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REVIEW

Early Direct and Indirect Impact of Quadrivalent HPV (4HPV) Vaccine on Genital Warts: a Systematic Review

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ABSTRACT

Introduction: Since 2007, many countries have implemented national human papillomavirus (HPV) vaccination programs with the quadrivalent HPV (4HPV) vaccine that has been shown to be efficacious in clinical trials involving 25,000 subjects. Two vaccine serotypes, HPV16 and 18, are responsible for cervical cancer and other HPV-related cancers, but the impact of the 4HPV vaccine on these cancers cannot be seen immediately as there is a considerable lag between infection with HPV and cancer development. The other two serotypes, HPV6 and 11, are responsible for genital warts (GWs), which develop within a few months after infection, making GWs an early clinical endpoint for the assessment of the impact of 4HPV vaccination.

Methods: We performed a systematic literature search in PubMed to identify all published studies on 4HPV vaccination, including those that assessed the impact of 4HPV vaccination programs on the incidence of GWs at a population level around the world.

Results: A total of 354 records were identified in the PubMed search. After screening and obtaining full papers for 56 publications, 16 publications presenting data on the impact or effectiveness of 4HPV vaccination on GWs were identified. These reported data on the impact or effectiveness of 4HPV in six countries [Australia ($n = 6$), New Zealand ($n = 2$), United States ($n = 3$), Denmark ($n = 2$), Germany ($n = 1$), and Sweden ($n = 2$)]. In Australia, no GWs

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were diagnosed in women aged <21 years who reported being vaccinated. A 92.6% reduction in GWs incidence was reported for all women in this age group, where the vaccine uptake rate (VUR) was 70% for 3 doses. The highest reductions were reported in countries with high VURs, mostly through school-based vaccination programs, although high VURs were obtained with some non-school-based programs.

Conclusion: The results are coherent with the GWs incidence reduction reported in clinical trials and are an early indicator of what can be expected for the long-term clinical impact on vaccine-type HPV-related cancers.

Keywords: 4HPV vaccine; Gardasil; Genital warts; Human papillomavirus; Quadrivalent human papillomavirus vaccine; Vaccine effectiveness; Vaccine impact

INTRODUCTION

Genital warts (GWs) are a sexually transmitted disease caused by human papillomavirus (HPV) and are the most common sexually transmitted disease in some countries [1, 2]. HPV6 and HPV11 are responsible for about 90% of the cases of GWs [3]. Worldwide, several million cases of GWs occur each year in both sexes, with a peak incidence between 20 and 24 years of age for females and between 25 and 29 years among males [4].

Genital warts usually occur about 6–12 months after the first infection with HPV [5]. However, in the placebo arms of two large randomized clinical trials assessing the quadrivalent HPV (4HPV) vaccine, the delay between PCR detection of HPV DNA and the occurrence of GWs was variable and could be as long as 2 years [3]. Data from the placebo group of these clinical trials show that GWs can spontaneously regress in up to 40% of cases [3]. Although GWs are not life-threatening, they are often associated with considerable psycho-sexual distress and represent an important financial and resource burden for the health system [6]. The estimates for the unit cost for a single GWs event are highly variable, depending on the type of episode (first occurrence, recurrent or persistent GWs), the management setting and type of consultation [general practice, genitourinary medicine (GUM), hospital, etc.], as well as the therapy used (medical treatment vs. surgery or other modalities) [7, 8]. A recent study in Italy reported that the most frequent cause for HPV-related hospitalization was GWs [9]. An economic analysis showed that the costs associated with GWs in men and females represented 24.3% (€70.9 million) of the total costs associated with HPV6/11/16/18 diseases in Italy. Most of the costs for 4HPV vaccination would have been covered by the prevention of GWs and the associated costs alone [10].

Two recombinant, virus-like particle (VLP)-based prophylactic HPV vaccines are currently available. One is a bivalent (2HPV) vaccine licensed for the prevention of premalignant cervical, vulvar and vaginal lesions and cervical cancer causally related to HPV16 or HPV18 in females. The other is a quadrivalent (4HPV) vaccine also licensed for the prevention of premalignant cervical, anal, vulvar and vaginal lesions and cervical and anal cancer related to HPV16 or HPV18. In addition, 4HPV is licensed for the prevention of GWs caused by HPV6 or HPV11 in both men and females [11].

Since 2006–2007, HPV vaccines have been licensed in over 133 countries and introduced into national immunization programs in at least 40 countries [12]. Over 169 million doses

of 4HPV have been distributed worldwide since its launch.

In the FUTURE I and II randomized clinical trials, 4HPV vaccine was shown to reduce the incidence of HPV6- and HPV11-related GWs in females aged between 15 and 26 years by 99% in a per-protocol susceptible population (females who were seronegative on day 1 and DNA negative on day 1 through month 7 to the respective HPV type, who received three doses of vaccine) [13]. A reduction of 62% was reported in an intent-to-treat population (females with past or current HPV exposure and those naïve to HPV who received >1 dose of vaccine) [13].

In countries that have implemented national vaccination programs against HPV, health economics models have estimated that the impact of these programs will only be seen for cervical cancer and other HPV-related cancers, at the population level, 30–50 years after the initiation of the vaccination program, due to the generally long time lag between infection and cancer [14, 15]. However, since HPV-related GWs develop rapidly after HPV infection, with a peak incidence between 20 and 35 years of age, the vaccine impact on their incidence should be visible earlier.

