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Research paper

Genital warts trends in Australian and overseas-born people in Australia: A cross-sectional trend analysis to measure progress towards control and elimination

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ABSTRACT

Background: Substantial declines in genital warts have been observed in countries with quadrivalent/nonavalent human papillomavirus (*q/n* HPV) vaccination programmes, with Australia showing the most pronounced and long-term reductions. No study has assessed progress towards elimination of genital warts in a nation-wide sample of patients, and migrants' contribution to population-level control of genital warts. We assessed Australia's progress towards genital warts elimination by examining trends in diagnoses in Australian- and overseas-born patients of sexual health clinics (SHCs) across Australia.

Methods: A cross-sectional trend analysis of new genital warts diagnoses among first-time patients of 34 SHCs, between 2004 and 2018, was performed. Rate ratios (RR) were calculated using Poisson regression models, for comparing trends in proportions of new genital warts diagnoses in Australian- and overseas-born patients during the pre-vaccination era (2004-2007) and the vaccination era (2008-2018), and by 2018 relative to 2004-2007.

Findings: A total of 439,957 new patients (Australian-born: 230,230; overseas-born: 209,727) were seen at SHCs, 6.4% were diagnosed with genital warts (Australian-born: 7.1%; overseas-born: 5.6%). By 2018, there had been a 64% reduction in the proportion of all SHC patients with a genital warts diagnosis relative to 2004-2007 (RR: 0.36, 95% CI: 0.35-0.38). The decline was more pronounced at 72% (RR: 0.28, 95% CI: 0.27-0.30) among Australian-born patients, with the greatest reduction in women and men aged <21 years, at 98% (RR: 0.02, 95% CI: 0.01-0.03) and 92% (RR: 0.08, 95% CI: 0.06-0.11), respectively. By 2018, there was a 49% reduction in the proportion of overseas-born patients diagnosed with genital warts (RR: 0.51, 95% CI: 0.48-0.54), and a 21% reduction in overseas-born patients from countries with no or bivalent HPV (bHPV) vaccination programme (RR: 0.79, 95% CI: 0.71-0.90).

Interpretation: The substantial reductions in Australian-born people is a testament to the efficacy of quadrivalent (*qHPV*) and nonavalent (*nHPV*) vaccines and the high and wide-spread vaccination coverage in Australia. However, population-wide elimination of genital warts in Australia is dependent on other countries initiating or expanding their own HPV vaccination programmes.

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Research in context

Evidence before this study

High and widespread coverage of a national quadrivalent human papillomavirus (qHPV) vaccination program in Australia has led to marked reductions in genital warts diagnoses in young Australian-born women and heterosexual men. Several countries have documented varying levels of declines in the incidence of genital warts among young people, since implementation of their qHPV programs, depending on the level of coverage.

We searched PubMed on May 13, 2021 for articles published between 2007–2021, to identify studies that evaluated the reduction in genital warts diagnoses in locally-born and immigrant population since the implementation of HPV vaccination programmes. We searched for terms “genital warts” AND “surveillance” AND “(human papillomavirus vaccination) OR “HPV vaccine)” AND “(immigrants” OR “overseas-born” OR “non-resident)”. The search yielded three articles. Two studies were from the United States pertaining to the knowledge and beliefs of overseas-born people on HPV vaccine. Only one study from Australia evaluated the difference in reduction of genital warts between locally-born and non-resident women only. This study investigated genital warts trend up until 2009, within two years of the implementation of the national HPV vaccination programme in Australia and restricted their analyses to just eight sexual health clinics (SHCs). Since 2009, many other countries have introduced their HPV programmes and therefore it is important to examine genital warts trends in overseas-born people from a larger sample of patients, over an extended period, 2007–2018, including both men and women. We did not identify any studies from other high-income countries that investigated the reduction in genital warts diagnoses at a population level, and difference in declines in locally-born versus overseas-born people in a nation-wide sample of patients, particularly people from countries with no or bivalent vaccination (bHPV) program.

Added value of this study

We analysed data on Australian- and overseas-born patients from 34 SHCs across Australia between 2004–2018. Our analysis shows that the proportion of patients with a genital warts diagnosis has declined by 64% in 2018 relative to the pre-vaccination period. The reduction was more pronounced in Australian-born patients (72%), with the greatest reduction in young women and men aged <21 years, at 98% and 92%, respectively. Reductions were more moderate among overseas-born patients (49%) and smaller among overseas-born patients from countries with no/bHPV vaccination program (21%).

Implications of all the available evidence

Our study provides important insights into the disparities in genital warts diagnoses between local and immigrant populations in Australia. Although large declines have been observed in young Australian-born people, population-wide elimination will require world-wide initiation and expansion of HPV vaccination programmes.

Introduction

Genital warts are flat or raised lesions in the anogenital area, approximately 95% of which are caused by the low-risk human papillomavirus (HPV) types 6 and 11.¹ Before the implementa-

tion of the National HPV Vaccination Programme in 2007, genital warts were one of the most common sexually transmissible diseases managed at sexual health clinics (SHCs) in Australia,² with major psychological impacts and costs.^{3,4} Prior studies have shown substantial decreases of over 90% and 80% in new genital warts diagnoses in young Australian-born women and heterosexual men, respectively, since the commencement of the HPV vaccination programme, suggesting a real potential for genital warts elimination.^{5,6} Likewise, a recent systematic review and meta-analysis examining the population-level impact of female-only HPV vaccination programmes in 14 high-income countries showed a 67% decline in genital warts in girls and 48% in boys aged 15–19 years.⁷ However, in high-income countries, the reduction in genital warts diagnoses at a population level, and difference in declines in locally- versus overseas-born people has not been investigated.

As of 2018, ~99 countries and territories had introduced an HPV vaccination programme.⁸ Australia implemented a nationally funded quadrivalent HPV (qHPV) vaccination programme in mid-2007 for schoolgirls aged 12–13 years and in 2013 for schoolboys aged 12–13 years, with catch-up programmes from 2007–2009 for girls/women aged 13–26 years, and a two-year catch-up for boys aged 14–15 years.^{9,10} The qHPV vaccine protects against two high-risk HPV types, 16 and 18, that are responsible for over 70% of cervical cancers, in addition to low-risk HPV types, 6 and 11.¹¹ In 2018, Australia replaced the qHPV vaccine with a nonavalent (nHPV) vaccine that protects against all four types in the qHPV vaccine plus five additional high-risk HPV types.¹¹ The HPV vaccine is provided free of charge to age-eligible citizens and overseas-born permanent residents, while people who are not 9–20 years old (the age eligible group) need to pay for it.¹² In Australia, the vaccination programme has attained high 3-dose HPV vaccine coverage of 80% in girls, and 76% in boys turning 15 years of age in 2017.¹³

