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Human papillomavirus vaccines effectiveness to prevent genital warts: A population-based study using health system integrated databases, 2009–2017

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ABSTRACT

Objectives: To assess the effectiveness of the HPV vaccines in preventing genital warts (GW) in women aged 14–23 years and to estimate the incidence of GW in the whole population aged from 14 to 65.
Design: Population-based retrospective cohort study using real-world data from the Valencia health system Integrated Databases (VID).
Study population: All subjects aged 14–65 years residing in the Valencia Region during 2009–2017 (n = 4,492,724), including a cohort of 563,240 females aged 14–23 years followed-up for the vaccine effectiveness (VE) estimations.
Main outcome measures: Incident cases of GW defined as the first activation of GW-related codes (ICD-9-CM 078.11 or ICD-10-CM A63.0) in hospital, primary and specialized care during the study period. Adjusted VE was estimated as (1-Relative Risk (RR)) × 100 by a negative binomial Bayesian model.
Results: There were 23,049 cases of GW in the overall population and 2,565 in the females' cohort 14–23 years old. The incidence rate (IR) (in 100,000 persons-year) was 69.1 (95% CI 68.21–69.99) in the population overall, being higher in men (72.73; 95% CI 71.45–74.04). The IR of GW was 104.08 (95% CI 100.79–108.94) in the cohort of young women. The RR of GW increased with age from 14 to 21 years, reaching a plateau from 21 to 23. The VE of a complete schedule was 74% (95% CrI 68–79) for quadrivalent HPV vaccine (HPV4v). No effectiveness was seen with a full vaccination course with the bivalent HPV vaccine (HPV2v) in girls up to 21 years old. GW IR tends to be higher in unvaccinated cohorts covered by HPV4v vaccine than in unvaccinated cohorts not covered by HPV4v vaccine.
Conclusions: A complete HPV4v vaccination schedule was 74% effective in reducing GW in our population. Our results also suggest an indirect protection to unvaccinated and HPV2v vaccinated girls.

1. Introduction

Human Papillomavirus (HPV) is responsible for the most common sexually transmitted infections, causing from genital warts (GW) to cervical, anogenital or oropharyngeal cancers. Among the more than 150 types of HPV sequenced, the low-risk genotypes 6 and 11 cause approximately 90% of cases of GW [1]. These lesions are very frequent and up to 10% of the population develop an episode during their lifetime. Although considered as benign disease, GW are associated with a negative impact on the psychological, social, and physical welfare, significantly impairing quality of life [2–4]. Due to its quick onset after infection, GW can be used as an intermediate disease outcome to assess a specific vaccination program impact shortly after introduction.

Among the current three licensed HPV vaccines there is a quadrivalent HPV vaccine (HPV 6, 11, 16, and 18) (HPV4v) available since 2007 which was followed by license of the bivalent vaccine (HPV 16 and 18) (HPV2v) and most recently, the nonavalent vaccine (HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58) (HPV9v). All three include the two most frequent high-risk HPV genotypes (HPV16/18, responsible for 70% of cervical cancer cases), and two

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of them (HPV4v and HPV9v) also include the low-risk genotypes HPV6/11 [5]. Efficacy [6–8] and effectiveness [9–12] of these HPV vaccines preventing HPV infection, GW and precancerous lesions has been proven in different clinical trials and post-authorization studies. Recently, their effectiveness preventing cervical cancer in two population-based studies in Sweden and Denmark has been also demonstrated [13,14].

Observational data showing the effectiveness of HPV vaccines in different real-world settings allows the identification of program characteristics that lead to the greatest reductions in HPV-related diseases. These data result extremely useful for decision-makers considering whether to introduce or modify HPV vaccination programs [9]. For example, vaccinating multiple age cohorts of girls (9–14 years old) when the vaccine is introduced in a country or vaccinating a single age cohort (for instance 12 years old) is a key policy issue, especially given the current shortage of vaccine supply in some places [15]. Most high-income countries had implemented vaccination of multiple-age cohorts, mainly through catch-up campaigns, leading to most of the published works reporting evidence from multiple-age cohort HPV vaccination programs [16–21]. However, although multi-cohort programs are expected to have a faster impact, it is expected that both strategies can lead to similar impact in the long term [22]. The paucity of observational studies in real-world settings implementing single-cohort HPV vaccination programs makes it difficult to measure its real impact [23].

In the Valencia Region (Spain), with around 5 million inhabitants and almost universal coverage of all citizens by the Public Health System (PHS), the HPV4v vaccine was used in the regional single-cohort vaccination program between 2008 and 2010 and was administered in a three-dose regimen to girls born in 1994 and 1995, when they were 14 years old. Thereafter, the HPV2v was used [24]. In a previous population-based study using the Valencia health system Integrated Databases (VID) [25] we assessed the effectiveness of the HPV vaccines in preventing GW in women aged 14–19 years between January 2009 and December 2014 [24]. The oldest immunized women in our cohort were 19 years old at the end of the follow-up period. The effectiveness of a three-dose regimen of the HPV4v preventing GW was 77%. Unvaccinated girls and those vaccinated with the HPV2v had similar risk of GW.

