Human papillomavirus in young women with *Chlamydia trachomatis* infection 7 years after the Australian human papillomavirus vaccination programme: a cross-sectional study

Eric P F Chow, Jennifer A Danielewski, Glenda Fehler, Sepehr N Tabrizi, Matthew G Law, Catriona S Bradshaw, Suzanne M Garland, Marcus Y Chen, Christopher K Fairley

Summary

Background The national quadrivalent human papillomavirus (4vHPV) vaccination programme was launched in Australia in April, 2007. In this study, we aimed to explore the prevalence of vaccine-targeted human papillomavirus (HPV) types contained in the 4vHPV and nine-valent HPV (9vHPV) vaccines detected in young women diagnosed with chlamydia.

Methods In this cross-sectional study, we identified specimens from women aged 25 years or younger who attended the Melbourne Sexual Health Centre (Melbourne, VIC, Australia) diagnosed with chlamydia. We calculated the prevalence of 4vHPV types (6, 11, 16, and 18) and the extra five 9vHPV types (31, 33, 45, 52, and 58 alone) excluding 4vHPV types, stratified by Australian financial year (and according to the prevaccination and postvaccination periods) and self-reported vaccination status, for all women, Australian-born women, Australian-born women aged 21 years and younger, and overseas-born women. We calculated adjusted prevalence ratios using binomial log linear regression.

Findings Between July 1, 2004, and June 30, 2014, we included 1202 women. The prevalence of 4vHPV types in Australian-born women decreased during this period (HPV 6 and 11: 2004–05 nine [16%, 95% CI 8–28] of 56 *vs* 2013–14 one [2%, 0–9] of 57, p<0·0001; HPV 16 and 18: 17 [30%, 19–44] *vs* two [4%, 0–12], p<0·0001). In Australian-born women aged 21 years and younger, HPV 6 and 11 prevalence remained at 0% for all years after 2008–09, and we detected HPV 16 and 18 in 5% or less of samples for the same period. In unvaccinated Australian-born women, we noted a significant decrease in 4vHPV types from 66 (41%, 95% CI 34–49) of 160 in the prevaccination period (from July 1, 2004, to June 30, 2007) to five (19%, 6–38) of 27 in the postvaccination period (July 1, 2007, to June 30, 2014; p=0·031), but not in the 9vHPV types, excluding 4vHPV (36 [23%, 95% CI 16–30] *vs* seven [26%, 11–46]; p=0·805).

Interpretation The three-dose vaccination coverage was sufficient for the 4vHPV types to almost disappear in Australian-born women aged 21 years or younger within 3 years of introduction of the national HPV vaccination programme. We noted strong herd protection, with a significant decrease in the prevalence of 4vHPV in unvaccinated women. The 4vHPV vaccination programme in Australia has been successful at protecting women against 4vHPV types.

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Introduction

Human papillomavirus (HPV) is one of the most common sexually transmitted infections worldwide, and women aged 25 years and younger are at high risk.[1,2] Worldwide HPV prevalence in women is estimated at about 10%, but substantial geographical variation exists, from 32% in eastern Africa to 6% in southeastern Asia.[1] HPV 16 and 18 are generally the two most common types.[1,3] Currently, three HPV vaccines are available worldwide. The bivalent HPV vaccine (Cervarix; GlaxoSmithKline, Boronia, VIC, Australia) can protect against HPV 16 and 18, whereas the quadrivalent HPV (4vHPV) vaccine (Gardasil; CSL, Parkville, VIC, and Merck, Macquarie Park, NSW, Australia) can protect against HPV 6, 11, 16, and 18. A nine-valent HPV (9vHPV) vaccine, which includes types 6, 11, 16, 18, 31, 33, 45, 52, and 58, protecting against the five additional high-risk cancer-causing HPV types, was approved by the US Food and Drug Administration in 2014 (Gardasil 9),[4] but is not currently used in Australia. A meta-analysis of 20 studies from nine high-income countries[5] showed that HPV 16 and 18 decreased in women by 68% and anogenital warts by 61% after introduction of HPV vaccines.

In April, 2007, Australia became the first country to introduce a free national HPV vaccination programme. Girls aged 12–13 years were eligible for the 4vHPV vaccine at school. The programme was free of charge, with a catch-up programme for women and girls aged 13–26 years through general practice and community immunisation clinics from July, 2007, to 2009.[6] The

Research in context

Evidence before this study

The authors of a systematic review and meta-analysis published in *The Lancet Infectious Diseases* to assess the effectiveness of the human papillomavirus (HPV) vaccine identified 20 studies from nine high-income countries measuring changes in the prevalence of HPV genotypes in women after a population-level vaccination programme. The prevalence of HPV 16 and 18 was noted to decrease in women by 68% after introduction of the HPV vaccine, and anogenital warts decreased by 61%, with a vaccination coverage of at least 50%. However, the related HPV 31, 33, and 45 types, and other high-risk types did not change after implementation of the HPV vaccination. No studies have sufficient follow-up to present the trend over time and therefore whether the pattern suggests that vaccination coverage was sufficient for elimination is not possible to establish. Several studies have monitored the HPV epidemic after introduction of the HPV vaccine in the general population. However, most of these studies were done in low-risk women and might have provided an overly optimistic conclusion of the HPV decrease in the population, in which a decrease would be easier to achieve than in high-risk women. The HPV epidemic needs to be monitored in high-risk individuals (eg, those with a high number of partners or diagnoses of a sexually transmitted infection) to see whether this population has a similar decrease.

Added value of this study

This study is the first to report the year-on-year trend in the prevalence of HPV in young, sexually active women diagnosed with chlamydia during a 10 year period. We have shown that the quadrivalent HPV types have almost disappeared in young women within 3 years of the vaccination programme.

