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Human papillomavirus detection in cervical neoplasia attributed to 12 high-risk human papillomavirus genotypes by region ☆

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ABSTRACT

Background: We estimated the proportion of cervical intraepithelial neoplasia (CIN) cases attributed to 14 HPV types, including quadrivalent (qHPV) (6/11/16/18) and 9-valent (9vHPV) (6/11/16/18/31/33/45/52/58) vaccine types, by region

Methods: Women ages 15–26 and 24–45 years from 5 regions were enrolled in qHPV vaccine clinical trials. Among 10,706 women (placebo arms), 1539 CIN1, 945 CIN2/3, and 24 adenocarcinoma in situ (AIS) cases were diagnosed by pathology panel consensus.

Results: Predominant HPV types were 16/51/52/56 (anogenital infection), 16/39/51/52/56 (CIN1), and 16/31/52/58 (CIN2/3). In regions with largest sample sizes, minimal regional variation was observed in 9vHPV type prevalence in CIN1 (~50%) and CIN2/3 (81–85%). Types 31/33/45/52/58 accounted for 25–30% of CIN1 in Latin America and Europe, but 14–18% in North America and Asia. Types 31/33/45/52/58 accounted for 33–38% of CIN2/3 in Latin America (younger women), Europe, and Asia, but 17–18% of CIN2/3 in Latin America (older women) and North America. Non-vaccine HPV types 35/39/51/56/59 had

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similar or higher prevalence than qHPV types in CIN1 and were attributed to 2–11% of CIN2/3.
Conclusions: The 9vHPV vaccine could potentially prevent the majority of CIN1-3, irrespective of geographic region. Notwithstanding, non-vaccine types 35/39/51/56/59 may still be responsible for some CIN1, and to a lesser extent CIN2/3.

1. Introduction

A 9-valent HPV (9vHPV) vaccine was licensed in 2014 in the United States and in 2015 in Canada, the European Union and Australia for the prevention of cervical, vulvar, vaginal, and anal cancers, their respective pre-cancerous lesions, and genital warts caused by HPV types 6/11/16/18/31/33/45/52/58 in females and males aged 9–26 years. The vaccine was developed to protect against cancer and precancer beyond what is already provided by the current quadrivalent vaccine (qHPV vaccine), which targets the high risk (HR) (i.e., cancerous) HPV types 16/18. The 9vHPV vaccine additionally targets the 5 next most common HPV types found in cervical cancer worldwide (HPV 31/33/45/52/58). Both the 9vHPV and qHPV vaccines also protect against the low risk (i.e., not likely to cause cancer) types 6/11 responsible for 90% of genital warts cases.

In a pivotal Phase III efficacy study, the 9vHPV vaccine prevented approximately 97% of cervical, vaginal and vulvar precancers caused by HPV 31/33/45/52/58. The vaccine also generated antibody responses to HPV6/11/16/18 that were non-inferior to those generated by the qHPV vaccine and had a favorable safety profile [1].

Approximately 90% of cervical cancers worldwide are attributed to infection with the 7 HR HPV types targeted by the 9vHPV vaccine (i.e., HPV16/18/31/33/45/52/58) [2,3]. A previous study of women in Brazil, Mexico, India and China also found that approximately 90% of cervical cancer cases in these countries are attributed to the 9vHPV types, with some minor regional variation in the proportion of these cancers attributed to HPV 31/33/45/52/58 (12–19% variability) [7]. Similarly, a previous study using qHPV clinical trial data found that approximately 85% or more of cervical intraepithelial neoplasia grade 3 (CIN3) and adenocarcinoma in situ (AIS), and approximately 50% of CIN1 lesions are attributed worldwide to the types targeted by the 9vHPV vaccine [4]. However, regional data on the proportion of CIN and AIS attributed to the 9vHPV vaccine types are sparse. Such data are essential for estimating the regional impact of HPV vaccines on the rates of cervical lesions. For example, the greatest impact of HPV vaccination is expected in low- and middle-income countries where the current qHPV and bivalent HPV vaccines targeting HPV16/18 are estimated to potentially reduce cancer risk by 40–50% at 70% vaccine uptake and where well organized screening programs are lacking [5–7].

Using data from the qHPV vaccine clinical trials, we estimated the proportion of CIN1-3 in North America, Latin America, Europe, Asia, and Oceania [8–11] attributed to the 14 HPV types tested in the trials (HPV6/11/16/18/31/33/35/39/45/51/52/56/58/59), as well as the proportion attributed overall to the 9vHPVvaccine types (6/11/16/18/31/33/45/52/58) and by the 9vHPV vaccine's constituent qHPV types (6/11/16/18) and 5 new types (31/33/45/52/58).

2. Materials and methods

2.1. Objective

The objective of this analysis was to determine the proportion of low and high grade cervical lesions (CIN1-3) attributed to the 9vHPV vaccine types (6/11/16/18/31/33/45/52/58), to the qHPV types (6/11/16/18), to the 5 new types targeted by the 9vHPV vaccine (31/33/45/52/58), as well as to 5 other measured non-vaccine HR HPV types (35/39/51/56/59), across the 5 regions studied.

2.2. Study designs and population

Data from 3 randomized double-blind, placebo-controlled clinical trials of the qHPV vaccine were used in this analysis. Protocols 013 and 015 included 17,622 women (8798 in placebo group) 15–26 years old from 23 countries enrolled between December 2001 and May 2003, while Protocol 019 included 3819 women (1908 in placebo group) 24–45 years old from 7 countries enrolled between June 2004 and April 2005. Participants in the trials were followed for approximately 4 years. As Protocols 013 and 015 enrolled only a small percentage of women above the age of 23, the age range for Protocol 019 was chosen to overlap with these studies. The proportions of subjects enrolled from the following regions for the younger and older age groups, respectively, are: North America (13%, 14%), Latin America (32%, 42%), Europe (51%; 13%), Asia (2%; 31%) and Oceania (2%, only included for women aged 15–26 years). Further details of subjects and patients with lesions and the countries included in these trials are provided in Supplementary Appendix Table A.1

The study designs, protocols, and results of the primary hypotheses for each of the studies have been previously described [8–10]. The studies were conducted in accordance with principles of Good Clinical Practice and were approved by the appropriate institutional review boards and regulatory agencies.

2.3. Analyses for infection

HPV anogenital infection prevalence was reported as one potential measure of HPV types circulating in the study population, and it can be compared to HPV types responsible for causing low and high grade cervical lesions. An endo/ectocervical swab (one specimen) and a combined labial/vulvar/perianal swab were obtained from all subjects across the trials. Prevalence of HPV infection at day 1 was assessed in the vaccine and placebo arms combined to increase precision (given the randomized nature of the trials, it is expected that the placebo arm infection prevalence will be similar to the prevalence in the combined trial arms). In each study, day 1 swabs were tested for 14 HPV types (6/11/16/18/31/33/35/39/45/51/52/56/58/59) using a PCR-based assay as previously described [12–14].

2.4. Cervical neoplasia diagnosis

All biopsies and excisional procedure specimens were tested for the 14 HPV types as previously described [4]. All specimens were processed and adjacent histological sections of each specimen were first read for clinical management by pathologists at a central laboratory (Diagnostic Cytology Laboratories, Indianapolis, IN) and then read for endpoint determination by a panel of up to 4 pathologists who were blinded to central laboratory and clinical diagnoses, treatment group, and HPV status. The following