It is important to survey the impact of any new vaccine. Although some registries and surveillance systems have been set up to monitor the impact of 4HPV vaccination on cervical cancer and other HPV-related diseases, they are heterogeneous and not implemented everywhere. In addition, these diseases, which take a certain time to develop, will only occur a long time after vaccine programs have been implemented. Since the impact of HPV vaccination on GWs will be seen earlier, the surveillance of their incidence and prevalence is a good indicator of the impact of vaccination on other vaccine-related HPV diseases and cancers. Data on the incidence and prevalence of GWs will not be available for all countries, as GWs are not a notifiable disease everywhere. However, some data can be obtained through sentinel surveillance systems for sexually transmitted infections or through the implementation of national networks using a sample of first-level 'sentinel' general practitioners or gynecologists, as has been done in Italy [16, 17]. Nevertheless, assessing the impact of HPV vaccination in a reliable and robust manner is easier in countries that have good surveillance systems for GW, e.g. United Kingdom (UK), Australia, and the Nordic countries.

The aim of the present review article is to summarize the published data reporting the early impact of HPV vaccination on GWs in countries that have introduced 4HPV into their national immunization programs. We specifically looked at countries where the 4HPV vaccine is recommended, either exclusively or not, since this is the only available vaccine licensed for the prevention of GWs via HPV6 and HPV11 included in the vaccine [11].

METHODS

As part of ongoing literature surveillance for publications on 4HPV, we had identified a number of studies assessing the impact of 4HPV vaccination programs on GWs. To verify that all the relevant studies had been identified, we performed a systematic literature search in PubMed from January 1, 2009 to August 21, 2014, using a combination of the following terms: papillomavirus; condylomata acuminata anogenital warts; genital warts; incidence; mass vaccination; vaccination methods; immunization/immunisation; real life; papillomavirus vaccines; HPV vaccine effectiveness; HPV vaccine impact; HPV

vaccination; ecological study HPV; reduction; impact; insurance claim review; military personnel, as free-text or MeSH terms.

Studies were eligible for inclusion in this review if they reported population-based data of vaccine impact. In addition, the 4HPV vaccine had to be included in the national immunization program; the publication had to report results from ecological studies of vaccine impact on GWs for defined pre- and post-vaccination periods; and the post-vaccination period had to start at least 1 year after the HPV vaccination program started. Publications reporting results for the same cohort at different post-vaccination periods were kept to assess the trends over time.

The analysis in this article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

RESULTS

A total of 354 records (after removal of duplicates) were identified in the PubMed search. After a first screen on titles and abstracts, full papers for 56 publications were analyzed and 16 publications presenting data on the impact or effectiveness of 4HPV vaccination on GWs were identified (Fig. 1). These reported data on the impact or effectiveness of 4HPV in 6 countries [Australia ($n = 6$) [18–23], New Zealand ($n = 2$) [24, 25], US ($n = 3$) [26–28], Denmark ($n = 2$) [29, 30], Germany ($n = 1$) [31] and Sweden ($n = 2$) [32, 33]] (Table 1). Since both impact and effectiveness publications assess the effect of vaccination programs on the incidence of the disease, both types of studies have been included. Fourteen of the studies used a before/after design or evolution over time to assess the change in GWs episodes after 4HPV vaccine introduction; two studies compared GWs in vaccinated and unvaccinated cohorts (Table 1).

The studies included in this review were performed in settings where the 4HPV vaccine was either the only vaccine available or it was used in >90% of the vaccinated population. The estimated vaccine uptake rates for ≥1 dose varied between the studies, from 25% in Sweden to 90% in Denmark (Table 1).

Some of the studies also reported that the incidence of GWs in men who have sex with men (MSM) was stable during the studied period [18, 20, 21]. Two studies reported that the incidence of other sexually transmitted diseases, chlamydia and genital herpes, increased or remained stable over studied period [18, 27].

In this review, we present data for the direct impact/effectiveness in vaccinated cohorts. We also present data for the indirect impact, or herd protection, in the unvaccinated population, since this contributes to the overall impact of the vaccine. The unvaccinated population has been divided further:

- Heterosexual men of a similar age who could have sex with vaccinated females and therefore could be expected to benefit from herd protection;
- Older females who are less likely to be vaccinated and older heterosexual men who are less likely to benefit from herd protection;
- MSM who are unlikely to have sex with vaccinated females, and at the time of the studies, male vaccination had not been recommended.

Due to the diversity of the study designs, the HPV vaccination programs and vaccine uptake rates, the results are presented country by country.