To our knowledge, apart from our previous work [24], only two additional studies from Catalonia and Canada have reported data on the population-level impact of a single-cohort HPV vaccination program on the incidence of GW. However, these works did not have individual-level data on HPV vaccination status [23,26]. The VID [25] offers the possibility of estimating vaccines effectiveness (VE) by linking individual-level data on vaccination status. Additionally, the utilization of HPV4v followed by HPV2v in different periods for different birth cohorts also allows evaluating the effectiveness of both vaccines in preventing GW in the same setting.

The aim of the present study is to enlarge the follow-up period of the previous work, estimating the effectiveness of the HPV4v and HPV2v vaccines to prevent GW in women aged from 14 to 23 years from 2009 to 2017 in the Valencia Region. Incidence rate (IR) of GW in the whole population aged from 14 to 65 years during the study period was also described.

2. Methods

2.1. Study design, population and setting

This is a population-based retrospective cohort study using real-world data from the VID [25], including subjects aged 14 to 65 years living in Valencia Region between 2009 and 2017. The inclusion date was defined as 1st January 2009 or the date on which 6 months have elapsed since the subject's enrollment in the Regional Health System (RHS), or the subject's fourteenth birthday, whichever occurred latest. The date of end of follow-up was defined as end of the study period (31st December 2017) or the date of exit of the RHS (including death), or their sixty-sixth birthday, whichever comes sooner.

For the study of the HPV vaccines effectiveness, a sub-cohort of women aged 14–23 years was followed up (corresponding to women of the eligible birth cohorts for HPV vaccination since the program implementation in 2008). Women vaccinated outside the vaccination program were excluded for the vaccine effectiveness estimation.

The Valencia region of Spain has a population of around 5 million inhabitants and >98% are covered by the PHS. The RHS is divided into 24 departments. Each of them includes at least 1 hospital, 1 specialty center, and a number of ambulatory care centers depending on the department. All recommended vaccines are fully paid for by the PHS; vaccines are bought every two years under a tender and any of the three available vaccines can be bought for the whole region.

2.2. Real world data: The Valencia healthcare Integrated Databases (VID)

We used the following registries from VID [25]: 1) the regional population-based administrative database (SIP), that collects and updates demographic data, health services assignment and usage of the health system; 2) the Ambulatory Care Information System (SIA), that contains medical information for each patient attended in the Primary Care (PC) setting (General Practitioners, GPs, and specialists); 3) the minimum basic data set (MBDS), that collects all diagnosis and procedures from hospitalizations; 4) Vaccine Information System (VIS) that provides vaccination status and information about all HPV vaccine doses administered both in public and many private healthcare centres. The data included are the type of vaccine, the batch number, the number of dose, the place and date of administration, and when applicable, if the individual is part of a risk group. Both SIA and MBDS used the International Classification of Diseases, Ninth Revision, Clinical Modification coding system (ICD-9-MC) for codification but MBDS changed to the International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) from 2016 onwards. All these registries can be linked at individual-level through a unique personal identification number [25,27].

2.3. Study procedures

An incident case of GW was defined as the first activation of diagnosis code ICD-9-CM 078.11 or ICD-10-CM A63.0 (Condyloma acuminatum) in hospital, primary care, and specialized outpatient consultations, including gynecology during the study period. Recurrent cases during the study period were no considered for the analysis.

HPV Vaccination status of women born from 1994 to 2003 was considered as a time-dependent variable. The following vaccination status were assessed for both, HPV4v and HPV2v: non-vaccinated (time until first dose or no dose registered); one-dose vaccinated (time from the date of first-dose registered); two-dose vaccinated (time from the date of second-dose registered); and complete schedule (time from the date of third-dose or second dose registered, depending on the recommendations). Of note, between 2008 and 2015, a three-dose HPV vaccination schedule was followed for 14 years old girls; from 2015 onwards, a two-dose schedule for 12 years old girls was followed [28]. The oldest immunized women with HPV2v in our cohort at the end of the

follow-up period were 21 years old. Women vaccinated outside the regional vaccination program were excluded (women vaccinated born before 1994).

Variables that are relevant to the disease or can impact on the incidence of GW were considered: age, sex, calendar year, urban/rural residence, social exclusion risk, nationality, health department (to control for variability in clinical practice) and immunocompromised condition (IC) (including HIV, immunodeficiency disorders and autoimmune diseases, cancer or organ transplantation which increase the risk of HPV infection [29]) (see supplementary table 1). Social exclusion risk was obtained from SIP, and its classification was based on multiple aspects such as unemployment, foreigner in irregular situation or without resources.

In order to evaluate a possible herd effect of the HPV vaccines, IR of GW were calculated by age in unvaccinated girls by birth cohorts as follows: the last eight birth cohorts not covered by the HPV vaccination programme (1985–1993), the two birth cohorts susceptible to be vaccinated with HPV4v (1994–1995) and the eight birth cohorts susceptible to be vaccinated with HPV2v (1996–2003).

