Early effect of the HPV vaccination programme on cervical abnormalities in Victoria, Australia: an ecological study

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Summary

Background **Australia introduced a human papillomavirus (HPV) vaccination programme with the quadrivalent HPV vaccine for all women aged 12–26 years between 2007 and 2009. We analysed trends in cervical abnormalities in women in Victoria, Australia, before and after introduction of the vaccination programme.**

Methods **With data from the Victorian Cervical Cytology Registry between 2003 and 2009, we compared the incidence of histopathologically defined high-grade cervical abnormalities (HGAs, lesions coded as cervical intraepithelial neoplasia of grade 2 or worse or adenocarcinoma in situ; primary outcome) and low-grade cytological abnormalities (LGAs) in five age groups before (Jan 1, 2003, to March 31, 2007) and after (April 1, 2007, to Dec 31, 2009) the vaccination programme began. Binary comparisons between the two periods were done with Fisher's exact test. Poisson piecewise regression analysis was used to compare incident rate trends.**

Findings **After the introduction of the vaccination programme, we recorded a decrease in the incidence of HGAs by 0·38% (95% CI 0·61–0·16) in girls younger than 18 years. This decrease was progressive and significantly different to the linear trend in incidence before introduction of the vaccination (incident rate ratio 1·14, 1·00–1·30, p=0·05). No similar temporal decline was recorded for LGAs or in older age groups.**

Interpretation **This is the first report of a decrease in incidence of HGAs within 3 years after the implementation of a population-wide HPV vaccination programme. Linkage between vaccination and screening registers is needed to confirm that this ecological observation is attributable to vaccination and to monitor participation in screening among vaccinated women.**

Funding **None.**

Lancet 2011; 377: 2085–92

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Introduction

Since the first prophylactic vaccine against human papillomavirus (HPV) was licensed in mid-2006, the quadrivalent vaccine (which provides protection against high-risk HPV types 16 and 18, and low-risk types 6 and 11, which cause 90% of genital warts) or bivalent vaccine (targeting HPV types 16 and 18) have been implemented in more than 28 countries as part of their national immunisation programmes and implemented at a sub-national level through donations in at least 17 developing countries.[1] Persistent infection with high-risk genital HPV types is needed for the development of cervical cancer, and HPV types 16 and 18 are detected in 70% of cervical cancers, half of high-grade cervical abnormalities (HGAs), and a quarter of low-grade cervical abnormalities (LGAs) worldwide.[2] Although the target age groups vary in different countries, the vaccine is aimed mainly at girls between the ages of 9 and 12 years because it is most effective when given before the onset of sexual activity, because it has no effect against HPV infection—which is transmitted sexually—once it has been acquired. Various countries have also chosen to implement short-term catch-up programmes aimed at older age groups, ranging from 13–18 years to 26 years.[3]

Australia was the first country to roll out an extensive, funded national HPV vaccination programme with the quadrivalent vaccine GARDASIL (Merck, Whitehouse Station, NJ, USA) in April, 2007, within the context of an already intensive and successful national cervical screening programme. The vaccination programme consists of a continuing component that targets 12–13-year-old girls in schools and two catch-up programmes, one for 13–17-year-old school girls, and one for 18–26-year-old women through general practice and community settings delivered between July, 2007, and December, 2009. In Victoria, the second most populous Australian state, the HPV vaccine programme in secondary schools began on April 16, 2007. Girls in school years 7 (ages 12–13 years), 10, 11, and 12 (ages 15–18 years) were offered vaccination in 2007, with the remaining two catch-up cohorts (aged 13–14 and 14–15 years in 2007) offered vaccine in 2008.[4] Vaccine coverage estimates from the National HPV Vaccination Program Register for the school programme in Victoria show a three-dose coverage of 79% in first-year high-school students and 71% in final-year high-school students.[4] A population-based telephone survey done in Victoria in early 2009 noted self-reported coverage rates of 74% for one dose, 69% for two doses, and 56% for three doses in young women aged 18–28 years.[5] These data indicate that the programme probably achieved high coverage.

