Fall in Genital Warts Diagnoses in the General and Indigenous Australian Population Following Implementation of a National Human Papillomavirus Vaccination Program: Analysis of Routinely Collected National Hospital Data

Megan A. Smith,1,2 Bette Liu,3,4 Peter McIntyre,5 Robert Menzies,5 Aditi Dey,5 and Karen Canfell2

1Sydney School of Public Health, University of Sydney, 2Prince of Wales Clinical School, 3School of Public Health and Community Medicine, UNSW, 4Sax Institute, Sydney, and 5National Centre for Immunisation Research and Surveillance, University of Sydney and Children’s Hospital Westmead, Australia

Background. Human papillomavirus (HPV) vaccination targeting females aged 12–13 years commenced in Australia in 2007, with catch-up vaccination of females aged 13–26 years continuing to 2009. Whole-population analyses, including effects on the Indigenous population, have not previously been reported.

Methods. All hospital admissions between 1999–2011 involving a diagnosis of genital warts were obtained from a comprehensive national database. We compared the age-specific rates before to those after implementation of the vaccination program, according to sex and other characteristics.

Results. Admission rates decreased from mid-2007 in females aged 12–17 years (annual decline, 44.1% [95% confidence interval [CI], 35.4%–51.6%]) and from mid-2008 in females and males aged 18–26 years (annual declines, 31.8% [95% CI, 28.4%–35.2%] and 14.0% [95% CI, 5.1%–22.1%], respectively). The overall reductions from 2006–2007 to 2010–2011 were 89.9% (95% CI, 84.4%–93.4%) for females aged 12–17 years, 72.7% (95% CI, 67.0%–77.5%) for females aged 18–26 years, and 38.3% (95% CI, 27.7%–47.2%) for males aged 18–26 years. Compared with the average annual number before program implementation, about 1000 fewer hospital admissions involved a warts diagnosis during 2010–2011. Reductions after program implementation were similar for Indigenous (86.7% [95% CI, 76.0–92.7%]) and non-Indigenous (76.1% [95% CI, 71.6%–79.9%]) females aged 15–24 years ($P_{\text{heterogeneity}} = .08$).

Conclusions. National population-based hospital data confirm previous clinic-based reports of a marked decline in genital warts diagnoses among young people in Australia after program implementation, including indirect benefits to males. The impact of HPV vaccination appears to be similar in young Indigenous and non-Indigenous females.

Keywords. human papillomavirus; HPV; vaccination; genital warts; condyloma acuminata; Australia; indigenous; impact; herd effect.

Australia implemented a national publicly funded vaccination program against human papillomavirus (HPV)
17 years, respectively, in 2007 [1]. Reported 3-dose uptake in the catch-up program delivered through primary care was lower (41% and 17% in females aged 18 and 26 years, respectively, in 2007), although underreporting to the NHVPR is likely for this component of the program [2, 3].

The quadrivalent HPV vaccine (Gardasil [Merck]; Whitehouse Station, NJ) is the only one used within the national program and provides protection against HPV 16, 18, 6, and 11. HPV 16 and 18 are implicated in several cancers, particularly cervical cancer [4]. HPV 6 and 11 are associated with approximately 90% of cases of anogenital warts [5].

Reductions in high-grade cervical abnormalities [6–8] and HPV prevalence in cervical specimens [9] after NHVP implementation have been previously documented in young women in Australia. Declines in genital warts in both females and males have been previously documented in Australia after NHVP implementation (and several other countries) [10]. However, previous studies in Australia have relied on a sentinel surveillance network of sexual health clinics, telephone surveys, or data on inpatient procedures for genital warts in private hospitals [11–14]. The aim of the current study was to perform the first assessment using national routinely collected data from a comprehensive population-based data set of hospital admissions involving a diagnosis of genital warts.