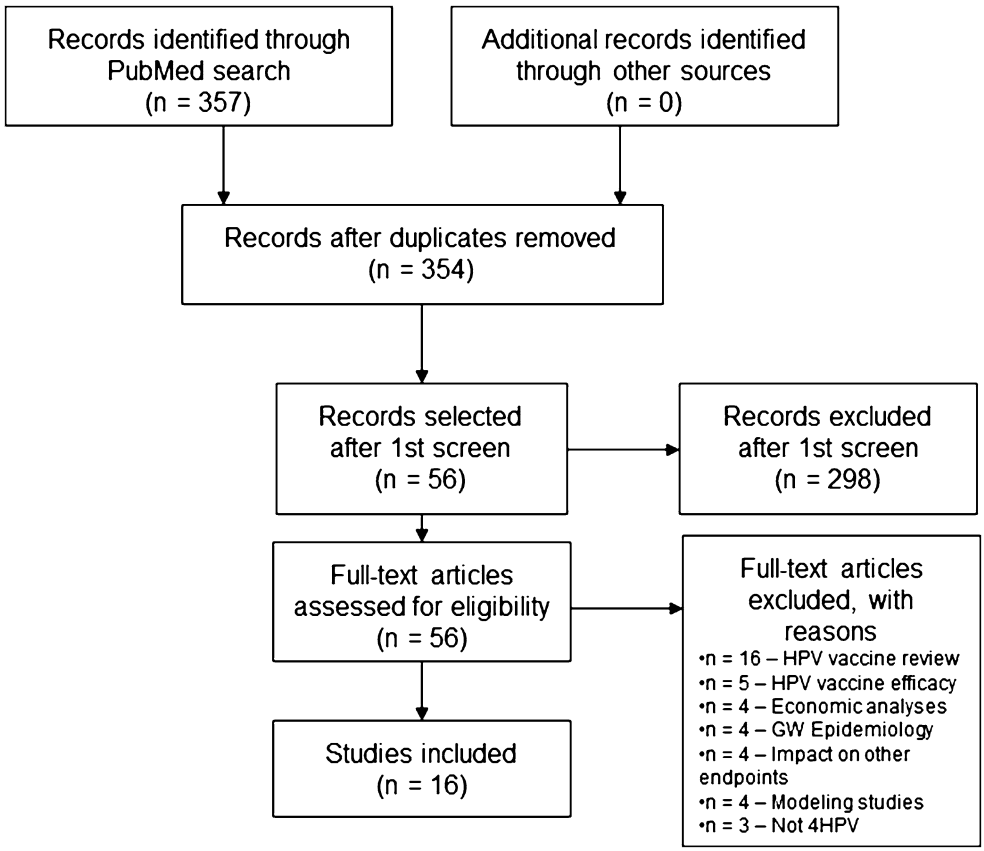

Fig. 1 PRISMA flowchart summarizing the results from the PubMed search. *4HPV* Quadrivalent HPV, *GW* Genital warts, *HPV* Human papillomavirus

Australia

Australia was one of the first countries to implement a fully funded national population-based 4HPV vaccination program in April 2007. The program provided free vaccination for females aged 12–13 years in schools. In addition, from July 2007 to December 2009 there was a catch-up program for females aged 13–18 years and another for females aged 18–26 years in the community. Since 2013, the vaccine program has been extended to males aged between 12 and 13 years. In 2007, it was estimated that vaccine uptake in eligible school-aged females was 70%; by 2011, approximately 80% had received one dose of vaccine and 70% had received three doses [34]. We identified two publications that reported data from the Melbourne Sexual Health Centre 1 year (2008) and 4 years (2011) after 4HPV introduction [20, 21] and two that reported data from eight Sexual Health Centers throughout Australia 2 years (2009) and 4 years (2011) after 4HPV introduction [18, 19] (Table 1). In addition, we identified one study comparing national population surveys on GWs in 2001 and 2011 and another that analyzed national hospital data for GWs [22, 23].

In the first report from Melbourne, the years analyzed were from January 2004 to December 2008 whereas in the later report they were from July 2004 to June 2011 [20, 21]. In addition, the subgroups analyzed were different. Despite these differences, rapid and significant declines

Table 1 Summary of published data (peer-reviewed) of genital warts reduction in countries with HPV vaccination programs including quadrivalent HPV vaccine

Country (region)/ References	Study design and setting	Vaccination program during the study/estimated vaccine uptake rate	Pre-/post-vaccine introduction periods [time since vaccine introduction (years)]	GW reduction in vaccine-targeted population (as defined in the study)	GW reduction in non-vaccine-targeted populations (as defined in the study)
Australia (Melbourne)					
Fairley [20]	Before/after study in one center (Melbourne Sexual Health Centre): all new female and male patients of any age in database	4HPV vaccine national program: From April 2007 school-based (12–13 years), community catch-up from Jul 2007 to Dec 2009 (females aged ≤26 years)/ 73% with 3 doses for females 12–13 years, 70% general coverage of target population	2004–2007/ 2008 (1)	Females <28 years: −25.1% (95% CI −30.5 to −19.3%) per quarter	Females ≥28 years: −4.7% (95% CI −13.9 to +5.4%) per quarter; MSW: −5.0% (95% CI −9.4 to −0.5%) per quarter
Read [21]	As above	As above	2004–2007/ 2007–2011 (4)	Females <21 years: OR (2004–2007): 1.11 (0.90–1.38); OR (2007–2011): 0.44 (0.32–0.58); OR for vaccinated females 2010–2011 vs. 2009–2010: 0.29 (0.13–0.65)	Females 22–29 years: OR (2004–2007): 1.12 (0.98–1.29); OR (2007–2011): 0.70 (0.62–0.80); MSW <21 years: OR (2004–07): 1.32 (0.92–1.90);OR (2007–11): 0.42 (0.31–0.60)