Implications of all the available evidence

In this study, we have shown the effectiveness of a national vaccination programme in Australia, which could be applicable to other worldwide settings. It provides, for the first time, an indication of whether a 70% coverage for a women and girls-only vaccination programme could be sufficient for 4vHPV types to almost disappear.

programme was expanded to include boys aged 12–13 years in February, 2013, with a catch up for ages 14–15 years up to December, 2014.[7] The 4vHPV vaccine is the only vaccine provided through this programme, although the bivalent vaccine is also licensed in Australia. The 4vHPV vaccine protects against HPV 6 and 11, which cause at least 90% of anogenital warts,[8] and HPV 16 and 18, which cause about 70% of cases of cervical cancer.[9,10] Furthermore, findings from several phase 3 clinical trials have shown cross-protection against non-vaccine-preventable HPV 31, 33, and 45.[11–13]

About 83% of girls aged 12–17 years in Australia have received at least one dose of HPV vaccine, and about 70% have received all three doses of vaccine.[6] Findings from several Australian studies in sexual health clinics[14–17] have shown a rapid reduction and near disappearance of genital warts in young Australian-born women of vaccine-eligible age after the vaccination programme, suggesting that this vaccine coverage could be greater than the critical vaccination threshold for HPV 6 and 11. However, HPV 16 and 18 might be more difficult to control through vaccination than are HPV 6 and 11 because they are asymptomatic and have a longer duration of infection and therefore a higher reproductive rate than HPV 6 and 11 do.[5,18] If HPV 16 and 18 do have higher reproductive rates than HPV 6 and 11, then a high coverage of HPV vaccination might be needed to achieve control and therefore decreases in genital warts cannot be used as proof of successful control of all HPV types. Mathematical models[19–21] have also predicted that HPV 16 and 18 will be more difficult to control than HPV 6 and 11, although, so far, no longitudinal data exist to support this finding. If this finding is true, then HPV 6 and 11 transmission could be largely controlled locally, but transmission of HPV 16 and 18 might persist.

To find out whether HPV 16 and 18 are more difficult to control than are HPV 6 and 11, HPV 16 and 18 infection in the postvaccination period need to be established. Investigators of a US[22] and an Australian[23] study have assessed this infection rate and although findings from both studies showed decreases in the 4vHPV types, the decreases were not greater for HPV 6 and 11 than for HPV 16 and 18.

The aim of this study was to establish annual trends and changes in detection of HPV types contained in the 4vHPV and 9vHPV vaccines in sexually active young women screened for and diagnosed with chlamydial infection in Australia during a 10 year period. Substantial and rapid decreases in 4vHPV types in high-risk women would suggest that changes in the low-risk general community were at least as marked. We hypothesised that a large reduction in 4vHPV types in Australian-born women would take place after implementation of the HPV vaccination programme compared with those who were born overseas who might not have access to free vaccine.

Methods

Study design and participants

Melbourne Sexual Health Centre (MSHC) is the major public sexual health clinic in Victoria, Australia, and all services are free of charge. MSHC provides about 35 000 consultations annually; about 13 000 consultations are with women (37%),[24] of whom about 34% are aged 25 years or younger and about 90% are

	Prevaccination			Postvaccination							Trend	
	2004–05	2005–06	2006–07	2007–08	2008–09	2009–10	2010–11	2011–12	2012–13	2013–14	Direction	p value
Total												
Total all	96 (100%)	113 (100%)	89 (100%)	95 (100%)	96 (100%)	147 (100%)	129 (100%)	117 (100%)	140 (100%)	180 (100%)	..	..
Total Australian born	56 (58%)	60 (53%)	44 (49%)	33 (35%)	34 (35%)	59 (40%)	43 (33%)	36 (31%)	46 (33%)	57 (32%)	..	..
Total Australian born ≤21 years old	31 (32%)	25 (22%)	25 (28%)	14 (15%)	16 (17%)	25 (17%)	20 (16%)	15 (13%)	20 (14%)	27 (15%)	..	..
Total overseas born	35 (36%)	44 (39%)	37 (42%)	53 (56%)	53 (55%)	80 (54%)	82 (64%)	75 (64%)	90 (64%)	113 (63%)	..	..
Self-reported HPV vaccination status*												
All who had HPV vaccine	..	..	..	..	..	10/17 (59% [33–82])	24/42 (57% [41–72])	29/80 (36% [26–48])	47/107 (44% [34–54])	65/138 (47% [39–56])	..	..
Australian born who had HPV vaccine	..	..	..	..	..	7/8 (88% [47–100])	17/18 (94% [73–100])	23/27 (85% [66–96])	26/35 (74% [57–88])	32/44 (73% [57–85])	..	..
Overseas born who had HPV vaccine	..	..	..	..	..	3/9 (33% [8–70%])	7/23 (30% [13–53])	5/50 (10% [3–22])	19/69 (28% [17–40])	28/87 (32% [23–43])	..	..
Any HPV type												
All	55 (57% [47–67])	76 (67% [58–76])	57 (64% [53–74])	66 (69% [59–79])	59 (61% [51–71])	93 (63% [55–71])	85 (66% [57–74])	75 (64% [55–73])	102 (73% [65–80])	121 (67% [60–74])	→	0·133
Australian born	33 (59% [45–72])	41 (68% [55–80])	28 (64% [48–78])	24 (73% [54–87])	20 (59% [41–75])	37 (63% [49–75])	28 (65% [49–79])	21 (58% [41–74])	34 (74% [59–86])	31 (54% [41–68])	→	0·680
Australian born ≤21 years old	17 (55% [36–73])	16 (64% [43–82])	15 (60% [39–79])	12 (86% [57–98%])	12 (75% [48–93])	15 (60% [39–79])	13 (65% [41–85])	9 (60% [32–84])	14 (70% [46–88])	15 (56% [35–75])	→	0·936
Overseas born	20 (57% [39–74])	29 (66% [50–80])	24 (65% [47–80])	37 (70% [56–82])	32 (60% [46–74])	50 (63% [51–73])	55 (67% [56–77])	49 (65% [53–76])	65 (72% [62–81])	83 (73% [64–81])	→	0·060
HPV 6 and 11												
All	13 (14% [7–22])	19 (17% [10–25])	18 (20% 12–30])	6 (6% [2–13])	8 (8% [4–16])	14 (10% [5–15])	11 (9% [4–15])	10 (9% [4–15])	8 (6% [2–11])	11 (6% [3–11])	↓	<0·0001
Australian born	9 (16% [8–28])	10 (17% [8–29])	12 (27% [15–43])	3 (9% [2–24])	2 (6% [1–20])	2 (3% [0–12])	1 (2% [0–12])	0 (0% 0–10])	0 (0% [0–8])	1 (2% [0–9])	↓	<0·0001
Australian born ≤21 years old	4 (13% [4–30])	3 (12% [3–31])	10 (40% [21–61])	1 (7% [0–34])	2 (13% [2–38])	0 (0% [0–14])	0 (0% [0–17])	0 (0% [0–22])	0 (0% [0–17])	0 (0% [0–13])	↓	<0·0001
Overseas born	4 (11% [3–27])	7 (16% [7–30])	6 (16% [6–32])	3 (6% [1–16])	3 (6% [1–16])	12 (15% [8–25])	10 (12% [6–21])	9 (12% 6–22])	8 (9% [4–17])	9 (8% [4–15])	→	0·300
HPV 16 and 18												
All	22 (23% [15–33])	31 (27% [19–37])	23 (26% [17–36])	25 (26% [18–36])	16 (17% [10–26])	25 (17% [11–24])	23 (18% [12–26])	24 (21% [14–29])	31 (22% [16–30])	19 (11% [6–16])	↓	0·001
Australian born	17 (30% [19–44])	21 (35% [23–48])	12 (27% [15–43])	10 (30% [16–49])	2 (6% [1–20])	3 (5% [1–14])	2 (5% [1–16])	2 (6% [1–19])	5 (11% [4–24])	2 (4% [0–12])	↓	<0·0001
Australian born ≤21 years old	9 (29% [14–48])	9 (36% [18–57])	7 (28% [12–49])	5 (36% [13–65])	1 (6% [0–30])	0 (0% [0–14])	0 (0% [0–17])	0 (0% [0–22])	1 (5% [0–25])	1 (4% [0–19])	↓	<0·0001
Overseas born	5 (14% [5–30])	8 (18% [8–33])	6 (16% [6–32])	13 (25% [14–38])	12 (23% [12–36])	22 (28% [18–39])	20 (24% [16–35])	20 (27% [17–38])	25 (28% [19–38])	16 (14% [8–22])	→	0·682

