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Review

Two-dose schedules for human papillomavirus vaccine: Systematic review and meta-analysis

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ABSTRACT

Simpler schedules for human papillomavirus (HPV) vaccine delivery could improve vaccine coverage and the effectiveness of cervical cancer prevention. The objective of this study was to systematically review evidence about the effects of two-dose compared with three-dose schedules for human papillomavirus (HPV) vaccine and to describe the uptake of two-dose HPV vaccination schedules globally. We searched PubMed, the Cochrane Central Registry of Controlled Trials, trials registers, and manufacturers' databases from their earliest date to February 2016. We selected randomised controlled trials and controlled clinical trials that directly compared HPV vaccine schedules with two or three doses. We extracted data on immunological and clinical outcomes and used meta-analysis where appropriate. We also described the use of two-dose HPV vaccine schedules globally. We screened 1464 items and included seven eligible noninferiority trials in 11 countries. In randomised comparisons amongst adolescent girls (three trials), geometric mean concentrations (GMC) of antibodies against HPV16 and HPV18 were non-inferior or inconclusive, up to 24 months after a two-dose compared with a three-dose schedule. One trial with a clinical outcome found no persistent HPV infections occurred after either two or three doses. In non-randomised comparisons, GMC were non-inferior or superior in adolescent girls receiving the two-dose schedule compared with women receiving the three-dose schedule for at least 21 months after vaccination. By February 2017, 23 low and middle income and 25 high income countries had adopted a two-dose HPV vaccination schedule. A two-dose HPV vaccine schedule provides satisfactory immunological outcomes in adolescent girls, but uptake globally is limited, particularly in countries with the highest burden of cervical cancer.

Contents

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1. Introduction

Vaccination against human papillomavirus (HPV) with schedules that are efficacious, simple and cheap could improve the effectiveness of cervical cancer prevention [1]. Persistent infection with HPV types 16 and 18 causes about 70% of cervical cancer [2]. An estimated 485,000 new cases of cervical cancer in 2013 caused 6.9 million disability adjusted life years, 85% in developing countries [3].

Simple immunisation schedules are essential to the optimisation of HPV vaccine effectiveness because the vaccine is given to adolescents, for whom health services are not well-developed [4]. In contrast, maternal and child health services are largely structured to facilitate delivery of infant and childhood vaccines. Reduced dose schedules for HPV vaccine have been suggested for several reasons. First, a subgroup analysis of a randomised controlled trial (RCT) in Costa Rica found that women who did not complete the planned three-dose schedule had similar rates of incident HPV 16/18 infection as those who received all three doses [5]. Second, two-dose schedules for hepatitis B vaccine in adolescents are as effective as three-dose schedules when the two doses are given at least six months apart [6,7]. The first vaccine dose stimulates a B cell response that primes the immune system ('prime' dose). Affinity-matured B cells then produce an anamnestic response after a booster ('boost'); affinity maturation takes at least four months to develop after the first prime dose(s) [7]. Third, it is hypothesised that ongoing exposure to HPV through sexual intercourse should sustain vaccine-induced antibody levels, through 'natural boosting' [7].

HPV vaccine presents challenges for evaluation and policy making for two main reasons. First, adolescent girls who have not yet had sexual intercourse are the target group for vaccination to prevent cervical cancer [8], but the pivotal RCT results enrolled women aged 15–26 years, because the outcome assessment required repeated endocervical sampling [9,10]. Second, the primary efficacy endpoint was a surrogate for invasive cancer, which takes decades to develop after initial HPV infection. RCTs showed high levels of protection against cervical intraepithelial neoplasia (CIN) grade two or above caused by HPV16 or HPV18 amongst women without detectable HPV antibodies when they were vaccinated [9,10]. HPV vaccine licensure for adolescents was based on 'immunological bridging' studies showing antibody responses in adolescents that were as good as or better than those in women after the standard three-dose schedule [11,12].

Two-dose schedules for the licensed HPV vaccines were first approved in 2014 [13]. In 2014, the World Health Organization (WHO) strategic advisory group of experts on vaccination concluded that evidence from immunological studies was sufficient to recommend a two-dose HPV vaccine schedule, with an interval of at least six months between doses, for girls aged under 15 years [14]. Although the International Agency for Research on Cancer recommended immunogenicity as a surrogate marker for vaccine efficacy against clinical disease caused by HPV16 and HPV18 in 2014 [15], doubts about the validity of the decision have been voiced [16]. The objectives of this study were to: describe the systematic review evidence that informed the WHO recommendation; review trial evidence published since the recommendation; and describe adoption of two-dose HPV vaccination schedules.

2. Methods

The systematic review followed a study protocol (Supplementary File 1). We follow the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines for reporting [17].

2.1. Inclusion and exclusion criteria

Population and study design: We defined primary study populations in (a) RCTs comparing eligible vaccine schedules including girls in the age range nine to 14 years; and (b) controlled trials with non-randomised comparisons of a two-dose schedule in girls *versus* a three-dose schedule in women aged 15 years and over, with the groups enrolled concurrently in the same geographic locations. Secondary study populations were adult women or men aged 15 years and over.

Intervention: bivalent vaccine against HPV types 16 and 18 (Cervarix®, GlaxoSmithKline) or quadrivalent vaccine against HPV types 6, 11, 16 and 18 (Gardasil®, Merck). We define HPV vaccination schedules, as follows: the first dose is a 'prime' dose, any second dose given <4 months later is a 'prime' dose, and any second or subsequent dose given ≥4 months after the prime dose is a 'booster' [7]. Results of trials of two-dose schedules of a 9-valent HPV vaccine [18,19] were not available when this review was done.

Comparisons: two doses *versus* three doses of the same vaccine and the same dosage (three-dose arm using a schedule recommended by WHO); and two doses *versus* two doses (prime-boost or prime-prime) with different intervals between doses (same vaccine and same dosage). We hypothesised that a prime-boost schedule would result in higher antibody levels than a prime-prime schedule [7].

Outcomes: immunological (antibodies in serum presented as geometric mean concentration, GMC, or percentage seropositive); or clinical (incident HPV infection, CIN2, CIN3, adenocarcinoma in situ, squamous cell carcinoma or adenocarcinoma, or genital warts). Neutralising antibody concentrations were measured using either a competitive Luminex immunoassay for quadrivalent vaccine (cLIA seropositive defined for HPV16 as ≥20 milliMerck units, mMU per mL, HPV18 ≥24 mMU per mL) or enzyme-linked immunosorbent assay for bivalent vaccine (seropositive defined for HPV16 as ≥8 ELISA units, EU per mL, HPV18 ≥7 EU per mL). We did not assess vaccine safety in this review.

2.2. Search strategy and study selection

We searched PubMed, the Cochrane Central Registry of Controlled Trials, clinical trials registers and manufacturers' websites. We also screened reference lists of included studies, abstracts from the European Research Organisation on Genital Infection and

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