Table 1 continued

Country (region)/ References	Study design and setting	Vaccination program during the study/estimated vaccine uptake rate	Pre-/post-vaccine introduction periods [time since vaccine introduction (years)]	GW reduction in vaccine-targeted population (as defined in the study)	GW reduction in non-vaccine-targeted populations (as defined in the study)
Australia (National)					
Donovan [19]	Before/after study in national surveillance network of eight sexual health centers: all new female and male patients of any age in database	As above	2004–2007/ 2007–2009 (2)	Eligible residents: 59% (95% CI 54–61%) reduction from 11.7% (2007) to 4.8% (2009)	MSW aged 12–26 years: 39.3% (95% CI 33–46%) reduction from 17.3% (2007) to 10.5% (2009); no change: non-resident eligible females, older resident females, and men, and MSMs
Ali [18]	As above	As above	Jan 2004–Jun 2007/Jul 2007–Dec 2011 (4)	Females <21 years: 92.6% reduction from 8.8% and 11.5% (2004 and 2007) to 0.85% (2011); summary rate ratio: 0.64 (0.59–0.69)	MSW <21 years: 81.8% reduction from 7.2% and 12.1% (2004 and 2007) to 2.2% (2011); summary rate ratio: 0.72 (0.65–0.81) No significant decline in females >21 years and MSW >21 years
Liu [23]	Before/after, country-wide telephone survey of females aged 18–39 years	As above	2001/2011 (4)	Females 18–30 years: 41% decrease, aOR = 0.59 (95% CI 0.39–0.89)	Females 31–39 years: 64% increase, aOR = 1.64 (1.05–2.54)

Table 1 continued

Country (region)/ References	Study design and setting	Vaccination program during the study/estimated vaccine uptake rate	Pre-/post-vaccine introduction periods [time since vaccine introduction (years)]	GW reduction in vaccine-targeted population (as defined in the study)	GW reduction in non-vaccine-targeted populations (as defined in the study)
Smith [22]	Before/after analysis of national hospital database (NHMD: ICD-10 code for GW as primary or contributing diagnosis) in men and females aged 12–69 years	As above	2006–2007/ 2010–2011 (4)	Females 12–17 years: 89.9% (95% CI 84.6293.4); females 18–26 years: 72.7% (95% CI 67.0–77.5); females 27–30 years: 42.1% (95% CI 26.1–54.6)	Females 31–69 years: no significant change; men 18–26 years: 38.3% reduction (95% CI 27.8–47.2); men 27–30 years: 21.2% reduction (95% CI 0.8–37.4%); men (other age groups): no significant change
New Zealand (Auckland)					
Oliphant [24]	Before/after study at one regional sexual health service (4 centers): All new female and male patients of any age in database	4HPV vaccine from Sep 2008 (school program: Feb 2009) for females aged 12–13 years, with initial catch-up until 2010 for those ≤20 years/ School program: 51.7%; overall 38% (1990–1991 cohort); 25% (1992–1996 cohort); 20% (1997 cohort)	Jan 2007–Dec 2008/Jan 2009–Jun 2010 (1.5)	Females <20 years: 62.8% reduction from 13.7% in 2007 to 5.1% in 2010	Men <20 years: 40.0% reduction (from 11.5 to 6.9%); male >20 years: 18.9% reduction (from 9.5 to 7.7%); females >20 years: 21.3% reduction (from 7.5 to 5.9%); (all changes from 2007 to 2010)

Table 1 continued

Country (region)/ References	Study design and setting	Vaccination program during the study/estimated vaccine uptake rate	Pre-/post-vaccine introduction periods [time since vaccine introduction (years)]	GW reduction in vaccine-targeted population (as defined in the study)	GW reduction in non-vaccine-targeted populations (as defined in the study)
Wilson [25]	National prescription database (PHARMAC) analysis for podophyllum resin-based products and imiquimod cream	As above	2002–2007/ 2011–2012 (3)	Largest reduction in females <20 years: 24.5% reduction (from 15.1% of prescription in 2007/2008 to 11.4% of prescriptions in 2011/2012)	Overall population: 18% reduction in podophyllum prescriptions/year (from 2007/2008 to 2011/2012) and 22% reduction in imiquimod prescriptions/ year (from 2009/2010 to 2011/2012)
US (National)					
Flagg [27]	Before/after study using a health insurance data (ICD-9: 078.11; 078.1; 078.10; 078.19; codes for benign anogenital neoplasms, codes for GW treatment): Females and males aged 10–39 years	HPV vaccination (4HPV; 2006 and 2HPV; 2009) recommended for females aged 11–12 years with catch-up to 26 years; late 2011 boys aged 11–12 years with catch-up to 21 years/In 2011 53% of females aged 13–17 years with ≤1 dose; 35% with 3 doses; low uptake for boys	2003–2005/ 2006–2010 (4)	Females aged 15–19 years: 37.9% decrease (from 2.9 in 2006 to 1.8 in 2010); females aged 20–24 years: 12.7% decrease (from 5.5 in 2007–2009 to 4.8 in 2010); females aged 25–29 years: 9.8% decrease (from 4.1 in 2009 to 3.7 in 2010); all values given in per 1,000 person-years	No reduction or small increase in other female age groups. In males (all ages grouped) incidence increased from 2003 to 2009, but did not increase in 2010; small decline in GW in men aged 20–24 years

