Effect on genital warts in Australian female and heterosexual male individuals after introduction of the national human papillomavirus gender-neutral vaccination programme: an analysis of national sentinel surveillance data from 2004–18

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Summary

Background In Australia, the government-funded human papillomavirus (HPV) vaccination programme was introduced in April, 2007, for girls and young women, and in February, 2013, for boys. As of Dec 31, 2018, all Australian-born female individuals younger than 38 years and male individuals younger than 21 years have been eligible for the free quadrivalent or nonavalent HPV vaccine. We aimed to examine the trends in genital wart diagnoses among Australian-born female and heterosexual male individuals who attended sexual health clinics throughout Australia before and after the introduction of the gender-neutral HPV vaccination programme in February, 2013.

Methods We did a serial cross-sectional analysis of genital wart diagnoses among Australian-born female and heterosexual male individuals attending a national surveillance network of 35 clinics between Jan 1, 2004, and Dec 31, 2018. We calculated prevalence ratios of genital warts, using log-binomial regression models, for the female-only vaccination period (July 1, 2007, to Feb 28, 2013), gender-neutral vaccination period (March 1, 2013, to Dec 31, 2018), and the whole vaccination period (July 1, 2007, to Dec 31, 2018) compared with the pre-vaccination period (Jan 1, 2004, to June 30, 2007).

Findings We included 121 038 men and 116 341 women in the analysis. Overall, we observed a 58% reduction (prevalence ratio 0·42, 95% CI 0·40–0·44) in genital wart diagnoses in female individuals and a 45% reduction (0·55, 0·53–0·57) in genital wart diagnoses in heterosexual male individuals after the introduction of the vaccination programme in 2007. The largest reduction in genital warts was observed in younger individuals, and there was a decreasing magnitude of reduction with increasing age (80%, 72%, 61%, 41%, and 16% reductions in female individuals aged 15–20 years, 21–25 years, 26–30 years, 31–35 years, and ≥36 years, respectively; 70%, 61%, 49%, 37%, and 29% reductions in male individuals aged 15–20 years, 21–25 years, 26–30 years, 31–35 years, and ≥36 years, respectively). Significant reductions observed in female individuals (0·32, 0·28–0·36) and male individuals (0·51, 0·43–0·61) aged 15–20 years in the female-only vaccination period were followed by a more substantial reduction in female individuals (0·07, 0·06–0·09) and male individuals (0·11, 0·08–0·15) aged 15–20 years in the gender-neutral vaccination period.

Interpretation The national gender-neutral HPV vaccination programme has led to substantial and ongoing reduction in genital warts among Australian female and heterosexual male individuals, with a marked reduction in young individuals who received the vaccine at school.

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Introduction

Human papillomaviruses (HPVs) are common viruses causing genital warts and HPV-related cancers, including cervical, anal, and oropharyngeal cancer in men and women. More than 90% of genital warts are caused by HPV types 6 and 11.[1] Before the introduction of HPV vaccination, genital wart was a commonly encountered sexually transmitted infection (STI) at sexual health clinics in Australia, with major psychosocial impacts and costs.[2]

HPV vaccination programmes have been implemented in numerous countries since 2006. These programmes have led to marked reductions in genital warts and HPV infections in young women.[3–6] Studies have also shown more modest reductions in genital warts and vaccine-targeted HPV genotypes in unvaccinated heterosexual

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Research in context

Evidence before this study

We searched PubMed and Embase electronic databases for English-language articles published between Jan 1, 2007, and April 26, 2020, with the terms ("human papillomavirus" OR "HPV") AND ("genital wart" OR "wart") AND "surveillance" on April 26, 2020. We chose the year 2007 because that was when some countries began to implement their HPV vaccination programmes.

In 2019, an updated systematic review and meta-analysis was published, examining the population-level effect on human papillomavirus (HPV) disease after the implementation of HPV vaccination programmes. It included 64 articles from 14 high-income countries, with 29 assessing the effect on anogenital warts after the implementation of the HPV vaccination programme. The meta-analysis showed that there was a 67% reduction in anogenital warts among girls aged 15–19 years and a 48% reduction among boys aged 15–19 years after the introduction of the HPV vaccination programme.

Australia was one of the first countries to implement a national HPV vaccination programme for girls and women in 2007, and included boys in 2013. Seven national studies reported the trends in genital warts in Australia before and after the implementation of the HPV vaccination programme in different populations and settings. One study of young Indigenous Australians reported the prevalence of genital warts between 2004 and 2014. Another study reported data for young women who attended general practice between 2002 and 2012. Three studies of national hospital data included data up to 2011. Two national studies of Australian heterosexual individuals attending sexual health clinics included data up to 2009 and 2011 from eight sexual health clinics, respectively. All published Australian studies only included genital wart data before the introduction of the gender-neutral HPV vaccination programme in 2013. We did not identify any published studies that reported the prevalence of genital warts in heterosexual men after the implementation of the gender-neutral HPV vaccination programme and compared with the female-only HPV vaccination programme in Australia and worldwide.