Australia's HPV vaccination programme includes the broadest funded catch-up age range in the world[3] and

overlaps with the age cohort presently eligible for cervical screening in Australia. The National Cervical Screening Program policy recommends one cervical cytology test every 2 years, beginning at age 18 years (or 2 years after onset of sexual activity, whichever is later) until age 69 years. The National Cervical Screening Program was established in 1991, and since that time both cervical cancer incidence and mortality have halved.[6] Participation rates in the programme are 61·2% of women every 2 years, 73·9% every 3 years, and 86·3% every 5 years.[7] Monitoring of the early effect of the vaccine in Australia is helped by the existence of state and territory Papanicolaou (Pap) test registers that record nearly all cervical cytology and histology results and the National HPV Vaccination Program Register, which was established to support and monitor the HPV vaccination programme.[8]

A rapid effect on infection with vaccine-targeted HPV types is predicted after the implementation of population-based HPV vaccination programmes.[9] Indeed, early data from sexual health clinics in Australia suggest that the incidence of genital warts in Victoria began to decrease in the first year of the vaccination programme.[10] However, because of the long lead-time between infection and development of malignant disease, the programme's effect on cancer incidence will take decades to assess. Hence monitoring of cervical abnormality rates in a country such as Australia, with a longstanding high-quality cervical screening programme, is especially important because the effect on these abnormalities is more proximal than, but closely related to, the development of cervical cancer, and the treatment of such lesions is associated with morbidity and cost.

See Online for webappendix

Here we present data from Victoria, reporting cervical abnormality rates in young women for the first 3 years (2007–09) after the introduction of a widely targeted population-based HPV vaccination programme.

	Before vaccination (Jan 1, 2003, to March 31, 2007)	After vaccination (April 1, 2007, to Dec 31, 2009)	Difference in proportions (95% CI)	p value
Number of women screened				
<18 years	13 620	5538	NA	NA
18–20 years	86 356	50 644	NA	NA
21–25 years	237 599	152 531	NA	NA
26–30 years	281 767	177 776	NA	NA
≥31 years	1 798 842	1 178 351	NA	NA
LGA incidence				
<18 years	1658 (12·2%)	691 (12·5%)	0·3% (–0·8 to 1·4)	0·6
18–20 years	9465 (11·0%)	5506 (10·9%)	–0·1% (–0·5 to 0·3)	0·6
21–25 years	18 671 (7·9%)	11 067 (7·3%)	–0·6% (–0·8 to –0·4)	<0·0001
26–30 years	14 049 (5·0%)	7810 (4·4%)	–0·6% (–0·7 to –0·5)	<0·0001
≥31 years	44 408 (2·5%)	23 106 (2·0%)	–0·5% (–0·47 to –0·54)	<0·0001
HGA incidence				
<18 years	109 (0·80%)	23 (0·42%)	–0·38% (–0·61 to –0·16)	0·003
18–20 years	1035 (1·20%)	593 (1·17%)	–0·03% (–0·15 to 0·09)	0·7
21–25 years	3639 (1·53%)	2609 (1·71%)	0·18% (0·10 to 0·26)	<0·0001
26–30 years	3561 (1·26%)	2542 (1·43%)	0·17% (0·10 to 0·24)	<0·0001
≥31 years	6320 (0·35%)	4397 (0·37%)	0·02% (0·01 to 0·04)	0·002

Data are number and percentage of women screened, unless otherwise stated. HGA=high-grade abnormality. LGA=low-grade abnormality. NA=not applicable.

Table 1: **Number of individuals screened and incidence of low-grade cervical cytological abnormalities and high-grade cervical histopathological abnormalities before and after introduction of the national human papillomavirus vaccination programme, by age group**

Methods

Data collection

The Victorian Cervical Cytology Registry (VCCR) is one of eight Pap test registries in Australia and promotes regular participation of women in the National Cervical Screening Program by sending reminder letters and enables the follow-up of women with abnormal Pap tests. In brief, follow-up of cervical abnormalities detected by screening programmes in Australia is guided by national recommendations,[11] with incident LGAs generally followed up with another smear test after 12 months to establish whether the abnormality has resolved or whether colposcopy is needed. Patients with HGAs or possible HGAs are immediately referred for colposcopy. The VCCR compiles statistics for the purpose of monitoring and research.

The VCCR receives timely data for almost all cervical cytology and cervical histopathology taken in Victoria, with a population of more than 2·7 million girls and women. Less than 1% of women request for their test results not to be held on the VCCR.[12] Cervical cytology results, coded by reporting laboratories with the Australian Standard Modified Bethesda coding schedule, are forwarded to the VCCR. Copies of relevant histopathology results are received from reporting laboratories and coded according to an in-house coding schedule, with most coding checked by a second staff member for quality assurance purposes.

