 vs 15.7 p1000py, IRR 1.07, 95% CI 0.99, 1.14, p=.08).

Figure 4: Cumulative incidence of high-grade histology in women aged 20–24 years by HPV vaccine dose (with at least one dose prior to 18 years in Dose 1–3 groups).

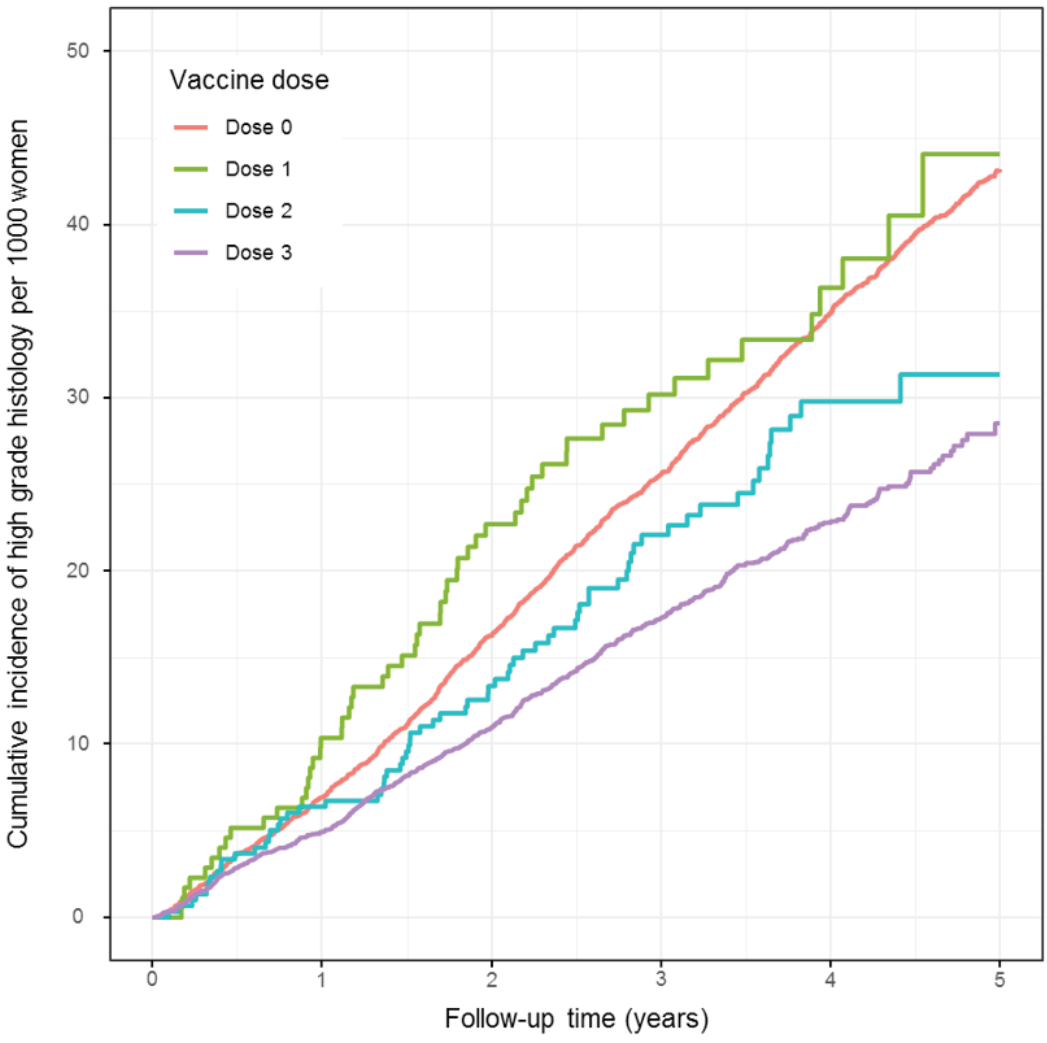


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Figure 5: Cumulative incidence of high-grade histology in women aged 20–24 years by ethnicity.

