Quadrivalent vaccine-targeted human papillomavirus genotypes in heterosexual men after the Australian female human papillomavirus vaccination programme: a retrospective observational study

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Summary
Background Australia introduced a national quadrivalent human papillomavirus (4vHPV) vaccination programme for girls and young women in April, 2007. The HPV genotypes targeted by the female vaccine could also affect the protection afforded to heterosexual men. We examined the prevalence of 4vHPV targeted vaccine genotypes and the nine-valent HPV (9vHPV)-targeted vaccines among sexually active, predominantly unvaccinated heterosexual men from 2004 to 2015.

Methods We did a retrospective, observational study of urine and urethral swab specimens from heterosexual men aged 25 years or younger attending the Melbourne Sexual Health Centre between July 1, 2004, and June 30, 2015, who tested positive for Chlamydia trachomatis. We extracted HPV DNA and used the PapType HPV assay to detect 14 high-risk HPV genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) and two low-risk genotypes (6 and 11). We calculated the prevalence of any HPV genotype, genotypes 6 or 11, genotypes 16 or 18, genotypes in the 4vHPV group (6, 11, 16, or 18), five additional genotypes in the 9vHPV group (31, 33, 45, 52, or 58), and non-vaccine-targeted genotypes (31, 33, 35, 39, 45, 51, 56, 58, 59, 66, or 68).

Findings We obtained data between July 1, 2004, and June 30, 2015, and did the data analysis in December, 2015. Of 1764 specimens obtained, we included 1466 in our final analysis (the others were excluded because they had indeterminate results or were duplicates). The prevalence of any HPV genotype and genotypes 31, 33, 45, 52, and 58 did not change from 2004–05 to 2014–15, but we noted reductions in genotypes 6 and 11 (from 12% [95% CI 6–21%], to 3% [1–7%], p=0·008) but not genotypes 6 and 11 (adjusted PR 0·50, 0·16–1·56; p=0·234) in the postvaccination period among Australia-born men, 4vHPV-targeted genotype prevalence decreased from 11 of 55 [20%, 95% CI 10–33%] to two of 74 [3%, 0–11%, p=0·008] but not genotypes 6 and 11 (adjusted PR 0·50, 0·16–1·56; p=0·234) in the postvaccination period among men who had arrived in Australia within 2 years from countries with a bivalent vaccine (2vHPV) programme (England, Scotland, Wales, Cook Islands, Northern Ireland, or the Netherlands), compared with the prevaccination period. No change was noted in 4vHPV genotypes in men born overseas in other countries.

Interpretation The marked reduction in prevalence of 4vHPV genotypes among mainly unvaccinated Australian-born men suggests herd protection has occurred from the female vaccination programme. Additionally, the decline in genotypes 16 and 18, but not genotypes 6 and 11, among overseas-born men predominately from countries with a 2vHPV vaccine programme suggests that these men received benefits from herd protection for genotypes 16 and 18 from their vaccinated female partners in their own countries. These reductions could translate to reductions in HPV-related malignant conditions in men, even in countries with female-only vaccination programmes.

Funding The Australian National Health and Medical Research Council Program.
Evidence before this study

We aimed to investigate the prevalence of quadrivalent human papillomavirus (HPV) targeted vaccine genotypes and the nine-valent HPV-targeted vaccine genotypes among sexually active, predominantly unvaccinated heterosexual men in Australia from 2004 to 2015. We searched MEDLINE and PubMed databases on May 2, 2016, for English-language articles published between Jan 1, 2004, and May 2, 2016, with the terms “human papillomavirus vaccination” and (“males” or “boys” or “men”) and (“prevalence” or “trend” or “decline” or “reduction” or “fall” or “herd immunity” or “herd protection”). We identified several studies that analysed changes in prevalence or incidence, or both, of genital warts in men, after implementation of female vaccination programmes from April, 2007. Significant reductions in genital warts were noted among young men in countries with high female vaccination coverage, which suggests herd protection against disease related to HPV genotypes 6 and 11. Additionally, we identified a Swedish study that assessed type-specific HPV prevalence among men participating in a chlamydia-screening programme 1 year after the implementation of a female vaccination programme; however, the investigators did not note any herd effects from female-only vaccination on HPV prevalence in men. We did not identify any studies that have measured the temporal changes in prevalence of HPV genotypes in men before and after implementation of female vaccination programmes.

