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Human papillomavirus vaccine effectiveness by number of doses: Systematic review of data from national immunization programs

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ABSTRACT

Background: Human papillomavirus (HPV) vaccines were first licensed as a three-dose series; a two-dose series is now recommended in some age groups and there is interest in possible one-dose vaccination.
Methods: We conducted a systematic literature review of HPV vaccine effectiveness by number of doses, including assessment of biases and impact of varying buffer periods (time between vaccination and outcome counting).
Results: Of 3787 articles identified, 26 full articles were assessed and 14 included in our review. All studies were conducted within the context of recommended three-dose schedules of bivalent (3) or quadrivalent HPV vaccine (11). Two evaluated effectiveness for prevention of HPV prevalence, six anogenital warts, and six abnormal cervical cytology or histology. Many studies found differences between three-, two- and one-dose vaccine recipients, indicating possible differences in HPV exposure prior to vaccination or in risk behavior. Adjusted or stratified analyses were conducted to control for potential confounding. All studies found significant vaccine effectiveness with three doses, 11 with two doses at various intervals, and six with one dose. Most studies showed a relationship (not always statistically significant) between effectiveness and number of doses, with greater decreases in HPV-related outcomes with three, followed by two and one dose(s). Few studies conducted formal comparisons of three vs fewer doses. Three of four studies that examined buffer periods found higher effectiveness and a smaller difference by number of doses with longer periods.
Conclusion: Most post-licensure studies report highest effectiveness with three doses; some found no statistically significant difference between two and three doses. Additionally, almost half found some effectiveness with one dose. Several biases impact estimates, with most biasing two- and one-dose results away from showing effectiveness. Future effectiveness studies, examining persons vaccinated prior to sexual activity and using methods to reduce potential sources of bias, can help inform vaccination policy.

1. Background

All three currently available human papillomavirus (HPV) vaccines were originally evaluated in clinical trials, licensed and recommended as a three-dose schedule (0, 1–2 and 6 months). However, interest in a reduced dose schedule arose soon after the first vaccines were licensed [1]. The high immunogenicity and efficacy observed in clinical trials with three doses and a post hoc analysis of one clinical trial stimulated interest in fewer doses [2]. Immunogenicity studies have been conducted with these available HPV vaccines and show non-inferior antibody response after two doses, administered 6–12 months apart, in young adolescents compared with three doses in women in the age group for which efficacy was demonstrated in clinical trials [3–5]. In 2014, the World Health Organization changed its guidance for number of doses

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and recommended a two-dose HPV vaccination schedule for girls starting the series at age 9 through 14 years [6]. In 2016, the Advisory Committee on Immunization Practices recommended a two-dose schedule in the United States for this age group [7]. Many countries in Europe, the Americas, and countries funded by Gavi, the Vaccine Alliance, either changed from a three-dose to a two-dose schedule in this age group, or introduced HPV vaccination with a two-dose schedule [8].

While immunogenicity trials have demonstrated non-inferiority of two HPV vaccine doses in young adolescents and were accepted by regulatory agencies, many effectiveness studies conducted in real world programs have largely shown lower effectiveness with fewer than three doses. We conducted a systematic review of the literature to: (1) summarize evidence about effectiveness of HPV vaccination by the number of doses, as measured in post-licensure studies, and (2) explore and discuss the main limitations and challenges of these studies.

2. Methods

2.1. Study selection

Studies were eligible if they fulfilled the following inclusion criteria: (1) reported effectiveness of HPV vaccination (bivalent or quadrivalent vaccine) on HPV infections, anogenital warts, or cervical abnormalities (based on cytological or histopathological results); (2) assessed effectiveness of HPV vaccination by the number of doses received (one, two, or three). We excluded studies if vaccine was administered as part of a randomized controlled trial (e.g., post hoc evaluations of clinical trials).

We searched Medline and Embase databases from January 1, 2007 to June 15, 2017 using a combination of Medical Subject Headings (MeSH) terms, title or abstract words, without restriction on the language of publications: (“papillomavirus vaccines”, “HPV vaccine”, “HPV vaccination”, “papillomavirus vaccine”, or “papillomavirus vaccination”) and (“program evaluation”, “immunization programs”, “population surveillance”, “sentinel surveillance”, “incidence”, “prevalence”, “rate”, “rates”, “effectiveness”, “doses”) and (“papillomavirus infections”, “HPV”, “uterine cervical neoplasms”, “cervical intraepithelial neoplasia”, “HPV related diseases”, “condylomata acuminata”, “genital warts”). The selection of eligible articles was performed independently by MD and NP on title and abstract first, and secondly on the full-text article.