(Table 1 continues on next page)

	Prevaccination			Postvaccination							Trend	
	2004–05	2005–06	2006–07	2007–08	2008–09	2009–10	2010–11	2011–12	2012–13	2013–14	Direction	p value
(Continued from previous page)												
HPV 31, 33, and 45												
All	9 (9% [4–17])	18 (16% [10–24])	15 (17% [10–26])	19 (20% [12–29])	15 (16% [9–24])	23 (16% [10–23])	16 (12% [7–19])	26 (22% [15–31])	23 (16% [11–24])	28 (16% [11–22])	→	0·401
Australian born	5 (9% [3–20])	10 (17% [3–20])	7 (16% [7–30])	3 (9% [2–24])	4 (12% [3–27])	8 (14% [6–25])	4 (9% [3–22])	4 (11% [3–26])	8 (17% [8–31])	4 (4% [2–17])	→	0·608
Australian born ≤21 years	4 (13% [4–30])	5 (20% [7–41])	4 (16% [5–36])	2 (14% [2–43])	2 (13% [2–38])	3 (12% [3–31])	1 (5% [0–25])	2 (13% [2–40])	2 (10% [1–32])	1 (4% [0–19])	→	0·097
Overseas born	4 (11% [3–27])	8 (18% [8–33])	6 (16% [6–32])	13 (25% [14–38])	10 (19% [9–32])	14 (18% [10–28])	11 (13% [7–23])	21 (28% [18–40])	13 (14% [8–23])	20 (18% [11–26])	→	0·836
HPV 52 and 58												
All	6 (6% [2–13])	21 (19% [12–27])	9 (10% [5–18])	15 (16% [9–25])	22 (23% [15–33])	29 (20% [14–27])	22 (17% [11–25])	15 (13% [7–20])	28 (20% [14–28])	36 (20% [14–27])	↑	0·027
Australian born	4 (7% [2–17])	12 (20% [11–32])	5 (11% [4–25])	5 (15% [5–32])	5 (15% [5–31])	14 (24% [14–37])	5 (12% [4–25])	3 (8% [2–22])	9 (20% [9–34])	7 (12% [5–24])	→	0·732
Australian born ≤21 years old	3 (10% [2–26])	5 (20% [7–41])	4 (16% [5–36])	1 (7% [0–34])	3 (19% [4–46])	5 (20% [7–41])	5 (25% [9–49])	1 (7% [0–32])	2 (10% [1–32])	3 (11% [2–29])	→	0·799
Overseas born	2 (6% [1–19])	9 (20% [10–35])	2 (5% [1–18])	7 (13% [5–25])	15 (28% [17–42])	13 (16% [9–26])	16 (20% [12–30])	10 (13% [7–23])	19 (21% [13–31])	26 (23% [16–32])	↑	0·039
9vHPV 31, 33, 45, 52, and 58 (excluding 6, 11, 16, and 18)												
All	13 (14% [7–22])	36 (32% [23–41])	20 (22% [14–33])	29 (31% [21–41])	33 (34% [25–45])	44 (30% [23–38])	33 (26% [18–34])	33 (28% [20–37])	47 (34% [26–42])	54 (30% [23–37])	↑	0·046
Australian born	8 (14% [6–26])	19 (32% [20–45])	9 (20% [10–35])	8 (24% [11–42])	8 (24% [11–42])	19 (32% [21–46])	9 (21% [10–36])	7 (19% [8–36])	15 (33% [20–48])	10 (18% [9–30])	→	0·834
Australian born ≤21 years old	6 (19% [7–37])	9 (36% [18–57])	5 (20% [7–41])	3 (21% [5–51])	4 (25% [7–52])	7 (28% [12–49])	6 (30% [12–54])	3 (20% [4–48])	4 (20% [6–44])	4 (15% [4–34])	→	0·451
Overseas born	5 (14% [5–30])	17 (39% [24–55])	8 (22% [10–38])	17 (32% [20–46])	22 (42% [28–56])	22 (28% [18–39])	23 (28% [18–39])	24 (32% [22–44])	30 (33% [24–44])	38 (34% [25–43])	→	0·267
Median number of male sex partners in the past 12 months												
All	2 (1–4)	3 (1–4)	2 (1–4)	3 (2–4)	2 (1–4)	2 (1–5)	2 (1–4)	3 (1–5)	3 (2–7)	3 (1–6)	↑	<0·0001
Australian born	2 (1–4)	3 (1–4)	2·5 (2–4)	3 (2–4)	3 (1–4)	4 (1–5)	3 (1–4)	3 (1–5)	3 (2–6)	4 (2–6)	↑	0·001
Overseas born	3 (1–4)	3 (2–5)	2 (1–4)	3 (2–4)	2 (1–3)	2 (1–4)	2 (1–5)	3 (1–5)	3 (1–7)	3 (1–6)	→	0·099
100% condom use with male sex partners in the past 12 months*												
All women	12/82 (15% [8–24])	8/100 (8% [4–15])	5/81 6% [2–14])	5/85 (6% [2–13])	9/82 (11% [5–20])	13/123 (11% [6–17])	15/101 (15% [9–23])	16/99 (16% [10–25])	20/129 (16% [10–23])	12/151 (8% [4–13])	→	0·301
Australian born	7/48 (15% [6–28])	2/55 (4% [0–13])	1/42 (2% [0–13])	1/31 (3% [0–17])	2/29 (7% [1–23])	6/54 (11% [4–23])	5/36 (14% [5–29])	4/31 (13% [4–30])	4/43 (9% [3–22])	2/47 (4% [1–15])	→	0·793
Overseas born	5/31 (16% [5–34])	4/42 (10% [3–23])	4/35 (11% [3–27])	2/46 (4% [1–15])	6/46 (13% [5–26])	7/64 (11% [5–21])	10/63 (16% [8–27])	10/62 (16% [8–28])	14/82 (17% [10–27])	8/94 (9% [4–16])	→	0·620