Added value of this study

In our study, we documented annual trends in HPV prevalence among young, sexually active, predominantly unvaccinated, heterosexual men diagnosed with chlamydia during an 11-year period. We described a striking fall in HPV genotypes 6 and 11, and 16 and 18 in Australian-born men after the introduction of a universal female vaccination programme. The declining prevalences of HPV genotypes 6 and 11 are consistent with reductions in genital warts in men reported in previous studies, but our findings also provide evidence that suggests herd protection from HPV genotypes 16 and 18. We also noted a decrease in genotypes 16 and 18, but not genotypes 6 and 11, in overseas-born men who had recently arrived from countries that have implemented a bivalent (2vHPV) vaccine programme against genotypes 16 and 18.

Implications of all the available evidence

In our study, we provide an indication of the effectiveness of Australia’s female vaccination programme against all four vaccine-targeted HPV infections in men. Additionally, the decline in HPV genotypes 16 and 18 in overseas-born men provides the first evidence suggesting herd effects in countries with high female coverage with the 2vHPV vaccine. The substantial reduction of vaccine-targeted HPV genotypes should, in time, translate to reduction in HPV-related malignancies in men, even in countries with female-only vaccination programmes.

Australian women after the introduction of the national female-vaccination programme, with a high HPV vaccine-initiation rate of 84% (receipt of at least one dose). Previous mathematical models predicted that reductions in the prevalence of HPV genotypes 16 and 18 will be slower and more difficult to control than that of genotypes 6 and 11. However, findings from an Australian study have shown that all four genotypes have rapidly decreased in sexually active young women after a few years of the vaccination programme.

Although findings from previous studies, done before the male programme began, have also shown a large decrease (roughly 90%) in genital warts in young Australian-born heterosexual men, presumably as a result of herd protection from the female-vaccination programme, the magnitude of its effect on HPV genotype prevalence in men is unknown. No studies have assessed the effect of female-only vaccination on HPV prevalence in men, and specifically to determine if reductions in the two oncogenic HPV genotypes 16 and 18 have occurred. Presumably, the HPV genotypes in the female vaccine will also influence the protection given to these heterosexual men.

In 2014, a new nine-valent HPV (9vHPV) vaccine was registered for use in the USA but is not currently available in Australia. The 9vHPV vaccine protects against five additional HPV genotypes: 31, 33, 45, 52, and 58. The aim of our study was to examine the annual trends in 4vHPV and 9vHPV vaccine-related genotypes among sexually active young men who tested positive for urethral Chlamydia trachomatis over an 11-year period. We stratified the data by country of birth and arrival time in Australia, to establish if there was evidence of herd protection among recent overseas travellers to Australia, with a particular focus on countries that used only the bivalent vaccine (2vHPV against genotypes 16 and 18) rather than 4vHPV.

Methods

Study design and participants

We did a retrospective, observational study of stored chlamydia-positive, urine and urethral swab specimens from heterosexual men aged 25 years or younger who attended the Melbourne Sexual Health Centre clinic (Melbourne, VIC, Australia) between July 1, 2004, and June 30, 2015 (heterosexual men were defined as men who had sex with a woman but not had sex with a man in the previous 12 months). The clinic is the largest public, sexual health service in Victoria, Australia, and provides about 35 000 consultations each year, about 10 000 (29%) of which are with heterosexual men. 28% of these heterosexual men are aged 25 years or younger and
more than 85% are screened for chlamydia, the most common sexually transmitted infection among heterosexual men in Australia. Findings from previous research have shown that chlamydia prevalence among heterosexual men presenting at the clinic remained at 7–9% between 2004 and 2014. Since 2004, all chlamydia-positive specimens have been routinely stored at −80°C, unless the patients declined to provide consent, which is rare. Ethical approval was obtained from the Alfred Hospital Ethics Committee (Melbourne, Australia; approval number 241/15).

Procedures
According to the Australian testing guidelines for sexually transmitted infections, we did most of the chlamydia screening with first-void urine samples, although a small proportion was tested by urethral swabs. For men with recurrent chlamydial infections over the study period, we used only the first positive specimen. We obtained demographic characteristics for each participant, including age, country of birth, the year they arrived in Australia if they were born overseas, and sexual behavioural data from the previous 12 months such as the number of female partners and 100% condom use.