Prior to NHVP implementation, cervical cancer incidence and mortality rates were 2.8 and 4.7 times higher in Indigenous females than in non-Indigenous females [7, 15]. Recent data from 2 Australian jurisdictions (Queensland and the Northern Territory) suggest that 3-dose uptake is lower in Indigenous females (by 15% and by 9%, respectively) [1, 16], but we have not identified any reports on the impact of HPV vaccination on disease in Indigenous Australians. Therefore, assessing outcomes in Indigenous women after NHVP implementation is of critical importance; a second aim of the current study was to examine whether the impact of the NHVP on genital warts diagnoses varied by Indigenous status [17].

METHODS

Data Sources

Data were obtained from the National Hospital Morbidity Database (NHMD), a comprehensive data set of admissions to virtually all public and private hospitals in Australia [18]. Data include, among other things, information on the age, sex, and Indigenous status of the individual; date of admission; primary and any contributing diagnoses, coded according to International Statistical Classification of Diseases, Tenth Revision, Australian Modification; (ICD-10-AM) and any procedures performed, coded according to the Australian Classification of Health Interventions. Population estimates were sourced from the Australian Bureau of Statistics [16, 19].

All NHMD admissions between 1 July 1999 and 30 June 2011 that included ICD-10-AM code A63.0 (anogenital warts) as a main or contributory diagnosis were included. Admission rates were derived per 100 000 individuals in the population, based on total admissions over a 12-month period (July–June) and estimates of the resident population mid-period [19]. The anatomical site of warts was ascertained on the basis of the site specified in the diagnosis and/or procedure codes recorded (Supplementary Table 1).

Analyses by Age and Sex

Admissions were categorized by sex and into 4 age groups (12–17, 18–26, 27–30, and 31–69 years), based on likely exposure of individuals to HPV vaccination and delivery methods during this period, with the youngest groups having high vaccine coverage and the oldest groups having minimal coverage [1, 2, 20]. Based on published coverage data and population estimates, estimated 3-dose coverage in females aged 12–17, 18–26, and 27–30 years in 2011 was 71%, 45%, and 25%, respectively (Supplementary Table 2) [1, 2, 19, 20]. Admissions in those aged <12 years or >69 years were excluded from the age-specific analyses.

Subgroup Analyses

Indigenous Status

As the accuracy of recording Indigenous status has varied over time and between jurisdictions, analyses by Indigenous status were restricted to the period after 30 June 2004 and to data from 6 of the 8 Australian jurisdictions (New South Wales, Victoria, Queensland, South Australia, Western Australia, and the Northern Territory), consistent with NHMD data analysis recommendations [17, 21, 22]. Because of the lack of Indigenous population estimates by single year of age and comparatively small numbers of admissions in Indigenous Australians, analyses by Indigenous status used modified age groups (15–24, 25–34, and 35–69 years). These age groups still broadly represent groups with moderate, low, and extremely low vaccination uptake, with estimated 3-dose uptake by the end of 2011 in all females in these age groups 56%, 16%, and 0%, respectively [1, 2, 19, 20].

Men Who Have Sex With Men (MSM)

While data on sexual behavior are not available from the NHMD, we examined trends in male admissions stratified according to whether the admission involved a diagnosis or treatment procedure code associated with anal warts or whether only nonanal sites were recorded (Supplementary Table 1), since anal HPV infections and HPV-related disease generally are more common in MSM [23, 24]. Admissions in which the warts site could not be ascertained were excluded from this subanalysis.

Cervical Screening

One quarter of warts admissions in women aged 18–26 years involved a procedure related to investigation or treatment of
screen-detected cervical abnormalities ("screening follow-up"; Supplementary Table 1 lists relevant procedures). Screening follow-up admissions might have been influenced by changes in cervical screening practices that occurred over the relevant period (including declining screening participation in younger women and variations in the way women with screen-detected abnormalities were managed) [7, 25]. Therefore, in a sensitivity analysis, we also examined trends after excluding "screening follow-up" admissions, to exclude the possibility that changes in cervical screening practices influenced the findings.

**Statistical Analyses**

Poisson and negative binomial regression were used to assess overall change in admission rates between the last year before NHVP implementation (July 2006–June 2007; hereafter, 2006–2007) and the most recent data available (July 2010–June 2011; hereafter, 2010–2011), by age group and sex. This was done to examine an a priori hypothesis that admission rates had changed in younger age groups since the NHVP commenced. Rate ratios after NHVP implementation were also calculated, which compared admission rates in each successive 12-month period from 1 July 2007, as well as the mean during 3 years after program implementation (1 July 2008–30 June 2011), to the mean during the 3 years before program implementation (1 July 2004–30 June 2007).