De-identified data were extracted from the VCCR for all screening-related episodes between Jan 1, 2001, and Dec 31, 2009. To minimise the prevalent pool effect,[13,14] which would result in prevalent lesions being regarded as incident because of an absence of preceding data, a clearance period of 2 years was applied to the data. We therefore analysed LGA and HGA incidence rates between 2003 and 2009.

The process of data exclusion from the analytical dataset is shown in the webappendix (p 1). Episodes that were not related to cervical diagnoses (eg, vaginal and non-cervical diagnoses) were excluded. Other exclusions included HPV DNA tests, non-diagnostic episodes (describing clinical procedures or treatment), and diagnoses obtained through colposcopy alone.

Data analysis

We aimed to find out whether the incidence of cervical abnormalities detected by screening has changed since

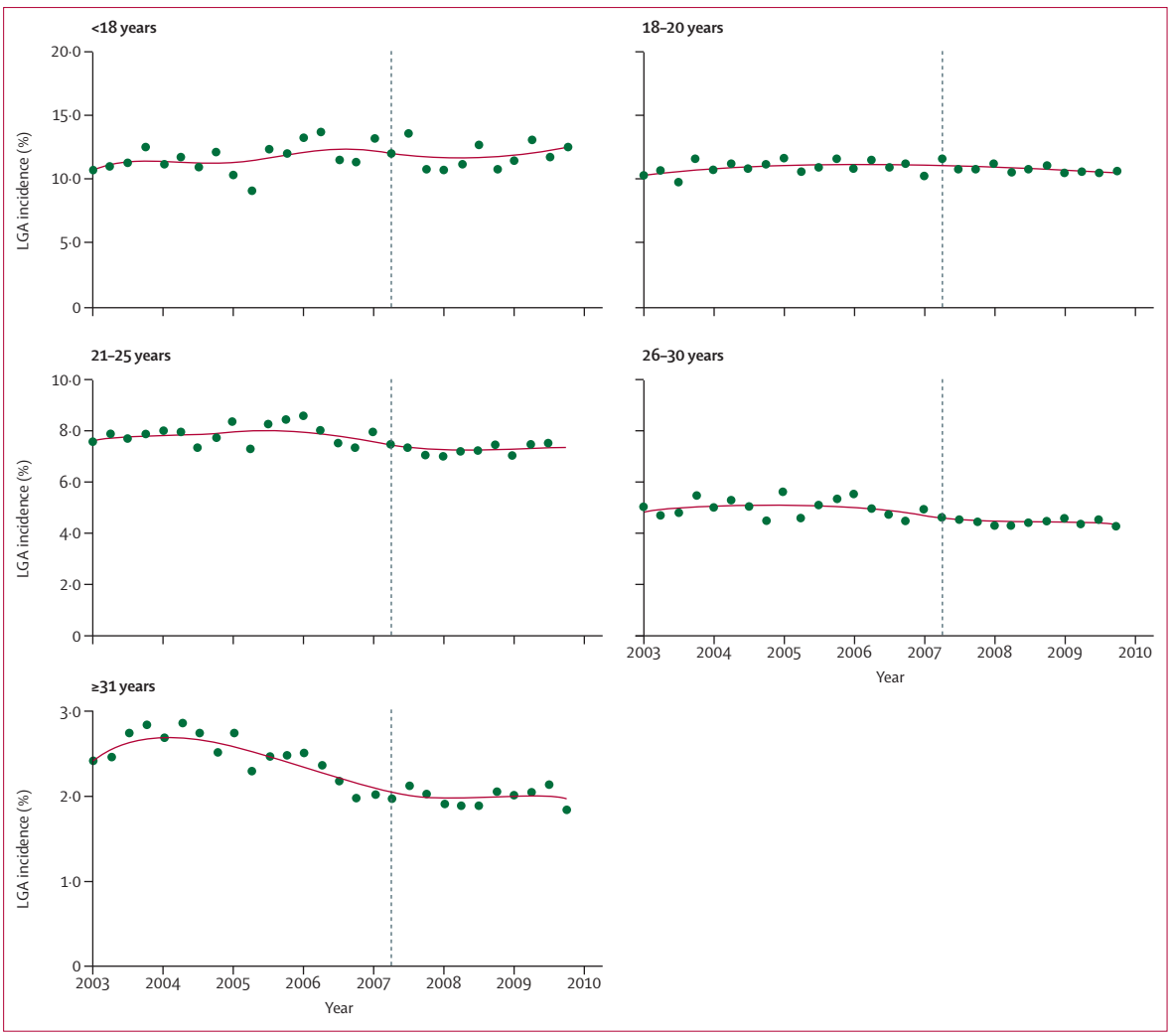

***Figure 1*: Incidence of low-grade cervical abnormalities, by age group**
Incidence of low-grade cervical abnormalities (LGA; green dots) is the number of new diagnoses within a 3-month period per 100 women tested. Lowess smoothing trends are shown with red lines. The vertical lines, at the start of the second quarter in 2007, signify the introduction of human papillomavirus vaccination.

the introduction of the HPV vaccination programme in April, 2007, compared with the 4 years before its introduction. The incidence of histopathologically defined HGAs was our primary outcome measure, and the incidence of cytologically defined LGAs was our secondary outcome measure.

An LGA was defined according to the results of Pap tests, coded with the Bethesda system. Low-grade squamous intraepithelial lesions and atypical squamous cells of undetermined significance were classified as cases of LGA.

Histopathology results were used to define cases of HGA and cancer. HGA included all lesions coded as cervical intraepithelial neoplasia of grade 2 or worse or adenocarcinoma in situ, with invasive cancers grouped separately, and according to the national data dictionary and Australian Institute of Health and Welfare classification system.[15] Cancer data are not presented in this paper because Victorian Cancer Registry data are not available for 2008 and 2009.

An LGA or HGA outcome was regarded as incident if it was a woman's first LGA or HGA diagnosis, or a woman's first abnormality that occurred at least 2 years (730 days) after a previous abnormality, with at least two negative tests in the intervening period.

A woman's first HGA diagnosis was also regarded as incident if it occurred after an LGA diagnosis, irrespective of test results in the intervening period. No event was defined as incident if it occurred after a cancer diagnosis, meaning that these records were excluded from the analysis. Incidence rates were defined as the number of incident events per 100 women tested within 3 months.

Statistical analysis

HGA and LGA incidence rates were estimated for 3-month periods and stratified by five age groups,