Added value of this study

In this study, we included 237 379 female individuals and heterosexual male individuals from 35 sexual health clinics across Australia between 2004 and 2018 and reported the annual trends in genital wart diagnoses. We found that the prevalence of genital warts continued to decline in Australian women and heterosexual men, with an ongoing reduction among those aged 15–20 years (from 9% in 2006 to <1% between 2016 and 2018). Furthermore, we noted there was a 49% reduction in genital wart diagnoses in young unvaccinated heterosexual men in the female-only vaccination period (2007–12), presumably because of herd protection from their vaccinated female partners, and there was an 89% reduction in genital wart diagnosis in the gender-neutral vaccination period (2013–18) compared with the pre-vaccination period as these male individuals (≤20 years) became eligible for the school-based HPV vaccination programme.

Implications of all the available evidence

Using national sentinel surveillance data, we showed an ongoing reduction in genital warts among Australian heterosexual individuals, with the largest reduction among young individuals aged 15–20 years, suggesting a near elimination of genital warts in this population in Australia. To our knowledge, this is the first study to suggest a population-level reduction in genital warts after the implementation of the gender-neutral HPV vaccination programme. Our results reinforce the 2018 WHO Strategic Advisory Group of Experts on Immunization's recommendation that a gender-neutral vaccination programme could be considered when it is feasible, affordable, cost-effective, and does not divert resources or vaccines from the primary target population.

men, presumably because of herd protection.[4–9] Drolet and colleagues[6] published a systematic review and meta-analysis in 2019 that examined the population-level effect on HPV prevalence and anogenital warts after the introduction of HPV vaccination programmes in 14 high-income countries, and concluded that, since 2006, there has been a 67% reduction in anogenital warts in girls aged 15–19 years and a 48% reduction in boys aged 15–19 years. Of the 29 articles reporting outcomes for anogenital warts in Drolet and colleagues' meta-analysis,[6] four studies from the USA and Australia included a small proportion of young vaccinated male individuals (aged <18 years) 1–2 years after implementation of the gender-neutral vaccination programme. Very few empirical studies have examined the effect of vaccine-preventable HPV genotypes among young men from the gender-neutral vaccination programmes, but sample sizes in these studies were relatively small.[8,9] Several modelling studies have predicted that implementation of a gender-neutral vaccination programme could provide additional public health benefits and protection, not only for men but also for women, and that this is likely to be cost-effective.[10,11]

In mid-2007, a government-funded ongoing national HPV vaccination programme was introduced in Australia for schoolgirls aged 12–13 years, with a 3-year catch-up programme for girls and women through to age 26 years until the end of 2009. From 2013, the programme was expanded to include schoolboys aged 12–13 years, with a 2-year catch-up programme through to age 15 years until the end of 2014. Three doses of quadrivalent HPV vaccine were given in the national programme between 2007 and 2018, but this was replaced by two doses of nonavalent HPV vaccine in 2019. The HPV vaccination

programme in Australia was rapidly adopted and high coverage has been achieved (80% coverage for girls and 76% coverage for boys turning 15 years in 2017).[12,13]

The primary aim of this study was to examine the effect on the diagnosis of genital warts in women and heterosexual men after the introduction of the gender-neutral HPV vaccination programme in 2013. We examined the diagnoses of genital warts in the female-only vaccination period (July 1, 2007, to Feb 28, 2013) and the gender-neutral vaccination period (March 1, 2013, to Dec 31, 2018) compared with the pre-vaccination period (Jan 1, 2004, to June 30, 2007).

Methods

Data collection

We did a serial cross-sectional study. Australia established the Genital Warts Surveillance Network (GWSN) in 2008.[14] 35 publicly funded sexual health clinics across Australia participated in the GWSN and were able to provide retrospective data for the period 2004–18. All sexual health clinics within the GWSN provide free walk-in HIV and STI testing and treatment. Demographic characteristics (eg, age, sex, and country of birth), sexual practices (eg, sex of sexual partners in the previous 12 months, had ever worked as a sex worker), injecting drug use in their lifetime, and clinical diagnosis of genital warts for all new patients who attended the GWSN sexual health clinics for the first time between 2004 and 2018 were recorded. De-identified patient data from each clinic were provided to the GWSN via regular and automated extraction of these data using specialised software called GRHANITE. Data collection methods did not change over time and the GSWN did not alter the data collection for these clinics.

Study population

All women and heterosexual men who were born in Australia and attended one of the sexual health clinics in the GWSN for the first time during the study period were included in this analysis. We excluded individuals who were born outside Australia because data on residency status and the number of years in Australia were not collected in most of the clinics, therefore we were unable to identify who was eligible for the Australian national HPV vaccination programme. We defined heterosexual men as men who reported sexual contact with women only in the previous 12 months. We excluded men who reported sexual contact with another man in the previous 12 months because they could have been exposed to HPV through sexual contact with men and were unlikely to have benefited from herd protection from the female-only vaccination programme.[15] We also excluded individuals who were intersex, transgender, gender-diverse, or of unknown sex because the numbers were too small for meaningful analysis.

