Quadrivalent human papillomavirus vaccination and trends in genital warts in Australia: analysis of national sentinel surveillance data

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Summary

Background **Quadrivalent human papillomavirus (HPV) vaccine has high efficacy in clinical trials but no reports describe its effects at a population level. From July, 2007, Australia was the first country to fund a vaccination programme for all women aged 12–26 years. We established a national surveillance network in Australia and aimed to identify trends in diagnoses of genital warts in 2004–09.**

Methods **We obtained standardised data for demographic factors, frequency of genital warts, HPV vaccination status, and sexual behaviour for new patients attending eight sexual health services in Australia between January, 2004, and December, 2009. We used χ^2 analysis to identify significant trends in proportions of patients diagnosed with warts in periods before and after vaccination began. Our primary group of interest was female Australian residents who were eligible for free vaccination, although data were assessed for patients ineligible for free vaccination, including women older than 26 years of age, non-resident women, and men.**

Findings **Among 112 083 new patients attending sexual health services, we identified 9867 (9%) cases of genital warts. Before the vaccine programme started, there was no change in proportion of women or heterosexual men diagnosed with genital warts. After vaccination began, a decline in number of diagnoses of genital warts was noted for young female residents (59%, $p_{trend}<0·0001$). No significant decline was noted in female non-residents, women older than 26 years in July, 2007, or in men who have sex with men. However, proportionally fewer heterosexual men were diagnosed with genital warts during the vaccine period (28%, $p_{trend}<0·0001$), and this effect was more pronounced in young men. By 2009, 65·1% of female Australian residents who were eligible for free vaccine reported receipt of quadrivalent or unknown HPV vaccine.**

Interpretation **The decrease in frequency of genital warts in young Australian women resulting from the high coverage of HPV vaccination might provide protective effects in heterosexual men through herd immunity.**

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Introduction

The clinical burden of genital warts has been increasing for decades;[1–4] the annual incidence is about 1% in young sexually active people.[3–5] Genital warts are notable for the emotional distress that they cause, particularly for young women,[6–8] and for their substantial cost to health systems.[5,9,10]

Human papillomavirus (HPV) types 6 and 11 cause up to 90% of cases of genital warts,[1,11] and are two of the four types targeted by the quadrivalent HPV vaccine (Gardasil, CSL Biotherapies, Melbourne, VIC, Australia). In clinical trials, this vaccine is safe and highly efficacious (90–100%) against persistent infection with HPV 6 and 11 and genital warts in women and men.[12–14]

In April, 2007, the Australian Government initiated a programme to vaccinate all girls from the age of 12 years with the quadrivalent HPV at no cost through existing school vaccination systems.[15] Additionally, in a catch-up programme, from July, 2007, free vaccine was made available to all female Australian residents in the community up to the age of 26 years through their family doctors and other primary health-care services.[16] The catch-up programme lasted until the end of 2009. The Australian Government and the vaccine manufacturer funded large advertising campaigns to promote the programme. Vaccine uptake in both the school-based and community-based programmes was rapid and a one-dose population coverage of around 80% and three-dose coverage of around 70% was achieved in the school-based programme.[17] The adult catch-up programme was implemented too quickly to establish adequate surveillance,[16] but population coverage was probably lower. In a study[18] done in a family-planning clinic 10 months into the catch-up programme, 58% of 15–26-year-old women had had at least one dose of HPV vaccine, mostly from their family doctor.

HPV vaccination was also approved in Australia for women aged 27–45 years and for boys and men aged 9–26 years, but these groups received no subsidy for the cost of the vaccine from either government or health-insurance companies, resulting in very low vaccination rates (<5%) in senior high school boys aged 15–17 years.[17]

HPV vaccination will probably result in declining rates of genital precancer and cancer attributable to HPV 16 or 18, disorders that typically have incubation periods lasting years or decades.[19,20] By contrast, the median incubation period for genital warts is around 3 months, although incubation can be 11 months or more,[21] so the time for an effect to be detectable on the incidence of genital warts is potentially much shorter than for cancer. A report[22] from one sexual health clinic in Melbourne showed a substantial local effect of the quadrivalent HPV vaccine against genital warts in young women, although because these data were from one service they might be biased and not generally applicable. Therefore, we established a sentinel surveillance system to monitor the effect of the quadrivalent HPV vaccine programme at a national scale.