We examined urine and urethral swabs that were stored at −80°C in BD Probtec swab diluent (Becton Dickinson Sparks, MD, USA) and previously tested positive for Chlamydia trachomatis DNA during the study period (2004–15). We extracted HPV DNA from the samples and assessed the adequacy of the samples as described previously. We detected and genotyped HPV using the PapType assay (Genera Biosystems, Scoresby, VIC, Australia) in accordance with version 10 of the PapType manual, and version 4.6.3 of Qplots. The PapType assay detects 14 HPV genotypes with high risk for cancer (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) and two low-risk genotypes (6 and 11).

Statistical analysis
We stratified the study period according to the Australian financial year, which runs from July 1 to June 30 of the following year, as in studies of genital warts. We stratified the men in our study according to their country of birth (ie, Australia vs overseas), a stratification that has been widely used in studies to assess the effect of vaccination on genital warts in heterosexual men in Australia. Australian-born men might be more likely to have sex with Australian-born women of younger or similar age because of assortative sexual mixing, and thus they would receive more herd protection from young Australian-born vaccinated women than would overseas-born men.

We calculated the prevalence of the following HPV genotype groups in each financial year: any HPV genotype (6 or 11), vaccine-targeted high-risk HPV genotypes (16 or 18), the 4vHPV-targeted genotypes (6, 11, 16, or 18), the additional five high-risk HPV genotypes present in the 9vHPV vaccine (31, 33, 45, 52, or 58), and non-vaccine-targeted high-risk HPV genotypes (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, or 68). We compared the HPV prevalences in all men, all Australian-born men, Australian-born men aged 21 years or younger, and overseas-born men.

We did a sensitivity analysis of Australian-born men aged 21 years or younger because all women aged 21 years or younger would have been eligible for the free HPV vaccine programme at school from 2007, thus men in this group were likely to receive the greatest herd protection. Similar analyses of the incidence of genital warts in heterosexual men have been published. We also did sensitivity analyses with urine samples alone. We calculated the median number of female sex partners and the proportion of men reporting 100% condom use with their female partners in the previous 12 months.

We calculated the 95% CIs of HPV prevalence and condom use on the basis of the exact binomial distribution. We used a χ² trend test to detect trends in HPV genotype prevalence over time and a non-parametric Jonckheere-Terpstra test to detect temporal trends in the median number of female partners. We calculated crude prevalence ratios (PR) for the postvaccination period compared with the prevaccination period as a reference for Australian-born men. Australian-born men aged 21 years or younger, men born in a country that had a 2vHPV vaccination programme for girls against genotypes 16 and 18 (ie, England, Scotland, Wales, Cook Islands, Northern Ireland, and the Netherlands) and who had arrived in Australia within the previous 2 years, and men born overseas in other countries. We also adjusted PRs for the number of female partners and condom use in the previous 12 months. We did all analyses with Stata version 13.1.

Role of the funding source
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
Between July 1, 2004, and June 30, 2015, 1764 specimens were obtained, of which we included 1466 in the final analysis (one specimen per man). We did the analysis in December, 2015. We excluded 160 specimens with indeterminate results for HPV testing and 138 duplicate samples. Most specimens were derived from first-void urine (1428 [97%]) and 38 (3%) specimens were urethral swabs. There were no significant differences in the detection of any HPV genotype (p=0.109) and 4vHPV (p=0.296) between the two specimen types (appendix).
Of the 1466 men, 633 (43%) were born in Australia, 768 (52%) were born overseas, and 65 (4%) had an unknown place of birth. The median age of all men was 23 years (IQR 21–24). The median number of female partners in the previous 12 months was five (IQR 3–10) and increased significantly over time for all men (from three [IQR 2–6] to five [3–11], \( p_{\text{uni}}<0.001 \); table 1). Only 76 (5%) of 1451 men reported 100% condom use with all their female partners in the previous 12 months and condom use remained stable over time (\( p_{\text{uni}}=0.9051 \)). Overseas-born men were slightly older than Australian-born men (median 23 years [IQR 22–24] vs 22 [21–24]).

