Vaccine xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Review

Systematic review of human papillomavirus vaccine coadministration☆

Alinea S. Noronha, Lauri E. Markowitz, Eileen F. Dunne*

Division of STD Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention, United States

ARTICLE INFO

Article history:
Received 27 August 2013
Received in revised form
21 November 2013
Accepted 12 December 2013
Available online xxx

Keywords:
Coadministration
Concomitant
HPV vaccination
Immunogenicity
Safety

ABSTRACT

Human papillomavirus (HPV) vaccination is recommended in early adolescence, at an age when other vaccines are also recommended. Administration of multiple vaccines during one visit is an opportunity to improve uptake of adolescent vaccines. We conducted a systematic review of safety and immunogenicity of HPV vaccines coadministered with other vaccines. Our review included 9 studies, 4 of quadrivalent HPV vaccine and 5 of bivalent HPV vaccine; coadministered vaccines included: meningococcal conjugate, hepatitis A, hepatitis B, combined hepatitis A and B, tetanus, diphtheria, acellular pertussis (Tdap), and inactivated poliovirus vaccines. Studies varied in methods of data collection and measurement of immunogenicity and safety. Noninferiority of immune response and an acceptable safety profile were demonstrated when HPV vaccine was coadministered with other vaccines.

Published by Elsevier Ltd.

1. Introduction

Two human papillomavirus (HPV) vaccines are licensed, and administered in three doses over six months [1,2]. The bivalent HPV vaccine provides protection against HPV 16 and 18 and the quadrivalent vaccine provides protection against HPV 6, 11, 16, and 18 [3]. In the United States, the Advisory Committee on Immunization Practices (ACIP) recommends routine HPV vaccination of girls with bivalent or quadrivalent vaccine and of boys with quadrivalent vaccine at ages 11 or 12 years. Other vaccinations recommended by ACIP at this age include meningococcal conjugate (MCV4), and tetanus, diphtheria, and acellular pertussis (Tdap) vaccines [4]. In addition, annual influenza vaccination is recommended for this age group and other vaccinations that adolescents might have missed when they were younger [4]. ACIP recommendations support HPV vaccine coadministration with other vaccines [4,5]. Until 2007, the only data on coadministration were with hepatitis B vaccine [6] and there are now additional studies [7–14]. We conducted a systematic review to evaluate the immunogenicity and safety of HPV vaccine coadministration.

2. Materials and methods

We searched the English language literature for HPV vaccine safety and efficacy studies evaluating coadministration. Specifically, we used the search terms “HPV vaccine” and “hepatitis A, hepatitis B, meningococcal conjugate, influenza, tetanus, diphtheria, pertussis, pneumococcal, BCG, typhoid, measles, mumps, and rubella, varicella, or poliovirus vaccine” or “coadministration, concomitant, or noninferiority”. This search yielded 139 abstracts, 10 were further reviewed as these studies had primary data, were randomized controlled trials, and had comparison groups; 9 of these studies were unique [6–14]. Studies met specific informed consent and international human subjects guidelines. For the 9 available studies, we extracted relevant data on immunogenicity to administered vaccines as well as safety evaluations. For HPV immunogenicity the according to protocol (ATP) population was assessed when possible.

3. Results

3.1. Study design and characteristics

Reviewed studies included one double blind [6] and eight open-label [7–14] randomized controlled trials, published between 2008 and 2012, with 144–1871 participants ages 9 through 25 years (Table 1). Four quadrivalent HPV vaccine studies [6–9] and five bivalent HPV vaccine studies [10–14] were included. HPV vaccines were coadministered with meningococcal conjugate vaccine

☆ The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

* Corresponding author at: Centers for Disease Control and Prevention, 1600 Clifton Road, MS E-02, Atlanta, GA 30333, United States. Tel.: +1 404 639 6184; fax: +1 404 639 8610.
E-mail address: dde9@cdc.gov (E.F. Dunne).

0264-410X/$ – see front matter. Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.vaccine.2013.12.037

Table 1
Randomized controlled trials of human papillomavirus (HPV) vaccine coadministration.

	First author, year (Ref)	*N*	Age range (mean), yrs	Sex	Study Groups					
					1	2	3	4	5	6
HPV4	Wheeler, 2008 [6]	1871	16–23 (20.4)	F	HPV4 + HepB	HepB + Placebo	HPV4 + Placebo	Placebo + Placebo		
	Vesikari, 2010 [7]	843	10–17 (12.1)	M, F	HPV4 + Tdap-IPV	HPV4 → Tdap-IPV				
	Aruguedas, 2010 [8]	1404	11–18 (13.9)	M,F	HPV4 + MCV4 + Tdap	Tdap → MCV4 → HPV4	MCV4 → Tdap → HPV4			
	Reisinger, 2010 [9]	1042	10–17 (12.6)	M,F	HPV4+ MCV4 + Tdap	HPV4 → MCV4 + Tdap				
HPV2	Garcia-Sicilia, 2010 [10]	655	10–18 (14.0)	F	HPV2 +Tdap-IPV	Tdap-IPV → HPV2	HPV2			
	Wheeler, 2011 [11]	1283	11–18 (13.4)	F	HPV2 + MCV4 + Tdap	Tdap → HPV2	HPV2	MCV4 → HPV2	HPV2 + MCV4 → HPV2 + Tdap	HPV2 + Tdap → HPV2 + MCV4
	Leroux-Roels, 2011 [12]	144	20–25 (22.2)	F	HPV2 + HepB	HepB				
	Schmeink, 2011 [13]	676	9–15 (11.4)	F	HPV2 + HepB	HepB	HPV2			
	Pedersen, 2012 [14]	779	9–15 (11.2)	F	HPV2 + HepA-HepB	HepA-HepB	HPV2			

