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Randomized controlled trial of two dosing schedules for human papillomavirus vaccination among college age males

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ABSTRACT

Background: Quadrivalent human papillomavirus (HPV) vaccine, for protection against sexually transmitted HPV infection, is licensed for females and males 9–26 years on a 3-dose schedule (0, 2, and 6 months; Standard schedule). Vaccine uptake has been low and catch-up vaccination of older adolescents using an alternate dosing schedule may increase coverage. This study tested the non-inferiority of the immunogenicity of an alternate dosing schedule (0, 2, 12 months) among college age males.
Methods: 220 18–25 year old males were randomly assigned to Standard or Alternate schedules. Blood samples were drawn immediately before Dose 1 and 2–6 weeks after Dose 3 and analyzed for antibody titers using a Luminex immunoassay. A value <1.5 for the upper 95% confidence interval (CI) bound of the Standard to Alternate schedule geometric mean titer (GMT) ratio was deemed non-inferior.
Results: Participants averaged 21.3 years old; 19.1% were non-white; completion rate was 93%. The anti-HPV titers for the Alternate schedule group were non-inferior to those of Standard schedule group for all four HPV vaccine virus types. Our results also demonstrated superiority of the Alternate schedule group for all four HPV vaccine virus types.
Conclusion: A delayed third dose at 12 months is immunologically non-inferior and superior for four HPV virus types. Using an alternate dosing schedule offers more flexibility to receive the 3-dose HPV vaccine and may result in higher vaccination rates among college-age males.

1. Introduction

In 2006, the Advisory Committee on Immunization Practices (ACIP) licensed quadrivalent human papillomavirus (HPV) vaccine for use among females ages 9–26 years [1]. During the ensuing years, an enormous body of literature has been published regarding the acceptability of the vaccine among physicians, parents, adolescents, adult men and women, as well as barriers to and facilitators of HPV vaccine uptake. In addition, the manufacturer undertook a public relations/educational campaign aimed at informing the public about the protection from cervical cancer provided by the HPV vaccine. Yet, HPV vaccination rates among females are lower than national goals of 80% [2]. In 2011, based on a survey of the U.S. population, only one third of girls 13–17 years of age had received ≥3 doses of HPV vaccine [3]. Some of the reported barriers to full HPV vaccination are cost of vaccine, the three-dose schedule at 0, 2 and 6 months and its attendant difficulties, parental reluctance to vaccinate their young daughters against a sexually transmitted virus, and lack of physician recommendation, among others [4,5].

Several facts indicate the need for another approach to prevention of HPV-related disease: (1) HPV infection represents more than 70% of all incident and prevalent cases of sexually transmitted infections in the US [6], translating to 17.9 million new infections annually among 15–24 year olds; (2) vaccination against HPV among females is not at sufficient levels to protect them from cervical cancer; and (3) an estimated 21,000 cancers in females and 12,000 cancers in males annually in the U.S. are HPV-related [7].

To address the need to also protect men from HPV related cancers and genital warts, the ACIP permitted quadrivalent HPV vaccine for use among male ages 9–26 years in 2009 [8], with full recommendations published in 2011 [9]. This action was also intended to increase protection of women against cervical cancer by reducing male-to-female spread of the virus. Some of the same barriers to vaccination of males have been reported including, less supportive provider attitudes toward vaccinating males than females [10], lack of provider recommendation [11], lack of knowledge about the vaccine, not perceiving risk of HPV infection or benefit of vaccination, and preference for vaccinating at an older age [12]. Early estimates of HPV vaccination uptake among males

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are low with only 8.3% of adolescent males receiving at least one dose in 2011 [3].

The three dose vaccination schedule has also been reported as a barrier to HPV vaccine uptake among males [5], as evidenced by the fact that only 28.1% of 13–17 year olds who have initiated the vaccination schedule have completed the series as of 2011 [13]. Adherence to the three dose vaccination schedule may be difficult for young men, because their frequency of contact with the health care system generally decreases at this age [14,15]. Among those 18–26 years old, university health services can provide easy access to vaccination and other preventive health services, but an academic calendar may not be conducive to completing the Standard schedule on time unless the first dose is administered early in the academic year. The purpose of this study was to test non-inferiority of an alternate administration schedule of 0, 2 and 12 months to the standard 0, 2 and 6 months schedule in a group of college-age men. We hypothesized that the immune response to the Alternate dosing schedule would be non-inferior to that of the Standard dosing schedule.

2. Methods

This study was approved by the University of Pittsburgh Institutional Review Board (PRO10070407) and registered at ClinicalTrials.gov as NCT01184079.

