Trends in genital warts diagnoses in New Zealand five years following the quadrivalent human papillomavirus vaccine introduction

Jeannie Oliphant, Joanna Stewart, Peter Saxton, Min Lo, Nicky Perkins, Daniel Ward

ABSTRACT

AIM: To investigate whether changes in rates of genital warts diagnosis at Auckland Sexual Health Service (ASHS), pre and post the quadrivalent human papillomavirus (4vHPV) vaccine introduction in late 2008, differed between clients vaccine-eligible and not eligible.

METHOD: All new clients attending ASHS from 2007 to 2013 were categorised as having genital warts or not. Generalised linear mixed models were used to compare differences in rates of change in diagnoses.

RESULTS: Overall, 43,480 were seen with genital warts diagnosed in 13.1%. The difference in rate of change over time in diagnosis pre- to post-vaccine differed in females vaccine-eligible to not (p=0.004). The relative risk of diagnosis per year pre-vaccine was 0.98 (0.84, 1.13) and post-vaccine 0.77 (0.74, 0.81) in those eligible compared to 0.87 (0.80, 0.95) and 0.95 (0.91, 0.98), respectively, in those not eligible.

This difference in change, between vaccine eligible or not, differed between males and females (p=0.02), with males considered eligible if the same aged female would have been. In males, no difference in rate change pre- to post-vaccine could be shown in those eligible or not (p=0.53).

CONCLUSION: In this study a population effect for women of the 4vHPV vaccine was demonstrated.

Since 2007, countries around the world have rolled out vaccination programmes using the quadrivalent human papillomavirus (4vHPV) vaccine. This vaccine provides protection against HPV types 6 and 11, which are responsible for the majority of genital warts, in addition to the oncogenic types 16 and 18 that can cause cervical cancer and penile cancer, respectively, for women and men, and oropharyngeal and anal cancers for both.1 Genital warts are an early indicator of HPV-related disease, but are not typically notifiable conditions, therefore studies investigating an early population response to the vaccine have examined rates of genital warts diagnoses among sexual health clinic attendees. These have found decreases in genital warts among vaccine-eligible young women in a number of countries, including the UK and Australia,2 with the latter reporting a 93% reduction over the five years following the introduction of a school-based HPV vaccination programme.3

In New Zealand the 4vHPV vaccine (Gardasil®) was made available on 1 September 2008 with the school-based arm of the vaccination programme commencing in February 2009 and an initial catch up programme through to the end of 2010 targeting women before they turned 20 years of age. The ongoing publically funded programme targets girls in year 8 of school (aged about 12 years) although the vaccine
is funded for young women up to the age of 20 years. There has been no publically funded vaccination programme for boys, although it is possible for males to purchase the vaccine privately. From January 2017 the New Zealand government’s drug purchasing agency is widening funded access to Gardasil® to both sexes up to and including age 26 years.4

A previous New Zealand study that investigated genital warts diagnoses in clients attending the Auckland Sexual Health Service (ASHS) noted a 63% decline in genital warts diagnoses for young women, 18 months into the New Zealand vaccination programme.5 We sought to update that analysis by examining rates of genital warts diagnoses over time in the same service up to five years after the vaccine introduction.

The aim of the study was to investigate whether the introduction of the 4vHPV vaccine had influenced the rate of genital warts diagnosed in females eligible to receive it, using those not eligible as a comparator. Secondary aims were to investigate whether any effect of the vaccine introduction was comparable in different ethnic groups and whether any effect of vaccine introduction seen in females was paralleled with one in males.

Method

The study setting was the ASHS, which is a regional service covering a large, urban, multicultural population with four clinics across Auckland. Patients access these clinics by self-referral or referral from other health providers and services are free of charge.

A retrospective review was undertaken extracting data on all new clients attending the ASHS between 1 January 2007 and 31 December 2013. For purposes of data extraction a new client was defined as an individual presenting to the service for the first time within the past five years.

The main variable extracted was whether or not there was a diagnosis of genital warts.

Genital warts are not a notifiable infection in New Zealand, but clinicians at the ASHS routinely enter diagnostic codes for each new diagnosis made for each client at each visit.

Demographic data is routinely collected for all new clients. Additional information included was: ethnicity (self-identified)—categorised NZ European, Māori, Pacific Peoples, Other; age—age at presentation; sex; month—time of presentation measured as number of months since January 2007; period—whether the date of presentation was pre- or post-vaccine (the time cut off point for pre- and post vaccine was taken at the start of 2009 as few could have had full protection for the vaccine prior to this time); eligible—whether they were eligible to receive vaccination (ie, aged less than 20 years of age at the time of the vaccine introduction). Males of the appropriate age were termed eligible if a female of the same age would be eligible.