Prior Australian based studies have primarily focused on reductions in Australian-born people, because of certainty that they had access to the subsidised vaccine and excluded overseas-born youth as they may not have been eligible.^{5,6} Some studies that investigated genital warts diagnoses in overseas-born people either restricted their analyses to non-resident women or analysed data from only one urban sexual health clinic thus limiting generalisability.^{14,15} Australia is a migrant country, with 30% of people born overseas, and nearly 200,000 new permanent migrants and over eight million short-term visitors arriving annually.¹⁶ With sexual mixing occurring among overseas- and Australian-born people,¹⁷ it is therefore important to evaluate genital warts trends in overseas-born people, particularly those from countries with no or bivalent (bHPV) vaccination programmes, which only protect against high-risk HPV types, 16 and 18. The other major gap in knowledge has been a lack of an epidemiologically defined threshold and a target timeframe to formally determine if genital warts have been eliminated. In response, in 2018–19 a modified Delphi study was conducted among experts in the Australian context.¹⁸ The study recommended the following thresholds if completion of HPV vaccination is $\geq 80\%$ coverage in the target population: (1) a 60% relative reduction in population-level genital warts incidence by 2021 (control milestone), (2) an 80% reduction by 2030 (control threshold), and (3) a 95% reduction by 2060 (elimination threshold). All thresholds were calculated taking into consideration genital warts incidence and HPV vaccination status of both Australian and overseas-born people.

With these thresholds set and endorsed by the expert group, we aimed to: 1) evaluate the difference in new genital warts diagnoses trends between Australian- and overseas-born people; and 2) assess Australia's progress in reaching genital warts control and elimination milestones/thresholds, including both Australian- and overseas-born people.

Methods

Data collection

In Australia a sentinel surveillance network to monitor trends in genital warts diagnoses was established in 2008.¹⁴ In this network of clinics, diagnosis of genital warts was based on clinical examination. Routine data on patients' demographics, including age, gender, place of birth (Australia / overseas) and clinical diagnosis of genital warts were collected from the 34 clinics that were able to provide retrospective data for the entire study period, 2004–2018. In addition, for overseas-born patients, information on name of country of birth, length of residence in Australia relative to their first SHC visit, and age at arrival in Australia was retrieved from a subset of four large clinics that had less than 10% missing data on year of arrival and name of country of birth. The demographic characteristics of the two groups of patients from the included four and excluded 30 clinics were compared to ascertain any risk of bias.

Study population

We included all first-time visits of patients of SHCs from January 2004 to December 2018. Patients were divided into two main groups, a) those who were born in Australia and b) those who were born overseas. Each group was stratified by gender (male, female and transgender people). Men and women were further stratified by age groups (<21, 21–30, 31–37, >37 years), corresponding to age cohorts in 2018 which defined differing eligibility to the national vaccine programme. We did not stratify transgender people by age due to small sample size. Each group was also stratified by reporting of men who had sex with men (MSM) in the previous 12 months, and sex work (see supplementary material). As of 2018, all Australian-born women and men aged <21 years had been eligible for the free HPV vaccination. During the 2007–2018 period, most (~93%) 21–30-year-old and some (~37%) 31–37-year-old Australian-born women had been eligible for free HPV vaccine at school or through the catch-up programmes,¹⁹ while none of the Australian-born women >37 years of age had been eligible for the free vaccine. [Figure 1](#) shows the eligible cohorts of Australian residents for the HPV vaccination programme in each year from 2007–2018, by age and sex.

To determine the relative reductions in the proportion of genital warts diagnoses in overseas-born patients from countries with or without an HPV vaccination programme, patients were further stratified by presence or absence of an HPV vaccination programme in their birth country during 2007–2018 using the World Health Organization's Immunization, Vaccines and Biologicals,' and HPV Information Centre's databases.^{20,21} To determine the type of HPV vaccine used, countries' vaccination programmes were searched on Google. Countries with a bHPV vaccination programme, countries that have recently announced but not implemented their HPV vaccination programmes (any type), and countries that only have a small-scale pilot HPV vaccination programme (any type), were categorised as countries with no/bHPV programme. To make conservative estimates, countries with mixed programmes (that is, both bHPV and q/nHPV), and countries where no information was available on the type of HPV vaccine available in their programmes were also categorised as countries with no/bHPV programme. Countries with q/nHPV programmes, countries that initially launched bHPV programmes but later implemented q/nHPV programmes were included in the q/nHPV group (Supplementary Box 1). We did not separately consider gender-neutral programmes in other countries and made a pragmatic decision to categorise countries together irrespective of their girls-only/gender-neutral strategies.

As the median incubation period of genital warts is ~3 months but can go as high as 11 months,²² a separate examination of recently arriving (within one year of arrival in Australia) overseas-born people and the resident overseas-born population is important to analyse the risk of genital warts importation. Therefore, the overseas-born patients were further stratified by the length of residence in Australia relative to their first SHC visit, (≤ 1 -year vs > 1 -year), with who arrived ≤ 1 year referred to as newly arrived overseas-born patients. In addition, to determine their likelihood of receiving free HPV vaccination in Australia or their home country, overseas-born patients were also stratified by age at arrival in Australia (<21, 21–30, 31–37, >37 years) (see supplementary material).

Statistical analysis

We divided our analyses into pre-vaccination (2004–2007) and vaccination (2008–2018) periods. We calculated the proportion of first-visit patients diagnosed with genital warts by dividing the number of new genital warts diagnoses by the total number of first-visit patients seen. Chi-squared test of proportions were used to test equality of proportions of categorical variables.

Poisson regression was used to model trends in the data for Australian- and overseas-born patients, stratified by gender, and age at diagnosis (<21, 21–30, 31–37, >37 years), and for men who reported male sexual contact in the previous 12 months and women who ever reported sex work (see supplementary material). We also modelled trends in overseas-born patients from q/nHPV and no/bHPV countries, stratified by duration of Australian residency (≤ 1 year, > 1 year relative to first SHC visit).

To investigate the first aim of evaluating the difference in new genital warts diagnoses trends between Australian- and overseas-born people, we calculated annual average rate of change, presented as rate ratios (RR), in the pre-vaccination and vaccination eras respectively, e.g.: RR of 0.90 signifies a 10% average annual decrease. We then tested for differences in these rates for respective categories of comparator groups using summary rate ratios (SRR), which were generated based on interaction terms between comparator groups and calendar year. Baseline differences were also generated and presented as SRRs in the supplementary material. Model fit was assessed using the deviance test statistic and negative binomial models were used in instances where potential overdispersion was indicated (see supplementary material). To investigate the second aim of assessing Australia's progress in reaching genital warts control and elimination milestones/thresholds, including both Australian- and overseas-born people, we calculated the difference in average pre-vaccination era rates of diagnosis compared to predicted 2018 rates of diagnosis. A p-value of less than 0.05 was considered statistically significant. Statistical analyses were performed in Stata Statistical Software (version 16.0; college station, TX: StataCorp LLC).