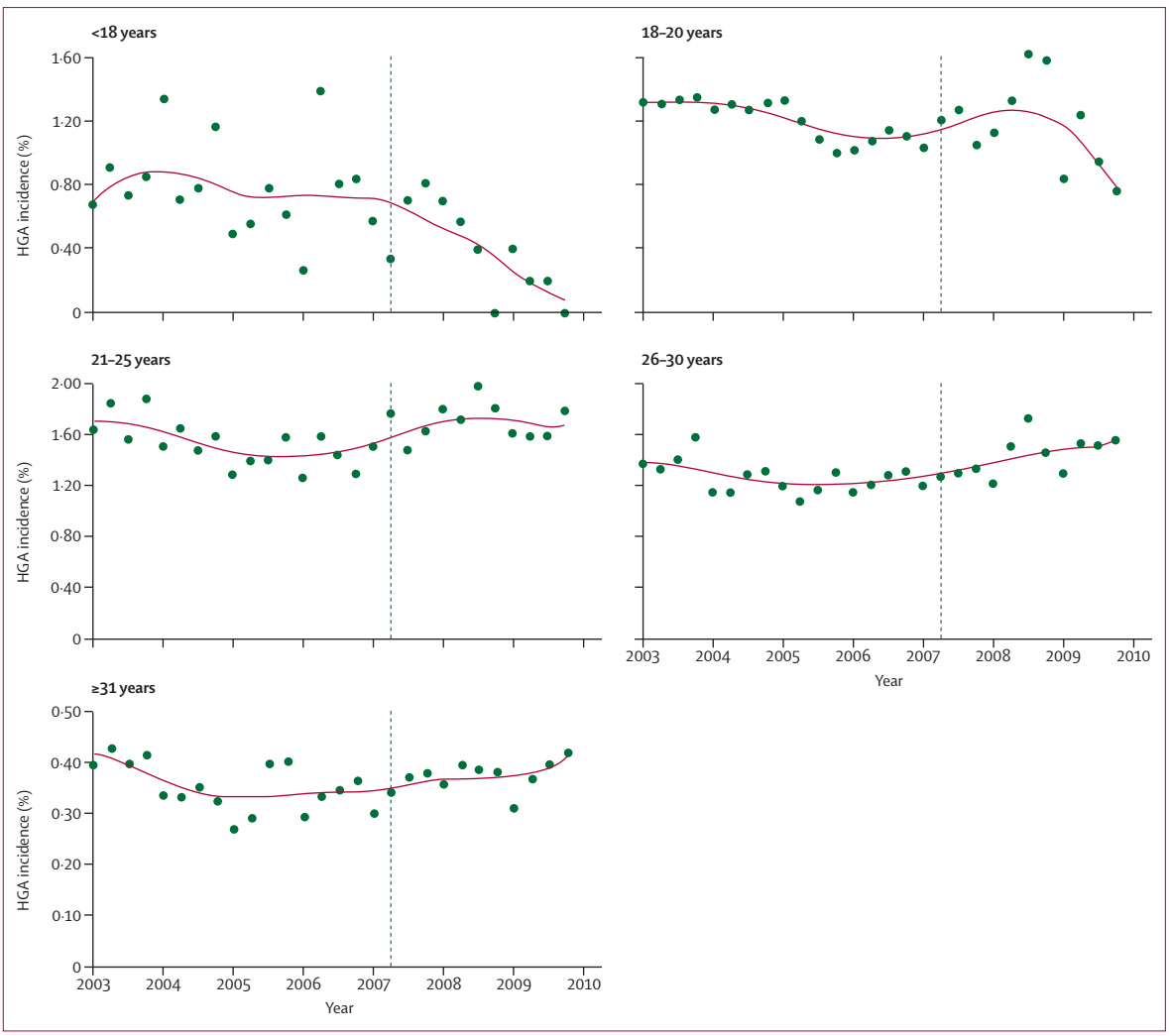

***Figure 2*: Incidence of high-grade cervical abnormalities, by age group**
Incidence of high-grade cervical abnormalities (HGA; green dots) is the number of new diagnoses within a 3-month period per 100 women tested. Lowess smoothing trends are shown with red lines. The vertical lines, at the start of the second quarter in 2007, signify the introduction of human papillomavirus vaccination.

	Aged <18 years			Aged 18–20 years		
	Incidence rate ratio	95% CI	p value	Incidence rate ratio	95% CI	p value
Before HPV vaccination (per 3-month interval)	0·99	0·96–1·02	0·5	0·99	0·98–1·00	0·1
After HPV vaccination (per 3-month interval)	0·87	0·78–0·97	0·01	1·00	0·98–1·02	0·8
Before *vs* after HPV vaccination	1·14	1·00–1·30	0·05	0·99	0·97–1·02	0·7

HPV=human papillomavirus.

***Table 2*: Comparison of trends in incident high-grade cervical abnormalities in the two youngest age groups, before and after introduction of the HPV vaccination programme**

which had different exposures to the vaccination programme (individuals aged ≤17 years, 18–20 years, 21–25 years, 26–30 years, and ≥31 years) and two periods: before vaccination (Jan 1, 2003, to March 31, 2007) and after vaccination (April 1, 2007, to Dec 31, 2009). Binary comparisons between the two periods for each age group were done with Fisher's exact test.

Temporal trend analysis was used to test the hypothesis that HGA would decrease more in younger age groups than in older age groups after the introduction of HPV vaccination in April, 2007, and that this decrease would be detected at a population level as a progressive decrease (negative slope) in HGA incidence. Lowess smoothing (bandwidth 0·5) was used to show incidence trends over time. A quantitative comparison of HGA temporal trends before and after vaccination was done with piecewise Poisson regression analysis.[16–18] In the context of a constant trend, the incidence rate ratio (IRR) was used as a measure of proportional change in incidence rate within a 3-month period. In the piecewise comparison of trends, IRR was used to estimate the

ratios of slopes for temporal trends before and after vaccination. StataSE (version 10) was used to do all statistical analyses.

Role of the funding source

There was no funding source for this study. MF, JMLB, and DMG had full access to data and JMLB had final responsibility for the decision to submit for publication.