Joinpoint Poisson analysis [26, 27] was also performed to assist in characterizing the timing of any changes, the annual percentage change (APC) in the rate of admissions, and whether any observed declines after NHVP implementation may represent the continuation of preexisting trends. Joinpoint analysis fits the simplest trend model (fewest changes in trends) consistent with the observed data. To avoid overfitting, we restricted analyses to a maximum of 2 joinpoints (3 trends) over the 12-year period.

Analyses were performed using SAS 9.3 (SAS Institute, Cary, NC) and Joinpoint 4.0.1 (Surveillance Research, National Cancer Institute, Bethesda, MD).

**RESULTS**

There were 39 350 admissions involving a diagnosis of genital warts (24 811 in females; 14 539 in males) recorded in the NHMD during July 1999–June 2011. The most common warts sites were vulval/vaginal in females (15 194 admissions [61.2%]) and anal/perianal in males (6959 admissions [47.9%]; Supplementary Table 3). The median age at admission over the analysis period was 26 years (interquartile range, 21–37 years) in females and 35 years (interquartile range, 26–46 years) in males (Table 1).

Age-standardized admission rates (across all ages) were lower in females in 2010–2011 than in 1999–2000 (11.4 vs 25.4 admissions per 100 000) but were relatively unchanged in males over the same period (11.5 vs 10.9 admissions per 100 000). Most admissions occurred in public hospitals (females, 62%; males, 52%).

**Age- and Sex-Related Trends in Admissions**

The median age at admission increased after the implementation of the NHVP, both in females (from 25 to 30 years) and...
females, similar results were seen in the rate ratios that compared 2010–2011 with the 3-year period before NHVP implementation (July 2004–June 2007; Figure 2).

Using the Joinpoint Poisson analysis to examine the timing of changes during 1999–2011, APCs in admission rates after NHVP implementation were significant for females aged 12–17 years from mid-2007 (APC, 44.1% decline; 95% CI, 35.4%–51.6%), and for females and males aged 18–26 years from mid-2008 (APC, 31.8% decline [95% CI, 28.4–35.2] and 14.0% decline [95% CI, 5.1%–22.1%], respectively) but not for females or males in any other age group. The rates and rapid reduction in females aged 12–17 years were driven by admissions in females aged 15–17 years (data not shown). There was no evidence of a change before NHVP implementation in females aged 12–17 years or in males aged 18–26 years. In females and males aged 27–30 years, a significant decline was observed from July 1999 to June 2011 (APC, 5.9% decline [95% CI, 3.8%–8.0%] and 4.3% decline [95% CI, 3.2%–5.5%], respectively), and there was no evidence of an additional reduction after NHVP implementation in either of these groups. In females aged 18–26 years, the best-fitting model estimated a small decline in admissions for genital warts between July 1999 and June 2004 (APC, 1.7% decline; 95% CI, 4.4%–3.0%), a larger decline between July 2004 and June 2008 (APC, 11.4% decline; 95% CI, 5.5%–16.9%), and finally a substantial decline between July 2008 and June 2011 (APC, 31.8% decline; 95% CI, 28.4%–35.2%). Thus, while admission rates appeared to be decreasing prior to the NHVP in females aged 18–26 years, the decline from July 2008 was significantly greater than that in the previous period (P < .001). This best-fitting model was a significantly better fit to the observed data than either a decline over the whole period or a decline that commenced earlier than mid-2008 (P < .0005 in both cases).

In the groups where changes were identified after NHVP implementation (females aged 12–26 years and males aged 18–26 years), the combined annual number of admissions associated with a diagnosis of genital warts reduced from an average of 1548 before implementation to 550 in 2010–2011 (Table 2).

