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Impact of quadrivalent human papillomavirus vaccine on genital warts in an opportunistic vaccination structure

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HIGHLIGHTS

- Opportunistic HPV vaccination caused 31% decrease in condyloma incidence in women.
- Opportunistic HPV vaccination caused 12% decrease in condyloma incidence in men.
- HPV vaccine is effective in reducing condyloma in opportunistic vaccination structure.

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ABSTRACT

Objective. Genital warts are the most common sexually transmitted disease and have a detrimental impact on quality of life. Genital warts could be prevented by prophylactic HPV vaccination. The objective was to study real-life benefit of opportunistic HPV vaccination on age and gender specific incidence of genital warts.

Methods. We performed a register-based population cohort study from publicly funded health-care provider in Israel. The incidence of genital warts was assessed during three time frame intervals: 2006–2008 (pre-vaccination effect period) 2009–2012 (early post-vaccination effect period) and 2013–2015 (late post-vaccination effect period), with an average annual number of members of 1,765,481, 1,906,774 and 2,042,678 in the years 2006–2008, 2009–2012 and 2013–2015, respectively.

Results. Among females, annual incidence of genital warts per 100,000 women decreased from 210.43 to 161.71 (OR 0.76, 95%CI 0.71–0.82, $p < 0.001$) and to 146.8 (OR 0.69, 95%CI 0.66–0.72, $p < 0.001$) between pre-vaccination period and early and late post-vaccination periods, respectively. Among males, annual incidence of genital warts per 100,000 men decreased from 262.85 to 232.40 (OR 0.88, 95%CI 0.83–0.93, $p < 0.001$) and to 234.01 (OR 0.88, 95%CI 0.86–0.91, $p < 0.001$) between pre-vaccination period and early and late post-vaccination periods, respectively.

Conclusions. There is a potential benefit in reducing incidence of genital warts even in opportunistic HPV vaccination structure. This information may be relevant for health-care providers in countries where national immunization programs do not include HPV vaccines.

1. Introduction

Genital warts or condyloma acuminata are caused by a sexually transmitted infection with low-risk Human Papilloma Virus (HPV) [1]. HPV types 6 and 11 are responsible for about 90% of genital warts [2]. HPV was disclosed to pose a significant burden in health (clinical and quality of life) as well as monetary terms for genital warts [3]. The quadrivalent HPV vaccine (Gardasil®, Merck, USA) has proven highly effective against infection with HPV types 6 and 11 and development of genital warts among women as well as men in clinical trials [4,5]. Vaccine implementation could be either opportunistic or as part of a national immunization program in which the vaccine is administered to females only or both females and males [6]. National immunization program vaccines are either recommended or imposed compulsory to entire or targeted population depending on risk assessment. In an opportunistic vaccination structure, the vaccines are not recommended or imposed compulsory for the entire population at risk, but are administered to appropriate individuals upon request. There is worldwide accumulating

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evidence that vaccine implementation as a part of national immunization program produces a significant decrease in genital warts incidence in vaccinated individuals with beneficial herd protection for unvaccinated population [7–13]. Still, as of August 2016, only about 60 countries in the world include HPV vaccines in their national immunization programs with varying coverage rates [14].

Two HPV vaccines are available in Israel: one is a bivalent vaccine (Cervarix®, Glaxo Smith Kline), protecting against "high risk" HPV types 16 and 18 and the other is a quadrivalent vaccine (Gardasil®, Merck), protecting against "high-risk" HPV types 16 and 18, as well as "low-risk" HPV types 6 and 11 [15]. Since its introduction in June 2007, the quadrivalent vaccine was available primarily for females and only through the private market and through supplementary health insurances provided by one of four independent health-care providers in Israel [15]. At that time (2007), a cost–utility analysis of vaccination against HPV in Israel, concluded that it was not cost-effective [16] and therefore it was not included in national immunization program. Accordingly, HPV vaccination was opportunistic until 2013, when it was introduced as a part of the national immunization program in schools at the age of 13 years for girls. In 2013, the bivalent vaccine was administered to girls, and since 2014 the quadrivalent vaccine has been administered to girls as part of the national immunization program. Subsequently since 2015 it is administered to boys as well. Even though the four health-care providers cover all Israeli residents, it is difficult to evaluate the rate or distribution of HPV vaccination in Israel in the opportunistic vaccination period due to the nature of the supplementary insurance and the private market [15]. Still, this opportunistic vaccination structure provides an opportunity to evaluate whether this type of setup is beneficial in reducing the incidence of genital warts. This information might be relevant for health-care providers in countries where national immunization programs do not include HPV vaccines.

This population based study aimed at evaluating the real-life benefit of an opportunistic HPV vaccination structure with regard to genital warts incidence according to age group and gender. The pre- and post-vaccination effect periods were chosen encountering the year of introduction of quadrivalent vaccine in Israel (June 2007), the year of expansion of indicated age for vaccination quadrivalent vaccine from 26 to 45 years (2012), the average timeline from HPV exposure to the development of genital warts is about 3 month [17], and the assumption that at least one year lag is needed to observe the effect of the vaccine [18].