2.1. Participants

From October 2010 through May 2011, men 18–25 years of age, were recruited using a variety of strategies including fliers, class announcements, recommendations by university health centers, emails to campus organizations, bus and campus newspaper advertisements, and targeted Facebook® advertisements. Potential participants were excluded if they had: more than four lifetime sexual partners, health problems that would interfere with the immune response or ability to complete the study, a hospitalization during the past year, hypersensitivity to yeast or HPV vaccine components, inability to complete the scheduled appointments, received HPV vaccine previously or if they were taking any immunosuppressive medications. Out of 311 men who were screened, 91 were excluded for not meeting inclusion criteria, leaving 220 enrollees of whom 204 completed the study.

2.2. Interventions

Participants read and signed informed consent forms prior to starting the study and completed eligibility screening forms before each dose of vaccine. Participants were randomized as they were scheduled for the initial visit using a simple random number sequence to determine the order of assignment into the Standard schedule or the Alternate schedule. Participants were aware of their group assignment. Following each vaccination visit, participants were screened for adverse events. Height and weight were measured at the final visit. Data collection and intervention schedules are shown in Table 1. Data collection was completed on May 29, 2012.

2.3. Sample processing and immunogenicity testing

Vaccine storage and delivery followed standard procedures. Blood samples were drawn immediately prior to the first dose and 2–6 weeks after the third dose into serum separator tubes. Samples were spun at 3200 rpm for 10–15 min and serum was transferred to labeled nunc cryovials. Cryovials were stored at −70 °C. Frozen nunc tubes were shipped on dry ice to the laboratory by an express carrier. Serology testing for each of the four HPV types was performed at PPD Vaccines and Biologics Laboratory (Wayne, PA) using a competitive Luminex immunoassay (cLIA) that measures type-specific antibodies to neutralizing epitopes on the virus-like particles (VLPs) as described in Dias et al. [16].

2.4. Objectives

In this randomized controlled trial, the primary goal was to determine whether the post Dose 3 geometric mean titers (GMTs) for men in the Alternate schedule group ($N = 111$) were non-inferior to those in the Standard schedule group ($N = 109$). Non-inferiority means that the difference in GMTs between the Standard and Alternate schedule groups was small enough to support the conclusion that Alternate schedule group also benefitted from HPV vaccination. That is, non-inferiority was demonstrated if the upper bound of the two-sided 95% confidence interval (CI) of the ratio of GMTs (Standard schedule GMT divided by the Alternate schedule GMT) was smaller than 1.5 [17,18]. Although our clinical trial was not intended to show superiority of the Alternate schedule to the Standard schedule, we also examined immunological response superiority, defined as, the lower bound of the two-sided 95% CI of the GMT ratio (Alternate schedule GMT divided by the Standard schedule GMT) larger than 1.0 [18].

2.5. Sample size

The formula used for calculating sample size was: $(1 + 1/u)(Z_\alpha + Z_\beta)^2\ \sigma^2/[\log(R_{GMT}) - \delta_0]$ [17] where u is the ratio of the size of the Standard schedule to Alternate schedule groups ($u = 1$, for equal size groups); one-sided alpha (0.025), that is divided by 4 to account for multiplicity of 4 serotypes, a non-inferiority margin (δ_0) equal to natural log(0.67), the expected ratio of geometric mean titers R_{GMT} set at 0.8, and a standard deviation of 1.26 (personal communication, Alfred J. Saah, 2007). Sample size for a power of 80% was calculated to be 75 participants in each arm [17], but was increased to 110 to allow for the possibility of dropouts and baseline seropositive participants.

2.6. Statistical analyses

Descriptive analyses of participants' characteristics were performed for all randomized participants at baseline, overall and comparing those randomized to each of the two dosing schedules. Participants who had anti-HPV serum cLIA levels ≥20 milliMerck units/mL (mM/mL) for HPV types 6 and 16, ≥16 mM/mL for type 11, and ≥24 mM/mL for type 18 were considered to be seropositive at baseline [19] and were excluded from further analyses only for the type(s) for which they were seropositive. Other participants dropped out of the study because of failing to: (1) receive Dose 2 or Dose 3 at all; or (2) return for Dose 2, Dose 3 or the final blood draw within their respective study-designated windows (see Table 1). These individuals were excluded from subsequent "per protocol" analyses.

Because post-vaccination antibody titers were skewed, the data were natural log-transformed and then used to calculate HPV type-specific GMTs and 95% CIs for each group [20]. One-way analysis of variance (ANOVA) was used to compare continuous variables while the Pearson Chi-square test was used to compare categorical variables. In addition, reverse cumulative distribution curves for each virus type were plotted to visualize the difference in the log-transformed titers between participants randomized into the Standard and Alternate dosing schedules.

To examine the association between HPV type-specific titers and the time between receiving Dose 2 and Dose 3, linear regressions were conducted using log-transformed titers as the dependent