### Men with any HPV genotype

<table>
<thead>
<tr>
<th>Year</th>
<th>All men (N=1466)</th>
<th>Australian-born men (N=633)</th>
<th>Overseas-born men (N=833)</th>
</tr>
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<tbody>
<tr>
<td>2004-05</td>
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</tr>
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<td>15/65</td>
<td>9/44</td>
<td>6/19</td>
</tr>
<tr>
<td>2008-09</td>
<td>12/63</td>
<td>7/49</td>
<td>5/14</td>
</tr>
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<td>2009-10</td>
<td>10/61</td>
<td>6/49</td>
<td>4/12</td>
</tr>
<tr>
<td>2010-11</td>
<td>9/59</td>
<td>6/46</td>
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<td>7/56</td>
<td>4/43</td>
<td>3/13</td>
</tr>
<tr>
<td>2013-14</td>
<td>6/55</td>
<td>3/44</td>
<td>3/12</td>
</tr>
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</table>

### HPV genotypes 6 or 11

<table>
<thead>
<tr>
<th>Year</th>
<th>All men (N=1466)</th>
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<th>Overseas-born men (N=833)</th>
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<td>9/78</td>
<td>5/73</td>
<td>4/25</td>
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<tr>
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<td>8/74</td>
<td>4/65</td>
<td>4/19</td>
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<td>2007-08</td>
<td>7/65</td>
<td>4/44</td>
<td>3/11</td>
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<td>2008-09</td>
<td>6/63</td>
<td>3/44</td>
<td>3/10</td>
</tr>
<tr>
<td>2009-10</td>
<td>5/61</td>
<td>3/46</td>
<td>2/9</td>
</tr>
<tr>
<td>2010-11</td>
<td>4/59</td>
<td>2/44</td>
<td>2/8</td>
</tr>
<tr>
<td>2011-12</td>
<td>3/57</td>
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<td>2012-13</td>
<td>2/56</td>
<td>1/44</td>
<td>1/6</td>
</tr>
<tr>
<td>2013-14</td>
<td>1/55</td>
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<td>0/5</td>
</tr>
<tr>
<td>2014-15</td>
<td>0/54</td>
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### HPV genotypes 16 or 18

<table>
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<th>Year</th>
<th>All men (N=1466)</th>
<th>Australian-born men (N=633)</th>
<th>Overseas-born men (N=833)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005-06</td>
<td>10/78</td>
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<td>4/25</td>
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<td>9/74</td>
<td>4/65</td>
<td>4/19</td>
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<tr>
<td>2007-08</td>
<td>8/65</td>
<td>4/44</td>
<td>3/11</td>
</tr>
<tr>
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<td>3/44</td>
<td>3/10</td>
</tr>
<tr>
<td>2009-10</td>
<td>6/61</td>
<td>3/46</td>
<td>2/9</td>
</tr>
<tr>
<td>2010-11</td>
<td>5/59</td>
<td>2/44</td>
<td>2/8</td>
</tr>
<tr>
<td>2011-12</td>
<td>4/57</td>
<td>2/43</td>
<td>2/7</td>
</tr>
<tr>
<td>2012-13</td>
<td>3/56</td>
<td>1/44</td>
<td>1/6</td>
</tr>
<tr>
<td>2013-14</td>
<td>2/55</td>
<td>1/44</td>
<td>0/5</td>
</tr>
<tr>
<td>2014-15</td>
<td>1/54</td>
<td>0/45</td>
<td>0/4</td>
</tr>
</tbody>
</table>

### Trend

- Increase, decrease, or none
- \( p_{\text{uni}} \) value

- Increase
- Decrease
- None

### Notes

- (Table 1 continues on next page)
Table 1: Annual trends in human papillomavirus genotypes and sexual behaviours in young heterosexual men in Australia
Mann-Whitney U test p<0·0001) but were otherwise similar with respect to the number of partners and condom use.

In all men, the prevalence of any HPV genotype at the end of the 11-year study period did not differ from that at the start (p<0·0001; table 1). However, we noted substantial reductions in genotypes 6 and 11 (p<0·0001) and 16 and 18 (p<0·0001) and 4vHPV-targeted genotypes (p<0·0001). The prevalence of genotypes 31, 33, 45, 52, and 58 at the end of the 11-year study period did not differ from that at the start (p<0·0001; table 1). The prevalence of non-vaccine-targeted high-risk genotypes increased over this period (p<0·0001).

Among 633 samples from Australian-born men, the prevalence of 4vHPV-targeted genotypes decreased from 2004–05 to 2014–15 (p<0·0001; table 1, figure). The prevalence of genotypes 6 and 11 together also declined in this period in Australian-born men, and more so for Australian-born men aged 21 years or younger, as did the prevalence of genotypes 16 and 18 (table 1). The prevalence of non-vaccine-targeted high-risk genotypes increased over the period in Australian-born men (p<0·0001).