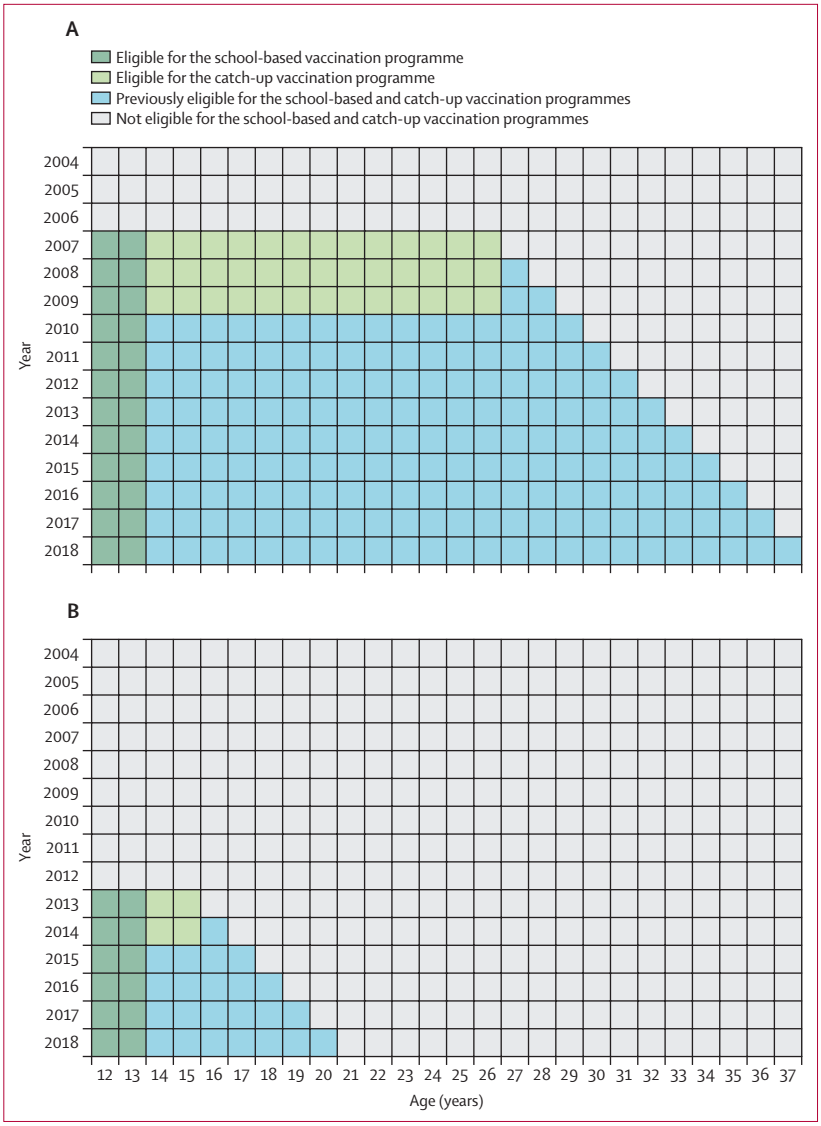

Figure 1: **Age cohort for the national quadrivalent human papillomavirus vaccination programme for female (A) and male (B) individuals**

Patients included in the analysis were categorised into five age groups, as follows: 15–20 years, 21–25 years, 26–30 years, 31–35 years, and 36 years or older. The eligibility for the HPV vaccination programme in each year by age is shown in figure 1. We used these age categorisations because all female individuals were eligible to receive the HPV vaccine at school and most male individuals aged 15–20 years were also eligible to receive the HPV vaccine. During the study period, all women aged 21–25 years would have been eligible for the HPV vaccine through the national vaccination programme. Most women aged 26–30 years and some women aged 31–35 years would also have been eligible for the HPV vaccine through the catch-up programme in the community. Most women aged 36 years or older were not eligible for the free HPV vaccine via the national

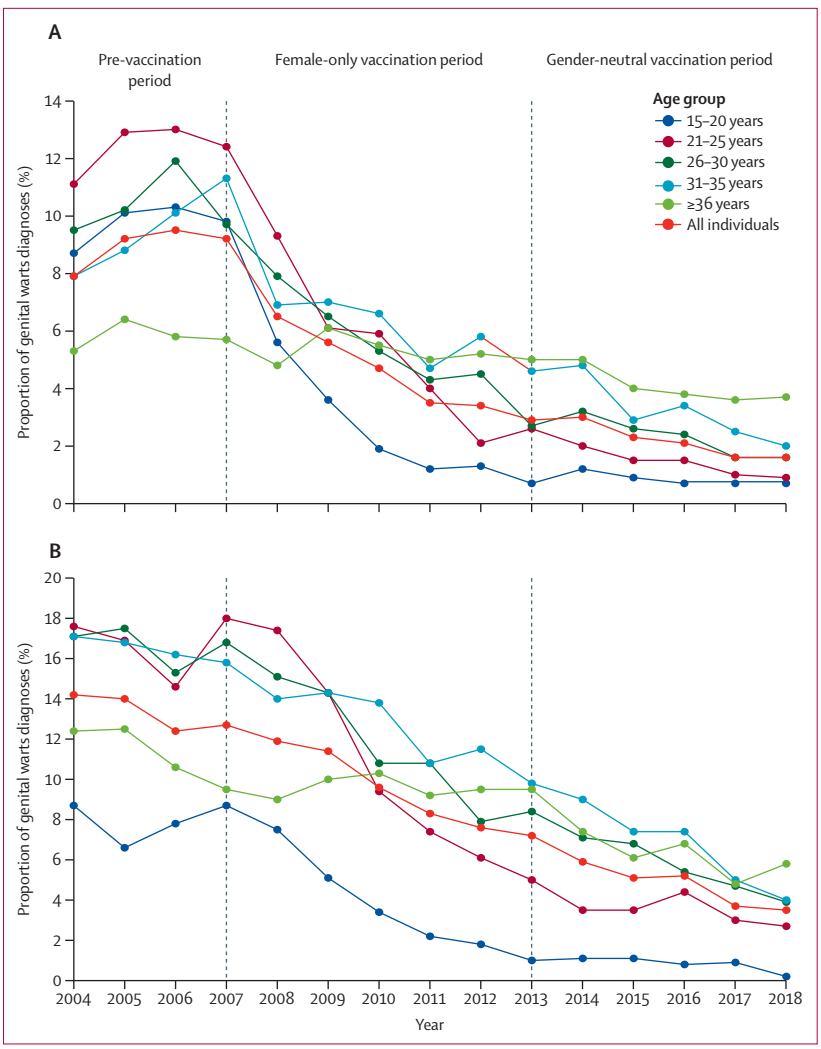

Figure 2: **Proportions of genital wart diagnoses in Australian-born female (A) and heterosexual male (B) individuals between 2004 and 2018**