Subgroups

Substantial reductions in admission rates after NHVP implementation were observed for females aged 15–24 years, and there was no evidence of variation by Indigenous status (P heterogeneity = .08; Table 3). Compared with admissions rates in 2006–2007, admission rates in 2010–2011 were estimated to have declined by 86.7% (95% CI, 76.0%–92.7%) in Indigenous females and by 76.1% (95% CI, 71.6%–79.9%) in non-Indigenous females. There were very few admissions in Indigenous males (43 aged 15–34 years), so these data could not be analyzed further. The 2 jurisdictions excluded from the Indigenous analysis represented a small proportion of admissions (3.7% of all admissions; 5.9% admissions in Indigenous Australians).
When admissions in males were stratified on the basis of whether they involved anal warts, the reductions in warts admissions observed in males aged 18–26 years appeared to be confined to admissions involving only nonanal sites (Table 3). Admissions for nonanal warts in 2010–2011 decreased by 55.0% (95% CI, 42.3%–65.0%), compared with 2006–2007, but there was no evidence of a reduction in admissions involving anal warts ($P = .38$).

When cervical screening follow-up admissions were excluded, the rate ratios and the overall reduction in admissions since 2006–2007 were very similar to those observed for all admissions in females aged 18–26 years (Table 3). While admission rates unrelated to cervical screening appeared to be decreasing in females aged 18–26 years prior to NHVP implementation (APC, 9.6% decline from mid-2005; 95% CI, 1.2%–17.3%), the decline from mid-2008 (APC, 34.5%; 95% CI, 29.7%–39.0%) was substantially and significantly greater than the trend in the preceding period ($P = .001$).

**DISCUSSION**

We analyzed population-based hospital admissions data and observed a substantial drop in admissions involving a diagnosis of genital warts since the introduction of the NHVP in Australia in 2007. The fall was most pronounced in younger female cohorts offered HPV vaccination, with a reduction in admissions of 90% in females aged 12–17 years and 73% in females aged 18–26 years. There has also been a substantial (38%) reduction in admissions of males aged 18–26 years, potentially representing indirect protection from the female-only vaccination program, since there was no change in this age group prior to mid-2008. We also observed a reduction in females and males aged 27–30 years in the period after NHVP implementation relative to the period before implementation; however, a decline in admissions in this age group appeared to commence prior to the implementation of the NHVP, and there was no evidence in the current analysis that HPV vaccination accelerated this trend.

Our results are consistent with and validate findings from previous studies in Australia, including those from a sentinel network of 8 sexual health clinics [11, 12] and an analysis of admissions to private hospitals [14] (private hospital admissions accounted for <50% of admissions in the current study). The rapid drop in the youngest age group reported here is consistent with that reported for the youngest age group in the sexual health clinic data [11]. In practice, our findings for this group reflect a rapid reduction in females aged 15–17 years, which is plausible because school-based programs in almost all jurisdictions commenced with vaccination of 15–17-year-old girls [28], the age group most likely to initiate sexual activity [29]. By July 2007, 2-dose coverage was estimated to be 76% in females aged 15–17 years (details of program roll out are available in Supplementary Table 2) [1, 19]. Our findings for young females (18–26 years) are also comparable with the reduction in all vaccine-included HPV type prevalence observed in a repeat cross-sectional survey of women aged 18–24 years [9].

A key result of the current analysis is our finding that the fall in genital warts admissions in young females (age, 15–24 years) after NHVP implementation has been comparable for Indigenous and non-Indigenous females. National data on HPV