The prevalence of genotypes 16 and 18 has remained at 0% for Australian-born men aged 21 years or younger for the last 3 years. No changes in the prevalence of any HPV genotype, or genotypes 31, 33, 45, 52, or 58, were noted for this subgroup (table 1).

Overall, the prevalence of 4vHPV-targeted genotypes was significantly lower in the postvaccination period (2007–08 to 2014–15) than in the prevaccination period (2004–05 to 2006–07) in Australian-born men (adjusted PR 0·37, 95% CI 0·22–0·60; p<0·0001) and Australian-born men aged 21 years or younger (adjusted PR 0·22, 0·10–0·47; p=0·001; table 2). The prevalence of any HPV genotypes and genotypes 31, 33, 45, 52, and 58 did not differ between the prevaccination and postvaccination periods (table 2). Similar trends were noted when urine samples alone were analysed (appendix).

No changes in prevalence were noted for either genotypes 6 and 11 or 16 and 18 in men born overseas in other countries. Similar trends were observed when urine samples alone were analysed (appendix).

Figure: Crude prevalences of human papillomavirus genotypes in heterosexual men from 2004 to 2015
Data stratified by all Australian-born men and Australian-born men aged 21 years or younger.

Figure: Crude prevalences of human papillomavirus genotypes in heterosexual men from 2004 to 2015
Data stratified by all Australian-born men and Australian-born men aged 21 years or younger.
To our knowledge, this is the first study in the world to assess the annual trends in HPV genotypes in men before and after the implementation of a female HPV-vaccination programme. A striking reduction occurred in HPV genotypes 6 and 11 and 16 and 18 in Australian-born men after the introduction of a universal female vaccination that targeted all four genotypes and achieved 84% coverage for at least one dose. These trends are consistent in magnitude with the reduction in genital warts in men from previous findings, but are the first evidence of herd protection from HPV genotypes 16 and 18. We also observed a decrease in genotypes 16 and 18, but not in genotypes 6 and 11, in overseas-born men who recently arrived from countries that have implemented the 2vHPV vaccine programmes (that target HPV genotypes 16 and 18). Our findings were from sexually active men with chlamydia who are at a higher risk of HPV, indicating that

### Data for prevalence are n/N (%, 95% CI). HPV=human papillomavirus. ·· = not applicable. *Prevaccination period defined as July 1, 2004, to June 30, 2007. †Postvaccination period defined as July 1, 2007 to June 30, 2015. ‡Prevalence ratios were adjusted for the number of female partners and condom use in the last 12 months.

#### Table 2: Human papillomavirus genotypes in unvaccinated Australian-born men before and after the national human papillomavirus vaccination programme

<table>
<thead>
<tr>
<th>Total number of men</th>
<th>Prevaccination period*</th>
<th>Postvaccination period†</th>
<th>Trend (increase, decrease, none)</th>
<th>Prevalence ratios (95% CI), p value</th>
<th>Adjusted prevalence ratios‡ (95% CI), p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australian-born</td>
<td>137</td>
<td>496</td>
<td></td>
<td>0·94 (0·69–1·30), 0·722</td>
<td>0·96 (0·69–1·32), 0·796</td>
</tr>
<tr>
<td>Australian-born &lt;21 years old</td>
<td>45</td>
<td>192</td>
<td></td>
<td>0·76 (0·48–1·20), 0·243</td>
<td>0·76 (0·47–1·22), 0·248</td>
</tr>
<tr>
<td>Overseas-born in England, Scotland, Wales, Cook Islands, Northern Ireland, or Netherlands and arrived from those countries within 2 years</td>
<td>17</td>
<td>250</td>
<td></td>
<td>0·94 (0·48–1·83), 0·857</td>
<td>0·93 (0·48–1·82), 0·840</td>
</tr>
<tr>
<td>Overseas-born (other)</td>
<td>84</td>
<td>403</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Any HPV genotype

| Australian-born                                          | 36/137 (26%; 19–4%)   | 123/496 (25%; 21–29%) | None                           | 0·94 (0·69–1·30), 0·722             | 0·96 (0·69–1·32), 0·796                     |
| Australian-born <21 years old                           | 16/45 (36%; 22–51%)   | 52/192 (27%; 21–34%)  | None                           | 0·76 (0·48–1·20), 0·243             | 0·76 (0·47–1·22), 0·248                     |
| Overseas-born in England, Scotland, Wales, Cook Islands, Northern Ireland, or Netherlands and arrived from those countries within 2 years | 6/17 (35%; 14–36%)   | 81250 (33%; 27–39%)  | None                           | 0·94 (0·48–1·83), 0·857             | 0·93 (0·48–1·82), 0·840                     |
| Overseas-born (other)                                   | 20/84 (24%; 15–34%)   | 111403 (28%; 23–32%)  | None                           | 1·16 (0·76–1·75), 0·490             | 1·13 (0·74–1·70), 0·575                     |

