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Estimation of the epidemiological burden of HPV-related anogenital cancers, precancerous lesions, and genital warts in women and men in Europe: Potential additional benefit of a nine-valent second generation HPV vaccine compared to first generation HPV vaccines

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ABSTRACT

Introduction: A second generation HPV vaccine has been developed for the prevention of anogenital cancers and precancerous lesions of the cervix, vulva, vagina, anus and of genital warts due to nine HPV types.

We estimated the annual burden of these diseases attributable to the nine HPV types compared to HPV types from first generation vaccines in women and men in Europe.

Material and methods: Incidence rates from the IARC database, cancer registries, the literature and Eurostat population data were used.

The burden attributable to the HPV types targeted by both vaccines was estimated by applying the relative contribution of the respective HPV types from epidemiological studies.

Results: In 2013, the number of new anogenital HPV-attributable cancers was 44,480 with 39,494 of these cases related to second vs. 33,285 to first generation vaccine types.

Among the 284,373 to 541,621 new HPV-attributable anogenital precancerous lesions 235,364–448,423 and 135,025–256,830 were estimated to be related to second and first generation vaccine types, respectively.

The annual number of new genital warts was 753,608–935,318, with 90% related to HPV6/11.

Conclusions: These data demonstrate how the large public health impact that was achieved by the first generation HPV vaccines could be further increased by second generation vaccines.

1. Introduction

The discovery of human papillomavirus (HPV) as the necessary cause of cervical cancer has led to the development of different prophylactic HPV vaccines. The International Agency for Research on Cancer (IARC) has identified twelve HPV types as carcinogenic to humans: HPV16/18/31/33/35/39/45/51/52/56/58/59 [1]. In addition to cervical cancer, HPV is responsible for a significant proportion of cancers and precancerous lesions of the vulva, vagina, and anus in women; cancers and precancerous lesions of the anus and penis in men; and a subset of head and neck cancers and genital warts in both sexes.

Two HPV vaccines have been licensed so far in Europe: the quadrivalent HPV vaccine, Gardasil® 9 (Sanofi Pasteur MSD)/ Silgard® (Merck Sharp & Dohme), and the bivalent HPV vaccine, Cervarix® (GlaxoSmithKline Biologicals). Both vaccines have reassuring safety profiles, as demonstrated in clinical trials, and are indicated for the prevention of cervical, vulvar and vaginal premalignant lesions and cervical cancer related to HPV16/18. The quadrivalent HPV vaccine is also indicated against premalignant anal lesions and anal cancer and protects against low-risk HPV6/11, which are responsible for about 90% of genital warts [2] and a fraction of precancerous lesions.

Abbreviations: AIN, anal intraepithelial neoplasia; CI, confidence interval; CI5, Cancer Incidence in Five Continents; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; IARC, International Agency for Research on Cancer; VIN, vulvar intraepithelial neoplasia; VaIN, vaginal intraepithelial neoplasia

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As it takes several decades for HPV infection to progress to cancer, it will be some time before the real effects of current HPV vaccination programs will be seen in terms of a reduced incidence of HPV-related cancers. In the meantime, in countries like Australia, where vaccination coverage is high, a reduction of 77% in the prevalence of infections with the HPV types targeted by the vaccines has been observed in young women [3], along with a 92.6% reduction in the incidence of genital warts ($p_{trend} < 0.0001$) [4]. Moreover, just 3 years after the implementation of the HPV vaccination program in Australia, the incidence of high-grade cervical precancerous lesions in women under 18 years of age decreased, from 0.85% in 2006 (1 year before vaccine introduction) to 0.22% in 2009 ($p=0.003$) [5]. This ecological observation was confirmed in two recent studies. One was a data-linkage study [6] that reported an adjusted vaccine effectiveness of 47.5% (95% confidence interval [CI]: 22.7–64.4%) to prevent cervical intraepithelial neoplasia (CIN) grade 3/adenocarcinoma in situ or worse among women who received all required doses of the quadrivalent vaccine (i.e., were fully vaccinated). The other study [7] reported a vaccine effectiveness of 46% (95% CI: 33–57%) for histologically confirmed high-grade cervical precancerous lesions among young women who were fully vaccinated before they initiated cervical cancer screening. Additionally, as a reflection of herd immunity, there has been a significant reduction in the frequency of genital warts in young men. In Australia, where there is an estimated 83% coverage of the first dose of HPV vaccine in girls aged 12–13 years, the reduction in the proportion of new genital warts cases among young men was in the order of 60% [8,9]. In 2013, Australia became the first country to implement a school-based vaccination program for boys aged 12–13 years. Currently the United States, Ireland, New Zealand, and Canada are also recommending HPV vaccination for boys.