Role of funding source

The funders had no role in study design or data collection, analysis, interpretation or writing of this article. The corresponding author and all co-authors had full access to all the data and had full responsibility to submit for publication.

Results

Demographic characteristics

Between 2004 and 2018, 441,913 new patients were seen in the 34 SHCs. Of these, 1,956 (0.04%) were excluded as 236 and 1,720 patients did not have a record of their place of birth and age at

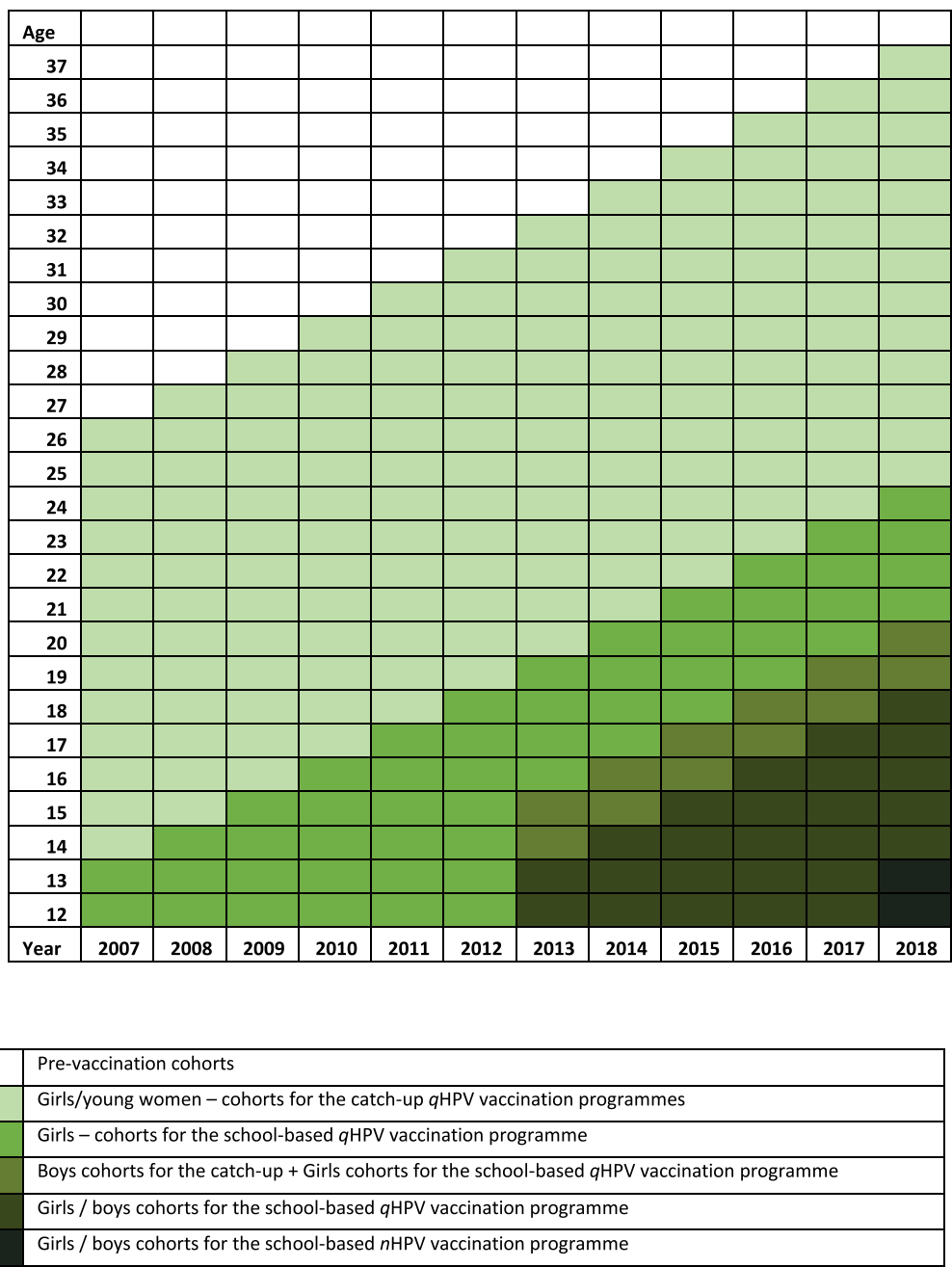


Figure 1. Age cohorts' eligibility for the National HPV Vaccination Programme in the permanent-resident / citizen population in Australia, by sex, 2007-2018

diagnosis, respectively. The remaining 439,957 patients were included in the analysis (Australian-born: 230,230; overseas-born: 209,727). Of these, 250,993 were men (Australian-born:138,604; overseas-born: 112,389), 188,094 were women (Australian-born: 91,292; overseas-born: 96,802), and 870 were transgender people (Australian-born: 334; overseas-born: 536) (Supplementary Table1a). The median age for all patients was 28 years (IQR: 23-36). The median age for patients with a diagnosis of genital warts was 28 years (IQR: 24-35). Of all men, 69,322 (27.6%) reported having sex with men (Australian-born: 37,934; overseas-born: 31,388), with a mean number of sexual partners of six in the previous 12 months. There were 25,403 (5.8%) patients who had ever worked as a sex worker (Australian-born: 9,184; overseas-born: 16,219) (Supplementary Table1b).

During 2004-2018, 28,079 (6.4%) new patients were diagnosed with genital warts (Australian-born: 16,334, 7.1%; overseas-born: 11,745, 5.6%). The proportion of men diagnosed with genital warts was significantly higher than women (men: 18,631, 7.4%; women: 9,431, 5.0%; $p < 0.01$) (Supplementary Table1a; Figure 2). Compared to overseas-born patients, Australian-born patients contributed 71% (7,534 / 10,611) of all new genital warts diagnoses in the pre-vaccination period ($p < 0.01$), and 50.4% in the vaccination period (8,800 / 17,468; $p < 0.01$).