#### Quadrivalent HPV vaccine-targeted genotypes 6, 11, 16, or 18

| Australian-born                                          | 24/137 (18%; 12–25%) | 52/192 (27%; 21–34%)  | Decrease                       | 0·76 (0·48–1·20), 0·243             | 0·76 (0·47–1·22), 0·248                     |
| Australian-born <21 years old                           | 10/45 (22%; 11–37%)   | 11/192 (6%; 3–10%)    | Decrease                       | 0·26 (0·12–0·57), 0·001             | 0·22 (0·10–0·47), 0·001                     |
| Overseas-born in England, Scotland, Wales, Cook Islands, Northern Ireland, or Netherlands and arrived from those countries within 2 years | 6/17 (35%; 14–36%)   | 31250 (33%; 27–39%)  | Decrease                       | 0·37 (0·18–0·77), 0·007             | 0·35 (0·19–0·61), 0·001                     |
| Overseas-born (other)                                   | 18/84 (22%; 14–30%)   | 111403 (28%; 23–32%)  | None                           | 0·98 (0·62–1·55), 0·767             | 0·97 (0·61–1·54), 0·783                     |

#### HPV genotypes 6 or 11

| Australian-born                                          | 14/137 (10%; 6–17%)   | 12/496 (2%; 1–4%)     | Decrease                       | 0·24 (0·11–0·50), 0·0001            | 0·22 (0·10–0·48), 0·0001                     |
| Australian-born <21 years old                           | 54/45 (11%; 4–24%)    | 14/192 (7%; 4–13%)    | Decrease                       | 0·23 (0·07–0·78), 0·017             | 0·20 (0·06–0·69), 0·011                     |
| Overseas-born in England, Scotland, Wales, Cook Islands, Northern Ireland, or Netherlands and arrived from those countries within 2 years | 2/17 (12%; 1–36%)    | 15/250 (6%; 3–10%)    | None                           | 0·51 (0·13–2·05), 0·343             | 0·50 (0·16–1·56), 0·234                     |
| Overseas-born (other)                                   | 6/84 (7%; 3–15%)      | 18/403 (4%; 3–7%)     | None                           | 0·63 (0·26–1·53), 0·303             | 0·63 (0·26–1·52), 0·306                     |

#### HPV genotypes 16 or 18

| Australian-born                                          | 12/137 (9%; 5–15%)   | 22496 (4%; 3–7%)      | Decrease                       | 0·51 (0·26–1·00), 0·049             | 0·50 (0·26–1·00), 0·048                     |
| Australian-born <21 years old                           | 5/45 (11%; 4–24%)    | 7192 (4%; 1–7%)       | Decrease                       | 0·33 (0·11–0·99), 0·047             | 0·33 (0·11–0·99), 0·049                     |
| Overseas-born in England, Scotland, Wales, Cook Islands, Northern Ireland, or Netherlands and arrived from those countries within 2 years | 5/17 (29%; 10–56%)  | 23/250 (9%; 6–13%)    | Decrease                       | 0·31 (0·14–0·72), 0·006             | 0·32 (0·14–0·74), 0·008                     |
| Overseas-born (other)                                   | 8/84 (10%; 4–18%)    | 21/403 (5%; 3–8%)     | None                           | 0·55 (0·25–1·19), 0·130             | 0·53 (0·24–1·16), 0·112                     |

#### HPV genotypes 31, 33, 45, 52, or 58

| Australian-born                                          | 5/137 (4%; 1–8%)     | 32496 (6%; 4–9%)      | None                           | 1·77 (0·70–4·45), 0·227             | 1·76 (0·68–4·43), 0·232                     |
| Australian-born <21 years old                           | 0/45 (0%; 0–8%)      | 16/192 (8%; 5–12%)    | –                               |                                     |                                             |
| Overseas-born in England, Scotland, Wales, Cook Islands, Northern Ireland, or Netherlands and arrived from those countries within 2 years | 0/17 (0%; 0–20%)    | 26/250 (10%; 7–15%)   | –                               |                                     |                                             |
| Overseas-born (other)                                   | 5/84 (6%; 2–13%)     | 30/403 (7%; 5–10%)    | None                           | 1·25 (0·50–3·13), 0·633             | 1·25 (0·49–3·14), 0·642                     |

