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## Effectiveness of HPV vaccines against genital warts in women from Valencia, Spain

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### ABSTRACT

**Objectives:** To assess the effectiveness of the HPV vaccines in preventing genital warts in young women.

**Design:** Population-based study using health databases.

**Setting:** Valencian Community (Spain).

**Participants:** All girls and women aged 14–19 years who were registered in the Valencian Community between January 2009 and December 2014 (n = 279,787).

**Main outcome measures:** Incident cases of genital warts were defined as the first activation of diagnosis code ICD-9-CM 078.11 (*Condyloma acuminatum*) in primary care and outpatient clinics during the study period.

**Results:** There were 612 cases of genital warts. The overall incidence rate was 75.8/100,000 person-years (95% CrI 69.7–81.8). There was a decrease in genital warts when female candidates to be vaccinated with quadrivalent HPV vaccine reached the age of 18 (in 2012), compared to previous years. Incidence of genital warts in unvaccinated women and those who received the bivalent vaccine was higher than in girls and women who received the quadrivalent HPV vaccine. The effectiveness of a three-dose regimen of the quadrivalent HPV vaccine was 77% (95 CrI: 66–85%), whereas that of a single dose was 61% (95 CrI: 20–87%). No effectiveness was seen with a full vaccination course with the bivalent HPV vaccine.

**Conclusions:** Three doses of the quadrivalent HPV vaccine were effective against genital warts in our population. Moreover, with low vaccine coverage the incidence of genital warts decreased only in the vaccinated.

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### 1. Introduction

Genital warts are a frequent sexually-transmitted disease (STD) [1]. It has been estimated that about 5–10% of the population will have at least one episode of genital warts during their lifetime [2–4]. The epidemiology of genital warts varies depending on age, gender, geographical area, and study methodology. A recent literature review has described an overall (females and males combined) annual incidence of genital warts (both new and recurrent) from 160 to 289/100,000 person-years [1]. Peak incidence occurs in women before 24 years of age and in men aged 25–29 years [1].

Genital warts have an important impact on the psychological, social and physical welfare of patients [5], significantly impairing their quality of life [6]. Furthermore, recurrences are frequent (around 20–30%) [7]. Over 90% of genital warts are related to HPV6/11 [8,9].

In Europe there are three licensed vaccines containing recombinant HPV L1 capsid proteins. All three include the two most frequent high-risk HPV genotypes (HPV16/18, responsible for 70% of cervical cancer cases), and two also include the low-risk genotypes HPV6/11 [10].

In subjects aged 16 and over enrolled in clinical trials, the efficacy of the quadrivalent HPV vaccine in preventing genital warts associated with HPV6 and 11 was 100% (95% CI 92–100) in women after a mean follow-up of 3 years [11], and 89.4% (95% CI 65.5–97.9) in men after a median follow-up of 2.9 years [12]. In the long-term follow-up studies, no case of diseases associated with the four types of HPV covered by the vaccine occurred within 9–10 years after vaccination [11].

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Post-authorization studies used different methodologies in geographical areas with different vaccination schedules [13–22]. These studies demonstrated the significant, and rapid, impact of the quadrivalent HPV vaccination: the incidence of genital warts diminished in the vaccinated population [8,23] and the disease was almost eradicated in vaccinated women under the age of 21 years, amongst whom the rate of vaccination coverage is high [14]. Significant herd immunity, protecting the unvaccinated population of both sexes, has been described when the vaccine coverage was over 50% [24]. In addition, the number of diagnoses of genital warts decreased in England two years after the onset of a vaccination programme with the AS04-adjuvanted HPV16/18 vaccine [25]. This vaccine does not contain the HPV genotypes 6 and 11.

In 2014 the Valencian Community in Spain had a population of 5 million, and its health system is organized into 24 health departments. All recommended vaccines are fully paid for by the National Health System; vaccines are bought every two years under a tender and any of the two available vaccines can be bought. The quadrivalent HPV vaccine was used only between 2008 and 2010 and was administered in a three-dose regimen to vaccinate girls born in 1994 and 1995, when they were 14 years old. Thereafter, the bivalent vaccine AS04-bHPV was used. The aim of the study was to assess the effectiveness of quadrivalent HPV and AS04-bHPV vaccines in preventing genital warts.