Statistical analysis

Statistical analysis was performed with SAS (version 9.2) software. Using a generalised linear model assuming a binary distribution and log link, comparison was made between the difference in the rate of change in proportion of visits to the ASHS with a diagnosis of genital warts from pre to post the introduction of the 4vHPV vaccine in females eligible and not eligible for vaccination.

The outcome was whether or not there was a diagnosis of genital warts. Explanatory variables included were age, month, period and eligible along with the interactions of eligible, month and period. The relationship of interest was the three-way interaction—ie, whether there was a difference in the change in slope over time from pre- to post-vaccine introduction in the cohort who became eligible for vaccine once released compared to those who were never eligible.

To investigate whether any effects observed differed for different ethnic groups, this analysis (in females) was also run, including ethnicity and its interactions with month, period and eligible with the four-way interaction the relationship of interest. Where a four-way interaction was detected the analysis was run separately for each ethnicity.

To investigate whether any effect of the vaccine introduction observed in females was also reflected in males a further analysis as described above was run,
including both males and females, with sex included as an additional explanatory variable, also with its interactions with month, period and eligible. The four-way interaction was the result of interest.

The effect size was assessed by estimating the genital wart diagnosis relative risk and 95% confidence intervals for the change from one year to the next, obtained from the estimates in the model. These relative risks were converted to those for a 12-month change to produce a meaningful estimate, although time was entered into the model as month.

Ethics approval for the study was granted by the Northern B Health and Disability Ethics Committee 15/NTB/71.

Results

Over the study time-period from 01/01/2007 to 31/12/2013, 43,480 new clients were seen at ASHS and genital warts were diagnosed in 5,711 (13.1%). Of the 19,894 female new clients seen, ethnicity was recorded as: NZ European 39.5%, Māori 15.1%, Pacific Peoples 13.0%, Other 32.5%. There were an unknown number of non-residents in the study group with the largest proportion likely to have been in the Other ethnic group. There was a general decrease across time in all groups presenting to ASHS in the diagnoses of genital warts (Table 1). While the graph in Figure 1 shows steady declines, based on the

Table 1: Annual number and proportion of first visit clients diagnosed with genital warts at time of presentation to ASHS.

<table>
<thead>
<tr>
<th>Year</th>
<th>n</th>
<th>Proportion (%)</th>
</tr>
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<tbody>
<tr>
<td>2007</td>
<td>5,648</td>
<td>17.2%</td>
</tr>
<tr>
<td>2008</td>
<td>6,001</td>
<td>15.6%</td>
</tr>
<tr>
<td>2009</td>
<td>6,037</td>
<td>14.6%</td>
</tr>
<tr>
<td>2010</td>
<td>5,351</td>
<td>13.8%</td>
</tr>
<tr>
<td>2011</td>
<td>6,754</td>
<td>12.4%</td>
</tr>
<tr>
<td>2012</td>
<td>6,837</td>
<td>11.0%</td>
</tr>
<tr>
<td>2013</td>
<td>6,852</td>
<td>8.6%</td>
</tr>
</tbody>
</table>

Figure 1: Proportion of new clients diagnosed with genital warts by sex and age, at time of presentation to ASHS with the Auckland HPV school vaccine programme starting in 2009.

Note from 2009 onwards an increasing proportion of females presenting to ASHS as >=20 years will have been <20 years at the time of the vaccine introduction and so been eligible for funded vaccination. Over time an increasing proportion of the group <20 years presenting to ASHS will have been vaccinated as part of the school programme.
Table 2: Modelled relative risk for change over time in genital warts diagnosis, from one year to the next, for females separated by eligibility for vaccination pre and post the introduction of the vaccine to New Zealand.

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eligible</td>
<td>0.98 (0.84–1.13)</td>
<td>0.77 (0.74–0.81)</td>
<td>p=0.004</td>
</tr>
<tr>
<td>not eligible</td>
<td>0.87 (0.80–0.95)</td>
<td>0.95 (0.91–0.98)</td>
<td></td>
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</tbody>
</table>

¹ the p value is testing whether the difference in the slope pre-vaccine compared to post-vaccine is different in those eligible for vaccination compared to those not.

Vaccination programme effect in eligible and not eligible females

For females, there was evidence of a difference in the pre- to post-vaccination era in the rate of change of the proportion of genital warts diagnoses in the vaccine-eligible cohort compared to the vaccine-ineligible cohort (p=0.004). As age at presentation to ASHS, further statistical analysis using a model that adjusted for the changing ages of the increasing numbers of those who would have been eligible to receive the funded vaccine over the study time-period provides a more refined estimate of the effect of the vaccine programme in New Zealand (Table 2–4).

Table 3: Relative risk for genital warts diagnosis from one year to the next for the vaccination eligible and not eligible cohorts for Pacific Peoples, Māori, NZ European and Other females pre and post the introduction of the vaccine to New Zealand.