A sensitivity analysis was performed for the estimation of the VE by excluding girls with less than 6 months elapsed between the date of last vaccination dose and diagnosis of GW. The use of this 6-month buffer period avoids considering cases of WG whose infection was prior to the date of vaccination.

2.4. Statistical analysis

A descriptive analysis included the vaccination coverage with the HPV4v and HPV2v, the GW incidence, the estimation of IR by age, year, vaccination state, and health department. It also included the time between the last vaccine dose (for a complete schedule vaccination) and the diagnosis of GW.

Incidence rates (number of subjects with an incident case of GW per 100,000 persons-years) were calculated dividing the number of incident GW cases by the person-at-risk over the study period. We considered the first occurrence of GW during the study period (2009–2017) as a GW incident case. Recurrent cases during the study period were not considered for the analysis. The person-time-at-risk ended at the date of the first event or the end of follow-up, whichever comes first. Follow-up time was split according to the time-varying covariates (calendar year, age, vaccination state and health department). Person-years were calculated as the sum of total person-time-at-risk divided by 365.25. 95% confidence intervals were calculated by the Exact Poisson method. For IR estimates by HPV2v vaccination status, the sub-cohort of girls aged 14–21 years corresponding to the highest ages reached by the cohorts covered by this vaccine (1996–2003) was considered.

A negative binomial Bayesian model was built to analyse incidences of GW and vaccine effectiveness. The model assumed that the number of incident cases of GW in the different observation units (counts aggregated by year, age, vaccination status, health department and IC) followed a negative binomial distribution. In addition to the vaccination status (exposure variable), the model was also adjusted by the following covariates: age, calendar year, health department and IC. Health department was included as a random effect to fit the differences in clinical practices and policies between health care areas, as they could influence GW diagnoses and vaccination. The calendar year was introduced to control the expected temporal variability in GW incidence. IC was also adjusted, including a wide range of diagnoses (shown in supplementary material 1) as it makes subjects more vulnerable to HPV infections. It should be noted that the covariates "age", "IC", "year", and "vaccination status" changed over time. Therefore, each subject contributed person-time to each combination of vaccination status, age group, IC, and year. The logarithm of the sum of times (person-years) of each observation unit acted as an offset term. For HPV2v VE estimates, the sub-cohort of girls aged 14–21 years corresponding to the peak ages reached by the cohorts covered by this vaccine (1996–2003) was considered.

VE for complete vaccination schedule was calculated as (1-RR) × 100; 95% credible interval (CrI), analogous to 95% confidence intervals in frequentist statistics was also reported. In a Bayesian context, the 95% CrI directly shows that the true estimation of the parameters lies within the range of CrI with a probability of 95%.

Ethical statement

The study protocol, observational in design and using retrospective anonymized non identifiable data transferred from the Valencia Ministry of Health to the research team according to the Spanish laws and institutional requirements, was approved by the Ethics Committee of Dirección General de Salud Pública / Centro Superior de Investigación en Salud Pública (CEIC DGSP-CSISP). The Valencia Health System Data Commission [25] granted permission for the transfer of specific anonymized data for the study development. Additionally, being that it is a retrospective study with 9 years of study period (2009–2017), it would have been not possible to get individual informed consent from the whole population studied (more than 4 million inhabitants). Based on Helsinki's Declaration (principle 32) and the Law of Biomedical Reseach in Spain (Art. 58.2), the Ethics Committee accepted the exemption.

3. Results

3.1. Overall incidence rates of GW

The study population included 4,492,724 subjects aged 14 to 65 years (49.6% female). Sample size, demographic characteristics, and distribution of cases of GW and IR by gender, age, calendar year, nationality, urban/rural residence and risk of social exclusion are listed in Table 1.

There were a total of 23,049 cases of GW. Of those, 12,162 (52.8%) were in men and 10,887 (47.2%) in women. IR of GW (in 100,000 persons-year) in the population overall was 69.1. IR was higher in men in all age groups except for those younger than 20 years (Fig. 1). IR of GW peaked at the age group of 20–29 years. It increased from 2009 to 2012 and decreased from 2013 onwards, when the first female candidates to be vaccinated with HPV vaccines reached the age of 18–19 years.

3.2. HPV vaccines effectiveness in women 14–23 years old

The study cohort for the evaluation of VE included 563,240 women aged 14–23 years (born between 1985 and 2003) (Fig. 2). We excluded 8,055 of them because they were vaccinated outside the vaccination program. 60.1% of women born in 1994 and 1995 were vaccinated (at least one dose) with HPV4v (0.7% of this cohort were vaccinated with HPV2v). 61.1% and 11.9% of women born between 1996 and 2003 were vaccinated (at least one dose) with HPV2v and HPV4v, respectively. Fig. 3 shows the vaccination coverage with at least one dose by year and vaccine type. In total, 186,068 women were vaccinated with one of the HPV vaccines.