Table 1 continued

Country (region)/ References	Study design and setting	Vaccination program during the study/estimated vaccine uptake rate	Pre-/post-vaccine introduction periods [time since vaccine introduction (years)]	GW reduction in vaccine-targeted population (as defined in the study)	GW reduction in non-vaccine-targeted populations (as defined in the study)
US (California)					
Bauer [26]	Analyses in a family planning administrative database (ICD-9: 078.10; 078.11; codes for GW treatment) for all patients	As above/in females aged 13–17 years; 56% received ≥1 dose	No comparison; study period 2007–2010 (4)	Females <21 years: 34.8% reduction (from 0.94 to 0.61%); females 21–25 years: 10% reduction (from 1.00 to 0.90%)	Men <21 years: 18.6% reduction from 2.65 to 2.16%; men 21–25 years: 11.2% reduction from 5.06 to 4.50%; stable or increase in other age groups
US (military service members)					
Nsouli-Maktabi [28]	Analyses in the Defense Medical Surveillance System for all individuals aged ≥17 years between 2000 and 2012 using ICD-9 code 078.1 in any diagnostic position	As above	2006/2012 (6)	Females <25 years: 40.1% reduction (from 3,575.6 to 2,143.2 per 100,000 person-years)	Females ≥25 years and all men: Stable from 2000 to 2010; increase in 2011–2012
Denmark (National)					
Baandrup [29]	Before/after study using data in national database; GWs (ICD-10 A63.0) in all ages and females and males	In Jan 2009 for females aged 12 years with catch-up from Oct 2008 for females up to 15-year old (1993–1995 birth cohorts)/82% and 81% for 3 doses in 1996 and 1997 birth cohorts; 85% in catch-up birth cohorts (1993, 1994, and 1995)	2006–2008/ 2009–2010 (2)	Females aged 16–17 years: 45.3% average annual decrease	Smaller decreases in older age groups of females up to 26–29 years; in men: stable incidence with a trend to decrease in some age groups, e.g., aged 22–25 years, average annual % decrease = 10.9%, but none statistically significant

Table 1 continued

Country (region)/ References	Study design and setting	Vaccination program during the study/estimated vaccine uptake rate	Pre-/post-vaccine introduction periods [time since vaccine introduction (years)]	GW reduction in vaccine-targeted population (as defined in the study)	GW reduction in non-vaccine-targeted populations (as defined in the study)
Blomberg [30]	Vaccine effectiveness study in 1989–1999 female birth cohorts; GWs (ICD-10 A63.0) in vaccinated and unvaccinated females	As above/for ≥1 dose: From 14% in 1989–1990 cohort to 90% in 1995–1996 cohort	NA/Mean follow-up: 3.1 years for vaccinated and 3.5 years for unvaccinated subjects	HR for GWs (vaccinated vs. unvaccinated) 0.12, 0.22, 0.25 and 0.62 for 1995–1996, 1993–1994, 1991–1992 and 1989–1990 birth cohorts, respectively	NA
Germany (National)					
Mikolajczyk [31]	Before/after study in a large healthcare database covering 8% of population: GWs (ICD-10 A63.0) in females and men aged 10–79 years	Mar 2007 for females aged 12–17 years (any HPV vaccine; 90% = 4HPV)/40% in 2008–2009 for females aged 16–18 years	2005–2007/ 2007–2008 (1)	By end 2008 reductions of 47, 45 and 35% in females aged 16, 17, and 18 years; estimated reduction per year: 34.8, 32.8 and 24.7% for same ages	In males, no evidence of decreased incidence, except some trend to decrease in those aged 16 and 17 years; general trend over time: increased incidence in GWs
Sweden (National)					
Leval [32]	Before/after study in national databases for those aged 10–44 years: GWs ICD-10 A63.0 (main and contributory discharge) and codes for GW treatment in prescribed drug database	May 2007 4HPV vaccination at subsidized cost for females aged 13–17 years/Aug 2011 in females aged 13–20 years: 25% ≥1 dose (>30% for females 15–18 years); highest coverage in females 18–19 years: 31.9%	2006/ 2007–2010 (3)	Decreased incidence in females aged 17–21 years: RR from 0.74 for 17 years and 0.83 for 21 years; reduction of 25% in GWs incidence in females 17–18 years	In other females aged 22–25 years: RR from 0.90 for 22 years to 0.77 for 25 years; in males incidence either stable or increased

Table 1 continued

Country (region)/ References	Study design and setting	Vaccination program during the study/estimated vaccine uptake rate	Pre-/post-vaccine introduction periods [time since vaccine introduction (years)]	GW reduction in vaccine-targeted population (as defined in the study)	GW reduction in non-vaccine-targeted populations (as defined in the study)
Leval [33]	Vaccine effectiveness study in national databases in females aged 10–44 years: GWs ICD-10 A63.0 (main and contributory) and codes for GW treatment in prescribed drug database; vaccination status from databases	As above	NA (3)	Highest effectiveness in females vaccinated at 10–13 years: 93%; 80, 71, and 48% in those aged 14–18, 17–19, and 20–22 years, respectively	No significant changes in other groups studied (e.g., 21% effectiveness for females aged 23–26 years, albeit not statistically significant)

4HPV quadrivalent HPV, *aOR* adjusted odds ratio, *CI* confidence interval, *DB* database, *GW* genital warts, *HPV* human papillomavirus, *HR* hazard ratio, *ICD* International Classification of Disease (number refers to the revision used), *MSM* men who have sex with men (homosexual men), *MSW* men who have sex with females (heterosexual men), *NA* not available, *NHMD* National Hospital Morbidity Database, *OR* odds ratio, *RR* relative risk

in the percentage of females and heterosexual men aged <30 years presenting with GWs were reported. In females aged <28 years, the percentage decreased 52.0%, from 12.7% in 2004–2007 to 6.6% in 2008, 1 year after vaccine introduction. From July 2010 to June 2011, 4 years after vaccine introduction, the percentages of females aged <21 years and 21–29 years with GWs were 1.9% and 3.7%, respectively. No decline was observed for females and heterosexual men aged ≥30 years, for MSM or for non-residents (who were not eligible for the 4HPV vaccination program).