Data are n (%), n/N (% [95% CI]), median (IQR), or n (% [95% CI]). All women include those with an unknown country of birth, therefore the total numbers of Australian-born and overseas-born women do not add up to the total number of women. HPV=human papillomavirus. 9vHPV=nine-valent HPV. *Data not available for all individuals.

Table 1: **HPV genotypes, sexual behaviours, and self-reported vaccination status**

screened for chlamydia. Testing for chlamydia is offered to all women at risk.[25] Since 2004, MSHC has routinely stored patients' specimens if they are positive for chlamydia for research. The clinic operates an opt-out consent process, so specimens are not stored for clients who decline to provide consent.

We identified specimens from women aged 25 years or younger who attended MSHC with a cervical or high vaginal swab sample positive for chlamydia. For women with repeat infections, we only used the first sample. Demographic and epidemiological data (number of male partners and 100% condom use with all partners in the past 12 months status) were collected at MSHC. A question was added about whether women had received the HPV vaccine from 2009 onwards. However, data from the National HPV Vaccination Program Register were not available to verify self-reported HPV vaccination status.

We obtained ethical approval from the Ethics Committee of Alfred Hospital, Melbourne, VIC, Australia (number 99/14), and Monash University, Melbourne, VIC, Australia (number CF14/1067 - 2014000455).

Procedures

Cervical and high vaginal swab samples in Becton Dickinson ProbeTec swab diluent (Becton Dickinson, Sparks, MD, USA), stored at –80°C, were previously tested for *Chlamydia trachomatis* DNA. We isolated DNA from known positive *C trachomatis* samples using the MagNA Pure 96 DNA and Viral NA small volume kit on an automated MagNA Pure 96 isolation and purification system (Roche Diagnostics, Mannheim, Germany) according to the manufacturer's protocol. We eluted nucleic acid into a final volume of 100 µL and used a quantitative β globin assay to assess sample adequacy after extraction as a standard laboratory procedure.[26]

We did HPV amplification and detection using the PapType high-risk HPV detection and genotyping kit (Genera Biosystems, Scoresby, VIC, Australia), according to the manufacturer's instructions. The PapType HPV assay includes solid-phase PCR amplification of 14 high-risk HPV genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68), two low-risk HPV genotypes (6 and 11), and an internal human control (myosin light chain 1 [MLC1]) to assess sample quantity and quality, using 10 µL of extracted DNA in a 20 µL PCR reaction. Amplified products acquire red fluorescence and are loaded onto silica beads distinguishable by size and fluorescent intensity with flow cytometry (Becton Dickinson Accuri C6; Becton Dickinson, Franklin Lakes, NJ, USA). We combined both cervical and vaginal specimens in the analysis.[27]

We analysed frequencies and prevalence of HPV genotypes as detection of any HPV genotype, vaccine-targeted wart-associated HPV 6 and 11, vaccine-targeted oncogenic HPV 16 and 18, the extra five HPV types within the 9vHPV types (31, 33, 45, 52, and 58 alone) excluding the 4vHPV types (6, 11, 16, and 18), and three HPV types that are phylogenetically associated with 4vHPV types 16 and 18 (31 and 33 associated with 16 and 45 associated with 18).