After HPV16/18, high-risk HPV31/33/35/45/52/58 are the six most frequently detected HPV types in invasive cervical cancer worldwide [10]. Merck has developed a second generation nine-valent HPV L1 virus-like particle vaccine (Gardasil® 9), which aims to protect against the seven high-risk HPV types (HPV16/18/31/33/45/52/58) most frequently responsible for cervical cancer development worldwide, and the low-risk HPV types (HPV6/11) responsible for about 90% of genital warts. Thus, the nine-valent vaccine is designed to protect against five 'new' high-risk HPV types (HPV31/33/45/52/58) that are not targeted by the quadrivalent or the bivalent vaccine. The vaccine is indicated to protect against premalignant lesions and cancers affecting the cervix, vulva, vagina and anus caused by vaccine HPV types as well as genital warts caused by specific HPV types.

In a Phase III study, the nine-valent vaccine prevented 97% of high-grade precancerous lesions of the cervix, vulva, and vagina caused by the five new high-risk HPV types (HPV31/33/45/52/58) [11]. The nine-valent vaccine also generated immune responses to HPV6/11/16/18 that were as good as or better than those generated by the quadrivalent vaccine.

The aim of this study was to estimate the annual burden of selected cancers, precancerous lesions, and genital warts attributable to the HPV types targeted by the second generation nine-valent HPV vaccine Gardasil 9® (high-risk HPV16/18/31/33/45/52/58, low-risk HPV6/11) in women and men in Europe in 2013, and to compare this to the estimated annual burden of the same lesions related to the HPV types targeted by the first generation HPV vaccines.

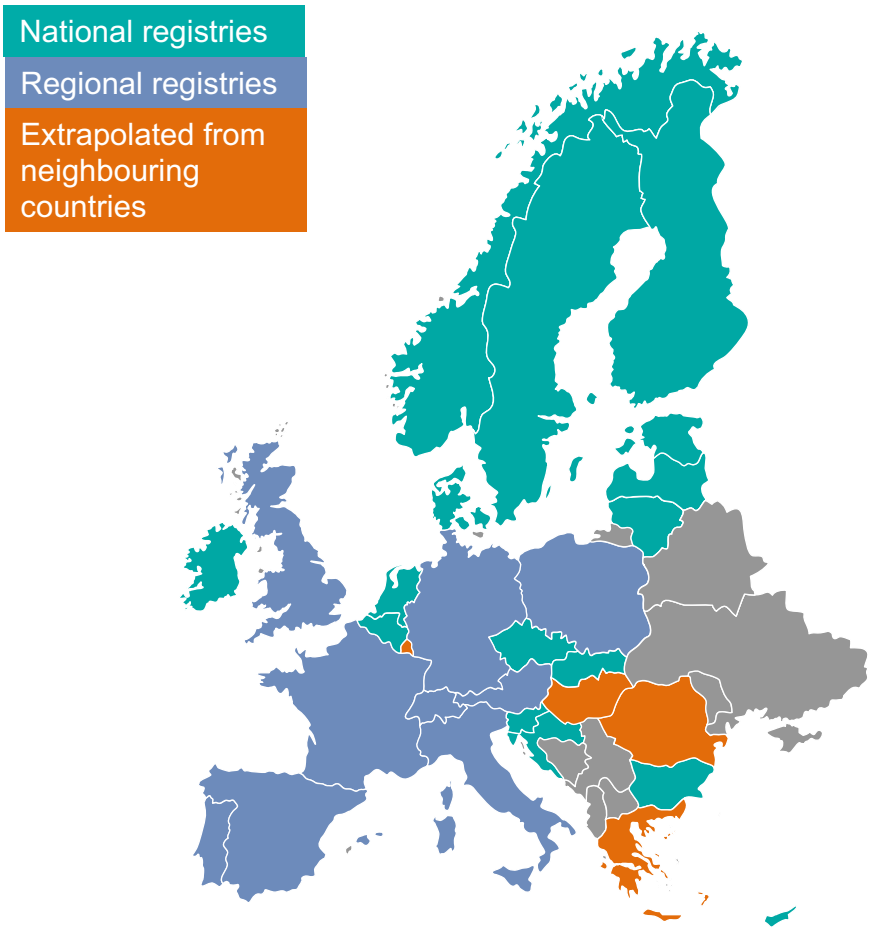

Fig. 1. Selected countries: European Medicines Agency region and Switzerland (32 countries).