The first report from the national study, involving eight sexual health services, including the Melbourne service, revealed a significant decrease of 59% [95% confidence interval (CI) 54–61%] for 4HPV-eligible females aged 12–26 years with GWs, from 11.7% in July to December 2007 to 4.8% in July to December 2009, 2 years after vaccine introduction. There was also a significant 39% (95% CI 33–46%) decrease for heterosexual men aged 12–26 years with GWs, in the same period [19]. No significant reductions were seen for non-resident females of eligible age, females and heterosexual men aged >26 years or MSM. The second report from this study, reporting data for up to 4 years after 4HPV vaccine introduction, showed a further decrease up to 92.6% in the percentage of females aged <21 years with GWs, from 11.5% in 2007 to 0.85% (i.e., 13 cases) in 2011 [18]. None of the 235 females aged <21 years who had been vaccinated were diagnosed with GWs. In females aged 21–30 years there was a 72.6% reduction of GWs, from 11.3% in 2007 to 3.1% in 2011. This study also confirmed the significant reduction of GWs in heterosexual men aged ≤30 years while confirming the absence of impact on older females, older heterosexual men and MSM. The decline in GWs contrasted with the increase in chlamydia infections and no change in genital herpes infections, over the same period. The comparison of national population-based surveys in 2001 and 2011 confirmed the decline in GWs and the increase in chlamydia infections [23]. The analysis of Australian national hospital data between 1999 and 2011 confirmed the reduction of GWs in young females and also in young men (herd protection), with a similar impact in indigenous and non-indigenous populations [22].

New Zealand

The 4HPV vaccine was introduced in New Zealand in September 2008 for females in year 8 (aged 11–12 years), with a catch-up program for females born after January 1, 1990 until the end of 2010. The estimated vaccine uptake rate in eligible females was 51.7% in 2009 for the Auckland District Health Board [24].

A retrospective study of new patients with GWs attending the Auckland Sexual Health Service between January 2007 and June 2010 showed a statistically significant reduction of 62.8% in females aged <20 years with GWs, from 13.7% in 2007 to 5.1% in 2010 and a reduction of 21.3% in females aged >20 years, from 7.5% in 2007 to 5.9% in 2010 (Table 1) [24]. A similar, but statistically non-significant, reduction was observed in young males. Another study used a prescription database (PHARMAC) to assess the impact on prescriptions for GW treatments (imiquimod and podophyllum) and as a surrogate outcome for GWs [25]. They reported the largest decrease in prescriptions in females aged under 20 years (Table 1).

United States

The 4HPV vaccine was introduced in the United States (US) in June 2006 for females aged 11–12 years with catch-up for those aged 13–26 years; in 2011, the recommendations were extended to males aged 11–12 years with catch-up for those aged 13–21 years [35, 36]. The uptake rate for ≥1 dose among adolescents aged 13–17 years in 2010 varied from 22.5% in the US Virgin Islands to 73.0% in Rhode Island with a national average of 48.7% [37]. In females and males aged 19–26 years, the uptake was 20.7% and 0.6%, respectively [38].

Three studies reported data showing the impact of 4HPV vaccination on GWs [26–28]. One study included 64 million person-years of data for subjects aged 10–39 years enrolled in about 100 health insurance plans throughout the US [27]. The results showed a significant decline in the prevalence of GWs 4 years after the introduction of 4HPV vaccination (2006–2010), from 2.9 per 1,000 person-years to 1.8 in females aged 15–19 years and from 5.4 to 4.8 in females aged 20–24 years. No decrease was observed for older females. In males aged 20–24 years there was a significant increase from 2.5 in 2003 to 5.0 in 2009 followed by a significant decrease to 4.6 in 2010. The other two studies were not national: one analyzed data from the Californian Public Family Planning Administrative Claims database and the other analyzed data from the Defense Medical Surveillance System, concerning US service members during their military service careers [26, 28]. The study in California reported a 34.8% decrease (0.94–0.61%; $P_{trend} < 0.001$) in GW diagnoses between 2007 and 2010 in females aged <21 years. Decreases were also reported in females aged 21–25 years (10.0% decline; $P_{trend} < 0.001$), males aged <21 years (18.6% decline; $P_{trend} < 0.001$), and males aged 21–25 years (11.2% decline; $P_{trend} < 0.001$) [26]. No change was reported for females or males aged >30 years. The study on US service members reported a marked decrease in the annual incidence rate of GWs from 2007 to 2010 among females aged <25 years [28]. The incidence rates of GWs remained relatively low and stable in females aged ≥25 years and men of all ages from 2000 to 2010, although there was an increase for these subjects between 2010 and 2012.