Results

Table 1 shows the number of individuals included in the analysis and incidence rates for LGA and HGA diagnoses before and after introduction of the vaccination programme. Although a decrease in LGA incidence was recorded in age groups 21–25 years, 26–30 years, and 31 years and older, analysis of temporal trends suggests that these changes are a continuation of long-term trends that began before vaccination (figure 1). Figure 1 also indicates no decrease in LGA incidence in individuals aged younger than 18 years or those aged 18–20 years after the introduction of the HPV vaccination programme.

We recorded a significant decrease of 0·38% (95% CI 0·61–0·16; p=0·003) in HGA incidence in women younger than 18 years, beginning shortly after introduction of the HPV vaccination programme (figure 2), with a reduction from 0·85% in 2006 (the year before vaccination) to 0·22% in 2009 (p=0·003). We recorded no significant change in incidence in women aged 18–20 years although figure 2 shows a non-linear decline in incidence. Small increases in incidence were recorded in women aged 21–30 years (0·17–0·18%, 95% CI 0·10–0·26; p<0·0001) and in those aged 31 years or older (0·02%, 0·01–0·04; p=0·002; figure 2). Trends in the prevalence of LGA and HGA by age group and time are shown in the webappendix (pp 2–3), and accord with trends shown in figure 2.

A quantitative comparison of linear trends also showed a significant decrease in HGA incidence after introduction of the vaccination programme in individuals aged 17 years or younger but no significant decrease in those aged 18–20 years (table 2). Figure 3 shows predicted HGA incidence trends from piecewise regression models for the two youngest age groups. In girls aged younger than 18 years, there is a progressive linear decrease in the HGA incidence rate after the introduction of the vaccination programme; in those aged 18–20 years, the HGA incidence trend after introduction of vaccination is non-linear, and the decline is smaller and seems delayed (figure 3).

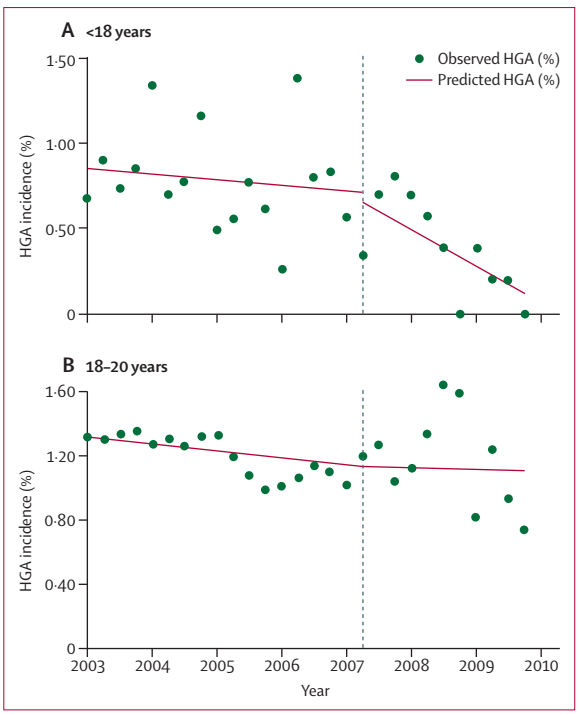

***Figure 3*: High-grade cervical abnormalities in individuals aged younger than 18 years (A) and 18–20 years (B)**

Incidence of high-grade cervical abnormalities (HGA; green dots) is the number of new diagnoses within a 3-month period per 100 women tested. Predicted incidences are shown with a red line. The vertical lines, at the start of the second quarter in 2007, signify the introduction of human papillomavirus vaccination.

Discussion

This ecological analysis reports a decrease in the incidence of high-grade cervical lesions in girls aged younger than 18 years in the 3 years after the start of the HPV vaccination programme in Victoria. This decrease began soon after the introduction of the vaccination programme. In women aged 18–20 years, a decrease in incidence seems to have begun about 1·5 years after vaccine introduction. Our finding that the decrease in HGA incidence occurred in the youngest vaccination cohort before it occurred in the older, catch-up cohorts (who were more likely to have been previously sexually experienced) reinforces the appropriateness of the targeting of prophylactic HPV vaccines to pre-adolescent girls.

