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Impact of baseline covariates on the immunogenicity of the 9-valent HPV vaccine – A combined analysis of five phase III clinical trials

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ABSTRACT

Background: The immunogenicity profile of the 9-valent HPV (9vHPV) vaccine was evaluated across five phase III clinical studies conducted in girls and boys 9–15 years of age and young women 16–26 years of age. The effect of baseline characteristics of subjects on vaccine-induced HPV antibody responses was assessed.

Methods: Immunogenicity data from 11,304 subjects who received ≥1 dose of 9vHPV vaccine in five Phase III studies were analyzed. Vaccine was administered as a 3-dose regimen. HPV antibody titers were assessed 1 month after dose 3 using a competitive Luminex immunoassay and summarized as geometric mean titers (GMTs). Covariates examined were age, gender, race, region of residence, and HPV serostatus and PCR status at day 1.

Results: GMTs to all 9 vaccine HPV types decreased with age at vaccination initiation, and were otherwise generally similar among the demographic subgroups defined by gender, race and region of residence. For all subgroups defined by race or region of residence, GMTs were higher in girls and boys than in young women. Vaccination of subjects who were seropositive at day 1 to a vaccine HPV type resulted in higher GMTs to that type, compared with those in subjects who were seronegative for that type at day 1.

Conclusions: 9vHPV vaccine immunogenicity was robust among subjects with differing baseline characteristics. It was generally comparable across subjects of different races and from different regions. Greater immunogenicity in girls and boys versus young women (the population used to establish 9vHPV vaccine efficacy in clinical studies) indicates that the anti-HPV responses generated by the vaccine in adolescents from all races or

Abbreviations: HPV, human papillomavirus; VLP, virus-like particle; 9vHPV, 9-valent human papillomavirus; cLIA, competitive Luminex immunoassay; GMTs, geometric mean titers; CI, confidence interval; mMU/mL, milli-Merck units per milliliter; qHPV, quadrivalent human papillomavirus

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regions were sufficient to induce high-level protective efficacy. This immunogenicity profile supports a widespread 9vHPV vaccination program and early vaccination.

1. Introduction

Human papillomavirus (HPV) is the cause of nearly all cervical cancers and a substantial proportion of anal, vulvar, vaginal, penile and oropharyngeal cancers; thus, it is responsible of approximately 5% of the global cancer burden [1]. The identification of HPV as a primary cause of anogenital cancers created an opportunity for cancer prevention through vaccination. First generation HPV vaccines, including the quadrivalent HPV (types 6/11/16/18) (qHPV) vaccine and the bivalent HPV (types 16/18) vaccine were initially developed [2]. A 9-valent HPV (types 6/11/16/18/31/33/45/52/58) (9vHPV) vaccine (Gardasil 9, Merck & Co., Inc., Kenilworth, NJ) was subsequently developed to provide protection against the HPV types already covered by the qHPV vaccine and the next five most common oncogenic types associated with cervical cancer worldwide (types 31/33/45/52/58) [3]. The 9vHPV vaccine could potentially prevent approximately 90% of cervical cancers, HPV-related vulvar, vaginal and anal cancers and genital warts worldwide [4–9]. The 9vHPV vaccine was licensed in 2014 in the US, in 2015 in Canada, the EU and Australia, and in 2015 and 2016 in other countries.

In a clinical trial conducted in women 16–26 years of age, the 9vHPV vaccine prevented infection and disease caused by HPV 31/33/45/52/58. It also induced anti-HPV 6/11/16/18 antibody responses that were non-inferior to responses induced by the qHPV vaccine; efficacy of the 9vHPV vaccine against infection and disease caused by HPV 6/11/16/18 was inferred based on these results [10–12]. In another clinical trial, the 9vHPV vaccine induced non-inferior antibody responses to HPV 6/11/16/18/31/33/45/52/58 in girls and boys 9–15 years of age vs. women 16–26 years of age; efficacy of the 9vHPV vaccine against infection and disease caused by the 9 vaccine HPV types in girls and boys 9–15 years of age was inferred based on these results [13].