There were 2565 cases of GW in this cohort, 281 of them in vaccinated women (127 and 164 with HPV4v and HPV2v, respectively). The overall IR was 104.08 (Table 2). Both the number of cases and IR increased with age. IR of GW increased from years 2009 to 2012 and it decreased from 2013 onwards. After adjustment (Supplementary material 2), the risk of GW increased with

Table 1
Demographic characteristics and distribution of genital warts (GW) cases and incidence rates (IR) by gender, age, nationality, urban/rural residence and risk of social exclusion for population 14–65 years old in the Valencia Region from 2009 to 2017 (n = 4,492,724).

Characteristics	Population (n = 4492724)	GW cases (n = 23049)	GW-IR (95% CI)
Gender N(%)			
Woman	2,230,242 (49.64)	10,887	65.44 (64.22–66.68)
Man	2,262,482 (50.36)	12,162	72.73 (71.45–74.04)
Age (years) N			
[a]14-16	659,659	211	14.6 (12.69–16.7)
[a] 17–19	678,060	1147	77.14 (72.74–81.74)
[a] 20–29	1,315,277	9310	164.52 (161.2–167.9)
30–39	1,662,783	6915	89.09 (87.01–91.22)
40–49	1,651,713	3456	45.76 (44.25–47.31)
50–59	1,370,060	1481	23.79 (22.6–25.04)
60–65	876,212	529	16.39 (15.02–17.85)
Calendar Year			
2009	4,067,613	2502	62.51(60.09–65.01)
2010	4,046,440	3034	76.78 (74.07–79.56)
2011	3,971,426	3257	83.9 (81.05–86.84)
2012	3,909,621	2941	78.61 (75.8–81.51)
2013	3,763,429	2388	64.86 (62.29–67.52)
2014	3,717,327	2215	61.21 (58.69–63.82)
2015	3,632,827	2238	62.94 (60.36–65.6)
2016	3,582,265	2196	62.69 (60.1–65.37)
2017	3,507,224	2278	66.57 (63.86–69.36)
Nationality N (%)	[b]**N = 4335493**		
Spanish	3,554,832 (81.99)	20,195	74 (72.98–75.02)
Other	780,661 (18.01)	2841	53.37 (51.42–55.37)
Rural N (%)	[b]**N = 4476484**		
No	4,372,177 (97.67)	22,733	69.86 (68.96–70.78)
Yes	104,307 (2.33)	312	40.84 (36.44–45.63)
Social exclusion N (%)	[b]**N = 4124858**		
No	3,565,670 (86.44)	18,729	68.42 (67.44–69.41)
Yes	559,188 (13.56)	4103	93.33 (90.5–96.23)
Health department			
1	88,785	208	32.85 (28.54–37.63)
2	267,210	959	49.68 (46.59–52.93)
3	160,518	854	70.73 (66.06–75.64)
4	128,805	775	79.51 (74.01–85.31)
5	322,318	1851	77.68 (74.18–81.30)
6	265,481	1445	71.05 (67.44–74.81)
7	253,786	1520	80.28 (76.30–84.42)
8	40,278	224	73.80 (64.46–84.13)
9	318,391	2225	92.59 (88.79–96.52)
10	247,063	1565	84.85 (80.70–89.16)
11	215,282	1055	63.95 (60.15–67.93)
12	159,762	842	71.33 (66.60–76.32)
13	162,388	526	46.17 (42.31–50.29)
14	163,016	638	50.91 (47.04–55.02)
15	113,013	409	47.15 (42.69–51.95)
16	191,248	721	55.06 (51.11–59.23)
17	208,089	996	66.22 (62.17–70.47)
18	161,613	802	65.22 (60.79–69.90)
19	243,511	1421	77.91 (73.91–82.06)
20	146,468	843	76.86 (71.76–82.22)
21	141,135	736	68.91 (64.02–74.07)
22	189,180	729	56.50 (52.47–60.76)
23	172,813	1001	75.59 (70.98–80.42)
24	132,571	704	69.33 (64.30–74.65)

[a] Including women and girls vaccinated against HPV.
[b] Number of subjects with available information for this category.

age until the age of 21, remaining without differences from 21 to 23 years old. Incidence of GW varied among health departments. Variations among years were not significant and the immunocompromised population had 87% higher risk of developing GW.

Table 3 shows the adjusted RR of GW by vaccination status. A complete vaccination schedule with HPV4v showed a VE of 74% (95% CrI: 68–79) preventing GW. No significant differences were found between the VE estimates according to the number of doses of HPV4v administered. However, the number of cases in partially vaccinated girls was so low (Table 2) that no further analysis could be performed (as reflected by the credible Intervals (CrI) being the most adjusted the one for the complete schedule). A complete vaccination schedule with HPV2v do not showed significant reduction in RR of GW when considering girls aged 14 to 21 years (the oldest girls covered by HPV2v during the study period) (Table 3). For those cases of GW in immunized women, the average time elapsed between the complete schedule of HPV vaccine and the activation of the diagnostic code for GW was 4.4 (SD ± 1.8) years, being 5.3 (SD ± 1.8) years for HPV4v vaccinated and 3.6 (SD ± 1.2) years for HPV2v.