The four large urban SHCs included in the sub-analysis represented 67% of all SHC consultations, and provided care to 168,372 / 209,727 (80.3%) of all overseas-born patients. See Supplementary Flowchart on the process of clinic selection. Patients from these four included clinics were comparable to patients from the 30 clin-

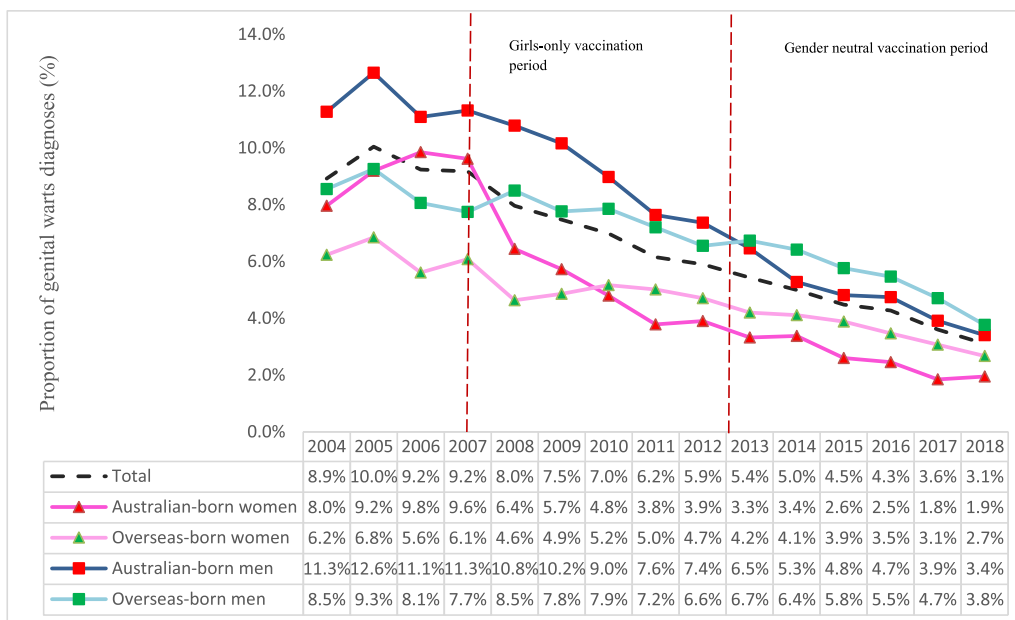


Figure 2. Proportions of genital warts diagnoses in all Australian- and overseas-born patients seen for the first time at sexual health clinics in Australia, by gender, between 2004-2018

ics that were excluded from the analysis in terms of gender, age and country of birth by type of HPV vaccination programme, including the proportion of migrants from the United Kingdom. The selected four clinics had a slightly higher proportion of MSM patients (Supplementary Table 2). Of the 168,372 patients from the selected clinics, 12,824 (7.6%) patients were excluded as 9,433 and 3,391 patients did not have a record on the name of country of birth and length of residence in Australia, respectively. The remaining 155,548 / 168,372 (92.4%) overseas-born patients were included in the sub-analysis (*q/nHPV* group: 105,465, 67.8%; *no/bHPV* group: 50,083, 32.2%). Of these, 87,520 / 155,548 (56.3%) were newly arrived patients, where the vast majority were from *q/nHPV* vaccine countries (*q/nHPV* group: 67,717, 77.4%; *no/bHPV* group: 19,803, 22.6%). In comparison, of the 68,028 / 155,548 (43.7%) that arrived >1 year from their first SHC visit, proportions of patients from the two group of countries were relatively similar (*q/nHPV* group: 37,748 (55.5%); *no/bHPV* group: 30,280 (44.5%)) (Supplementary Tables 3 and 4). The median age at arrival for newly arrived patients was 26 years (IQR:23-30), whereas for those who arrived >1 from their first SHC visit it was 23 years (IQR: 14-29 years). Of the total overseas-born patients included in the sub-analysis, 36,395 / 155,548 (23.4%) were aged <21 years at arrival in Australia (*q/nHPV* group: 22,021, 60.5%; *no/bHPV* group: 14,374, 39.5%), and 95,640 / 155,548 (61.5%) were aged 21-30 years (*q/nHPV* group: 70,221,73.4%; *no/bHPV* group: 25,419, 26.6%).

Overall trends, stratified by place of birth

In the pre-vaccination period, the proportion of genital warts diagnoses in Australian-born patients increased from 9.7% in 2004 to 10.6% in 2007, with a 2% average annual increase (RR: 1.02, 95% CI: 1.00-1.04) (Table 1; Supplementary Table 1a). During this period, no significant difference was observed in the proportion of patients diagnosed with genital warts for Australian- as compared to overseas-born patients (SRR: 1.05, 95% CI: 0.99-1.11). The different baseline levels at the start of the pre-vaccination and vaccination periods in Australian- versus overseas-born patients are presented in Supplementary Table 5.

In the vaccination period, an 11% (RR: 0.89, 95% CI: 0.89-0.90) and 7% (RR: 0.93, 95% CI: 0.93-0.94) average annual decrease was observed in the proportion of genital warts diagnoses in Australian- and overseas-born patients, respectively. During this period this decrease in the proportions of genital warts diagnoses was 5% per annum greater in Australian-born patients as compared to overseas-born patients (SRR: 0.95, 95% CI: 0.94-0.96) (Table 1).

By 2018, there had been a 64% (RR: 0.36, 95% CI: 0.35-0.38) relative reduction in genital warts diagnoses in all patients since the baseline of 2004-2007 (Figure 3). When stratified by place of birth, a 72% (RR:0.28, 95% CI: 0.27-0.30) and 49% (RR: 0.51, 95% CI: 0.48-0.54) relative reduction in genital warts diagnoses was observed in Australian-born and overseas-born patients, respectively (Figure 3).

Trends in women, stratified by place of birth and age

Of the 188,094 women, 9,431 (5.0%) were diagnosed with genital warts (Australian-born: 5,135, 5.6%; overseas-born: 4,296, 4.4%). Results presented for women focus on the vaccination-era declines, with the pre-vaccination declines explained in Supplementary Box 2.

In the vaccination period, a 12% (RR: 0.88, 95% CI: 0.87-0.90) and 6% (RR: 0.94, 95% CI: 0.93-0.95) average annual decrease was observed in the proportion of genital warts diagnoses in Australian- and overseas-born women, respectively (Table 1). This downward trend was seen for all age groups of Australian- and overseas-born women except >37 years old women (Table 1; Supplementary Figure 1). This decrease in the proportions of genital warts diagnoses was greater for all age groups of Australian-born women than the overseas-born women except for women aged 31-37 and >37 years where no difference was observed (SRR: 0.96, 95% CI: 0.92-1.00; SRR: 0.99, 95% CI: 0.95-1.04, respectively). In the vaccination period, a 14% (RR: 0.86, 95% CI: 0.78-0.96) average annual decrease was observed in the proportion of genital warts diagnoses in Australian-born female sex workers, while no trend was seen in overseas-born female sex workers (Supplementary Table 6).