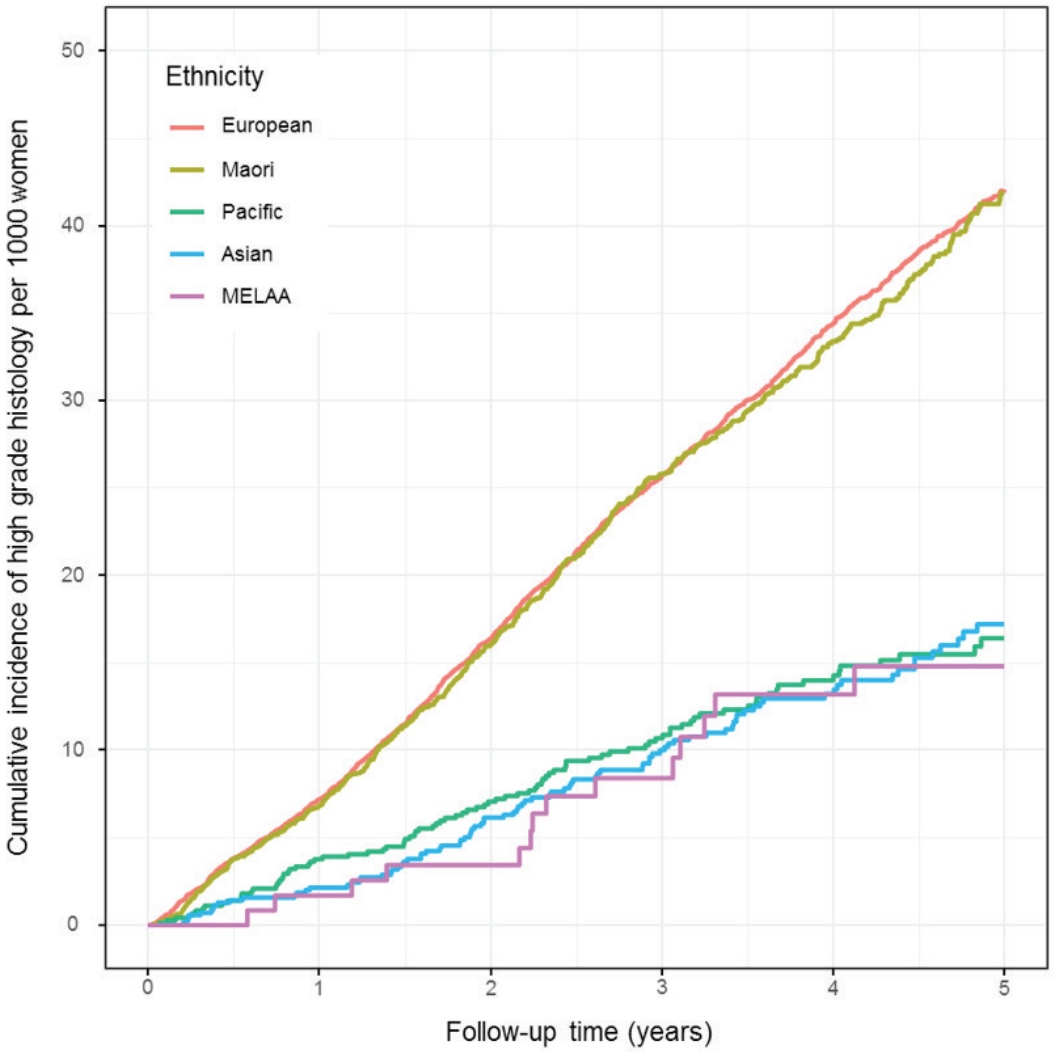

Table 2: Incidence of high-grade and low-grade cytology and histology by vaccination status.

	High-grade					Low-grade				
	Person-years of observation	N	Incidence per 1,000 person years (95% CI)	Incident rate ratio (95% CI)	p	Person-years of observation	N	Incidence per 1,000 person years (95% CI)	Incident rate ratio (95% CI)	p
Cytology										
Unvaccinated	174,742	1,981	11.3 (10.8, 11.8)	1.00		155,076	10,074	65.0 (63.7, 66.2)	1.00	
Late vaccinated	65,761	640	9.7 (9.0, 10.5)	0.86 (0.79, 0.94)	<0.001	56,727	3,470	61.2 (59.2, 63.2)	0.94 (0.91, 0.98)	0.002
Vaccinated prior to 18 years	133,895	1,135	8.5 (8.0, 9.0)	0.75 (0.70, 0.80)	<0.001	119,179	7,937	66.6 (65.1, 68.1)	1.03 (0.99, 1.06)	0.10
Histology										
Unvaccinated	175,748	1,537	8.7 (8.3, 9.2)	1.00		173,379	2,718	15.7 (15.1, 16.3)	1.00	
Late vaccinated	66,091	535	8.1 (7.4, 8.8)	0.93 (0.84, 1.02)	0.12	64,757	1,082	16.7 (15.7, 17.7)	1.07 (0.99, 1.14)	0.08
Vaccinated prior to 18 years	134,563	813	6.0 (5.6, 6.5)	0.69 (0.64, 0.75)	<0.001	132,909	1,768	13.3 (12.7, 13.9)	0.85 (0.80, 0.90)	<0.001