## 2. Methods

This is a population-based study using Valencia's health databases. We assembled a cohort that included all the girls and women aged between 14 and 19 years registered in the Valencian Community between January 2009 and December 2014.

### 2.1. Data sources and linkage of registries

Databases used were SIA, SIP and SIV. Database managers made available the data included in each database following a request from the authors. SIA (*Sistema de Información Ambulatoria*) registers all ambulatory medical visit to the National Health System, and physicians record diagnoses using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) [26]. This database was used to identify incident cases of genital warts supplying information on all ambulatory visits that included the ICD-9 code 078.11. SIP (*Sistema de Información Poblacional*) includes socio-demographic data of all population of the Valencian Region, such as birthdate, area of residence, social status, etc. It was used to identify our target population and provided data relating to all the female population aged 14–19 years in the Valencian Community, including birthdate and health department. Finally, vaccination status was retrieved from SIV (*Sistema de Información Vacunal*) [27], that provided information about all HPV vaccine doses administered in public health system centres as well as in many private vaccination centres. Data from SIV included type and batch of the vaccines and date of administration. All these databases can be linked through the SIP number, a unique number identifying each resident (previously anonymised by the administrators of the databases) in the Valencian Community [26,28]. More information on these databases can be found in previous papers [26–28].

Girls and women were included in the cohort if they were aged from 14 to 19 years in January 2009, or on the day of entry into SIP, or on their fourteenth birthday, whichever occurred latest. Follow-up ended when they left Valencia (data of deletion from SIP), on either their twentieth birthday or their death, at the end of the

study (31 December 2014), or on the first activation of the diagnosis code for genital warts, whichever occurred first.

An incident case of genital warts was defined as the first activation of diagnosis code ICD-9-CM 078.11 (*Condyloma acuminatum*) in primary care and outpatient clinics during the study period. Recurrent cases were excluded.

Variables that are relevant to the disease or can impact on the incidence of genital warts were considered: age, calendar year, and health care department (to control for clinical practice variability).

Vaccination state was a time-dependent variable and different states were considered: 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 completely vaccinated (time from the date of third-dose registered).

### 2.2. Statistical analysis

A descriptive analysis included the vaccination coverage with the quadrivalent and bivalent vaccines, the genital wart incidence, the age of cases, the estimation of incidence rate by age, year, vaccination state, and health department, as well as the corresponding confidence intervals using the Poisson exact method. It also included the time between the third dose and the diagnosis of genital warts.

In addition, a Bayesian model of Poisson regression was built to analyse incidences of genital warts and vaccine effectiveness. The response variable was the number of incident cases of genital warts in the different observation units (counts by year, age, vaccination state, and health department). The model was adjusted and studied the effect of the covariates “vaccination state”, “age”, “healthcare department”, and “year”. The last two covariates were included as random effects.

It should be noted that the variates “age”, “year”, and “vaccination state” changed over time. Therefore, each subject contributed person-time to each combination of vaccination state, age group, and year. The sum of times of each observation unit acted as the “exposition or control” variate within the models, i.e., ones that impacted directly on mean response, because there is a natural assumption that the more person-years, the greater the likelihood of cases of genital warts.

Vaccine effectiveness is presented as risk ratios (RR) with 95% credible intervals (CrI), analogous to 95% confidence intervals in frequentist statistics. In a Bayesian context, the 95% CrI directly shows that the true RR lies within the range of CrI with a probability of 95%.

The study protocol and programming code are accessible via <https://www.dropbox.com/sh/q3csvit381sgyo8/AAA3u9e2r12VrhUzujm1IFha?dl=0>.

The study was approved by the Ethics Research Committee of the Dirección General de Salud Pública/Centro Superior de Investigación en Salud Pública, that permitted the codified linkage of the databases. All the study was conducted in accordance to the Good Epidemiological Practice (November 2007) of the International Epidemiological Association [29].

## 3. Results

The study cohort included 279,787 girls and women, who provided 809,864 person-years. The vaccination coverage of three doses of quadrivalent HPV vaccine in women born in 1994 and 1995 was 44.9%. In addition, 13.1% of the girls and women born between 1996 and 2000 were vaccinated with this vaccine. Vaccine coverage with AS04-adjuvanted bivalent HPV vaccine was

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