By 2018, there had been an 82% (RR: 0.18, 95% CI: 0.17-0.20) and 51% (RR: 0.49, 95% CI: 0.46-0.54) relative reduction in geni-

Table 1

Average annual trends with rate ratios (RR) in diagnosis of genital warts in Australian- and overseas-born patients seen for the first time at sexual health clinics in Australia with ratio of change or summary rate ratios (SRR) in the pre-vaccination (2004–2007) and vaccination (2008–2018) periods, stratified by gender and age groups

Gender	Age (years)	Place of birth	Pre-vaccination period		Vaccination period		
			Average annual trend RR (95% CI), p value	Ratio of difference Australian vs overseas-born patients SRR (95% CI), p value	Average annual trend RR (95% CI), p value	Ratio of difference Australian vs overseas-born patients SRR (95% CI), p value	
All genders	Overall	Australia	1.02 (1.00–1.04), p=0.02	1.05 (0.99–1.11), p=0.06	0.89 (0.89–0.90), p<0.01	0.95 (0.94–0.96), p <0.01	
		Overseas	0.97 (0.93–1.01), p=0.13		0.93 (0.93–0.94), p<0.01		
Women	Overall	Australia	1.07 (1.03–1.10), p<0.01	1.09 (1.03–1.16), p <0.01	0.88 (0.87–0.90), p<0.01	0.93 (0.92–0.95), p <0.01	
		Overseas	0.97 (0.92–1.02), p=0.34		0.94 (0.93–0.95), p<0.01		
	< 21 years	Australia	1.05 (0.98–1.12), p=0.13	1.05 (0.90–1.22), p=0.48	0.81 (0.76–0.86), p<0.01	0.88 (0.81–0.96), p <0.01	
		Overseas	0.99 (0.86–1.14), p=0.93		0.91 (0.86–0.96), p<0.01		
	21–30 years	Australia	1.05 (1.00–1.10), p=0.03	1.11 (1.01–1.21), p <0.01	0.84 (0.82–0.86), p<0.01	0.89 (0.87–0.91), p <0.01	
		Overseas	0.94 (0.88–1.01), p=0.11		0.93 (0.92–0.94), p<0.01		
	31–37 years	Australia	1.11 (1.01–1.21), p=0.03	1.19 (1.01–1.41), p=0.03	0.92 (0.90–0.95), p<0.01	0.96 (0.92–1.00), p=0.08	
		Overseas	0.92 (0.80–1.06), p=0.26		0.96 (0.93–0.98), p<0.01		
	>37 years	Australia	1.04 (0.93–1.17), p=0.49	1.02 (0.83–1.24), p=0.83	0.99 (0.97–1.02), p=0.63	0.99 (0.95–1.04), p=0.87	
		Overseas	1.01 (0.86–1.19), p=0.81		0.99 (0.96–1.03), p=0.86		
	Men	Overall	Australia	0.99 (0.96–1.02), p=0.42	1.03 (0.96–1.10), p=0.35	0.89 (0.88–0.90), p<0.01	0.95 (0.94–0.96), p <0.01
			Overseas	0.95 (0.91–1.00), p=0.10		0.93 (0.92–0.94), p<0.01	
< 21 years		Australia	1.11 (1.00–1.24), p=0.04	1.19 (0.91–1.34), p=0.19	0.78 (0.75–0.81), p<0.01	0.87 (0.82–0.93), p <0.01	
		Overseas	0.93 (0.73–1.18), p=0.56		0.88 (0.84–0.93), p<0.01		
21–30 years		Australia	1.01 (0.97–1.05), p=0.56	1.05 (0.98–1.12), p=0.12	0.87 (0.86–0.88), p<0.01	0.94 (0.92–0.96), p <0.01	
		Overseas	0.96 (0.91–1.01), p=0.14		0.92 (0.91–0.93), p<0.01		
>37 years	Australia	0.96 (0.91–1.01), p=0.10	0.99 (0.89–1.10), p=0.86	0.91 (0.89–0.92), p<0.01	0.97 (0.94–0.99), p=0.03		
	Overseas	0.96 (0.88–1.05), p=0.43		0.93 (0.91–0.95), p<0.01			
Trans-gender	Overall	Australia	1.27 (0.41–3.93), p=0.68	0.34 (0.04–2.64), p=0.30	0.90 (0.72–1.13), p=0.35	1.08 (0.78–1.50), p=0.62	
		Overseas	3.72 (0.67–20.54), p=0.13		0.82 (0.65–1.04), p=0.11		

Note: Poisson regression models used except where overdispersion detected, in which case negative binomial models were used. Deviance test statistics of models included in S. Table 7.

tal warts diagnoses in Australian- and overseas-born women since the pre-vaccination period, respectively (Figure 3). The greatest decrease was in Australian-born women aged <21 years, where a 98% (RR: 0.02, 95% CI: 0.01–0.03) relative reduction in the proportion of genital warts diagnoses was observed.

Trends in men, stratified by place of birth and age

Of the 250,993 men, 18,631 (7.4%) were diagnosed with genital warts (Australian-born: 11,191, 8.1%; overseas-born: 7,440, 6.6%). Results presented for men focus on the vaccination-era declines, with the pre-vaccination declines explained in Supplementary Box 2.

In the vaccination period, an 11% (RR: 0.89, 95% CI: 0.88–0.90) and 7% (RR: 0.93, 95% CI: 0.92–0.94) average annual decrease was observed in the proportion of genital warts diagnoses in Australian- and overseas-born men, respectively (Table 1). This downward trend was seen for all age groups of Australian and overseas-born men, except >37 years old overseas-born men (Table 1; Supplementary Figure 2). This decrease in the proportions of genital warts diagnoses was greater for all age groups of Australian-born men as compared to the overseas-born men, except for men aged >37 years where no difference was observed (SRR: 0.97, 95% CI: 0.94–1.01). In the vaccination period, a 12% (RR: 0.88, 95% CI: 0.86–0.90) and 9% (RR: 0.91, 95% CI: 0.89–0.93) average annual decrease was observed in the proportion of genital warts diagnoses in Australian- and overseas-born MSM patients, respectively (Supplementary Table 6).

By 2018, there was a 69% (RR 0.31, 95% CI: 0.29–0.33) and 48% (RR: 0.52, 95% CI: 0.49–0.56) relative reduction in genital warts diagnoses in Australian-born and overseas-born men since the pre-vaccination period, respectively (Figure 3). The greatest decrease was in Australian-born men aged <21 years, where a 92% (RR:

0.08, 95% CI: 0.06–0.11) relative reduction in the proportion of genital warts diagnoses was observed.

Trends in transgender people, stratified by place of birth

Overall, of the 870 transgender people, 17 (2.0%) were diagnosed with genital warts (Australian-born: 8, 2.4%; overseas-born: 9, 1.7%). In the pre-vaccination and vaccination periods, no trends were seen for Australian- and overseas-born patients (Table 1). There was no difference between Australian- and overseas-born patients in pre-vaccination and vaccination periods (Table 1; Supplementary Figure 3).