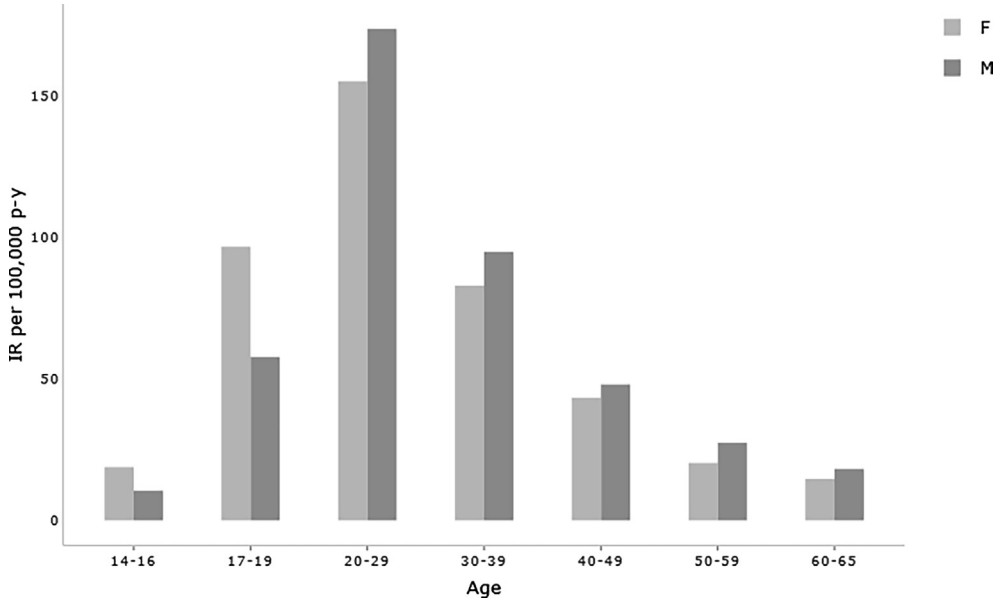

Fig. 1. Incidence rates (IR) of GW by gender and age group for population 14–65 years old in the Valencia Region from 2009 to 2017 (n = 4,492,724).

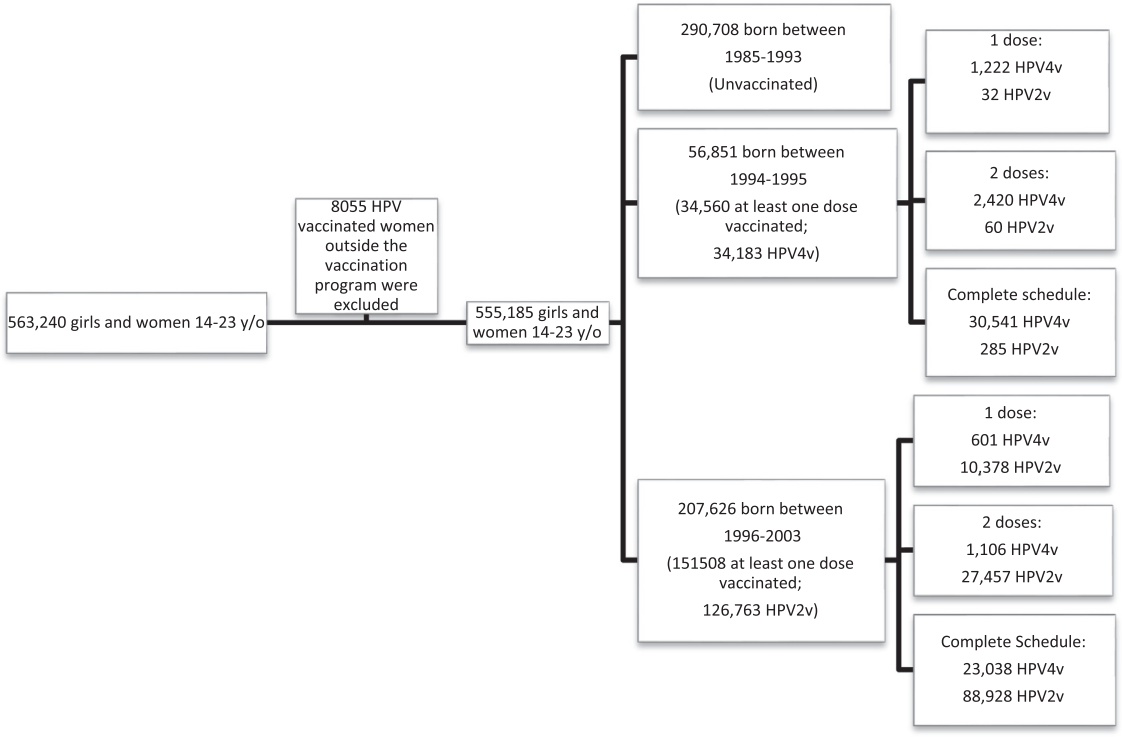

Fig. 2. Flow chart for HPV vaccines effectiveness estimations in girls and women 14–23 years old**.** Note: The 1985–1993 birth cohorts are those prior to the implementation of the vaccination program, the 1994–1995 birth cohorts were covered by the HPV4v vaccination program and the 1996–2003 birth cohorts were covered by the HPV2v vaccination program.