Denmark

The 4HPV vaccine was licensed in Denmark in October 2006 and since January 2009 it has been offered free of charge to all females aged 12 years, with catch-up in females aged up to 15 years. In 2012, the 4HPV vaccine uptake for ≥1 dose was between 87% and 90% and 82% and 81% for three doses for the first two birth cohorts and 85% in the catch-up campaign [29, 30].

Two studies that used data from the Danish National Patient Register have been published [29, 30]. The register contains information on all hospitalizations and outpatient consultations, including GWs. One study reported the incidence of GWs in Denmark and the other reported the effectiveness of 4HPV vaccination for preventing GWs [29, 30]. The greatest impact was reported for females aged 16–17 years with a decrease from 381.5 per 100,000 in the second half of 2008 to 39.8 per 100,000 in the first half of 2011, representing an average annual percentage decrease of 45.3%. In other age groups there was a significant but more gradual decrease reported from 2009 [29]. There was a

non-significant reduction in the incidence of GWs in all age groups of men, with the greatest reduction in those aged 22–25 years.

In the second study, all females in the 1989–1999 birth cohorts were identified and information about their HPV vaccination status was obtained for the period 2006–2012 [30]. In this study 248,000 out of the 399,967 females (62.2%) were vaccinated. After a median follow-up of 3.1 and 3.5 years for the vaccinated and unvaccinated females, respectively, the relative risks of GWs in females who had received ≥1 dose of 4HPV compared with unvaccinated females were 0.12 (0.04–0.36), 0.22 (0.15–0.33), 0.25 (0.19–0.32), and 0.62 (0.50–0.76) for those born in 1995–1996, 1993–1994, 1991–1992, and 1989–1990, respectively (P for trend < 0.0001). No GWs occurred among vaccinated females in the youngest birth cohort (1997–1999).

Germany

In Germany, HPV vaccination for the prevention of cervical cancer was recommended for females aged between 12 and 17 years in March 2007. Although the type of vaccine was not specified in the German Standing Vaccination Committee (STIKO) recommendation, about 90% of the doses sold in Germany were 4HPV. In 2008–2009, the vaccine uptake rate was about 40% in females aged 16–18 years [31].

Data from one large health insurance company in Germany showed a reduction in the incidence of anogenital warts in females aged 16 (47%), 17 (45%), and 18 (35%) years at the end of 2008, soon after the recommendation for HPV vaccination [31]. There was no evidence of a reduction in incidence in older females and males.

Sweden

From May 2007, 4HPV vaccine has been available at a subsidized cost for females aged 13–17 years; vaccination was, therefore, administered in clinics and costs were incurred by the females or their parents. It was estimated that 25% of females aged 13–20 years had received ≥1 dose of 4HPV [32]. Vaccine uptake rates were highest in those aged 18–19 years (31.9%) and those aged 13–17 years (24.7%) [33].

Two studies reported results from the analysis of data extracted from the Swedish Prescribed Drug and the National Patient Registers to identify GW episodes in the population aged between 10 and 44 years between 2006 and 2010 [32, 33]. One of the studies showed significant decreases in the incidence of GWs in females aged 15–25 years from 2006 to 2010 ($P < 0.001$ test for trend); the decrease was highest (>25%) in those aged 17 and 18, with significant decreases up to 25 years [32]. No significant trends over time were observed for males ($P = 0.71$ test for trend).

The second study reported a vaccine effectiveness of 76% (95% CI 73–79%) among females who received three doses of vaccine with the first dose before 20 years [33]. The effectiveness was highest in those vaccinated before 14 years (93%) compared with 71% between 17- and 19-year old and 48% between 20- and 22-year old.

DISCUSSION

This summary of published data provides evidence that there is a rapid reduction in the incidence of GWs after the implementation of 4HPV vaccination, at least, in the target population, despite the differences in study

designs, populations studied, and 4HPV vaccine implementation and uptake. The results for the trends of other sexually transmitted diseases that increased or remained stable suggest that the reduction in GW incidence is unlikely to be explained by changes in sexual health education or in sexual behavior [18, 29].

Results from the study in Sweden suggest that vaccination at an early age results in higher protection, with the highest effectiveness for vaccination at 10–13 years [33]. The younger the subjects are at vaccination, the less likely they are to have been in contact with HPV, and therefore, the more likely they will be protected with a prophylactic vaccine such as 4HPV vaccine.

The results from this review also provide some evidence for possible herd protection in unvaccinated populations of men and older females, particularly in settings with high vaccine uptake rates [18]. However, herd protection was not seen in all countries (e.g., Denmark) suggesting that factors other than vaccination, for example, population dynamics could contribute to herd protection [29]. A study in Australia using a national general practice database, published after our literature search had been done, reported a reduction of 61% in GW management rate in vaccine-eligible females for the post-vaccination period (July 2008–June 2012) but no change in older females or in males of any age [39].The US Centers for Disease Control and Prevention reported that male HPV infections are responsible for about one-third of the total expected burden of HPV-associated cancers, emphasizing how universal vaccination could be beneficial by providing direct protection [40]. Certain populations, such as MSM, will not benefit from herd protection from a female HPV vaccine program. Thus, it is reasonable to consider universal HPV vaccination programs to provide direct protection to all individuals, irrespective of their gender [41]. Despite the considerable indirect effects seen in Australia, the Australian government has implemented a publically funded program for 4HPV vaccination in boys aged 12–13 years, with a 2-year catch-up program for boys aged 14–15 years [42]. In early 2014, Austria started a vaccination program for both boys and females [43, 44]. In the UK, the Joint Committee on Vaccination and Immunization is considering extending the HPV vaccination program; a group of parliamentarians with a special interest in public health published an open letter in support of extending to the program to males [45].