Trends in overseas-born people, stratified by length of residence in Australia and type of HPV vaccination programme in birth countries

Of the 87,520 newly-arrived patients, 4,790 (5.4%) were diagnosed with genital warts (*q/n*HPV countries: 4,115, 6.1%; *no/b*HPV countries: 675, 3.4%) (Supplementary Tables 3 and 4). Of the 68,028 patients who arrived >1 year, 4,084 (6.0%) were diagnosed with genital warts (*q/n*HPV countries: 2,549, 6.8%; *no/b*HPV countries: 1,535, 5.1%). Results presented for overseas-born people focus on the vaccination-era declines, with the pre-vaccination declines explained in Supplementary Box 2.

In the vaccination period, an 8% (RR:0.92, 95% CI: 0.91–0.93) and 7% (RR: 0.93, 95% CI: 0.92–0.95) average annual decrease was seen in warts diagnoses in overseas-born patients from *q/n*HPV countries who had newly arrived in Australia and those who arrived >1 year, respectively. No trend was observed in people from *no/b*HPV countries irrespective of their length of residence (Table 2). The proportions of genital warts diagnoses in patients from *no/b*HPV countries were 7% (SRR: 1.07, 95% CI: 1.04–1.10) per annum greater in newly-arrived patients and 6% (SRR: 1.06, 95%

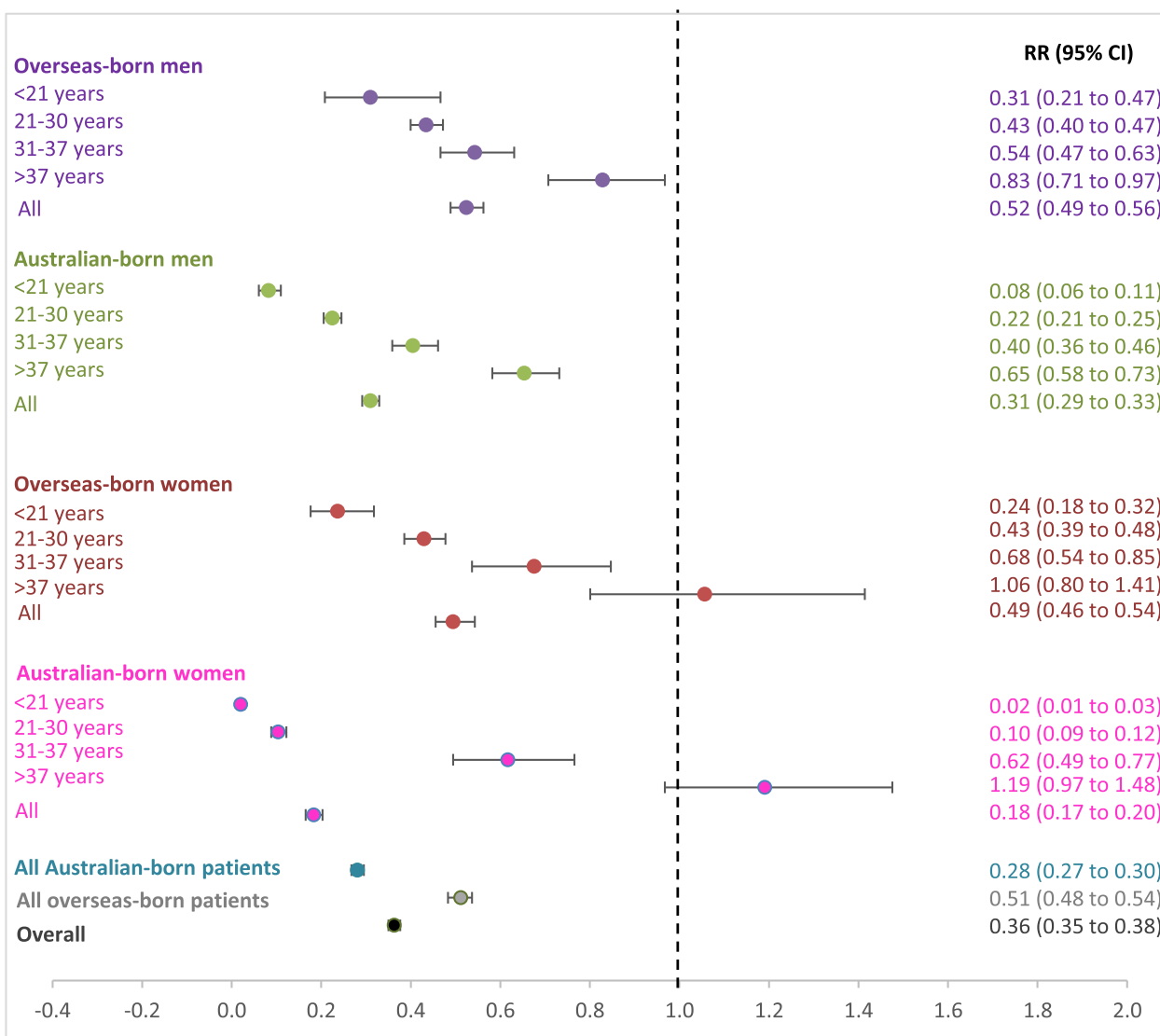


Figure 3. Rate ratios (RR & 95% CI) of genital warts diagnoses among Australian- and overseas-born patients seen for the first-time at sexual health clinics in Australia, by 2018 in comparison with a fitted average baseline (2004-2007), by gender and age groups

Table 2

Average annual trends with rate ratios (RR) in diagnosis of genital warts in overseas-born patients seen for the first time at sexual health clinics in Australia with ratio of change or summary rate ratios (SRR) in the pre-vaccination (2004-2007) and vaccination (2008-2018) periods, stratified by length of residence in Australia and country of birth according to the type of HPV vaccination programme

Length of residence relative to the first SHC visit	Country of birth by type of HPV programme	Pre-vaccination period		Vaccination period	
		Average annual trend RR (95% CI), p value	Ratio of difference No/bHPV vs q/nHPV countries SRR (95% CI), p value	Average annual trend RR (95% CI), p value	Ratio of difference No/bHPV vs q/nHPV countries SRR (95% CI), p value
≤1 year	q/nHPV	0.88 (0.84-0.94), p<0.01	1.07 (0.92-1.26), p=0.33	0.92 (0.91-0.93), p<0.01	1.07 (1.04-1.10), p <0.01
	No/bHPV	0.96 (0.83-1.10), p=0.56		0.98 (0.96-1.01), p=0.22	
>1 year	q/nHPV	0.99 (0.94-1.06), p=0.98	0.95 (0.85-1.06), p=0.39	0.93 (0.92-0.95), p<0.01	1.06 (1.03-1.08), p <0.01
	No/bHPV	0.95 (0.87-1.04), p=0.29		0.99 (0.97-1.01), p=0.35	

Note: Poisson regression models used except where overdispersion detected, in which case negative binomial models were used. Deviance test statistics of models included in S. Table 7.