---

**Table 2. Rate and Number of Admissions for Genital Warts per 100 000 Population, by Age and Sex, Before and After Implementation of the National HPV Vaccination Program (NHVP)**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Rate</td>
<td>No.</td>
<td>Rate</td>
<td>No.</td>
<td>Rate</td>
<td>No.</td>
</tr>
<tr>
<td>Female</td>
<td>12–17 y</td>
<td>17.9</td>
<td>145</td>
<td>3.4</td>
<td>28</td>
<td>8.1</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>18–26 y</td>
<td>84.8</td>
<td>1059</td>
<td>32.1</td>
<td>444</td>
<td>67.9</td>
<td>891</td>
</tr>
<tr>
<td></td>
<td>27–30 y</td>
<td>38.7</td>
<td>213</td>
<td>26.6</td>
<td>164</td>
<td>37.5</td>
<td>214</td>
</tr>
<tr>
<td></td>
<td>31–69 y</td>
<td>15.0</td>
<td>754</td>
<td>13.6</td>
<td>731</td>
<td>12.4</td>
<td>643</td>
</tr>
<tr>
<td>Male</td>
<td>12–17 y</td>
<td>0.7</td>
<td>6</td>
<td>1.1</td>
<td>9</td>
<td>0.5</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>18–26 y</td>
<td>26.6</td>
<td>345</td>
<td>20.1</td>
<td>291</td>
<td>25.4</td>
<td>349</td>
</tr>
<tr>
<td></td>
<td>27–30 y</td>
<td>25.4</td>
<td>140</td>
<td>19.7</td>
<td>124</td>
<td>21.2</td>
<td>122</td>
</tr>
<tr>
<td></td>
<td>31–69 y</td>
<td>14.5</td>
<td>723</td>
<td>14.0</td>
<td>744</td>
<td>12.6</td>
<td>648</td>
</tr>
</tbody>
</table>

$^a$ 3-year mean calculated over July 2004–June 2007.

$^b$ 3-year mean calculated over July 2008–June 2011. June 2007 was selected as the end of the period before NHVP implementation, as it was extremely unlikely that any females in the initial target age group included in the ongoing and catch-up program (age, 12–26 years) would have received all 3 doses prior to July 2007. The primary-care-based catch-up for older females commenced in July 2007; the school-based program commenced from April 2007 and was rolled out over 2 years.
vaccine uptake by Indigenous status are not available, because Indigenous status is not a mandatory reporting field in all jurisdictions; however, data from 2 jurisdictions suggest that 3-dose uptake in females aged 12–17 years in 2007 was higher for all females than for Indigenous females (by 15% in Queensland and 9% in the Northern Territory) [1, 16]. In Queensland, this observation appears to be driven by lower rates of course completion in Indigenous females [1], whereas in the Northern Territory this appeared to be because Indigenous females were less likely to start the vaccine course [1]. It is possible that uptake in Indigenous females in the other 6 jurisdictions (collectively representing 60% of the female Indigenous population aged 10–14 years) may be more comparable to that in non-Indigenous females. Although more data are required, it is alternatively or additionally possible that 2-dose vaccination confers substantial and comparable protection to 3-dose protection and that the effects of coverage differences relating to course completion differences are therefore small [30]. It is also possible that our findings may have been influenced by changes in ascertainment of Indigenous status over time and/or by the exclusion of jurisdictions with poorer quality data on Indigenous status (although the 2 excluded jurisdictions, Australian Capital Territory and Tasmania, compose a very small proportion of the national population). Longer-term follow-up will be required to establish whether this effect is sustained and whether the findings of this analysis are representative of the jurisdictions excluded from the analysis by Indigenous status. However, our study provides provisional evidence and reassurance that Indigenous females are benefiting from the implementation of the NHVP to an extent comparable to that for non-Indigenous females. To our knowledge, this is the first analysis that has examined the impact of HPV vaccination according to Indigenous status and the only ecological study internationally that has examined the impact of HPV vaccination in female subgroups who are disadvantaged in terms of health based on individual-level characteristics, although a prior ecological study of cervical abnormalities examined impact by patterns of ethnicity and poverty in the woman’s area of residence [31].

A strength of this study is that it uses national routinely collected data from a comprehensive population-based data set. To our knowledge, this represents the largest data set analyzed for trends in genital warts after NHVP implementation in Australia.