After excluding GW cases during the 6-month buffer period in the sensitivity analysis, the estimation of VE was not significantly modified (75%; CrI: 70–80 for HPV4v).

Figure in Supplemental Material 3 shows the IR of GW by age in unvaccinated girls of the last eight birth cohorts not covered by the HPV vaccination program (1985–1993), the two birth cohorts susceptible to be vaccinated with HPV4v (1994–1995) and the eight birth cohorts susceptible to be vaccinated with HPV2v (1996–2003). IR of GW tends to be higher in unvaccinated girls in the pre-vaccination cohorts than in unvaccinated girls in the vaccine-covered cohorts. Despite the wide confidence intervals due to the small number of girls in the vaccine-covered cohorts who reach the ages of highest incidence of WG during the study period (especially in the HPV2v covered cohorts, born 1996–2003), these results suggest an indirect protection through a herd effect to unvaccinated girls.

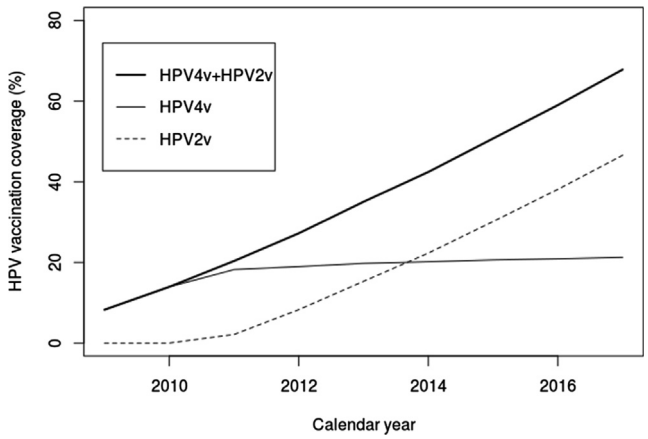

Fig. 3. HPV vaccination coverage by year for at least one dose HPV2v, HPV4v and HPV4v or HPV2v.

4. Discussion

To our knowledge, this is the first population-based study assessing the HPV2v and HPV4v VE in preventing GW in the same setting using individual-level data over a period of 9 years. In 2017 our group reported a VE of 77% in preventing GW for a three-dose regimen of the HPV4v vaccine in a population 14–19 years old. But no effectiveness was observed in the population with a full vaccination course with the HPV2v vaccine [24]. The present study updates and strengthens the previous evidence expanding the follow-up period to 14–23 years old. Despite the potential increase in sexual activity in the current cohort, the effectiveness preventing GW for the complete HPV4v vaccination schedule was 74%, and no significant protection against GW was found for HPV2v vaccination schedules in girls up to 21 years. The lower IR of GW in unvaccinated girls covered by HPV vaccination programs than in unvaccinated girls not covered by HPV vaccination programs suggests a potential indirect protection through a herd effect using a single-cohort vaccination program.

The impact of HPV vaccination on GW incidence has been investigated in several studies around the world, reporting significant decreases of GW diagnoses in vaccinated girls and women [9,23]. Among them, very few have reported data on the population-level impact of single-cohort HPV vaccination programs [24,27] and none reported VE using individual-level data. Concretely, Brotons *et al.* [23] have recently showed a decline of 61% of GW incidence among women aged 16–19 years who were eligible for HPV vaccination in Catalonia. In contrast, a 6.5% decline in GW incidence among women aged 18–20 years was reported in a Canadian study [26]. Both studies used aggregated data, calculating the decrease between the cohorts not eligible for HPV vaccination and the eligible cohorts [23], or that between pre- and post-vaccination periods [26]. However, the use of individual-level data performed in our work, allows associating the vaccination status of each person with their diagnostic records, giving accuracy concerning causality between vaccination status and GW risk. These advantageous conditions have enabled us to estimate 74% effectiveness in the prophylaxis of GW using a single-cohort HPV4v vaccination program.

When analysing IR of GW in unvaccinated girls from cohorts covered and uncovered by HPV vaccine programs, our results suggest an indirect protection through a herd effect to unvaccinated girls. Nevertheless, it must be highlighted the small number of girls in the vaccine-covered cohorts who reach the ages of highest incidence of WG during the study period (especially in the HPV2v covered cohorts, born 1996–2003). In a *meta*-analysis conducted by Drolet and colleagues [9] they compared (among other) the impact of single and multi-cohort vaccination programs from different countries on the RR of GW between the pre-vaccination and post-vaccination periods. They showed greater reductions in GW diagnoses for multi-cohort rather than single-cohort vaccination in high-coverage countries. However, as discussed by Brotons and Bruni [22], the impact of single-cohort strategies was underestimated since in the three single-cohort studies analysed, vaccinated cohorts had not yet reached ages assessed in the *meta*-

Table 2
Incidence rates (IR) of genital warts by age, year, vaccination status and health department in women 14–23 years old in the Valencia Region from 2009 to 2017. Women vaccinated outside the vaccination program were excluded (women born before 1994 and vaccinated).