Discussion

To our knowledge, this is the first study in the world to assess the annual trends in HPV genotypes in men before and after the implementation of a female HPV-vaccination programme. A striking reduction occurred in HPV genotypes 6 and 11 and 16 and 18 in Australian-born men after the introduction of a universal female vaccination that targeted all four genotypes and achieved 84% coverage for at least one dose. These trends are consistent in magnitude with the reduction in genital warts in men from previous findings, but are the first evidence of herd protection from HPV genotypes 16 and 18. We also observed a decrease in genotypes 16 and 18, but not in genotypes 6 and 11, in overseas-born men who recently arrived from countries that have implemented the 2vHPV vaccine programmes (that target HPV genotypes 16 and 18). Our findings were from sexually active men with chlamydia who are at a higher risk of HPV, indicating that...
the herd protection from HPV in men was substantial. The magnitude of the reductions suggests that malignancies associated with genotypes 16 and 18 in men will substantially decrease in countries with quadrivalent or 2vHPVvaccine programmes in women.

Our results show that both genotypes 6 and 11, and 16 and 18, declined rapidly in Australian-born men after only a few years of the vaccination programme, and are broadly consistent with the findings from a similar Australian study of the prevalence of 4vHPV-targeted genotypes among women (adjusted PR 0·12 for genotypes 6 and 11, and 0·24 for genotypes 16 and 18) after adjusting for individual sexual risk. These findings are also consistent with the magnitude of the decline observed in the prevalence of genital warts among largely unvaccinated heterosexual men and largely vaccinated women. Furthermore, although the overall prevalence of any HPV genotype in all men remained unchanged over time, the prevalence of non-vaccine-targeted high-risk genotypes increased over the study period in both Australian-born and overseas-born men.

HPV genotypes 16 and 18, but not genotypes 6 and 11, significantly reduced in overseas-born men who predominantly came from countries with national 2vHPV vaccine programmes only. This finding suggests that these men acquired herd protection from genotypes 16 and 18 from their female partners vaccinated with the 2vHPV vaccine in their own countries, which have high proportions of vaccine coverage: Netherlands (61%), England (86%), and Scotland (92%). If these men had had sexual contact with Australian women vaccinated with the 4vHPV vaccine, they might have benefited even further. Our findings are also consistent with those from a UK study showing a continuing decrease in HPV genotypes 16 and 18, but an increase in genotypes 6 and 11 in women.

4vHPV genotypes did not change in overseas-born men who came from countries that have implemented universal female 4vHPV vaccination despite seeing changes in men from countries with the 2vHPV vaccine programmes. In fact, a substantial proportion of men who arrived in Australia within a 2-year period before their consultation were born in countries that had introduced the 4vHPV vaccine programme. However, we might not have noted this benefit because many of these countries either started the vaccination programme recently (eg, Sweden in 2012) or have low vaccine coverage (eg, France <30%, USA and Germany 40%, and New Zealand 56%). An important challenge for monitoring HPV surveillance in men is the identification of optimum sampling techniques. The HPV detection rate varies across different urogenital sites (eg, glans, foreskin, urethra, scrotum, and shaft) and no agreement has been reached as to which urogenital site is the best for HPV detection in men. Most specimens in our study were urine samples, which have a lower reported sensitivity (41%) for HPV detection compared with penile swabs.

Findings from studies in the USA, where circumcision rates are higher, suggest lower detection rates of human genomic DNA markers in urine; however, most men aged younger than 25 years in Australia and some from the UK are not circumcised (85% uncircumcised in Australia, 13% uncircumcised in the UK). We did not obtain the circumcision status of the men in our study, which therefore shares the problem noted in other HPV-surveillance programmes that we used a specimen-collection method with imperfect sensitivity. However, this limitation should not have affected our ability to detect trends or reductions because the same sample type was used consistently throughout the study and the inclusion criteria did not change. Although only a small proportion of samples overall were urethral swabs (3%), the proportion of urethral swab samples versus urine samples was similar in the prevaccination and postvaccination periods. Additionally, similar trends in HPV prevalence were noted when urine samples alone were analysed (appendix). However, we acknowledge that not detecting a particular HPV genotype (eg, genotypes 16 and 18 were not detected among men aged ≤21 years between 2012 and 2015) does not signify the absence of that genotype.