Statistical analysis

Findings from a previous Australian study[23] showed that the prevalence of 4vHPV decreased from 28·7% in the prevaccination period to 6·5% in the postvaccination period in women attending family planning clinics. To detect a reduction of 4vHPV between the prevaccination and postvaccination periods, a minimum sample size of 108 was needed in each period (power 0·8; α=0·05).

We stratified the study period according to the Australian financial year, which runs from July 1 to June 30 of the following year. We further stratified according to the prevaccination (from July 1, 2004, to June 30, 2007) and postvaccination (July 1, 2007, to June 30, 2014, to cover the female catch-up programme that started in July, 2007) periods. We then calculated the number and prevalence of HPV genotypes in each financial year across three groups (all women, Australian-born women, and overseas-born women). We stratified

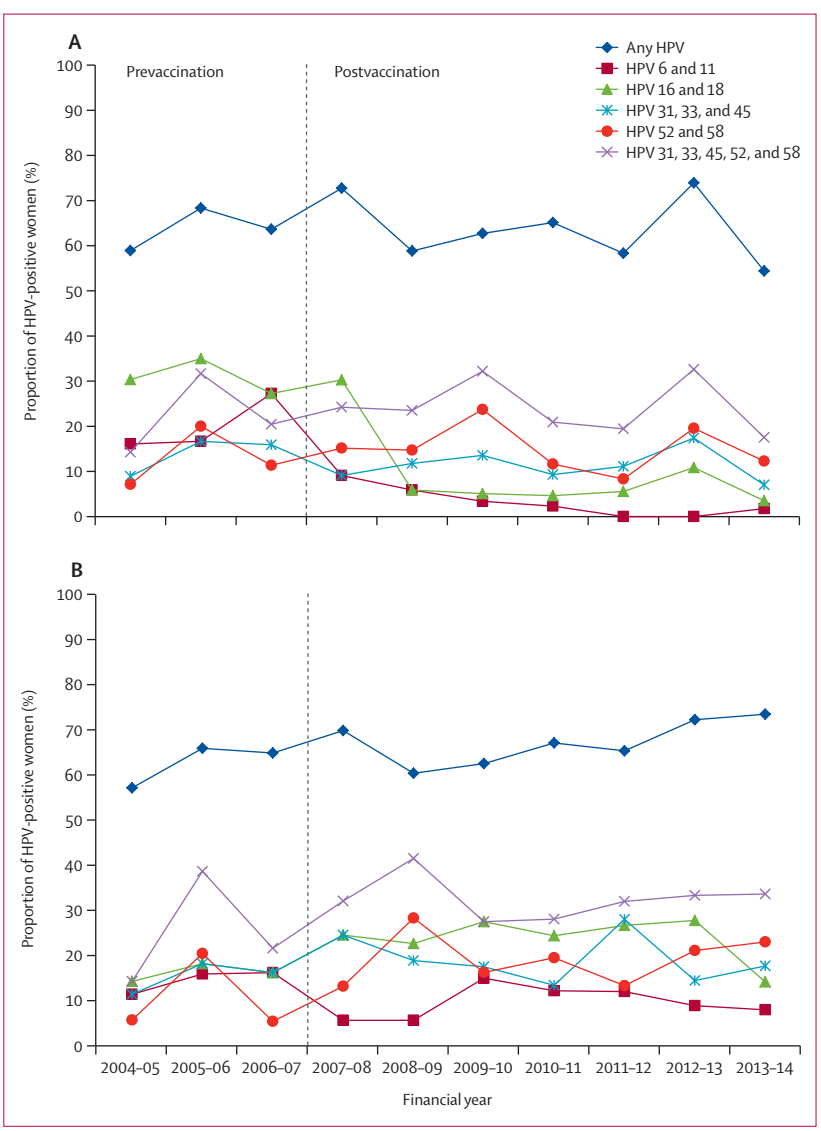

Figure 1: **Crude HPV genotype prevalence in all women, stratified by (A) Australian-born and (B) overseas-born women**

The dashed line represents when the HPV vaccination programme began. HPV=human papillomavirus.

individuals by country of birth because only Australian citizens or permanent residents are eligible for the HPV vaccination programme. We also analysed Australian-born women aged 21 years or younger because these women had all been eligible (aged 12–13 years) to receive the free HPV vaccine at school from April, 2007, onwards, and most of these women would have received the vaccine before they started having sexual intercourse. We also stratified data by self-reported HPV vaccination status.

We assessed the effectiveness of vaccine against prevalent HPV 6, 11, 16, and 18 infections using binomial log linear regression, adjusting for self-reported sexual behaviours and anatomical sampling of women in the prevaccination and postvaccination periods. We calculated adjusted prevalence ratios (aPRs) and 95% CIs for HPV 6, 11, 16, and 18 infections in both Australian-born and overseas-born women. We adjusted for sexual behaviours because these are the strongest predictors of HPV infection. Findings from a previous study[28] showed that some differences in detection of any HPV types between vaginal and cervical specimens exist, but not in detection of any carcinogenic HPV type. Although our sample did not show any differences between detection of HPV 6 and 11 and of HPV 16 and 18, we adjusted anatomical sampling to avoid any potential confounding.

We tested differences in detection of HPV genotypes during the 10 year period using a χ^2 trend test or Fisher's exact test. We calculated 95% CIs of the estimates on the basis of the exact binomial distribution. We tested temporal changes in median number of sex partners using a non-parametric Jonckheere-Terpstra test. We tested differences in mean number of sex partners between vaccinated and unvaccinated women with an independent *t* test. We used a Hosmer-Lemeshow test to assess the goodness of fit of the model for prediction of prevalence ratios. We used a significance level of 0·05 for all statistical tests and did all analyses using Stata version 13.1. We interpreted the flow cytometry data with QPlots4 (4.6.0.2248 research use only; Java virtual machine version 1.7.0_25) software.