CI: 1.03-1.08) per annum greater in those who arrived >1 year, as compared to patients from q/nHPV countries.

By 2018, the overseas-born patients from the q/nHPV and no/bHPV countries showed a 57% (RR:0.43, 95% CI: 0.41-0.47) and 21% (RR: 0.79, 95% CI: 0.71-0.90) reduction in the proportion of genital warts diagnoses since the pre-vaccination period, respectively (Figure 4). When stratified by length of residence, more pro-

nounced reductions relative to the baseline were observed in the newly-arrived patients than those who arrived had >1 year: patients from q/nHPV countries at a 61% (RR: 0.39, 95% CI: 0.36-0.43) vs a 48% reduction (RR: 0.52, 95% CI: 0.47-0.58); and patients from no/bHPV countries at a 27% (RR: 0.73, 95% CI: 0.59-0.91) vs no reduction (RR: 0.87, 95% CI: 0.75-1.00).

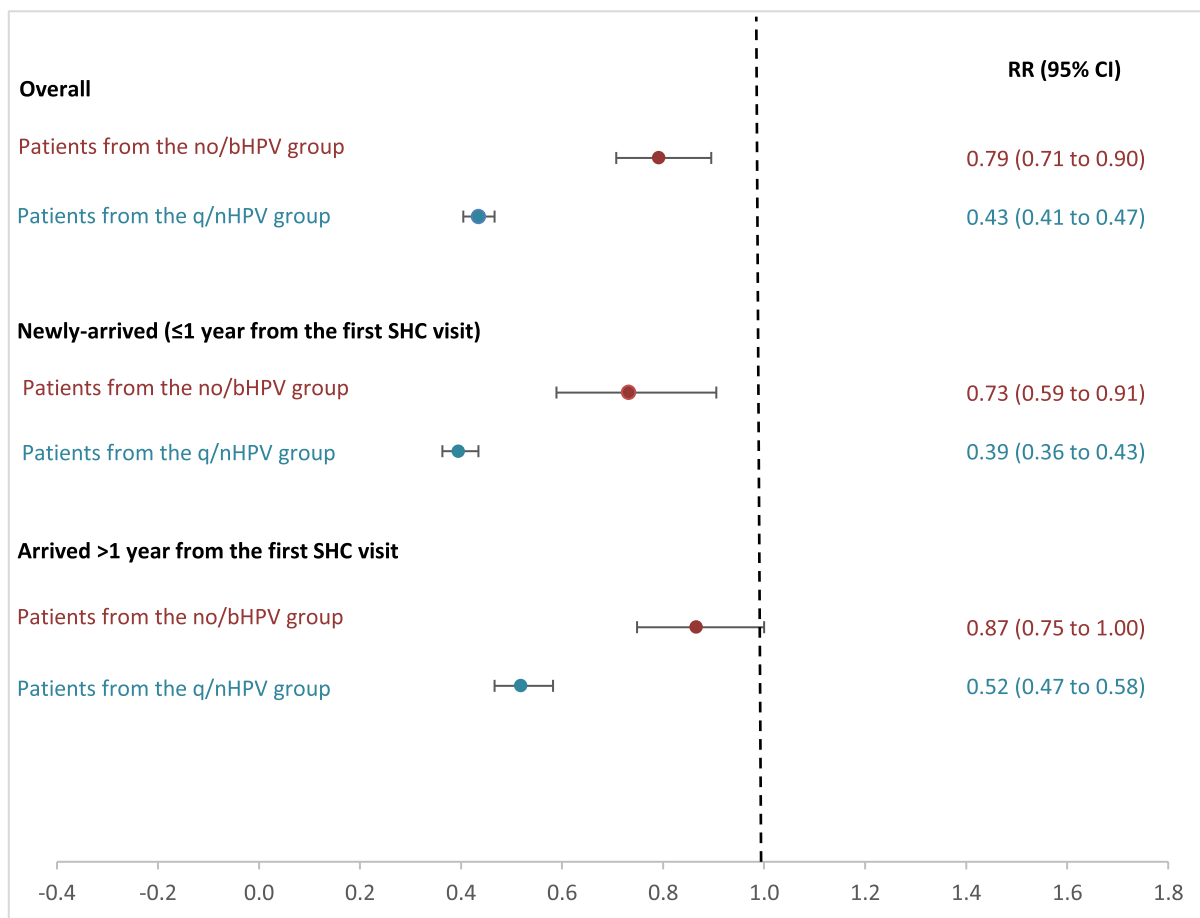


Figure 4. Rate ratios (RR & 95% CI) of genital warts diagnoses among overseas-born patients seen at a selected four sexual health clinics, by 2018 in comparison with a fitted average baseline (2004-2007), by grouping according to the type of HPV vaccination programme in birth country and length of residence in Australia.

Discussion

Our study examining genital warts diagnoses in attendees of Australian SHCs demonstrated marked declines in both Australian- and overseas-born patients, 11 years since the implementation of a national HPV vaccination programme. By 2018, a 64% reduction in genital warts diagnoses was observed in all SHC patients, relative to an average baseline of 2004-2007, surpassing the 2021 control milestone of a 60% reduction.¹⁸ This decline was more pronounced in Australian-born patients with a 72% reduction as compared to 49% in all overseas-born patients, 57% in overseas-born patients from countries with *q/nHPV* and just 21% in overseas-born patients from countries with *no/bHPV* vaccination programme. The elimination threshold of a 95% relative reduction in genital warts diagnoses since the baseline was exceeded by Australian-born women aged <21 years, at 98%. Our study provides important insights into the disparities in genital warts diagnoses between local and immigrant populations. Although large declines have been observed in young Australian-born people, population-wide elimination will require world-wide expansion of HPV vaccination programmes.

We observed that several Australian-born patients' groups exceeded the 2030 genital warts control threshold of an 80% relative reduction, including Australian-born women overall, Australian-born women aged 21-30 years, and Australian-born men aged <21 years. Importantly, Australian-born women <21 years of age did not achieve zero genital warts diagnoses. This observation is in line with the results of the Delphi study that defined elimination of genital warts as a public health problem and not as an absolute elimination of the disease,¹⁸ with the latter unlikely due to two

factors. First, a small proportion of genital warts are caused by non-vaccine HPV types.²³ Second, some degree of ongoing transmission of wart-causing HPV will continue in non-vaccinated individuals, mainly due to importation of genital warts via international travel to and travellers from high-prevalence countries.¹⁸ As highlighted in the Delphi study, elimination of genital warts will take a long time in Australia, mainly due to continued importation, which underscores the need to increase global HPV vaccination coverage.