2. Materials and methods

The quadrivalent HPV vaccine was introduced in Israel in June 2007 and the vaccination was opportunistic, as it was not covered by the National Health Insurance Act. Its introduction was promoted by its manufacturer focusing on prevention of cervical cancer. At first it was indicated for females aged 9 to 26 years and in the year 2012 it was expanded to females aged 9 to 45 years. During the opportunistic vaccination period, the vaccines were administered to adequate individuals upon request.

The state of Israel provides health services for all residents of the country subject to the National Health Insurance Law. The comprehensive health services are delivered by four independent health-care providers. The current report summarizes data from Maccabi Healthcare Services, the second largest publicly funded health-care provider in Israel during three time frame intervals, namely 2006–2008 (pre-vaccination effect period) 2009–2012 (early post-vaccination effect period) and 2013–2015 (late post-vaccination effect period). Entire Maccabi Healthcare Services population was included in the analysis, with average annual number of members of 1,765,481, 1,906,774 and 2,042,678 in the years 2006–2008, 2009–2012 and 2013–2015, respectively.

We retrospectively examined trends in rates of genital warts diagnoses from data that were obtained from a Maccabi Healthcare Services database containing medical record information including all outpatient visits to community health centers. The dataset in the database was described previously in details [3]. Briefly, all physicians operating in Maccabi Healthcare Services use a nationwide network of computerized medical record. The database is not only a billing tool but also a central data repository, retaining historical records of patient demographic, clinical and resource-utilization data. Double records, non-Israeli citizens, other sources of artifacts and irrelevant data were filtered out, and the reliability of the data was re-assessed. Main outcome measure was the diagnosis of genital warts. The study protocol was approved by the Institutional Review Board Committee of Maccabi Healthcare Services.

Analysis of data was carried out using Epiinfo 7 (Centers for Disease Control and Prevention, Atlanta, GA). We compared the proportion of patients diagnosed as having genital warts in the two study periods by the chi-square (χ^2) test, and determined the odds ratios along with 95% confidence intervals. Analysis was also performed after stratification for age groups and gender. Absolut risk reduction was calculated in rate per 100,000 subjects per year. All tests were two-sided and considered significant at $p < 0.05$.

3. Results

There were 12,497, 14,962 and 11,600 new cases of genital warts in the years 2006–2008, 2009–2012 and 2013–2015, respectively. Among females, the annual incidence of genital warts per 100,000 women decreased from 210.43 to 161.71 (OR 0.76, 95%CI 0.71–0.82, $p < 0.001$) between pre-vaccination period (years 2006–2008) and early post-vaccination period (years 2009–2012) and to 146.8 (OR 0.69, 95%CI 0.66–0.72, $p < 0.001$) between pre-vaccination period (years 2006–2008) and late post-vaccination period (years 2013–2015) with an absolute risk reduction of 48.72 and 63.62 cases per 100,000 women per year between pre-vaccination period and early and late post-vaccination periods, respectively. The annual incidence of genital warts per 100,000 women decreased from 161.71 to 146.8 (OR 0.90, 95%CI 0.84–0.97, $p < 0.001$) between early post-vaccination period (years 2009–2012) and late post-vaccination period (years 2013–2015) with an absolute risk reduction of 14.91 cases per 100,000 women per year.

Among males, the annual incidence of genital warts per 100,000 men decreased from 262.85 to 232.40 (OR 0.88, 95%CI 0.83–0.93, $p < 0.001$) between pre-vaccination period (years 2006–2008) and early post-vaccination period (years 2009–2012) and to 234.01 (OR 0.88, 95%CI 0.86–0.91, $p < 0.001$) between pre-vaccination period (years 2006–2008) and late post-vaccination period (years 2013–2015) with an absolute risk reduction of 30.45 and 28.84 cases per 100,000 men per year between pre-vaccination period and early and late post-vaccination periods, respectively. The difference between annual incidence of genital warts per 100,000 men between early post-vaccination period (years 2009–2012) and late post-vaccination period (years 2013–2015) was not statistically significant: 232.40 and 234.01, respectively (OR 1.006, 95%CI 0.94–1.06, $p = 0.81$). The annual incidence of genital warts per 100,000 subjects between pre-vaccination period (years 2006–2008) and late post-vaccination period (years 2013–2015) decreased by 31% (95%CI: 28%–34%) in females compared to 12% (95%CI: 9% to 14%) in males ($p = 0.006$).

Comparison of new cases of subjects with warts and its incidence per 100,000 subjects per year between pre-vaccination and early post–vaccination periods in females and males is presented in Table 1. Comparison of new cases of subjects with warts and its incidence per 100,000 subjects per year between early post-vaccination and late post–vaccination periods in females and males is presented in Table 2. Comparison of new cases of subjects with warts and its incidence per 100,000 subjects per year between pre-vaccination and late post–vaccination periods in females and males is presented in Table 3. The incidence of genital warts in females by age group and vaccination effect periods are described in Fig. 1. The incidence of genital warts in males by age group and vaccination effect periods are described and Fig. 2. The greatest absolute risk reduction was in the 19–24 years age group.

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