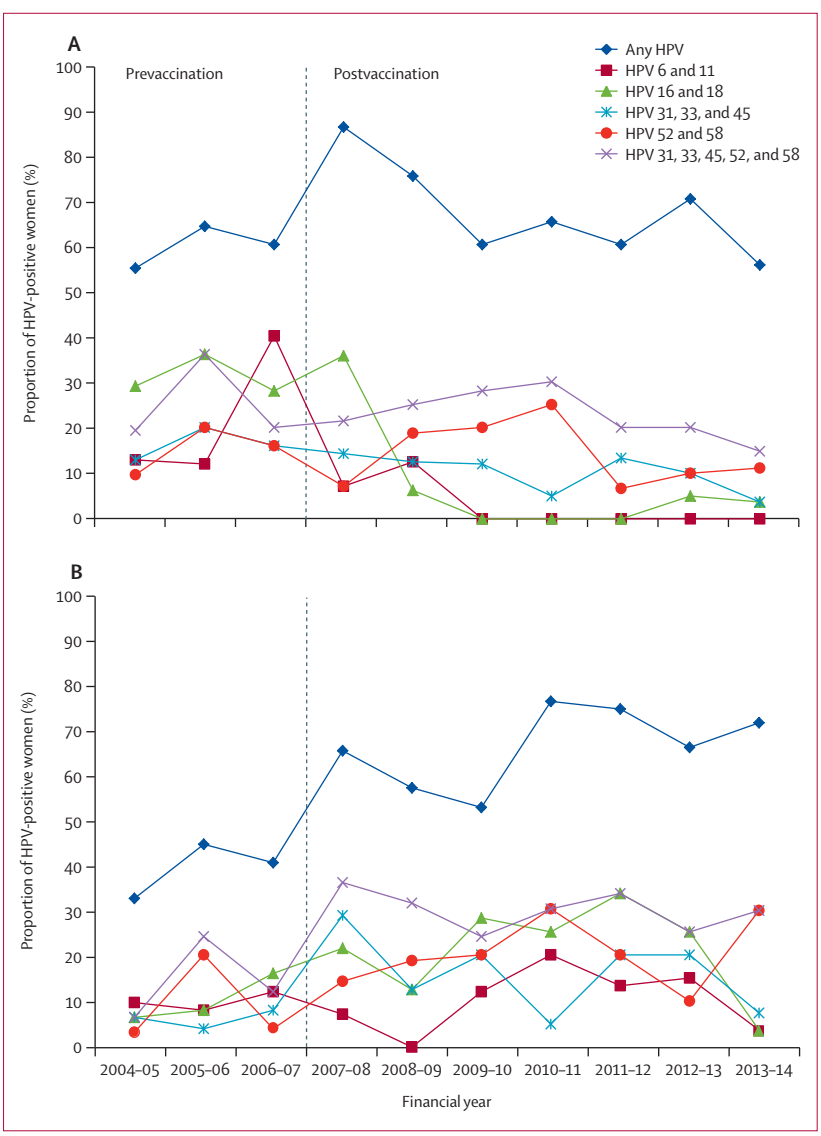

Figure 2: **Crude HPV genotype prevalence in women aged 21 years and younger, stratified by (A) Australian-born and (B) overseas-born women**
The dashed line represents when the HPV vaccination programme began. HPV=human papillomavirus.

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, 2014, 1301 specimens were eligible (after we excluded 101 specimens that were from the same individual). Of these, 1203 women agreed to consent for retention and storage of their specimen for research purposes. All of these specimens had HPV DNA detection and genotyping done—only one specimen was non-assessable and so we excluded it from the analysis. The remaining 1202 specimens (938 cervical and 264 vaginal samples) were positive for both human DNA controls (β globin and MLC1) and so we included them in this analysis. We noted no significant difference between detection of HPV 6 and 11 (cervical 84 [9%] of 938; high vaginal 34 [13%] of 264; p=0·058) and 16 and 18 (cervical 177 [19%] of 938; high vaginal 62 [23%] of 264; p=0·097) between cervical and high vaginal swab specimens.

468 women were born in Australia (39%), 662 were born overseas (55%), and we had no information for 72 (6%). The median age of women was 22 years (IQR 20–24). 1045 women were never married (87%); 61 were married, divorced, or in a de-facto relationship (5%); and we did not have information for 96 (8%). The median number of male sex partners in the past 12 months in these women

rose significantly over time (table 1). However, the proportion reporting 100% condom use with male partners in the past 12 months remained stable over time.

The prevalence of any HPV type in all women remained stable during the past 10 years (table 1). The prevalence of 4vHPV types, however, decreased rapidly within 3 years of the vaccination programme commencing. We noted no significant temporal changes in HPV 31, 33, and 45. From 2009–10 to 2013–14, 175 (46%) of 384 women self-reported that they had received at least one dose of HPV vaccine.

The mean number of male sex partners for all women in the past 12 months was the same for both vaccinated (4·6, SD 4·7) and unvaccinated (4·2, 3·6) women in the postvaccination period (p=0·321), and the proportion of 100% condom use did not differ between vaccinated (16 [10%] of 160; 95% CI 6–16) and unvaccinated (24 [13%] of 192; 8–18) women (p=0·462). However, the prevalence of 4vHPV was significantly lower in vaccinated (13 [7%] of 176; 4–12) than in unvaccinated (66 [31%] of 210; 25–38) women (p<0·0001). Additionally, vaccinated women had a significantly lower prevalence of HPV 31, 33, and 45 than did unvaccinated women (20 [11%] of 176; 7–17 *vs* 47 [22%] of 210; 17–29; p=0·004), but we noted no differences in the prevalence of samples with at least one of the 9vHPV types excluding 4vHPV types between vaccinated (48 [27%] of 176; 21–34) and unvaccinated (71 [34%] of 210; 27–41) women (p=0·166).