Although the 2HPV vaccine does not contain HPV6 or HPV11, an unexpected result was reported from an ecological study in the UK. 2HPV vaccination was introduced in September 2008 for females aged 12–13 years with catch-up for those up to 18-year old. The vaccine uptake was reported to be >80% in the routine cohorts and about 40% or more in the oldest catch-up cohorts [46]. It was reported that there were reductions in diagnoses of GW in GUM clinics of 13.3% in females aged 16–19 years from 2008 to 2011. The results from a recent analysis suggested that the reported reduction in GW diagnoses in the UK could be partially due to the recent introduction of asymptomatic screening pathways whereby testing for sexually transmitted diseases is offered to asymptomatic patients without an examination by a clinician, leading to up to 12.3% of GWs being missed [47]. In addition, a study performed between October 2010 and June 2012 in the UK, using PCR-confirmed HPV, reported that while there was a reduction in HPV 16/18 infections in the post-vaccination period, no such reductions were seen for HPV6/11 infections in females aged 16–21 years [48].

Another study in Scotland where the 2HPV vaccine uptake was 91% also demonstrated that while 2HPV vaccination significantly reduced vaccine type and related type HPV infections, there were no reductions in the prevalence of HPV6/11 infections [49]. Results from ad hoc analyses for persistent infection in samples collected during the large randomized clinical trial on 2HPV showed that the vaccine reduced persistent infection with HPV6 by 34.9% in females naïve for all HPV types [50]. However, no reduction was observed for HPV11 in this population and no reduction was observed for HPV6 or HPV11 in the total vaccinated population comprising all subjects who had received ≥1 dose of 2HPV, irrespective of their HPV status at enrollment. An analysis of the HPV types present in GWs in the placebo groups of two randomized clinical trials of 4HPV showed that while HPV6/11 were present in 86.0% (447/520) of the GWs analyzed in which HPV was detected, HPV16/18 were also present in 13.4% (64/478) of these lesion [3].

In September 2012, the UK switched to the 4HPV vaccine in their program. Due to direct protection against HPV 6 and 11 conferred by 4HPV, greater reductions in the incidence of GWs are expected to be observed; and this will also accompanied by reductions in HPV6 and HPV11 infections. In the US, 4 years after 4HPV vaccine introduction, in females aged 14–19 years, a decline of 56% (11.5–5.1%) of vaccine-type HPV infection was reported despite a low vaccine uptake rate; vaccine effectiveness for ≥1 dose was estimated to be 82% [51]. In Germany, where the vaccine uptake is also low, a similar decline of 54.5% (22.4–10.2%) in HPV16/18 infections has been reported in females aged 20–21 years [52]. Recently in Belgium, the results from a retrospective study between September 2009 and January 2012 in females aged 15–19 and 20–24 years showed a significant decrease in HPV 16 infection in the younger age group, with a similar-sized reduction for HPV18, which was not significant [53]. In the older age group, where HPV vaccination uptake is lower, the incidence remained stable over the period, suggesting that the observed decrease is due to HPV vaccination.

While the first indication of the clinical impact of HPV vaccination has been shown by the reduction in the incidence of GWs, the impact on the incidence of cervical abnormalities that can give rise to pre-cancerous and cancerous cervical lesions is suggestive of a long-term clinical impact. Recent data, including two reviews, showing a significant reduction in the incidence of cervical abnormalities in countries where 4HPV was introduced early and with high vaccine uptake have been published [54–59].

The studies presented in this review are either analysis of national or very large regional databases. Some of the studies reported the vaccination status of the subjects and so provided effectiveness data. Although some of the studies included present the classical potential limitations of database-based and ecological studies, including erroneous coding, underreporting to the databases and potential biases, they allow a pragmatic approach to continual assessment of national vaccination programs. Another possible limitation that should be acknowledged is the potential publication bias, which is inherent to literature reviews. However, the authors feel, that as this is an area of high interest, the studies are reported. After the end of the literature search and the submission of the paper we identified an additional study that was not included in the formal review but presented in the discussion. Since GWs are not notifiable diseases in all

countries, dedicated surveillance programs have not been implemented as they have been for some diseases, such as invasive pneumococcal diseases and influenza [60].

Despite their limitations, these results show that 4HPV vaccination programs have the potential to significantly reduce the burden associated with GWs. Some models, based on data from clinical trials and estimates for the high burden of GWs to healthcare systems, predict that vaccination costs can be offset by reductions in GW disease costs [10]. The studies in this overview can be used to verify the reliability of published models on the timing of reduction of such diseases and the possible impact of vaccination programs in countries with no surveillance systems. In summary, the data from these international studies (6 countries, 3 different continents) summarized in this review give an encouraging view of the early clinical impact of introducing 4HPV into national vaccination programs.

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Compliance with ethics guidelines. The analysis in this article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

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