vaccination programme. Furthermore, all heterosexual men aged 21 years or older were not eligible to receive the HPV vaccine from the national vaccination programme during the study period.

Ethical approval for the project was provided by the human research ethics committees at Alfred Hospital (248/17), 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 Australian Aboriginal Health Ethics Committee (885), and St Vincent's Hospital (08/051). As our study analyses de-identified data collected under the auspices of public health surveillance, individual patient consent was not required. Individuals could opt out of the surveillance network.

Statistical analysis

We stratified the study into three periods, as follows: pre-vaccination (Jan 1, 2004, to June 30, 2007), female-only vaccination (July 1, 2007, to Feb 28, 2013), and gender-neutral vaccination (March 1, 2013, to Dec 31, 2018). The numbers and proportion of patients diagnosed with genital warts were calculated for each time period and stratified by sex and age group. The 95% CIs for the proportions were calculated using the binomial exact method. We used a log-binomial regression model to estimate the average annual trend (ie, mean annual change in the percentage of genital warts) for each sex and age grouping in all three predefined time periods. We calculated the prevalence ratios of genital warts for the female-only vaccination, gender-neutral vaccination, and whole vaccination periods, using the pre-vaccination period (Jan 1, 2004, to June 30, 2007) as the reference group. The percentage of genital wart diagnoses in each calendar year was also calculated. We calculated the difference in the percentage of genital wart diagnoses between Jan 1, 2006 (ie, the last year in the pre-vaccination period), and Dec 31, 2018 (ie, the last year in the post-vaccination period), to indicate the changes in percentage of genital warts diagnoses 11 years after the implementation of the vaccination programme.

All statistical analyses were done using STATA (version 14.2).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Jan 1, 2004, and Dec 31, 2018, 576 578 new patients attended the participating sexual health clinics. 339 199 individuals were excluded: 286 746 (84·5%) were born outside Australia, 51 307 (15·1%) were men who have sex with men, 345 (0·1%) did not have a record of their country of birth, and 801 (0·2%) were intersex, transgender, gender-diverse, or had unknown sex.

The remaining 237 379 Australian-born patients (121 038 heterosexual men and 116 341 women) were included in the study. The median age was 29 years (IQR 22–39) and 12 863 (5·4%) patients were recorded as Indigenous. 8394 (3·5%) individuals had ever injected drugs and 9696 (4·1%) had ever worked as a sex worker. 16 920 (7·1%) individuals were diagnosed with genital warts and the proportion of heterosexual men diagnosed with genital warts (10 848 [9·0%] of 121 038 men) was significantly higher than for women (6072 [5·2%] of 116 341 women; p<0·0001).

6072 (5·2%, 95% CI 5·1–5·3) of 116 341 Australian-born women were diagnosed with genital warts. The overall proportion of Australian-born women with genital warts decreased by 84% 11 years after the vaccination programme. We found a 19% mean annual reduction in