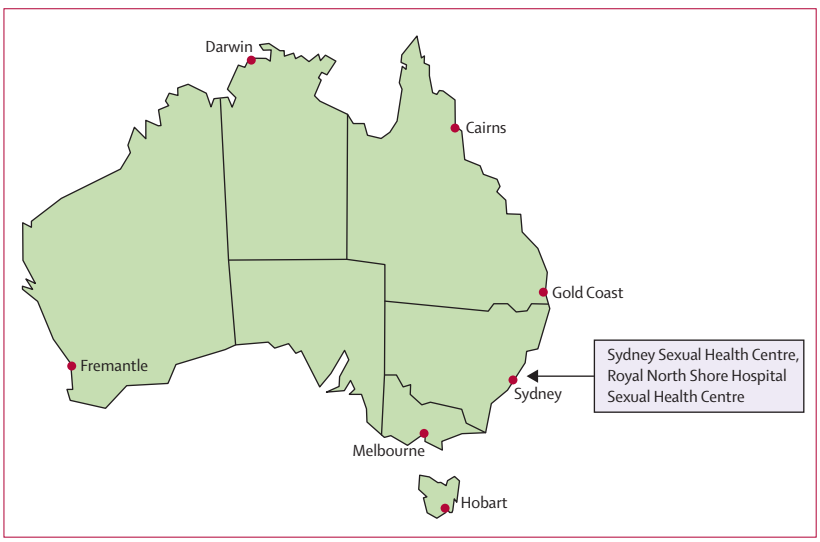

Figure 1: **Sexual health services recruited to the new sentinel surveillance system**

Methods

Data collection

We recruited eight clinical sites in dispersed locations around Australia (figure 1) to our sentinel surveillance system. All sites were free public urban specialist sexual health services, chosen because of their size and location and because their computerised patients' data systems obtained standardised demographic, clinical, and behavioural information that were available retrospectively to the beginning of 2004.

As an additional variable, we asked the two largest clinics, the Sydney Sexual Health Centre (Sydney, NSW, Australia), and the Melbourne Sexual Health Centre (Melbourne), to record the HPV vaccination status of consecutive new patients from 2009. If patients reported having been vaccinated they were asked to identify what type of vaccine (quadrivalent or bivalent) they had received.

Our primary group of interest was women aged 12–26 years who were permanently resident in Australia in July, 2007, when the community catch-up arm of the national free HPV vaccination programme began.

Because the clinics do not record residency status, non-residents were defined as people who arrived in Australia in the year they attended the clinic for the first time or the preceding calendar year. Even if they were born in another country, patients who reported arriving in Australia before this cutoff were assumed to be Australian residents and, if they were women who were young enough, to be eligible for free vaccination. Non-resident status is of interest because some countries have had a lower or slower HPV vaccine uptake than in Australia or have opted to provide the bivalent HPV vaccine, which provides no protection against HPV 6 or 11. The cutoff age for free or subsidised vaccination for adult women is also lower than 26 years in some other countries.