Discussion

Main findings

Compared with unvaccinated women, women who had at least one dose of the quadrivalent HPV vaccine prior to age 18 years had a 25% lower incidence of high-grade cervical cytology and 31% lower incidence of high-grade cervical histology when they were aged 20–24 years. For women vaccinated after 18 years, there was a 14% lower incidence of high-grade cytology compared with unvaccinated women; however, there was only a small relative decrease in high-grade histology rates within the time frame of the study.

Māori and Asian women in our cohort of screened women were less likely to be vaccinated prior to 18 years than European women while Pacific women had similar vaccination coverage to European women. There was no evidence of a difference in the incidence of high-grade histology between European and Māori women, either overall or after taking vaccination status into account. In contrast, Pacific and Asian women had lower rates of high-grade histology than European women.

We classified women as vaccinated prior to 18 years if they had had at least one dose of the HPV vaccine prior to age 18. However, most vaccinated women (89%) did receive all three doses and there was no substantial difference in the results if we excluded women who had had fewer than three doses.

Strengths and limitations

Missing data

Data was included from all women who consented to have their data held in either the NCSP or NIR. A small number of women may have consented for their data to be held on one register but not on the other, which could lead to incorrect assumptions being made about a woman (eg, cervical cytology history but no evidence of HPV vaccination [despite having received the HPV vaccine]). However, the number of women who would have been eligible for the audit but opted off either register is likely to be very small.[17]

During the audit period, 3–6% of the New Zealand population aged 20–25 years were recent immigrants (arrived within the past 12 months).[22] Some young immigrants may have been vaccinated prior to their arrival in New Zealand, but not recorded as vaccinated on the NIR. If a large enough number of young HPV-vaccinated immigrant women were included in NCSP register data and misclassified as unvaccinated, this could lead to an underestimate of the impact of vaccination on cervical cell abnormalities.

Our analyses took an inclusive approach to identifying Māori women (ie, the analyses included as Māori any woman who self-identified as Māori in any ethnicity response). However, ethnicity recording is not always accurate and there will inevitably be women who identify as Māori but who are not recorded as such. In addition, while screening coverage for Māori women (of all ages) is improving (increasing by about 8% between 2010 and 2017), coverage continues to be 20–25% lower than in non-Māori.[17] Thus, this study may underestimate the real incidence of high-grade abnormalities in young Māori women.

The potentially largest proportion of missing data will be from women who had neither an HPV vaccination nor a smear (but otherwise would have met the inclusion criteria for the study). These women would not be recorded in either register and, thus, were not included in the audit. While, the proportion of eligible women and girls receiving the HPV vaccine is slowly increasing in New Zealand, since the programme commenced in 2008, an estimated 39–56% of eligible women have not received the HPV vaccine.[18] In addition, only 52% of eligible women 20–24 years were screened in the three years prior to 31 December 2015.[23]

A factor that may impact our results is whether screening participation is different for those women who have undergone HPV vaccination. The data around this is conflicting.[24] HPV vaccination was associated with higher rates of screening participation in the US,[25] UK,[26,27] and Sweden[28] but decreased screening participation in Australia.[29] Unfortunately, we do not currently have the data to investigate this factor in young New Zealand women.

Exposure to HPV 16 or 18

Our analysis was limited to women born 1990–1994, as only women born in 1990 or later were eligible for the HPV vaccine and only those born in or before 1994 were

old enough to have been aged 20–24 years during the audit period. Women in our study who were born in 1990 had the most follow up data (ie, five years) as they were aged 20–24 years throughout the entire audit period. In contrast, women born in 1994 only turned 20 years in 2014, and thus, were limited to 1–2 years follow-up. The women with the most follow-up data (ie, those born in 1990–1991) were primarily 17 or 18 years old when vaccinated, meaning that a proportion of those women may have already been exposed to HPV16/18 prior to vaccination.

Women vaccinated over the age of 18 appeared to have limited benefit, however we cannot exclude a benefit for these women with longer-term follow-up as, although disease from existing infections was not prevented, further new infections will be.