The strengths of our analyses are that we have almost complete population-based data about cervical-screening-related outcomes on the VCCR. Coding of histopathological abnormalities was done with the national standard classification, and a 6-month period was allowed for reporting of histology to the register and checking of data. Our definition of incident abnormalities was conservative, requiring both an extended time interval and two negative tests after a previous abnormality for new lesions to be defined as incident. Prevalence trends in our study were similar to the incidence trends and support the robustness of the findings. Our definition of the period after vaccination was also conservative because we defined this phase as starting at the introduction of the vaccination programme, rather than after the first date (4 months after its introduction) when women could

Panel: Research in context

Systematic review

We systematically searched Medline and PreMedline on Nov 9, 2010, with the search terms ("HPV vaccination" OR the subject heading "Papillomavirus vaccines") AND ([the subject heading "cervical intraepithelial neoplasia" OR "CIN"] OR 'impact') with a publication date from Jan 1, 2006, onwards (the first HPV vaccine was licensed in 2006). We identified 418 articles but identified no population-based post vaccination reports on cervical intraepithelial neoplasia.

Interpretation

Our study is the first to report the effect of a national human papillomavirus vaccination programme on cervical abnormalities at a population level. With data from a state-based cervical screening register, we have shown a decrease in high-grade cervical abnormalities in young women after the implementation of the vaccination programme.

have completed the three-dose course. This starting point allows for some vaccine effectiveness after receipt of one to two doses of prophylactic HPV vaccines, which is biologically plausible.[19]

The main limitation of our analysis is that it is ecological in nature, and therefore a causal link between the recorded decrease in incidence and the vaccination programme cannot necessarily be ascribed. To substantiate these findings, cervical cytology data should be linked to HPV vaccination register data to enable analysis of cervical abnormality rates and participation rates by vaccination status. Monitoring of the effect of the vaccine is complex and needs data from several sources regarding cancer and abnormality rates, participation in screening, adverse events, and HPV typing of cancers and abnormalities.[20] However, we believe that our findings have strong biological plausibility and that the specific temporal association, differential by age (which is related to both coverage and likelihood of sexual activity and therefore HPV exposure before vaccination), suggests that the vaccination programme caused the decrease. Data from cohort studies and HPV vaccine trials indicate that the time from incident infection with HPV types 16 or 18 to development of cervical intraepithelial neoplasia of grade 2 or worse is often less than 12 months.[21,22]

New guidelines for the management of abnormalities detected by screening were adopted in Australia in 2006.[11] These new guidelines were more conservative than the previous guidelines in the management of women with LGAs and are unlikely to have had an effect on the reported incidence of HGAs specifically in younger women; neither guidelines have specific recommendations targeting women aged 20 years or younger. Little is known about the characteristics of women who attend Pap screening before the recommended starting age in Victoria. However, few young women were screened—on average, 2000–3000 per year between 2003 and 2009. These women could have been screened because of a misinterpretation of the screening policy or they could have been at higher-than-average risk for HPV infection and cervical intraepithelial neoplasia. Some individuals could have been screened too early because they were sexually active early in mid-adolescence, meaning they would have received vaccination after they had become sexually active. However, this possibility could not explain our findings because the vaccine would be less effective for such individuals. Similarly, if they were screened early because they were deemed at high risk, we would expect the lesion prevalence to be higher not lower in those women. One scenario that could contribute to a decrease in incidence is if young women at high risk are preferentially no longer being screened. We believe such a scenario is unlikely for the following reasons: no significant decrease was apparent in the older catch-up cohorts; all vaccinated cohorts were targeted with the same information about the need for screening after vaccination; and the decrease in screening rates in younger women occurred before the introduction of the vaccination programme.

Understanding of the possible effect of vaccination on screening behaviour is important to exclude differential screening in vaccinated and unvaccinated women as an explanation for recorded changes in lesion prevalence. Widespread publicity that accompanied the vaccination roll-out emphasised the importance of continued screening, and a Victorian population-based telephone survey in 2009 found that 96% of women aged 18–28 years knew that Pap tests were still needed after vaccination.[5] In Victoria, as in the rest of Australia, overall cervical screening participation by the target group of women aged 20–69 years has been stable for about a decade. However, in women younger than 35 years, a gradual decrease in participation has been recorded in the past decade.[7] In Victoria, 58% of women aged 20–24 years and 70% of women aged 25–29 years had a Pap test between 2007 and 2009, compared with 62% of women aged 20–24 and 74% of women aged 25–29 years between 2004 and 2006.[12] Reasons for this decrease are unclear but reported barriers to screening for young women include young women having a low awareness of the purpose of cervical screening, perceiving that the test would be embarrassing or painful, and reporting a lack of time or not even having thought of having a Pap test.[23] There has also been an increase in the population of eligible women in Victoria, and a delay in health-service use in young women newly migrated to Victoria could be a contributing factor. A gradual decrease in the number of women who were screened too early (before 18 years of age) is evident in Victoria, perhaps as a result of increased efforts in education for practitioners; this improvement in compliance with screening recommendations is not temporally related to the introduction of the vaccination