One of the limitations of this study is that, as for several other studies of the impact of HPV vaccination programs [6, 12, 14, 32–38], it is ecological and information about the vaccination status of the individuals was not available. A future analysis of linked data from the NHVPR and NHMD would be valuable in providing stronger evidence that the declines are due to HPV vaccination. Nevertheless, the declines in admissions here are both substantial and specific in terms of both the age groups affected and the timing in relation to the implementation of the NHVP. Furthermore, these declines are in contrast with observed increases among younger people in gonorrhea, chlamydial infection, and Chlamydia trachomatis positivity rates among those tested over a similar period [39–42], suggesting that changes in sexual risk behavior are unlikely to explain the observed declines in genital warts. The declines are also unlikely to be fully explained by the small declines observed in 27–30-year-old males, as these did not change over the period and partnering with younger females (12–17 years) is likely to be comparatively rare [29, 43]. Another limitation is that hospital admissions data only capture a subset of genital warts, as these are mostly managed in general practice and sexual health clinics [44, 45]. Based on published estimates for average incidence rates in Australia during 2000–2006, the admission rates observed in this hospital data in the same period represent approximately 8%–11% of new cases in females and 3%–5% of new cases in males aged <30 years.

Figure 2. Ratio of admission rates after implementation of the National HPV Vaccination Program, relative to mean admission rates before program implementation (July 2004–June 2007), by age, in females (A) and males (B). The asterisk denotes the reference category, which is the mean prevaccination admission rate (during July 2004–June 2007) for that age group. Rate ratios are not shown for males aged 12–17 years because of a small number of admissions.
Another possible explanation for the observed decline is that treatments for warts (eg, topical treatments or other nonsurgical methods) may have been increasingly performed outside of hospital settings over the period after NHVP implementation. However, this is unlikely to fully explain the substantial declines seen here, for a number of reasons. First, it is likely that such changes would affect all age groups, not only the younger age groups as observed here. Second, the availability and price of topical treatments did not change substantially over this period [14]. Third, similar declines to those we have described here have been observed in a national network of sexual health clinics in Australia, suggesting that treatments have not shifted to these sites [11]. While it is possible that treatments may have moved from both hospitals and sexual health clinics toward primary care, this seems unlikely to fully explain the observed declines, as they are both substantial and confined to certain age groups. Similarly, while we were unable to distinguish between incident and recurrent diagnoses of genital warts, it is unlikely that the number of recurrent diagnoses would vary over time and do so only within particular age groups. We also cannot exclude the possibility that there were changes in coding practice, but it would be expected such changes would affect all groups.

As in other studies including inpatient data, we did not distinguish between admissions in which warts were coded as a primary or a contributory diagnosis [38, 46]. We did this because coding of warts in the primary diagnosis field has not been consistent over time [47–49]. It is possible that any changes in rates of admissions in which warts are a coincident diagnoses may have affected our findings, but we would not expect these changes to be so precisely aligned with the age groups that are targeted and likely to be affected by the HPV vaccination program.

In summary, this national population-based study demonstrates a marked decline in admissions involving a diagnosis of genital warts in young females (age, 12–26 years) and young males (age, 18–26 years) in Australia since the implementation of the NHVP, including a very pronounced (90%) reduction in females aged 12–17 years. These declines are consistent with and strengthen other evidence that suggests that the program has had a rapid and substantial impact on genital warts in young people, including some indirect benefits to males from the female vaccination program. This study also provides the first indication that the impact of HPV vaccination in young Indigenous females is comparable to that in non-Indigenous females in Australia.

**Supplementary Data**

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://jid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary materials, except those of limited length, are subject to copyright. Copyright notices for the supplementary materials are printed at the end of the main article.
data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Acknowledgments. We thank Han Wang (National Centre of Immunisation Research and Surveillance) for assistance with data management and coding.

Financial support. This work was supported by the National Health and Medical Research Council Australia (grants CDF APP1007994 [to K.C.] and CDF APP1081473 [to B.L.]). The National Centre for Immunisation Research and Surveillance is supported by the Australian Government Department of Health, the NSW Ministry of Health, and the Children’s Hospital at Westmead.

Potential conflicts of interest. B. L. holds shares in bioCSL, distributor of the HPV vaccine Gardasil in Australia. P. M. is an investigator on a survey of HPV seroprevalence in Australia that is partly funded by bioCSL. K. C. is a principal investigator in a new trial of primary HPV screening in Australia that is supported by Roche Molecular Systems and Ventana. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References