	January–June, 2004	July–December, 2004	January–June, 2005	July–December, 2005	January–June, 2006	July–December, 2006	January–June, 2007	July–December, 2007	January–June, 2008	July–December, 2008	January–June, 2009	July–December, 2009	Total
Women (overall)	317/3707 (8·6%)	293/3514 (8·3%)	317/3703 (8·6%)	330/3776 (8·7%)	318/3674 (8·7%)	324/4038 (8·0%)	376/4365 (8·6%)	324/4086 (7·9%)	272/4393 (6·2%)	206/4460 (4·6%)	258/4609 (5·6%)	205/4597 (4·5%)	3540/48 922 (7·2%)
Female Australian residents eligible for free HPV vaccination*	128/1178 (10·9%)	140/1171 (12·0%)	144/1199 (12·0%)	171/1543 (11·1%)	180/1554 (11·6%)	207/1849 (11·2%)	212/1810 (11·7%)	183/1743 (10·5%)	137/1644 (8·3%)	86 /1676 (5·1%)	109/1774 (6·1%)	78/1641 (4·8%)	1775/18 782 (9·5%)
Female non-residents†	40/427 (9·4%)	34/390 (8·7%)	38/439 (8·7%)	47/491 (9·6%)	41/553 (7·4%)	34/452 (7·5%)	65/717 (9·1%)	46/635 (7·2%)	59/878 (6·7%)	48/862 (5·6%)	60/1114 (5·4%)	57/1047 (5·4%)	569/8005 (7·1%)
Men (overall)	572/4672 (12·2%)	512/4465 (11·5%)	526/4802 (11·0%)	544/4909 (11·1%)	539/4974 (10·8%)	508/5189 (9·8%)	542/5334 (10·2%)	531/5409 (9·8%)	525/5528 (9·6%)	493/5643 (8·7%)	562/6043 (9·3%)	473/6193 (7·6%)	6327/63 161 (10·0%)
Heterosexual men	428/2986 (14·3%)	405/2925 (13·8%)	411/3043 (13·5%)	414/3143 (13·2%)	410/3077 (13·3%)	393/3123 (12·6%)	411/3275 (12·5%)	410/3325 (12·3%)	405/3573 (11·3%)	377/3678 (10·3%)	459/4076 (11·3%)	351/3932 (8·9%)	4874/40 156 (12·1%)
Men who have sex with men	118/1281 (9·2%)	77/1061 (7·3%)	96/1268 (7·6%)	104/1201 (8·7%)	90/1353 (6·7%)	80/1300 (6·2%)	99/1455 (6·8%)	87/1297 (6·7%)	96/1447 (6·6%)	77/1385 (5·6%)	79/1562 (5·1%)	104/1587 (6·6%)	1107/16 197 (6·8%)
Total	889/8379 (10·6%)	805/7979 (10·1%)	843/8505 (9·9%)	874/8685 (10·1%)	857/8648 (9·9%)	832/9227 (9·0%)	918/9699 (9·5%)	855/9495 (9·0%)	797/9921 (8·0%)	699/10 103 (6·9%)	820/10 652 (7·7%)	678/10 790 (6·3%)	9867/112 083 (8·8%)

Data are number of cases of genital warts/first-time users of sexual health services (%). HPV=human papillomavirus. *Aged 12–26 years in July 2007. †Arrived in Australia in the year listed or previous calendar year.

Table 1: **Cases of genital warts among first-time users of sexual health services, 2004–09**

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We analysed data for genital warts in men by the sex of their sexual partners in the previous 12 months. Men who have sex with men (MSM) reported sex with at least one man, but might have also had female partners. Heterosexual men reported sex with women only.

Data were forwarded electronically from the eight surveillance sites to the National Centre in HIV Epidemiology and Clinical Research (Sydney) for analysis. We only analysed patients attending any of the services for the first time between January, 2004, and December, 2009, who had not previously been diagnosed with genital warts. Diagnosis was based on clinical appearance. We obtained data for demographic and behavioural variables consisting of age, sex, sex of their sexual partners, country of birth, and, if born in another country, year of arrival in Australia.

Statistical analysis

We divided the study period into blocks of 6 months and calculated the proportion of patients diagnosed with genital warts in every block by dividing the total number of new diagnoses by the total number of new patients. The prevaccination period was from January, 2004, to June, 2007, and the vaccination period was from July, 2007, to December, 2009. We used χ^2 tests to identify significant trends in proportions of patients diagnosed with warts in the prevaccination and postvaccination periods. Statistical analyses were done with Stata version 10.0, and $p<0{\cdot}05$ was regarded as significant. Ethical approval was obtained from all local research ethics committees and from the University of New South Wales (Sydney).

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. Only the National Centre in HIV Epidemiology and Clinical Research (Sydney) had access to all the data in the study and the corresponding author had final responsibility for the decision to submit for publication.

Results

From January, 2004, to December, 2009, 112 083 new patients (48 922 women and 63 161 men) attended one of the sexual health services in the surveillance network, and 9867 (9%) had a first diagnosis of genital warts (table 1). The mean age of women, overall, was 28 years (SD 9·34) and of men, overall, was 32 years (11·12). The mean age of women diagnosed with warts in the pre-vaccine period was 25 years (SD 6·59), while the modal age was 19 years.