	Pre-vaccination period (Jan 1, 2004, to June 30, 2007)			Female-only vaccination period (July 1, 2007, to Feb 28, 2013)			Gender-neutral vaccination period (March 1, 2013, to Dec 31, 2018)		
	n/N (%)	Mean annual trend (95% CI)	p value	n/N (%)	Mean annual trend (95% CI)	p value	n/N (%)	Mean annual trend (95% CI)	p value
Australian-born female individuals									
15–20 years	740/7581 (9·8%)	1·08 (1·00–1·16)	0·044	348/11 096 (3·1%)	0·64 (0·59–0·69)	<0·0001	74/10 363 (0·7%)	0·94 (0·82–1·07)	0·33
21–25 years	776/6422 (12·1%)	1·04 (0·97–1·12)	0·28	458/7622 (6·0%)	0·72 (0·68–0·76)	<0·0001	156/10 651 (1·5%)	0·82 (0·74–0·90)	<0·0001
26–30 years	450/4374 (10·3%)	1·05 (0·96–1·15)	0·29	380/6567 (5·8%)	0·83 (0·78–0·89)	<0·0001	161/6789 (2·4%)	0·87 (0·79–0·96)	0·0054
31–35 years	442/4893 (9·0%)	1·03 (1·03–1·23)	0·011	361/5325 (6·8%)	0·86 (0·81–0·92)	<0·0001	145/4161 (3·5%)	0·83 (0·75–0·93)	0·0005
≥36 years	681/11 867 (5·7%)	1·02 (0·94–1·10)	0·64	543/10 146 (5·4%)	0·98 (0·93–1·03)	0·38	357/8484 (4·2%)	0·92 (0·86–0·98)	0·0091
All individuals	3089/35 137 (8·8%)	1·07 (1·03–1·10)	0·0003	2155/43 137 (5·0%)	0·81 (0·79–0·83)	<0·0001	828/38 067 (2·2%)	0·86 (0·83–0·90)	<0·0001
Australian-born heterosexual male individuals									
15–20 years	230/2953 (7·8%)	1·00 (0·87–1·14)	0·96	240/6008 (4·0%)	0·69 (0·63–0·75)	<0·0001	58/6741 (0·9%)	0·84 (0·72–0·98)	0·024
21–25 years	837/5003 (16·7%)	0·97 (0·91–1·05)	0·48	850/7834 (10·9%)	0·76 (0·73–0·79)	<0·0001	391/10 955 (3·6%)	0·90 (0·85–0·96)	0·0008
26–30 years	721/4340 (16·6%)	0·95 (0·88–1·03)	0·23	806/6844 (11·8%)	0·85 (0·81–0·89)	<0·0001	510/8630 (5·9%)	0·86 (0·81–0·91)	<0·0001
31–35 years	757/4602 (16·4%)	0·95 (0·88–1·02)	0·18	810/6162 (13·1%)	0·91 (0·87–0·95)	<0·0001	391/5499 (7·1%)	0·83 (0·78–0·89)	<0·0001
≥36 years	1752/15 124 (11·6%)	0·90 (0·86–0·95)	<0·0001	1536/15 839 (9·7%)	1·00 (0·97–1·03)	0·95	959/14 504 (6·6%)	0·90 (0·86–0·93)	<0·0001
All individuals	4297/32 022 (13·4%)	0·93 (0·90–0·96)	<0·0001	4242/42 687 (9·9%)	0·88 (0·87–0·90)	<0·0001	2309/46 329 (5·0%)	0·87 (0·85–0·89)	<0·0001

Data are presented as n/N (%), unless otherwise indicated, where N represents the total number of patients attending the clinics for the first time, n represents the number of genital wart diagnoses, and % represents the proportion of genital warts diagnoses. July 1, 2007, was used as a cutoff for the start of the female-only vaccination period as the school-based vaccination for girls aged 12–13 years started rollout in April, 2007, and a catch-up vaccination programme for female individuals aged 18–26 years started in July, 2007. March 1, 2013, was used as a cutoff for the start of the gender-neutral vaccination period as the school-based vaccination period for boys started in February, 2013. The pattern of change in diagnoses was described using univariate log-binomial regression models, with the number of diagnoses as the outcome and the calendar year as the independent variable. Results are presented as average annual trends (mean annual proportional change in rate). Models were separately fitted for the three vaccination periods.

Table: **Mean annual trends in diagnosis of genital warts among Australian-born women and heterosexual men at sexual health clinics in Australia between 2004 and 2018**

the female-only vaccination period from 826 (9·5%) of 8659 individuals in 2006 (pre-vaccination period) to 242 (3·4%) of 7069 individuals in 2012, and a 14% mean annual reduction in the gender-neutral vaccination period, to 105 (1·6%) of 6703 individuals in 2018 (figure 2; table; appendix p 3).

Among female individuals aged 15–20 years, all of whom were eligible for vaccination, diagnosis of genital warts decreased by 93% 11 years after the vaccination programme. There was a 36% average annual reduction in the female-only vaccination period, from 209 (10·3%) of 2037 individuals in 2006 (pre-vaccination) to 25 (1·3%) of 1974 individuals in 2012 (female-only vaccination; (figure 2; table; appendix p 3). In the gender-neutral vaccination period, there was a 6% mean annual reduction, although this was not significant (p=0·33), dropping further to 13 (0·7%) of 1815 individuals in 2018, and remaining below 1% in the last 4 years between 2015 and 2018 (figure 2; table; appendix p 3). Among women aged 31–35 years who were eligible for the catch-up programme, diagnoses of genital warts decreased by 80% 11 years after the vaccination programme. We found a 14% mean annual reduction in the female-only vaccination period, from 126 (10·1%) of 1247 individuals in 2006 (pre-vaccination) to 50 (5·8%) of 859 individuals in 2012 (female-only vaccination), and a 17% mean annual reduction in the gender-neutral vaccination period to 11 (2·0%) of 548 individuals in 2018 (figure 2; table; appendix p 3). Among women aged 36 years and older who were not eligible for the vaccination programme, there was no significant change in the annual trends of genital wart diagnoses in the pre-vaccination period (p=0·64) and female-only vaccination period (p=0·38). However, we found an 8% mean annual reduction in the gender-neutral vaccination period (table).

When comparing the whole vaccination period with the pre-vaccination period, we observed a 58% reduction (prevalence ratio 0·42, 95% CI 0·40–0·44) in genital wart diagnoses among all Australian-born female individuals, and the reduction in the gender-neutral vaccination period (0·25, 0·23–0·27) was greater than in the female-only vaccination period (0·58, 0·55–0·62; figure 3). The magnitude of the reduction decreased with increasing age, and female individuals aged 15–20 years had the largest reduction in genital warts in the female-only vaccination (prevalence ratio 0·32, 95% CI 0·28–0·36), gender-neutral (0·07, 0·06–0·09), and whole vaccination (0·20, 0·18–0·23) periods. When comparing the pre-vaccination period with the female-only vaccination period, we found no significant reduction in genital warts among women aged 36 years and older in the female-only vaccination period (prevalence ratio 0·93, 95% CI 0·84–1·04). However, there was a significant reduction in genital wart diagnoses in this age group in the gender-neutral vaccination period (0·73, 0·65–0·83).