Our study has several limitations. First, it was done at one urban sexual health service in Melbourne, which might not be representative of all men in the state or the country. Second, risk behaviours are changing over time with an increase in the number of partners; however, these changes would only increase the HPV risk and bias towards not seeing an effect of vaccination, which further supports the notion that the real decrease in HPV from our findings is due to the implementation of the vaccine programme, but not related to individual-level sexual behaviour. Third, our study only contained a few men who came from a country with a 2vHPV vaccine programme; therefore, the study had little power to detect these changes and we were unable to examine the changes in HPV prevalence in each year for this group. Furthermore, the effect of the reduction before and after the vaccination period might have been underestimated in our study because all these countries introduced the 2vHPV vaccine programme after Australia did in 2007 (England, Northern Ireland, and Scotland introduced it in 2008, the Netherlands in 2010, and the Cook Islands in 2011). Thus, a substantial proportion of men included in the postvaccination period would not have received herd protection because of the absence of a female-vaccination programme in their own countries. Fourth, we did not obtain and check the vaccination status of the men in our study, but we assumed that most men would not have been vaccinated because most would not have been eligible for the school-based male programme, by age, when it was launched in 2013. Although the USA was one of the first countries to introduce a universal male HPV-vaccination programme, men who were born in the USA only accounted for 2%
of our cohort and vaccine coverage of men in the USA is
low (ie, 35% for at least one dose and 14% for at least
three doses).26 Finally, estimates in some of our analyses
had wide CIs because of the small numbers of men in
the subgroups, and thus the data should be interpreted
cautiously. For example, there was a low PR (0·51) and
wide CI (0·13–2·05) for reductions in HPV genotypes 6
and 11 among the 267 men who arrived in Australia
within 2 years.

Our findings show that with the high coverage (84% for
at least one dose)27 of female vaccination within the
programme, the 4vHPV vaccine genotypes 6, 11, 16,
and 18 have significantly reduced among unvaccinated
Australian-born men, suggesting that men acquire herd
protection for these genotypes from vaccinated women.
Additionally, HPV genotypes 16 and 18 decreased, but
not 6 and 11, in overseas-born men recently arrived
in Australia from countries with a 2vHPV vaccine
programme, suggesting men from these countries
acquire the herd protection for genotypes 16 and 18 only
from contact with vaccinated women in their own
countries.

Contributors
EPPFC and CKF designed the study. JAD and SNT did the laboratory
testing. GF obtained, identified, and stored samples. EPPFC and DAM
were involved in data analysis and data interpretation. CSB, SMG, MYC,
SNT, and CKF assisted with data interpretation. DAM did the literature
review. EPPFC, DAM, and CKF drafted the manuscript. EPPFC, DAM,
SNT, JAD, GF, CSB, SMG, MYC, and CKF critically reviewed it for
important intellectual content and read and approved the final version.

Declaration of interests
EPPFC is supported by the Early Career Fellowships from the Australian
National Health and Medical Research Council (number 1091226). EPPFC
has received educational grants from Seqirus and bioCSL to assist with
education, training, and academic purposes in human papillomavirus
research. DAM has received educational grants from Seqirus to assist with
education, training, and academic purposes in human papillomavirus
research. CKF has received honoraria from CSL Biotherapies and Merck
Biotherapies. CKF also owns shares in CSL Biotherapies, which markets
Gardasil. SNT and SMG are investigators in a national prevalence study of
cervical cancer tissue that is receiving unrestricted funding from CSL
Biotherapies, which is the supplier of human papillomavirus vaccine in
Australia. SMG has received advisory board fees and grant support from
CSL Biotherapies and GlaxoSmithKline, and lecture fees from Merck,
CSL Biotherapies, and Merck, which is the supplier of human papillomavirus
type 16 in Australia. SMG has received educational grants from Seqirus and
bioCSL to assist with education, training, and academic purposes in human
papillomavirus research. EPFC and CKF designed the study. JAD and SNT did the
literature review. EPPFC, DAM, and CKF drafted the manuscript. EPPFC, DAM,
SNT, JAD, GF, CSB, SMG, MYC, and CKF critically reviewed it for
important intellectual content and read and approved the final version.

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