Until the HPV vaccination programme began in July, 2007, the proportion of women and heterosexual men diagnosed with genital warts was stable ($p_{trend}=0{\cdot}96$). Thereafter, female Australian residents who were eligible for free vaccination were progressively less likely to be diagnosed with genital warts, with the proportion

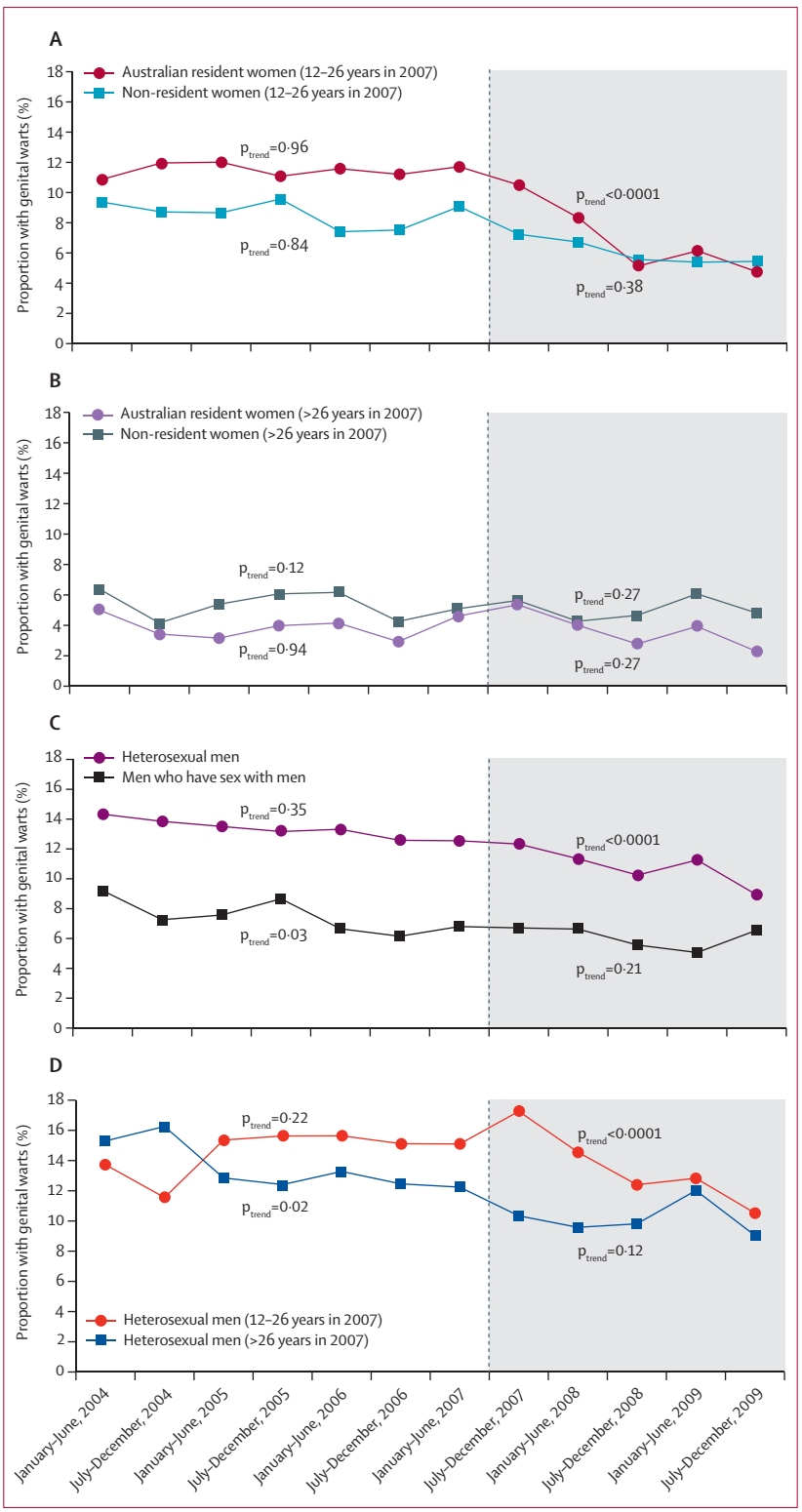

Figure 2: **Proportion of people presenting to sexual health services with genital warts, 2004–09**
p values for trend are for the prevaccine period or within vaccine period (grey region). (A) Women eligible (aged 12–26 years in July, 2007) for free quadrivalent HPV vaccine in Australia, by residency status. (B) Women not eligible (aged older than 26 years in July, 2007) for free quadrivalent HPV vaccine in Australia, by residency status. (C) Men with genital warts, by sex of sexual partners. (D) Heterosexual Australian men with genital warts, by age group.