10 848 (9·0%, 95% CI 8·8–9·1) of 121 038 heterosexual men were diagnosed with genital warts. Overall, genital wart diagnoses among all heterosexual men decreased by 71% 11 years after the female-only vaccination programme. There was a 12% mean annual reduction in

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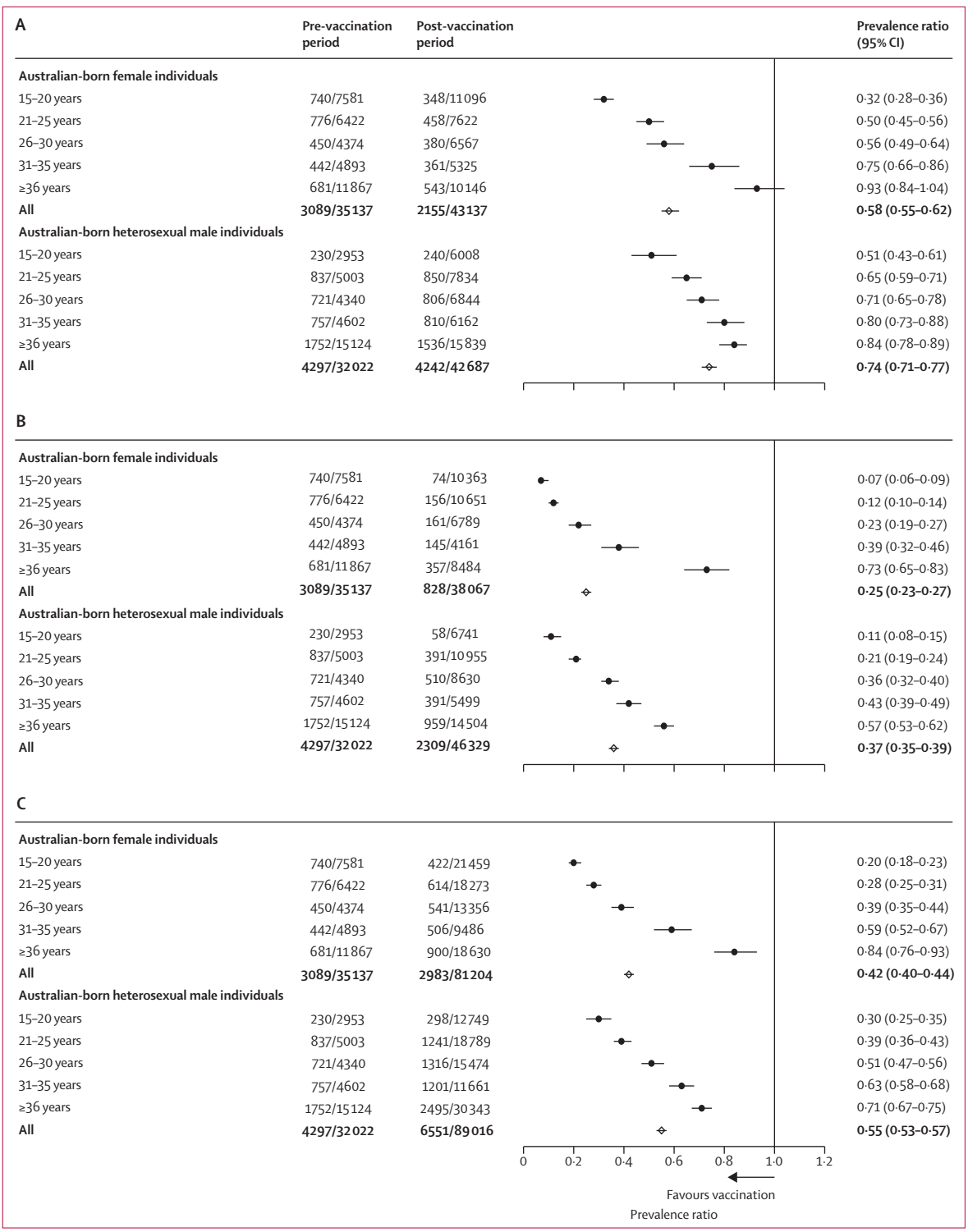

Figure 3: **Prevalence ratios of genital wart diagnoses in Australian-born female and heterosexual male individuals after the introduction of the female-only vaccination programme (A), gender-neutral vaccination programme (B), and whole vaccination programme (C) compared with the pre-vaccination period**

the female-only vaccination period from 1030 (12·4%) of 8317 individuals in 2006 (pre-vaccination period) to 594 (7·6%) of 7768 individuals in 2012, and a 13% mean annual reduction in the gender-neutral vaccination period to 285 (3·5%) of 8043 individuals in 2018 (figure 2; table; appendix p 4).