The prevalence of any HPV type in 468 Australian-born women remained stable during the study period (table 1 and figure 1). We noted a substantial decrease in HPV 6 and 11 within 3 years of the vaccine programme commencing. We noted a similar decrease in HPV 16 and 18. We did not note any significant temporal changes in detection of the 9vHPV types excluding 4vHPV. Furthermore, HPV 6 and 11 (aPR 0·12, 95% CI 0·05–0·28) and 16 and 18 (0·24, 0·15–0·39) were significantly lower in the postvaccination period than in the prevaccination period, after adjustment for the number of sexual partners, condom use, and anatomical sampling sites. We noted a larger reduction in 4vHPV types in Australian-born women aged 21 years or younger than in all Australian-born women (table 1 and figure 2). We did not note any significant changes in detection of 9vHPV types excluding 4vHPV types, or in HPV 31, 33, and 45.

105 (80%) of 132 Australian-born women reported having received the HPV vaccine. Only one (1%, 95% CI 0–5) of these women had HPV 6 and 11, whereas five (5%, 2–11) had HPV 16 and 18, which was much lower than in unvaccinated Australian-born women before the vaccination programme commenced (table 2). In the postvaccination period, the prevalence of 4vHPV was significantly lower (p=0·047) in vaccinated women (six [6%] of 105; 95% CI 2–12) than in unvaccinated women (five [19%] of 27; 6–38). However, we did not note any significant difference in the prevalence of any HPV type (69 [66%] of 105; 56–75 *vs* 15 [56%] of 27; 35–75; p=0·328), HPV 31, 33, and 45 (12 [11%] of 105; 6–19 *vs* one [4%] of 27; 0–19; p=0·303), or 9vHPV excluding 4vHPV (24 [23%] of 105; 15–32 *vs* 7 [26%] of 27; 11–46; p=0·737). We noted a greater reduction in 4vHPV in unvaccinated Australian-born women aged 21 years and younger than in all Australian-born women, although the trend for all Australian-born women was more significant (table 2). The prevalence of HPV 6 and 11, and 31, 33, and 45 decreased to 0% in the postvaccination period, although the decreases were not significantly different (table 2).

The prevalence of any HPV type in 662 overseas-born women did not significantly change (table 1 and figures 1 and 2). Additionally, we did not note any changes in the prevalence of HPV 6 and 11, 16 and 18, and 31, 33, and 45, and 9vHPV excluding 4vHPV types. HPV 6 and 11 (aPR 0·65, 95% CI 0·38–1·11) and 16 and

	Prevaccination*	Postvaccination†	Trend	p value
Any HPV				
Australian born	102/160 (64% [56–71])	15/27 (56% [35–75])	→	0·519
Australian born ≤21 years old	48/81 (59% [48–70])	6/12 (50% [21–79])	→	0·550
4vHPV				
Australian born	66/160 (41% [34–49])	5/27 (19% [6–38])	↓	0·031
Australian born ≤21 years old	33/81 (41% [30–52])	1/12 (8% [0–38])	↓	0·050
HPV 6 and 11				
Australian born	31/160 (19% [14–26])	2/27 (7% [1–24])	→	0·175
Australian born ≤21 years old	17/81 (21% [13–31])	0	→	0·114
HPV 16 and 18				
Australian born	50/160 (31% [24–39])	3/27 (11% [2–29])	↓	0·037
Australian born ≤21 years old	25/81 (31% [21–42])	1/12 (8% [0–38])	→	0·168
HPV 31, 33, and 45				
Australian born	22/160 (14% [9–20])	1/27 (4% [0–19])	→	0·208
Australian born ≤21 years	13/81 (16% [9–26])	0	→	0·206
HPV 52 and 58				
Australian born	21/160 (13% [8–19])	6/27 (22% [9–42])	→	0·237
Australian born ≤21 years old	12/81 (15% [8–24])	2/12 (17% [2–48])	→	1·000
HPV 31, 33, 45, 52, and 58				
Australian born	36/160 (23% [16–30])	7/27 (26% [11–46])	→	0·805
Australian born ≤21 years old	20/81 (25% [16–36])	2/12 (17% [2–48])	→	0·725

Data are n/N (% [95% CI]). *160 Australian-born women and 81 Australian-born women aged 21 years or younger. †27 Australian-born women and 12 Australian-born women aged 21 years or younger.

Table 2: **HPV genotypes in unvaccinated Australian-born women before and after the national HPV vaccination programme**

18 (1·33, 0·84–2·10) types did not differ after adjustment for the number of sexual partners, condom use, and anatomical sampling sites. 62 (26%) of 238 overseas-born women reported receiving HPV vaccine. The prevalence of 4vHPV in unvaccinated women in the postvaccination period did not differ from that of women in the prevaccination period (59 [34%, 95% CI 27–41] of 176 *vs* 32 [28%, 20–37] of 116; p=0·284). In the postvaccination period, the prevalence of 4vHPV was significantly lower in vaccinated women than in unvaccinated women (seven [11%, 5–22] of 62 *vs* 59 [34%, 27–41] of 176; p=0·001), but we noted no significant difference in any HPV (47 [76%, 63–86] of 62 *vs* 126 [72%, 64–78] of 176; p=0·522) or 9vHPV excluding 4vHPV (21 [34%, 22–47] of 62 *vs* 62 [35%, 28–43] of 176; p=0·847) types.

Discussion

Transmission of both low-risk and high-risk 4vHPV vaccine types decreased rapidly and almost disappeared when vaccination commenced, with a coverage of about 70% in women vaccinated before sexual activity (ie, 21 years of age or younger in 2013–14 or 14 years of age in 2007–08). This trend is similar to what mathematical models predicted 10 years ago.[29] This study is strengthened by the fact that the study population consisted of sexually active women diagnosed with chlamydia in which the likelihood of HPV infection is greater than in the community on average. These trends are remarkably consistent with reductions in genital warts in women who were vaccinated before starting sexual intercourse and bode well for substantial decreases in HPV-related cancers in women. Findings from an Australian study[30] done in the postvaccination period agree with ours, showing that only 1·6% of community-based young women who were sexually active when they were vaccinated were 4vHPV positive.