	HPV vaccine			No HPV vaccine
	Quadrivalent	Bivalent	Unknown	
Eligible female Australian residents (n=1203)	308 (25·6%)	23 (1·9%)	475 (39·5%)	397 (33·0%)
Eligible female non-residents (n=1327)	147 (11·1%)	8 (<1%)	60 (4·5%)	1112 (83·8%)
Eligible age women with unknown residency status (n=113)	25 (22·1%)	4 (3·5%)	21 (18·6%)	63 (55·8%)
Older women not eligible for free vaccine (n=1361)	99 (7·3%)	7 (<1%)	47 (3·4%)	1208 (88·8%)
Overall	579	42	603	2780

Data are number (%). Women aged 12–26 years in mid-2007 were eligible age for free quadrivalent HPV vaccine in Australia; women older than 26 years in mid-2007 were not eligible for vaccine. HPV=human papillomavirus.

Table 2: **Self-reported HPV vaccination status of 4004 consecutive new female patients, 2009**

declining from 11·7% in July–December, 2007, to 4·8% in July–December, 2009 (59%, 95% CI 54–61; $p_{trend}<0·0001$; figure 2). A decline in the proportion of women with genital warts was noted in all clinics (data not shown).

The proportion of new cases of genital warts in non-resident women of eligible age declined from 7·2% to 5·4%, during the vaccination period, although this decline was not significant (25%, 95% CI 13–19; $p_{trend}=0·38$; figure 2). By contrast, the proportion of women older than 26 years old (residents and non-residents) diagnosed with genital warts did not differ before or during the vaccination period (figure 2). The proportion of MSM newly diagnosed with genital warts declined from 9·2% to 6·6% before the HPV vaccine programme (28%, 20–37; $p_{trend}=0·03$), but the trend did not continue through the vaccination period ($p_{trend}=0·21$; figure 2).

The proportion of heterosexual men diagnosed with genital warts declined in the vaccine period from 12·3% to 8·9% (28%, 95% CI 24–33; $p_{trend}<0·0001$; figure 2). For heterosexual Australian resident men aged 12–26 years in July, 2007, this decline (from 17·3% to 10·5%) was significant (39%, 33–46; $p_{trend}<0·0001$), but frequency of genital warts did not fall significantly for men older than 26 years (from 10·3% to 9·0%; 13%, 95% CI 11–18; $p_{trend}=0·12$; figure 2).

During 2009, HPV vaccination status was routinely reported in two clinics in Sydney and Melbourne, and 4004 (79%) of 5044 consecutive new female patients reported their HPV vaccination status (table 2). Of 1203 female Australian residents aged 12–26 years in July, 2007, 806 (67%) reported previous HPV vaccination; 783 (65·1%) received quadrivalent or unknown HPV vaccine. By contrast, only 153 (11%) of 1361 resident women who were older than 26 years at start of vaccination and 215 (16%) of 1327 non-resident women of eligible age reported previous HPV vaccination. Vaccination statuses were too infrequently reported for men for the data to be meaningful.

Discussion

We show that there was a substantial decline in diagnosed cases of genital warts in young Australian women with a high coverage of free quadrivalent HPV vaccination. No significant decrease was noted in female non-residents or in women older than 26 years at commencement of vaccination in July, 2007. The strong correlation between reported vaccine coverage and apparent population effect shows the efficacy of quadrivalent vaccine against HPV 6 and 11 infections and consequent disease.[12,14] Although such an effect has been predicted on the basis of modelling the effect of vaccination against HPV type 16,[19,20] this study is the first to show that the vaccine is efficacious in practice at a national scale (panel).

The proportion of younger eligible women diagnosed with genital warts might have been approaching a low plateau by 2009 after a more pronounced decline early in the vaccination programme. Our data seem to show that rate of decline is slowing, which is consistent with the models[19,20] of HPV 16 transmission that suggest a much more gradual decline might be expected in the next few decades, and that some genital warts will occur unless vaccination is universal.

Because the median age of the women attending the Australian sexual health services for the first time was 26 years, our findings are more likely to be effects of the community-based catch-up arm of the HPV vaccination programme than the effects of the school-based arm. Nevertheless, because the modal age of women with genital warts in attending these clinics was 19 years before school vaccination programmes began, by 2009 the school-based HPV-vaccination programme should have been having an increasing effect. The decline in proportion of people with genital warts contrasted with increased rates of chlamydia[23] and no reported change in frequency of genital herpes.[22]

Our data for vaccination rates complement the few published studies[15,17,18] about population coverage for the catch-up programme in Australia. However, caution is needed when interpreting these coverage data. Recollection of vaccines by patients can be unreliable; however, women in this study were adults and the vaccination event was recent so recall was expected to be good. Nevertheless, the Australian HPV vaccination programme only provided free quadrivalent vaccine, so we cannot explain why 1·5% of eligible women reported receiving the bivalent vaccine, other than as a result of imperfect recall. Because the HPV vaccine was marketed as a cancer vaccine, the finding that many people could

not recall whether they had a quadrivalent or bivalent vaccine is not surprising.