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Among male individuals aged 15–20 years who were eligible for the gender-neutral vaccination programme from 2013, the diagnosis of genital warts decreased by 97% 11 years after the introduction of the female-only vaccination programme. There was a 31% mean annual reduction in the female-only vaccination period, from 71 (7·8%) of 916 individuals in 2006 (pre-vaccination) to 21 (1·8%) of 1177 individuals in 2012 (female-only vaccination). In the gender-neutral vaccination period, there was a 16% mean annual reduction, dropping further to three (0·2%) of 1253 individuals in 2018 and remaining below 1% in the last 3 years of the study period (figure 2; table; appendix p 4). Among men aged 21 years and older who were not eligible for the vaccination programme throughout the study period, the diagnosis of genital warts was relatively high (ranging from 10–18%) in the pre-vaccination period. However, there was a 24% mean annual reduction among men aged 21–25 years, a 15% mean annual reduction among men aged 26–30 years, and a 9% mean annual reduction among men aged 31–35 years in the female-only vaccination period (table). There was a 10% mean annual reduction (from 5·0% to 2·7%; p=0·0008) in men aged 21–25 years, a 14% mean annual reduction (from 8·4% to 3·9%; p<0·0001) in men aged 26–30 years, and a 17% mean annual reduction (from 9·8% to 4·0%; p<0·0001) in men aged 31–35 years in the gender-neutral vaccination period (table). We found no change in the diagnosis of genital warts among men aged 36 years and older in the female-only vaccination period (324 [9·5%] of 3393 individuals in 2007 and 242 [9·5%] of 2549 individuals in 2012) but diagnoses dropped to 133 (5·8%) of 2287 individuals in 2018, with a 10% mean annual reduction in the gender-neutral vaccination period (table; appendix p 4).

When comparing the whole vaccination period (July 1, 2007, to Dec 31, 2018) with the pre-vaccination period (Jan 1, 2004, to June 30, 2007), we found a 45% reduction in genital wart diagnoses in all Australian-born men (prevalence ratio 0·55, 95% CI 0·53–0·57), and the reduction in the gender-neutral vaccination period (0·37, 0·35–0·39) was greater than in the female-only vaccination period (0·74, 0·71–0·77; figure 3). The magnitude of the reduction in men decreased with increasing age, and there was a significant reduction in genital wart diagnoses in all age groups in both the female-only and gender-neutral vaccination periods. Young male individuals aged 15–20 years had the largest reductions in genital warts in the female-only (prevalence ratio 0·51, 95% CI 0·43–0·61), gender-neutral (0·11, 0·08–0·15), and whole vaccination (0·30, 0·25–0·35) periods, compared with the pre-vaccination period.

Discussion

In this study, we observed a significant and ongoing reduction in genital warts in both Australian-born female individuals and heterosexual male individuals 11 years after introduction of the national HPV vaccination programme. Further to the female-only vaccination period, substantial reductions in genital warts were observed among heterosexual male individuals and female individuals aged 15–20 years during the gender-neutral HPV vaccination programme. Our data show that the percentage of genital wart diagnoses in this age group has remained at less than 1% in the last 3 years of the study period, suggesting near-elimination of genital warts in young Australian-born women and heterosexual men. The rapid and dramatic reductions in genital warts in both female individuals and heterosexual male individuals reflect the success of the national HPV vaccination programme, including the 3 years of catch-up programmes in female individuals.[16] The largest reduction in genital wart diagnoses was observed in young individuals aged 15–20 years, with a 68% reduction in female individuals and a 49% reduction in heterosexual male individuals after the female-only vaccination programme period (from July 1, 2007, to Feb 28, 2013). There was a 93% reduction in female individuals and an 89% reduction in heterosexual male individuals after the gender-neutral vaccination period (from March 1, 2013, to Dec 31, 2018).

Our findings are consistent with our previous report that examined trends in the proportion of genital wart diagnoses until 2011.[4] The present study provides an update of the annual trends in diagnosis of genital warts in Australian-born women and heterosexual men until 2018, which was more than 11 years after the introduction of the national HPV vaccination programme. More clinics in more diverse locations were also included in this analysis compared with the previous study (35 clinics *vs* eight clinics).[4] Both studies found a significant reduction in genital warts in both female individuals and heterosexual male individuals younger than 30 years.

The proportion of genital warts among young female and male individuals aged 15–20 years remained below 1% in the last 3 years of the study period, reaching 0·7% in female individuals and 0·2% in male individuals in 2018, equating to only 16 diagnoses in 2018. Although vaccination status data were unavailable, these 16 diagnoses are likely to have been in unvaccinated individuals, who might have acquired HPV from exposure in Australia or travel overseas. In Australia, HPV vaccine coverage is high at 80%, but still below the global target of 90%, and travel of young people to countries without HPV vaccination programmes is common. Additionally, previous studies have shown that a small proportion of genital warts is caused by HPV genotypes other than HPV6 or HPV11.[17,18] However, we only included clinically diagnosed genital warts in this study, and do not have genotyping data for genital warts diagnosed at these clinics, which makes it difficult to assess what proportion of the remaining warts was attributable to non-vaccine HPV genotypes.

The largest reduction in genital warts in the vaccination period was observed among male individuals aged 15–20 years, as most individuals in this age group were eligible for the school-based gender-neutral vaccination programme introduced in 2013, which is consistent with predictions using mathematical modelling.[19] Previous studies in Australia have shown that reductions in genital wart diagnoses and the prevalence of HPV vaccine-preventable types should be expected in unvaccinated heterosexual men because of herd protection in the female-only vaccination period.[4,5,7,8,20,21] However, herd protection cannot be proved in ecological studies, such as the present study, hence we can only presume that the reduction was due to herd protection, as suggested in previous studies. Our study provides novel data showing a further decline in genital warts in young heterosexual men at the population level after the introduction of the school-based gender-neutral vaccination programme.