2.2. Data extraction

Two authors (NP and LM) independently extracted the main study characteristics and outcomes using standardized forms. Any discrepancy between the two independent extractions was resolved by MD. The main study characteristics included the country, study design, age of study population at vaccination and outcome assessment, sample size according to the number of doses received, case definition, and statistical analyses (procedure used to assign the number of doses, and adjustment for potential confounders). Information on use of buffer periods (lag time between vaccination and counting of outcomes) was also collected. Buffer periods delay the case counting to attempt to exclude conditions caused by a prevalent infection at the time of vaccination.

Sources of bias in post-licensure studies examining the impact of HPV vaccination by number of doses include: (1) differences in the characteristics and age at vaccination between groups vaccinated with different number of doses; (2) likelihood of prevalent infection at vaccination; and (3) interval between the first and second dose of the HPV vaccine among two-dose vaccine recipients. Therefore, information on how authors dealt with these potential sources of bias was also extracted. Since one of the aims of this systematic review was to discuss the limitations of these studies, no studies were excluded on the basis of the methodological quality.

The main outcome was effectiveness of HPV vaccination comparing the incidence or prevalence of HPV-related endpoints between individuals vaccinated with different number of doses (three vs none, two vs none, one vs none, three vs two, three vs one, two vs one) of quadrivalent or bivalent vaccine. Results are presented as crude or adjusted risk ratios (RR) or odds ratios (OR). Of note, because eligible studies used different buffer periods or age groups at vaccination and at outcome assessment, it was not possible to pool results from the studies.

3. Results

The literature search identified 3787 articles, from which 26 full articles were assessed. After reading full texts, 12 articles were excluded, leaving 14 in our review (Fig. 1) [9–22]. These publications were from eight different countries, published from 2013 through 2017: Australia (three), Scotland (three), United States (two), Sweden (two), and one each from Belgium, Canada, Denmark, and Spain (Table 1). All evaluations were conducted within the context of a recommended three-dose schedule of either bivalent HPV vaccine (three) or quadrivalent HPV vaccine (eleven). Articles included analyses of effectiveness for prevention of HPV infection (two), anogenital warts (six), and cervical cytological or histological abnormalities (six) (Table 2 and Appendix).

Recognizing the potential for confounding, all investigators attempted to control for or stratified by potentially important variables, such as age at vaccination; however, limited other variables were available in most studies (Table 1). Four studies also evaluated the impact of different buffer periods and four evaluated different intervals between doses for two-dose vaccine recipients.

3.1. HPV prevalence

The two studies that reported vaccine effectiveness for reduction of prevalent vaccine type infection (HPV 16 or 18) were both from Scotland, conducted in the context of a three-dose bivalent HPV vaccination program that had achieved high coverage in the routine and catchup target age groups. The studies used residual cervical screening samples obtained at first screen of 20–21 year-olds and national vaccine registry data. Most two-dose vaccine recipients received doses at a one-month interval. Kavanagh et al. found statistically significant effectiveness for three doses, aOR = 0.43 (95% CI 0.34, 0.55); but not two doses, aOR = 0.68 (95% CI 0.42, 1.12); or one dose, aOR = 0.95 (95% CI 0.51, 1.76) [9]. There were few one- or two-dose vaccine recipients. In the second study, Cuschieri et al. over-selected women partially vaccinated [10]. Compared with three-dose vaccine recipients, partially vaccinated women were older than those fully vaccinated and differed by socioeconomic status. Statistically significant effectiveness was found for three doses, aOR = 0.27 (95% CI 0.20, 0.37); two doses, aOR = 0.45 (95% CI 0.29, 0.69); and one dose, aOR = 0.52 (95% CI 0.31, 0.83). Neither study performed a formal comparison of effectiveness of three doses vs fewer doses; confidence intervals for the effectiveness estimates of three, two and one dose(s) overlapped.

3.2. Anogenital warts

The six evaluations of anogenital wart outcomes were retrospective cohort studies from five different countries that had introduced quadrivalent HPV vaccination [11–16]. Only one study presented characteristics of women by number of doses [12]

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