Our study did not yield true population-based data on genital warts. Nevertheless, as the clinics were large and geographically dispersed, we believe that the decline in presentations with genital warts shows a profound decline in incidence of genital warts in young women across Australia. In a representative sample of Australian adults, 17% reported that the diagnosis and treatment of their warts occurred in public sexual health services.[24]

Our clinic-based sample might be biased against detection of a decline in incidence of genital warts. In recent years, and in the context of re-emerging epidemics of curable sexually transmissible infections, Australian sexual health clinics have been required to target priority populations such as MSM.[25] Low-risk, asymptomatic heterosexuals seeking screening for sexually transmitted infection are increasingly triaged to family doctors, whereas heterosexuals with symptoms (eg, warts) are not. Additionally, recipients of HPV vaccine would have less need for a sexual health service (diminishing the clinic denominator) and not all genital warts are caused by HPV 6 and 11. The active encouragement of asymptomatic MSM to attend for sexual health screening[25] might also explain the gradual decline in genital warts in the prevaccination period.

Some women were misclassified as eligible or ineligible for free vaccination. Some resident (as defined in this study) women who had been in Australia for more than 2 years would have been long-term international students or women with working visas who would not have been eligible for free vaccine. We did not obtain data on patients' residency statuses. However, such misclassification would have tended to weaken our finding of a decline in genital warts in resident Australian women in the eligible age-range.

Very few Australian men (<5%) have received HPV vaccine.[17] However, a declining proportion of young (aged ≤26 years in 2007) heterosexual men—but not MSM or older heterosexual men–were diagnosed with genital warts during the vaccine period. From this finding we postulate that young heterosexual men had reduced incidence of HPV type 6 and 11 infections (and consequently genital warts) largely because of reduced exposure to these infections in young women (ie, through herd immunity). However, these men would remain susceptible to HPV types 6 and 11 and at risk of infection from women who have not had the quadrivalent vaccine. The 500 000 young heterosexuals (often called backpackers) who visit Australia every year, many of whom are not vaccinated or who have had the bivalent vaccine, might have a proportionally larger role than they do at present in the epidemiology of genital warts in Australia.[26]

MSM are not benefiting from the HPV vaccine programme because they do not have access to subsidised vaccine and they are exposed to other unvaccinated men.[27]

Panel: Research in context

Systematic review

We systematically searched Medline and Embase with the search terms "HPV vaccination" AND ("genital warts" OR "condylomata acuminata"), and identified only one population-based report[22] that was based on data from one of our sentinel sites.

Interpretation

Our study is the first to document the national population effect of the quadrivalent human papillomavirus (HPV) vaccine. By use of data from a national sentinel surveillance system, we show that the national HPV vaccination programme in Australia had a substantial effect on the clinical burden of genital warts.

The high morbidity in MSM attributable to HPV-related disease, including anal cancer,[28] and the possible role of anal warts in facilitation of transmission of HIV,[29] means that this group should be considered in future HPV-vaccination programmes.

We hope that our findings of national population benefit from the quadrivalent HPV vaccine, showing much the same efficacy as in clinical trials, will be followed by widespread reductions in infection and disease from oncogenic HPV 16 and 18. This reduction might already be underway, but will take longer to document than did decreased incidence of genital warts.[14]

Contributors

BD, CKF, and AEG designed and were principal investigators of the study, with assistance from RG and DGR. NF, HW, HA, and RG collated and analysed data. BD wrote the first draft and all authors contributed to the final report.

Conflicts of interest

CKF owns shares in CSL Biotherapies. CKF, AEG, DGR, RG, and BD have received honoraria from CSL Biotherapies. BD and RG have received honoraria from Sanofi Pasteur MSD. BD is a member of an advisory board for GlaxoSmithKline and CSL Biotherapies. DGR receives funding from an Australian Research Council Linkage Grant for which CSL Biotherapies is a partner organisation. AEG has been on the speakers' bureau and has received honoraria from Merck.

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