HPV infection is a global health concern; prophylactic HPV vaccination is included in the national immunization programs of at least 80 countries [14], and used in diverse settings worldwide. It is anticipated that the 9vHPV vaccine will be widely licensed and recommended. Thus, it is useful to evaluate the impact of demographic parameters on the immunogenicity of the 9vHPV vaccine. Of relevant note, a similar study examining the impact of demographic parameters on the immunogenicity of the qHPV vaccine was published shortly after the initial licensure of the qHPV vaccine [15]. This report summarizes a combined analysis of five Phase III clinical trials conducted in girls and boys 9–15 years of age and women 16–26 years of age to examine antibody responses in subgroups for which individual studies may have had limited sample size. Thus, these analyses are novel and may be of interest to many as the 9vHPV vaccine becomes more widely available. Immunogenicity of the 9vHPV vaccine in young men 16–26 years of age was not included in these analyses; it will be the topic of another report so that the additional complexities specific to that population (i.e., lower HPV antibody responses in men having sex with men than in heterosexual men [16,17]) can be fully explored.

2. Materials and methods

2.1. Enrollment and vaccination

An analysis of the combined immunogenicity database of Phase III studies submitted to regulatory agencies in support of the licensure of the 9vHPV vaccine was conducted. This analysis included 11,304 subjects who received 9vHPV vaccine in five Phase III studies (Table 1). These studies contained three separate populations: virginal girls 9–15 years of age, virginal boys 9–15 years of age, and young women 16–26 years of age, most of whom were sexually active. Eligible subjects received a 3-dose vaccination regimen given as intramuscular injections at day 1, month 2 and month 6. Each study was conducted in accordance with principles of Good Clinical Practice and was approved by the institutional review board at each participating institution and by regulatory agencies. Written informed consent was provided by all adult subjects and by a parent or legal guardian of subjects who were minors, assent was also obtained from minors in conformity with

Table 1
Phase III studies of the 9vHPV vaccine contributing to the combined immunogenicity analysis.

Study	Key objectives	Experimental arm	Control arm	Included in analyses[a]
001	Immunogenicity, efficacy vs. qHPV	Women age 16–26 years randomized to 9vHPV vaccine (N=6799)[b]	Women age 16–26 years randomized to qHPV vaccine (N=6799)[b]	N=6792[b,c]
002	Adult-to-adolescent immunobridging	Girls and boys age 9–15 years (N=2604) enrolled to receive 9vHPV vaccine	Women age 16–26 years enrolled to receive 9vHPV vaccine (N=470)	N=3066
005	Co-administration with Menactra/Adacel	Girls and boys age 11–15 years randomized to concomitant arm (N=621)	Girls and boys age 11–15 years randomized to non-concomitant arm (N=620)	N=618[d]
007	Co-administration with Repevax	Girls and boys age 11–15 years randomized to concomitant arm (N=526)	Girls and boys age 11–15 years randomized to non-concomitant arm (N=528)	N=528[d]
009	qHPV-to-9vHPV immunobridging	Girls age 9–15 years randomized to 9vHPV vaccine (N=300)	Girls age 9–15 years randomized to qHPV vaccine (N=300)	N=300[c]

Study 001: NCT00543543 [10].
Study 002: NCT00943722 [13].
Study 005: NCT00988884 [22].
Study 007: NCT01073293 [23].
Study 009/GDS01C: NCT01304498 [12].

[a] Subjects who received at least one vaccination with 9vHPV vaccine. A total of 11,304 subjects who received at least one 9vHPV vaccination are included in these analyses. Most subjects (97.7% [11,046 of 11,304]) received the three vaccinations.

[b] Subjects who received the low-dose, mid-dose or high-dose formulation of 9vHPV vaccine during the dose selection portion of the study [10,43] are not included; immunogenicity results in these subjects are reported in [44].

[c] Subjects randomized to the 9vHPV vaccine who received ≥1 dose of vaccine.

[d] Subjects randomized to the non-concomitant arm who received ≥1 dose of 9vHPV vaccine. Subjects randomized to the concomitant arm of studies 005 and 007 are not considered in this report; immunogenicity results in these subjects are reported in [22,23].