programme and is unlikely to explain our findings, because the denominator is screened women. As the cohorts vaccinated before becoming sexual active enter screening, data linkage between the vaccine and Pap registers will provide information about screening participation in both vaccinated and unvaccinated women, and will be crucial to confirm the emerging trends in the incidence of cervical abnormalities reported in this study.

We recorded no significant decrease in incidence of LGAs, which are a subset of acute HPV infections. Although HGAs are strongly associated with the detection of HPV types 16 and 18 (detected in >50% of all patients, probably more in young women),[24] LGAs are associated less strongly with detection of HPV types 16 and 18 (about 25%; HPV types 6 and 11 are detected in about 10%).[25] All 40 genital HPV types can lead to low-grade Pap test abnormalities, and most young women have concurrent infections with more than one type.[26] Furthermore, physiological changes such as inflammation and atrophy can closely mimic the appearance of LGAs.[27] Therefore, a reduction in infection with HPV types 16 or 18 might not result in a demonstrable decrease in the detection of LGAs on Pap tests. An intention-to-treat analysis from the phase 3 quadrivalent vaccine trials of more than 17 000 women aged 15–26 years recorded a statistically significant 19% reduction of any HGAs (with an average follow-up of 3·6 years), but a non-significant reduction in any Pap abnormality (11·3% reduction; difference 1·32 per 100 person-years at risk, 95% CI 0·74–1·90).[28] Although an eventual decrease in LGAs because of vaccination in HPV-naive cohorts is predicted,[29] these data emphasise that cervical abnormalities will continue to occur in vaccinated women in the future.[26]

We are aware of no other study to document the possible effect of a national HPV vaccination programme on cervical abnormalities at a population level (panel). We have shown a decrease in the incidence of HGA in young women after the implementation of the vaccination programme, and that this decrease occurred soon after vaccination. This finding suggests an urgent need to review the age at which cervical screening is begun in Australia and in other countries with national vaccination programmes that begin screening of women at a young age, because cost-effectiveness of screening will decrease for the youngest age groups screened. In countries that screen women at an older age, the effect of the vaccination will take longer to be seen. During the study period, we recorded no decrease in incidence of LGAs in women younger than 21 years (in whom LGA incidence was greater than 10%), which was to be expected because of the lower proportion of abnormalities that are due to vaccine preventable types. Long-term gradual decreases in LGA rates were, however, noted in women older than 21 years. Although more time and linked data analyses by vaccination status are now needed to substantiate these ecological results, our findings are a timely reminder that cervical screening programmes will need to adapt and respond to a post-vaccination environment in which lesion prevalence will decrease, accelerating the need to define workable screening algorithms, especially in vaccinated populations.[30]

Contributions

JMLB, DMG, and MF designed and were principal investigators of the study, with assistance from MS, GC, and CLM. MF prepared and analysed incidence data. Data interpretation was led by DMG, JMLB, and MS, with statistical interpretation by MF. JMLB and DMG wrote the first draft and all authors contributed to the final report.

Conflicts of interest

JMLB, DMG, and MS are investigators on an Australian Research Council Linkage Grant, for which CSL Biotherapies is a partner organisation. JMLB was an investigator on a national HPV prevalence study that received partial, equal, and unrestricted funding from CSL Biotherapies and GlaxoSmithKline. GC, MF, and CLM declare that they have no conflicts of interest.

Acknowledgments

We thank Grace Zampogna (VCCR) for her assistance with variable definitions and appreciate the methodological advice received from Ian Gordon (Statistical Consulting Centre, University of Melbourne, Victoria, Australia), Karen Canfell (NSW Cancer Council, NSW, Australia), and Carolyn Nickson (University of Melbourne, Victoria, Australia). The VCCR is fully funded by the Victorian Government and operated by the Victorian Cytology Service.

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