Ref = reference number. *N* = total number of participants that were vaccinated in the according to protocol analysis population. Age range = age range of study participants. + = vaccine is coadministered at same time. → = vaccine is administered one month later. – = vaccine is combined in same suspension. HPV4 = quadrivalent HPV vaccine, Gardasil [6–9]. HPV2 = bivalent HPV vaccine, Cervarix [10–14]. Tdap = tetanus, diphtheria, acellular pertussis vaccine, Adacel [11] and Boostrix [8,11]. Tdap-IPV = tetanus, diphtheria, acellular pertussis vaccine combined with inactivated poliovirus vaccine, Repevax [10] and Boostrix-IPV [12]. MCV4 = conjugated meningococcal quadrivalent vaccine, Menveo [8,9] and Menactra [11]. HepB = hepatitis B vaccine, Enregix-B [12,13]. HepA-HepB = combined hepatitis A and hepatitis B vaccine, Twinrix [14].

in three studies, Tdap vaccine in three studies [8,9,11], combined Tdap and polio vaccines in two studies [7,10], hepatitis B vaccine in two studies [6,13], and combined hepatitis A and B vaccine in one study [14]. Studies were conducted in Europe [7,8,10,12–14], the United States [9,11] and Costa Rica [12]. One study evaluated the clinical trial data on quadrivalent HPV vaccine conducted in 5 continents [6].

In all quadrivalent HPV vaccine studies except for one, control groups received quadrivalent HPV vaccine one month apart from non-HPV study vaccines [7–9]; one study administered quadrivalent HPV vaccine at the same time as a placebo vaccine [6]. In all bivalent HPV vaccine studies except for one, control groups only received HPV vaccine [10,11,13,14]. In one study, HPV vaccine was coadministered with hepatitis B vaccine and there was no comparison that received HPV vaccine alone [12].

3.2. Immune response

Most study vaccines were coadministered with just the first dose of HPV vaccine except for the studies of coadministration with hepatitis B and combined hepatitis A and B vaccines in which coadministration occurred at dose 2 [12], and dose 3 [6,13,14] and in one arm of another study in which HPV was coadministered with MCV4 and Tdap for dose 1 and dose 2 respectively [11]. We present results from antibody measured one month after the third HPV vaccine dose. All studies measured seroconversion or seroprotection, defined as the percent of the study participants with antibody titer or antibody concentration above a threshold [6–14]. Threshold values for serologic correlates of protection were used for all antibody responses except HPV and pertussis (for which no correlates exist). Noninferiority was determined compared to the control group and included assessments of geometric mean titers (GMTs) or geometric mean concentration (GMC) ratio (coadministration/control group) and/or the seroconversion rate difference (coadministration group – control group) [6–14].

3.2.1. HPV immunogenicity

Quadrivalent and bivalent HPV vaccine coadministration studies used serologic assays developed for HPV vaccine clinical studies. For studies of the quadrivalent HPV vaccine, the Competitive Luminex immunoassay (cLIA) reported in milli Merck Units per milliliter (mMU/mL) was used [15]; for studies of the bivalent HPV vaccine, an enzyme linked immunosorbant assay (ELISA) reported in ELISA units per milliliter (EU/mL) was used [16]. Analyses were limited to those persons seronegative to the respective HPV vaccine type, or stratified by baseline serostatus. All studies with a control group that received HPV vaccine alone reported seroconversion rates greater than 99.5% and noninferior geometric mean titers (GMTs) for all vaccine HPV types in the HPV vaccine coadministered groups (Table 2). The difference in serologic assays prevents GMT comparisons between quadrivalent and bivalent HPV vaccine studies.

3.2.2. Immunogenicity of other study vaccines

Antibody titers were determined by ELISA for tetanus, diphtheria, pertussis, and hepatitis A and B, functional serum bactericidal assay for meningococcal and neutralization titers for poliovirus [6–14]. The seroconversion or seroprotection threshold were consistent across studies, except for pertussis (diphtheria and tetanus: >0.1 IU/mL, meningococcal: ≥4-fold rise in antibody, poliovirus and meningococcal conjugate: >1:8 titer, hepatitis A: ≥15 mIU/mL, and hepatitis B: ≥3.3 IU/mL for seroconversion and ≥10 mIU for seroprotection) [8–11]. Pertussis studies measured anti-pertussis toxin (anti-PT), anti-filamentous hemagglutinin (anti-FHA), anti-pertussis fimbriae (anti-FIM), and anti-pertussis pertactin (anti-PRN) [8–11]. The definition of noninferiority