By contrast with our previous study,[4] we observed an emerging trend of declining genital wart diagnoses in women and men older than 30 years in the female-only vaccination period and a further reduction during the gender-neutral vaccination period; however, this reduction was not observed in women older than 30 years between 2007 and 2011 in our previous study.[4] As of 2018, a substantial proportion of women aged 30–35 years would have been vaccinated against HPV via the catch-up programme and might create herd protection to protect unvaccinated heterosexual men in older age groups against genital warts and HPV. We found a significant reduction in the diagnosis of genital warts in women aged 36 years and older. Most women in the 36 years and older age group were not eligible for the vaccination programmes (ie, only women aged 36 years in 2017 or those aged 37 years in 2018 were eligible for the catch-up programme when they were aged ≤26 years in 2007–09), which suggests that unvaccinated older individuals also have benefited from the vaccination programme through herd protection due to high vaccination coverage in younger individuals.

It is important to note that this study aimed to examine the impact of the gender-neutral HPV vaccination programme on genital warts in heterosexual men. Previous studies have shown that young gay, bisexual, and other men who have sex with men have a high prevalence of HPV-related diseases.[22,23] Unlike heterosexual men, gay, bisexual, and other men who have sex with men are less likely to receive herd protection from vaccinated women because of their sexual practices. Empirical data and mathematical modelling have shown reductions in genital warts and vaccine-preventable HPV genotypes in young gay, bisexual, and other men who have sex with men after implementation of the gender-neutral vaccination programme.[11,24] Further studies are needed to assess the effect of the gender-neutral HPV vaccination programme and time-limited targeted catch-up programmes for gay, bisexual, and other men who have sex with men in Australia.[15]

This study has limitations. First, it was done on attendees at sexual health clinics, a population that might not be generalisable to the entire Australian heterosexual population. However, our conclusions are consistent with findings from previous studies in general practice and hospital settings.[25–27] There was a substantial drop in the number of women attending the clinics over time, which was because women at increased risk of contracting an STI or who presented with symptoms were being prioritised at the participating clinics. Thus, asymptomatic women were being triaged out to other health services (eg, general practices) because of heavy clinical load at the sexual health clinics. Therefore, our results might have underestimated the magnitude of the decrease in genital wart diagnoses in the general population.[28] HPV vaccination status data were not routinely collected in most clinics because recollection of a vaccine given at age 12–13 years might be unreliable; therefore, we were unable to do a sensitivity analysis to examine the differences in genital wart diagnoses between vaccinated and unvaccinated individuals. However, other studies have examined the effectiveness of HPV vaccination in women.[5,29] A previous study reported that 75% of Australian-born women self-reported receiving HPV vaccination in 2013–14 at a specific clinic within the GWSN, and this clinic contributed 23% of the data in the present study.[5] Finally, only Australian-born individuals were included in this analysis. Some individuals who were born overseas and migrated as children or young adults might have been eligible for the vaccination programme and been in Australia when the programme was implemented. Further studies will be required to investigate the trends in genital warts in migrant populations. The country of origin, year of arrival in Australia, and whether the country of origin has an HPV vaccination programme will need to be considered in the analysis.

In conclusion, our data showed a substantial and ongoing reduction in genital warts in Australian-born women and heterosexual men, supporting the success of the national HPV vaccination programme in Australia over the past decade. We observed a significant reduction in genital warts among heterosexual men after the addition of the male quadrivalent HPV vaccination programme. Future monitoring studies on vaccine-preventable genotypes and HPV-related cancers are required for evaluating the benefits of the gender-neutral vaccination programme.

Contributors

BD, CKF, RJG, DGR, and AEG designed and were principal investigators of the study. TV was involved in data management and extraction. EPFC did the preliminary data analysis, prepared the figures, and wrote the first draft of the manuscript, with edits from AC. AC did the data preparation and analysis. AC and TV have accessed and verified the data. All authors were involved in data interpretation and contributed to the final version of the manuscript. The corresponding author had full

access to all the data in the study and had final responsibility for the decision to submit for publication. Not all authors had access to all data, as only authorised research personnel with expertise in data analytical skills were granted access, in accordance with approvals from our institutional research ethics board.

Declaration of interests

EPFC has received educational grants from Seqirus Australia and bioCSL to assist with education, training, and academic purposes in human papillomavirus (HPV) research. EPFC has received speaker's honoraria from Merck and has been the principal investigator on Merck investigator-initiated studies and received funding for HPV studies. EPFC is supported by an Australian National Health and Medical Research Council Emerging Leadership Investigator Grant (GNT1172873). CKF has received research funding from CSL Biotherapies, owns shares in CSL Biotherapies, and is a co-investigator on Merck investigator-initiated studies. BD, DGR, and AEG have received occasional speaker's honoraria from Merck. BD, LK, DAM, and RJG have been investigators on the Extended Surveillance of Genital Warts Program funded by the Australian Government Department of Health, outside the submitted work. BD, AEG, and DGR have received funding from Seqirus Australia for genital wart surveillance. DGR has received occasional speaker's honoraria from CSL Biotherapies. LK, DAM, and RJG have received funding from Seqirus Australia for a Delphi study on genital wart elimination. DAM reports travel grants from Seqirus and travel funding and honoraria to her institution from Merck Sharp & Dohme, outside the submitted work. All other authors declare no competing interests.

Data sharing

The data supporting the findings of this study are available within the Article and its supplementary materials.

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