Mean age of HPV vaccination decreased across each birth cohort in this study. Decreasing age of vaccination is likely to be associated with decreasing risk of pre-vaccination exposure to HPV. Thus, the impact of vaccination may be greater in later birth cohorts in this study and in later birth cohorts not evaluated in this study.

The herd effect is an important confounding factor to consider. Once there are a large number of vaccinated women within the population, the prevalence and transmission of vaccine HPV types will decrease. This herd effect offers protection to unvaccinated women. We have recently shown a substantial decrease in the proportion of unvaccinated young women with CIN2 who are HPV16/18 positive (66% in 2013 vs 17% in 2016).[13] Decreased HPV16/18 prevalence in unvaccinated young women has also been reported in the Australia[10,11] and Scotland.[12] The herd effect will be enhanced by the inclusion of HPV vaccination for males in New Zealand from 2017.

As age at first vaccination is influenced by birth cohort, and if incidence rates are dropping over time (due to herd effect), then those born earlier (and thus vaccinated later) will also be at higher risk of exposure (regardless of vaccination status). Factors such as a decreased mean age of vaccination and the introduction of the nonavalent HPV vaccination may lead to an even greater impact of the HPV vaccine on rates of high-grade cervical cell abnormalities in vaccinated women over time. There have also been increased rates of HPV vaccination in New Zealand, and coupled with the inclusion of HPV vaccination for males in New Zealand in 2017, both these factors may enhance the herd effect in New Zealand.

HPV vaccine effectiveness

The quadrivalent HPV vaccine has been demonstrated to be almost 100% effective in preventing HPV 16- or 18-related cervical abnormalities. In this study, women vaccinated prior to 18 years showed only a 31% reduction in high-grade abnormalities and little consistent reduction in low-grade abnormalities. This can be expected because while ~50–60% of high grade abnormalities in an unvaccinated population are associated with HPV 16 or 18,[5,6] a recent study of New Zealand women found that only 22% of high-grade abnormalities were positive for *only* HPV 16 and/or 18, with the remainder associated other high-risk HPV types.[6] Low-grade abnormalities are less likely to be associated with HPV 16 or 18 and therefore the impact of vaccination on the incidence of these abnormalities will be substantially less.

A US population-based study was undertaken following the 2007 introduction of the HPV vaccine. They showed an 11% annual decrease in CIN2 and a 41% annual decrease in CIN3 between 2007 and 2014 in adolescent women (aged 15–19 years).[16] They also noted a 6% annual decrease in CIN2 in women (aged 20–24 years) but no decrease in CIN3 in this age group. The individual HPV vaccination status of women was not evaluated.

An Australian study considered HPV vaccination status and found that compared with unvaccinated women, at least one dose of quadrivalent HPV vaccine was 26% effective against high-grade cervical abnormalities in young women attending their first cervical cytology screen, while the vaccine was 46% effective in fully vaccinated young women.[14] Similarly, a Scottish study observed a 50% decrease in CIN2 and 55% decrease in CIN3 among fully vaccinated women at their first cervical screen at age 20 or 21.[30] Therefore, the most substantial effects were seen in studies reporting decreases in high-grade cervical abnormalities in young fully-vaccinated women attending their first cervical cytology screen.

Conclusion

HPV vaccination has led to a significant reduction in high-grade abnormalities in women vaccinated prior to 18 years in New Zealand, which in turn can be expected to impact on rates of cervical cancer as this cohort ages. In this cohort of screened women, Māori were less likely to be vaccinated but, if vaccinated, vaccination offered similar protection for Māori and non-Māori women. As time progresses, we can expect the decreasing age of vaccination and higher coverage to increase the impact of vaccination and this will be further amplified by the herd effect. In 2017, the nonavalent vaccination became available, fully-subsidised, in New Zealand for both boys and girls. This vaccine will provide protection against the majority of disease-causing HPV types and vaccination of boys will compound the herd effect. The vaccination programme offers opportunities to reduce the incidence of, and inequities from, cervical cancer. This study also demonstrates that both HPV-vaccinated and unvaccinated women develop high-grade cervical disease and this underlines the need for cervical screening in both HPV-vaccinated and unvaccinated women and for the impact of HPV vaccination to continue to be monitored.

Competing interests:
Author CI reports a travel grant from Seqirus Ltd to present at a scientific meeting during the conduct of the study. Author MS is the Clinical Lead for Pathology with the National Cervical Screening Programme in the Ministry of Health in New Zealand. Author BL reports personal fees and non-financial support from CSL Biotherapies (NZ) Ltd and, outside the submitted work, she sits on the Pfizer board for women's health menopause.

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