Characteristics	Cases	IR (95% CI)
Overall	2565	104.08(100.79–108.94)
Age		
14	25	10.62(6.87–15.68)
15	36	15.3(10.72–21.19)
16	73	30.84(24.17–38.78)
17	137	57.39(48.18–67.85)
18	241	100.05(87.82–113.51)
19	332	136.05(121.8–151.5)
20	369	148.66(133.88–164.63)
21	421	167.19(151.6–183.95)
22	447	174.7(158.88–191.67)
23	484	185.74(169.56–203.05)
Year		
2009	348	111.52(100.11–123.88)
2010	383	128.12(115.61–141.62)
2011	358	124.51(111.94–138.1)
2012	380	138.7(125.11–153.38)
2013	271	101.92(90.14–114.8)
2014	233	89.53(78.4–101.8)
2015	204	80.14(69.52–91.92)
2016	190	75.99(65.57–87.6)
2017	198	81.08(70.18–93.19)
Health department		
1	20	46.47(28.39–71.78)
2	102	74.26(60.55–90.15)
3	90	104.6(84.11–128.58)
4	103	165.37(134.98–200.56)
5	224	103.44(90.34–117.91)
6	142	96.2(81.03–113.39)
7	177	125.77(107.93–145.73)
8	20	107.5(65.67–166.03)
9	218	118.79(103.54–135.64)
10	169	125.28(107.11–145.66)
11	132	112.36(94.01–133.24)
12	83	99.93(79.6–123.88)
13	65	84.06(64.88–107.15)
14	74	84.36(66.24–105.9)
15	51	83.12(61.89–109.29)
16	101	112.28(91.45–136.43)
17	110	99.89(82.1–120.39)
18	75	85.6(67.33–107.31)
19	185	124.12(106.88–143.35)
20	84	107.12(85.44–132.62)
21	80	94.95(75.29–118.17)
22	80	96.41(76.45–119.99)
23	107	116.77(95.69–141.1)
24	73	96.25(75.45–121.02)
Vaccination status[a]		
0-Unvaccinated	2274	141.63(135.87–147.58)
1HPV4v	4	18.58(5.06–47.56)
2HPV4v	13	28.65(15.26–49)
Complete Schedule HPV4v	110	28.26(23.23–34.06)
1HPV2v	14	34.46(18.84–57.82)
2HPV2v	37	45.02(31.7–62.05)
Complete Schedule HPV2v	113	42.98(35.43–51.68)

CI: confidence interval; IR: incidence rate per 100,000 person-year.
[a] doses of quadrivalent or bivalent HPV vaccine. For estimates by HPV2v vaccination status, the sub-cohort of girls aged 14–21 years corresponding to the highest ages reached by the cohorts covered by this vaccine (1996–2003) was considered.

Table 3
Relative risk of GW by vaccination status (adjusted model).

Vaccination status	RR	95% CrI
HPV4v vaccine		
No vaccine	1	
1 dose	0.25	0.08–0.56
2 doses	0.40	0.22–0.65
Complete schedule	0.26	0.21–0.32
HPV2v vaccine*		
No vaccine	1	
1 dose	1.74	0.96–2.87
2 doses	1.49	0.99–2.14
Complete schedule	0.89	0.69–1.12

RR, Relative Risk; CrI, Credible Interval
Note: RR of GW for the adjustment variables are shown in Supplementary material 2.
* For HPV2v VE estimates, the sub-cohort of girls aged 14–21 years corresponding to the peak ages reached by the cohorts covered by this vaccine (1996–2003) was considered.

analysis for HPV endpoints. In the absence of further population-based studies with individual-level data assessing the HPV VE and impact on preventing GW, our results suggest that the overall effect of single-cohort vaccination programs could impact in unvaccinated females and some herd effect could be expected during the first nine years. Conversely, impact and herd effect of multi-age cohort vaccination strategies becomes apparent long before.

As described before [30], in our overall population (14–65 years old) the age group 20–29 showed the highest risk of developing GW. However, a reduction in the IR of GW by year was observed from 2013 onwards, when the first cohort to receive HPV4v reached the age of 18 to 19 years. This reduction observed when the eligible cohorts to be vaccinated reached the ages of initiation of their sexual contacts could be reflecting again, an impact containing the characteristic increasing trend in these age groups.

The majority of vaccinated girls and women in Valencia received the complete vaccination schedule (three-dose for 14 years old girls since 2008 and two-dose for 12 years old girls from 2015 onward), resulting in few cases in partially vaccinated women. Despite the wide confidence intervals due to small numbers (only 4 cases of GW in the one dose vaccinated with HPV4v), VE estimations for HPV4v were comparable regardless of the number of doses administered. Previous publications have evidenced that one dose of HPV4v vaccine may be as effective as two or three in preventing HPV infections and related diseases [31–34]. In 2018, the World Health Organization (WHO) Director General announced his commitment to eliminate cervical cancer, with HPV vaccination as a priority [35]. However, the costs of setting up a multi-dose HPV vaccination program remain a barrier for a global mass vaccination campaign. One dose vaccination would significantly reduce program costs and requirements and it could be one of the viable strategies on the way of achieving the elimination of cervical cancer as a public health problem. However, our results should be interpreted with caution and further research on this issue is needed.