Our results are consistent with those of a previous study done of women aged 18–24 years attending family planning clinics in Australia,[23] which showed that the prevalence of 4vHPV types has decreased from 28·7% in the prevaccination period (2005–07) to 6·5% in the postvaccination period (2010–11), with a three-dose vaccine coverage of 55%. Sweden launched the publicly funded 4vHPV school-based vaccination programme in 2012. Soderlund-Strand and colleagues[31] analysed samples of young women before and after introduction of the 4vHPV vaccine, and although the study had a short follow-up of only 1 year, findings showed that the prevalence of HPV 6 decreased from 7·0% to 4·2%, HPV 16 fell from 14·9% to 8·7%, and HPV 18 decreased from 7·9% to 4·3% between 2008 and 2013 in women aged 13–22 years attending chlamydia screening, with a 75% vaccine coverage. This rapid decrease is consistent with the remarkably rapid fall that we noted within 2 years of commencement of the vaccine programme. This decline occurred despite women in our study having a higher number of male partners (median of two to three) than in women in the general Australian community (median of one)[32] in the past 12 months. Of particular note, women reported an increasing number of partners during the cohort, showing increased transmission pressure for HPV; however, despite this finding, 4vHPV types remained rare. This trend is consistent with results from another Australian study[33] showing that the incidence of high-grade cervical abnormalities decreased by 0·38% (with a preintervention and postintervention incidence rate ratio of 1·14) in young girls after the vaccination programme began. Our findings also show a significant fall in the prevalence of 4vHPV types from the prevaccination to the postvaccination period in unvaccinated Australian-born women, suggesting that these unvaccinated women are obtaining a strong herd protection effect of reduction of the pool of infectious virus in the community, presumably predominantly via men having sex with young vaccinated women. We noted no herd protection effect in overseas-born women, most of whom would have not been vaccinated, which is consistent with a study in the USA.[34] This might relate to sexual networks in overseas university students who tend to have sexual partners from their own country, low power, or biased self-reported vaccination status.

Theoretically, the prevalence of non-vaccine-preventable 9vHPV types should not change between the prevaccination and postvaccination period. Consistent with previous findings,[23] we found that the prevalence of HPV 31, 33, and 45 was significantly lower in fully vaccinated women than in unvaccinated women in the postvaccination period, suggesting that vaccinated women would have benefited from a cross-protection effect. In view of the fact that we did not verify vaccination status in these women and the number of participants was small, further studies with a large sample size and verified vaccination status are needed to substantiate any cross-protection from the 9vHPV vaccine.

Our study has several limitations. First, it was done at a single sexual health clinic only in sexually active young women diagnosed with chlamydia, which might not be representative of changes in other Australian women at lower risk than those in this study. The changes that we noted, however, are likely to be more marked in lower-risk women because their risk of acquisition is lower.[23,35] Second, the sexual risk of women with chlamydia might have increased during the study period, and we did note an increasing number of sex partners in these women over time. Indeed, a sentinel surveillance programme in Victoria has shown a rise in prevalence in women, supported by rises in chlamydia notifications in women, which have risen from 177 per 100 000 in 2004 to 391 per 100 000 in 2013.[36] However, if this risk did increase, then the effect of vaccination would actually be stronger than that we reported. Third, a small proportion of Australian-born girls would have received vaccination from April to June, 2007, during the school-based programme (we included this period in the prevaccination period because

this study monitors HPV at a community-based level, and the actual date of implementation varied in different states and schools in the country, therefore we decided to use July, 2007, as a cutoff because the vaccine would definitely be available by this time), which could have biased our study towards not showing an effect of vaccination. Fourth, we did not validate self-reported vaccination status through the National HPV Vaccination Program Register because we did not obtain patients' consent to check vaccination status through the registry, so recall or misclassification bias could be associated with these self-reported behaviours. Fifth, some overseas-born women might have been eligible for the HPV vaccine, but we were not able to distinguish these women. Finally, estimates in some analyses had wide confidence intervals from small numbers of women and should be interpreted cautiously.

Contributors

EPFC and CKF designed the study. JAD and SNT did laboratory testing. GF collected and stored samples. EPFC, CKF, JAD, SNT, and GF analysed data. MGL provided statistical advice for data analysis. EPFC, CKF, MGL, CSB, SMG, and MYC interpreted data. EPFC and CKF drafted the report, and all authors critically revised it for important intellectual content and read and approved the final version.

Declaration of interests

EPFC has received a conference sponsorship from bioCSL and is supported by the Early Career Fellowships from the Australian National Health and Medical Research Council (number 1091226). CKF has received honoraria from CSL Biotherapies and Merck, and research funding from CSL Biotherapies. CKF owns shares in CSL Biotherapies, which is the manufacturer of Gardasil. SNT and SMG are investigators in a national prevalence study of cervical cancer tissue that is receiving unrestricted funding from bioCSL, which is the supplier of human papillomavirus (HPV) vaccine in Australia. SMG has received advisory board fees and grant support from CSL and GlaxoSmithKline, and lecture fees from Merck, GlaxoSmithKline, and Sanofi Pasteur. SMG has received funding through her institution (Royal Women's Hospital) to do HPV vaccine studies for Merck Sharp & Dohme and GlaxoSmithKline. SMG is a member of the Merck Global Advisory Board and the Merck Scientific Advisory Committee for HPV. MYC has been an investigator for investigator-initiated research grants from Merck Sharp & Dohme. MGL receives unrestricted grants from Boehringer Ingelhiem, Gilead Sciences, Merck Sharp & Dohme, Bristol-Myers Squibb, Janssen-Cilag, and ViiV HealthCare. All other authors declare no competing interests.

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