<table>
<thead>
<tr>
<th>Female</th>
<th>Pre vaccine 2007–2008</th>
<th>Post vaccine 2009–2013</th>
<th>p value¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pacific Peoples</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eligible</td>
<td>1.03 (0.69–1.5)</td>
<td>0.67 (0.58–0.77)</td>
<td>p=0.28</td>
</tr>
<tr>
<td>not eligible</td>
<td>0.97 (0.77–1.23)</td>
<td>0.86 (0.78–0.96)</td>
<td></td>
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<tr>
<td>Māori</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>eligible</td>
<td>1.00 (0.75–1.32)</td>
<td>0.71 (0.64–0.80)</td>
<td>p=0.01</td>
</tr>
<tr>
<td>not eligible</td>
<td>0.79 (0.62–1.01)</td>
<td>1.02 (0.92–1.12)</td>
<td></td>
</tr>
<tr>
<td>NZ European</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eligible</td>
<td>0.99 (0.80–1.24)</td>
<td>0.78 (0.73–0.83)</td>
<td>p=0.01</td>
</tr>
<tr>
<td>not eligible</td>
<td>0.83 (0.73–0.94)</td>
<td>0.96 (0.91–1.01)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eligible</td>
<td>0.86 (0.56–1.32)</td>
<td>0.90 (0.81–1.00)</td>
<td>p=0.75</td>
</tr>
<tr>
<td>not eligible</td>
<td>1.00 (0.82–1.2)</td>
<td>0.95 (0.89–1.02)</td>
<td></td>
</tr>
</tbody>
</table>

¹ the p value is testing whether the difference in the slope pre-vaccine compared to post-vaccine is different in those eligible for vaccination compared to those not, within ethnic group.
shown in Table 2, for females the proportion of clients diagnosed with genital warts each year was fairly stable in the vaccine-eligible cohort pre-vaccine (RR=0.98), but has decreased markedly post the introduction of the vaccine (RR=0.77). In comparison the non-eligible females showed a small decrease in proportion of genital warts diagnoses both pre- and post-vaccine (RR=0.87 and RR=0.95, respectively).

Comparison of vaccination programme effect in different ethnic groups in females

There was evidence that the eligibility difference in change of slope pre and post the vaccine introduction differed by ethnic group (p=0.02), therefore the analysis was run separately for each ethnic group. A difference in the change in decline in those eligible compared to not eligible was demonstrated in Māori and NZ European. While it could not be demonstrated in Pacific Peoples this was because of a small decrease also occurring in those not eligible. The increase in the decline in genital wart rates from before to after the vaccine introduction was similar in Māori, Pacific Peoples and NZ Europeans. The observed ethnic interactions were largely due to the Other group where the change from pre to post was similar in those eligible and ineligible for vaccination (Table 3). It is likely that this group contained many non-residents who may not have been vaccinated prior to arrival and were not able to access funded vaccination in New Zealand.

Comparison on vaccination programme effect for males and females

When comparing males and females (males defined as eligible for vaccine if a female of the same age would be eligible) there was evidence that the difference in the change over time pre- to post-vaccination in those eligible or not for vaccination differed in males and females (p=0.02). The analysis was therefore also run separately for males. For males, although the difference in the estimated rate of decrease of genital warts diagnoses from pre-vaccine introduction to post the introduction of the vaccine was slightly greater in those eligible compared to those not eligible (Table 4), this difference could not be shown to be significant (p=0.53).

Discussion

While there were already signs of the rates of diagnosis of genital warts declining prior to the 4vHPV (Gardasil®) vaccine introduction in New Zealand, the speed of decline in females eligible for the vaccine increased more after the vaccine introduction than it did in those not eligible, with the faster decline being consistent with a vaccine effect. A parallel pattern to the female pattern of difference in decline over time in those eligible or not for the vaccine could not be shown in males considered eligible if a female of the same age was eligible. No difference in the pattern in eligible and non-eligible males was able to be shown, and any increase in rates of

Table 4: Modelled relative risk for change over time in genital warts diagnosis, from one year to the next, for males separated by eligibility for vaccination pre and post the introduction of the vaccine to New Zealand.

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Male eligible²</td>
<td>0.93 (0.72–1.19)</td>
<td>0.84 (0.79–0.89)</td>
<td></td>
</tr>
<tr>
<td>Male not eligible</td>
<td>0.95 (0.88–1.02)</td>
<td>0.96 (0.93–0.98)</td>
<td>p=0.53</td>
</tr>
</tbody>
</table>

¹ the p value is testing whether the difference in the slope pre-vaccine compared to post-vaccine is different in those eligible for vaccination compared to those not.
² For males the group ‘eligible’ were those where a female of the same age would have be eligible.
decline after vaccine introduction compared to before was small. This would imply that if there were any potential benefits for males under the current vaccination programme in New Zealand, they are small. In the post-vaccination period, declines in genital warts diagnoses among vaccine eligible women were witnessed for all ethnicities with the exception of an “Other” ethnicity, which likely included more non-New Zealand residents.