Declines in Australian-born younger age groups reflect eligibility for the free HPV vaccine from the national HPV vaccination programme. In comparison, of the overseas-born patients aged <21 years at arrival in Australia, 39% were from *no/bHPV* group of countries and only a proportion of them are likely to have permanently migrated to Australia when they were children and thus would have been eligible for free vaccination. Nonetheless, most overseas-born patients aged <21 years (61%) and 21-30 years (73%) at arrival in Australia were from countries with *n/q* HPV vaccination programmes, making them likely eligible for vaccination in their home countries. Thus, the declines in genital warts diagnoses in overseas-born people aged <30 years are likely a mixed effect of vaccination and herd protection.

In older age groups of men, genital warts reductions likely reflect a greater benefit of herd protection in heterosexual men. Older heterosexual men are likely to experience herd protection as evidence suggests this group tend to have younger sexual partners,²⁴ who are more likely to be vaccinated. The larger reduction in Australian-born men aged 31-37 years may be due to their likelihood of forming sexual relationships with Australian-

born younger women as people tend to form assortative sexual relationships with those from their own countries and ethnic background.¹⁷ The lack of difference between Australian- and overseas-born women aged 31–37 and >37 years is not surprising as only a proportion (~37%) of Australian-born women were eligible for vaccination via the catch-up programmes for the former group, while neither of the latter groups were eligible for free HPV vaccine.

As expected, we did not observe any average change in the vaccination period for patients in the no/bHPV group of countries, irrespective of their length of residence. Nonetheless, a decrease by 2018 was observed relative to the baseline of 2004–2007 in those who had newly arrived in Australia. Backpackers and international students form a sizable proportion of overseas-born people aged <30 years in Australia,¹⁸ and while the majority (~78%) of backpackers are from q/nHPV countries, most (~72%) international students are from no/bHPV countries.¹⁸ In our study, most (62%) newly-arrived patients from no/bHPV countries were aged 21–30 years, and of them, a substantial proportion is likely to be international students. International students in Australia tend to form social networks that are not solely made up of fellow students from their home countries, rather a mix of other international and local students.²⁵ Therefore, the reduction in proportions of genital warts diagnoses observed in newly arrived patients from no/bHPV countries by 2018 is likely due to herd protection from sexual partnerships with local and international students from q/nHPV countries.

When interpreting these findings, there are some limitations to consider. Sexual health clinics in Australia cater to high-risk and priority populations, such as female sex workers and MSM,²⁶ as well as non-resident overseas-born patients who are not eligible for Medicare (Australia's universal health insurance scheme to provide health services at low/no cost to all Australians).²⁷ Most low-risk populations engage in care at general practice (GP) clinics.¹⁴ Nonetheless, as the SHCs service a large population and are geographically dispersed, the declines in genital warts presentation observed in our study likely reflect declines in genital warts diagnoses across Australia. This is further supported by a prior study that used nationally representative GP data and showed significant reductions in genital warts diagnoses in vaccine age-eligible women.²⁸ In addition, we may have underestimated the overall impact of vaccination in overseas-born patients from countries with q/nHPV vaccination programmes. We grouped the overseas-born patients by the type of vaccination programme in the home country based on the global estimates on the number of countries that have introduced HPV vaccination programmes as of 2018 and did not consider the different timelines at which countries introduced their programmes. In doing so, we grouped the countries that recently introduced their programme and therefore have not yet seen its impact together with those that introduced their programmes as early as 2007 and have recorded substantial genital warts declines.

Lastly, although the four large urban SHCs included in our sub-analysis provided care to over 80% of all overseas-born patients, we may have slightly overestimated the decreasing trend in genital warts diagnoses in these patients. These four clinics had a higher proportion (29.6% versus 21.4%) of MSM amongst men as compared to those from the 30 excluded clinics, as the majority of MSM people live in urban settings, and as shown in our results, there was a reduction in genital warts diagnoses in MSM in the vaccination period. MSM patients have different health-seeking behaviours in Australia as compared to the general population, as most MSM seek consultations for screening rather than symptomatic reasons.²⁹ Therefore, reductions in genital warts in MSM patients may have been an artefact of an increasing denominator. However, overall, as most (85%) migrants live in major cities in Australia,³⁰ we believe excluding overseas-born patients from SHCs

in the regional/rural settings would have had a minimal impact on our findings.

Our study has demonstrated a remarkable 64% overall reduction in genital warts diagnoses in patients attending SHCs in Australia by 2018, which is a testament to the efficacy of qHPV and nHPV vaccines and the high and wide-spread vaccination coverage in Australia. Nonetheless, a sizable proportion of the Australian population is comprised of migrants from countries with no/bHPV vaccination programme, and as evident from our study, this subgroup has much lower declines in genital warts. Therefore, until worldwide access to HPV vaccination is attained, a migrant country like Australia is unlikely to achieve population-wide elimination of genital warts. Future genital warts surveillance systems should consider including migrant patients in their analyses and continue to monitor progress towards elimination.

Contributors

LK, SM, BD and RJG conceived the idea for the study. All authors contributed in the design of methodology. TV contributed in data management and extraction. HM and LK performed data analyses. TV and LK verified the data. BD, SM and RJG advised on analysis and interpretation. LK wrote the first draft, prepared the figures and tables, and made the subsequent revisions based on co-authors' feedback. All authors contributed to subsequent drafts. All authors have read and agreed to the published version of the manuscript.

Declaration of competing interests

BD, RJG, DGR, CKF, AEG and LK report grants from Australian Government Department of Health and Seqirus Australia during the conduct of the study. BD, RJG, LK and SM have received funding during 36 months prior to the submitted work from Seqirus Australia to conduct the Delphi study on genital wart elimination. DGR reports research funding support and honoraria from CSL Ltd, outside the submitted work, and more than 36 months prior to the submitted work. CKF owns shares in CSL Ltd. TV reports personal fees from NSW Health, outside the submitted work. DM reports grants from Australian Government Department of Health, non-financial support from MSD and Roche Diagnostics, outside the submitted work. EPFC reports grants from Merck & Co, grants from National Health and Medical Research Council, grants from Seqirus Australia, personal fees from Merck & Co, outside the submitted work. HM has no conflict of interest to disclose.

Ethical Approval

Ethics approval for this study was obtained by the Human Research Ethics Committees at Alfred Hospital (218/17), Central Australia Human Research Ethics Committee at Flinders University (CA-19-3355), Northern Territory Department of Health and Menzies School of health (08/47), University of Tasmania (H0016971), Aboriginal Health and Medical Research Council (1099/15), ACON (2015/14), Victorian AIDS Council / Thorne Harbour Health (VAC REP 15/003), Western Australia Aboriginal Health Ethics Committee (885), and St. Vincent's Hospital (08/051). Individual consent from the patients was not obtained as we used non-identifiable aggregated data.

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Data sharing statement

Study data supporting the findings are available in the supplementary document.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.lanwpc.2021.100251](https://doi.org/10.1016/j.lanwpc.2021.100251).

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