The risk of GW after full vaccination course with the HPV2v vaccine showed a non-significant small decrease. These results are in disagreement with some previous studies conducted in England that showed a decrease in the incidence of GW in young girls and heterosexual men. However, these results must be interpreted with caution as they were ecological analysis and the variations in diagnoses of GW are potentially due to factors other than the vaccine [36–38]. Our previous study assessing individual-level data on HPV vaccination did not showed any protective effect of HPV2v against GW in concordance with results from Czech Republic [24,39]. The non-significant low reduction in the RR of GW observed in girls vaccinated with a complete HPV2v in the present study could be due to a possible herd protection from the HPV4v vaccine given to the more than 20% of girls in these cohorts (1996–2003), as suggested previously [9,10,23]. It should also be noted that women vaccinated with HPV2v only reached 21 years of age during the study period, which has been taken into account in the adjusted model for the RR of GW estimation.

5. Strengths and limitations

The strengths of this study include the population-based design, the large sample and the individual-level data. The VID have proven to be very reliable in the surveillance of vaccine preventable diseases [25,27], as well as in the assessment of vaccine safety [40] and effectiveness [41]. Using registries, we were able to identify GW episodes treated in hospitals, primary care and outpatient clinics (including gynaecologists) all over the Valencia Region, thus allowing a more complete outcome determination than studies relying on self-report or patient files from a single clinic for example. In addition, changes in the vaccine used in the regional vaccination program (HPV4v or HPV2v) allowed us to estimate the effectiveness in preventing GW for both vaccines in the same setting and population.

Among the limitations of the study, there is the possibility of biases because the data collected routinely was not created for research. Some cases of GW may not have been registered and some vaccine doses could have been missed, which could lead to some degree of underestimation. Approximately 17% of the population has dual health insurance coverage (both public and private health insurance) in The Valencia Region [42]. In the case of people with dual health coverage, it is common for them to visit private doctors but to seek drug treatments covered by the publicly funded health system. In that case, doctors need to activate the corresponding ICD code to prescribe the drug to treat it and these cases of GW are registered in the databases we have access for. Regarding vaccination status, it was retrieved from Vaccine Information System (SIV) that provides information about all HPV vaccine doses administered both in public and most of the private healthcare centres. Due to the universal coverage of the Spanish PHS and the gratuity of the vaccines, only the 2.7% of the registered HPV vaccine doses were administered in the private setting. Therefore, with these considerations and given that the underestimation applies to the entire study period, with no differences in time or vaccination status anticipated in the previous study, our results are unlikely to have been affected by this potential limitation. Moreover, differences in local practices have been controlled for by the health department. VE estimations in partially vaccinated girls could be biased as it corresponds to the youngest girls and those who have been "at risk" for the shortest time periods, as many of them received the second dose 6 months after the first one. This, together with the low number of GW cases in partially vaccinated girls (four cases in 1 dose HPV4v), prevented us from performing any further analysis and categorically stating that vaccination with one dose of HPV4v is effective in preventing GW.

6. Conclusions

A complete HPV4v vaccination schedule was 74% effective in preventing GW in girls 14 to 23 years old. Non-significant effectiveness was observed for complete HPV2v schedule in girls up to 21 years old. Indirect protection through a herd effect is suggested for unvaccinated and probably for HPV2v vaccinated girls. These results provide real-world evidence supporting the possibility of achieving the WHO goal of eliminating HPV-related diseases, including GW as its first manifestation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Contributorship

AOS is the guarantor of the paper, taking responsibility for the integrity of the work as a whole, from inception to published article.

CMQ contributed to study conception and design; data acquisition, analysis, and interpretation; drafting the article and final approval of the version to be published. CMQ takes responsibility for the integrity of the data and the accuracy of the data analysis and serves as principal author.

MLL contributed to data acquisition, data cleaning, analysis and interpretation; drafting the article and revising it critically for important intellectual content; and final approval of the version to be published. MLL takes responsibility for the integrity of the data and the accuracy of the data analysis.

CMQ and MLL have equally contributed to this work.

VRC discussed the results and approved the final version.

AOS and JDD contributed to study design; drafting the article or revising it critically for important intellectual content; and final approval of the version to be published.

All authors have read and approved the manuscript.

Competing interest declaration

CMQ, JDD, AOS and MLL have attended to several congresses whose registration, travel and accommodation costs have been covered by GSK and MSD. VRC have no conflict of interest. JDD and his institution received research grants from GSK and MSD related to the HPV vaccine. JDD also acted as advisor for these vaccines to GSK and MSD.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2021.11.062.

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