The major strength of this study was the large data set available for analysis and the availability of data for a period of time before the introduction of the vaccine. While only genital warts diagnoses at sexual health clinics in Auckland were examined, which are not representative of the total New Zealand population, Auckland contributes substantially to the overall population of the country. Data from other sources such as decreasing prescriptions dispensed for imiquimod and podophyllum products in New Zealand support the findings of this study.

This study has several limitations. It is an ecological study so cannot comment on causality of genital wart reduction. The reduction in genital warts diagnoses among young people may also be due to changing patterns of behavior with less school aged youth in New Zealand reporting being sexually active in 2012 compared to five years earlier. Indeed a decline was observed prior to the vaccine introduction. However, statistical analysis demonstrated significantly greater reductions of genital warts diagnoses pre- to post-vaccine introduction in the vaccine-eligible cohort of young women compared to those not eligible, which would tend to support a role for the 4vHPV vaccine.

ASHS clinic data did not include information on the vaccination status of clinic attendees. Future research linking data from the National Immunisation Register (NIR) and diagnostic codes related to National Health Index (NHI) would be of interest. In addition data could not be extracted separately for men who have sex with men (MSM), which may have provided further information.

The 83.4% reduction in genital warts diagnoses, from just prior to the vaccine introduction (2008 to 2013), in New Zealand is less than the 92.6% reduction seen in young women in Australia, five years into their 4vHPV vaccination programme. However, the vaccination coverage in that study was reported as being 73% for 12–13 year olds compared with 56% in Auckland for the 1993 birth cohort.

New Zealand HPV vaccination coverage information is derived from the NIR. Ministry of Health data on the cumulative vaccination coverage from the start of the programme on 1st September 2008 through to 31st December 2013 for each birth cohort was reviewed. Ethnicity in the reports is categorised into Māori, Pacific Peoples or Other, with the denominator figure derived from New Zealand census-estimated population projections in order to assess vaccination coverage. The majority of females in the Other category are of NZ European ethnicity, although in Auckland, Asian young people also make a significant contribution to the population.

Thus in the Auckland region, the birth cohort of young women born in 1993 who were aged between 14 and 20 years over the study period of 2007 to 2013 had a vaccination coverage to the end of 2013 for all three vaccines of 48% for Māori, 68% for Pacific Peoples and 51% for Other. These vaccinations occurred as part of the initial catch up programme. There was a trend for vaccination rates to improve for Māori and Pacific Peoples over time with no change for the category Other. For the birth cohort of young women born in 1999 (turning 14 years in 2013), who would have predominately been vaccinated in year 8 at school, the vaccination coverage was 62% for Māori, 77% for Pacific Peoples and 52% for Other.

It is anticipated that HPV vaccination programmes will have the potential to reduce ethnic and socioeconomic disparities of HPV related disease. In New Zealand cervical cancer incidence rates are higher for Māori women so that it is important that any interventions such as HPV vaccination are effective for this population. Recent modelling showed that HPV vaccination is a pro-equity intervention in New Zealand for Māori women, provided vaccine coverage is not lower for this population group.

In Auckland, HPV vaccination coverage was notably higher for Pacific and Māori young women. While it is difficult to make
any further comment on the basis of this study it is encouraging that Māori and Pacific young women had larger decreases in genital warts diagnoses post-vaccine introduction (93.4% each) followed by NZ European (80.2%), (data not shown).

Vaccine coverage has been shown to be an important predictor of population response in a recent meta-analysis. Only countries with high vaccine coverage for females showed significant reductions in genital warts diagnoses for young men with no evidence of any herd effect in countries with low vaccine coverage.10–11

Despite a slightly quicker rate of decline in the rates of genital warts diagnoses over time post-vaccine introduction compared to pre-introduction for young men in this study, the reduction was not shown to be statistically different when compared to older men. While there are other possible explanations to account for this finding, such as changing reasons for young men to present to sexual health clinics over time, it may also be that the vaccination rates across the study population were not high enough to provide more than a small herd immunity effect for young men.

The findings of this study would suggest that publicly funding Gardasil® vaccination for males is needed to ensure equitable prevention of HPV related disease in New Zealand. In particular men who have sex with men, who are at higher risk of HPV related anal cancer,12 would not have benefited from the current vaccination programme.

The findings of this study support an early and equitable population effect of the HPV vaccination programme for young women in New Zealand. The authors applaud the decision to extend the funded programme to include males and anticipate that this is likely to have a significant impact on continuing to reduce HPV-related disease in New Zealand.

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Dr Oliphant reports a grant from Seqirus, following the completion of the study.

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