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Review

Systematic review of human papillomavirus vaccine coadministration☆

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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, 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.

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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.

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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 [9] and Boostrix [8,10]. Tdap-IPV = tetanus, diphtheria, acellular pertussis vaccine combined with inactivated poliovirus vaccine, Repevax [7] and Boostrix-IPV [10]. MCV4 = conjugated meningococcal quadrivalent vaccine, Menveo [8] and Menactra [9,11]. HepB = hepatitis B vaccine, Engerix-B [12,13]. Recombivax HB [6]. HepA-HepB = combined hepatitis A and hepatitis B vaccine, Twinrix [14].

in three studies, Tdap 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 primarily in Europe [7,10,12–14], the United States [9,11] and Costa Rica [8]. 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 vaccine 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) [7–11]. The definition of noninferiority

Table 2
Human papillomavirus (HPV) 6/11/16/18 geometric mean titers (GMT) and seroconversion, HPV vaccine alone and coadministered.

	Ref	Coadministered vaccine	Mean age, yrs	HPV GMTs (% Seroconversion)											
				HPV16			HPV 18			HPV 6			HPV 11		
				HPV alone		HPV coadministered	HPV alone		HPV coadministered	HPV alone		HPV coadministered	HPV alone		HPV coadministered
HPV4[a]	[6][c]	HepB	20.4	2160	(100)	2172 (100)	434	(98.9)	443 (99.6)	507	(100)	533 (100)	751	(99.6)	772 (100)
	[7]	Tdap-IPV	12.1	6508	(99.7)	5836 (100)	1309	(100)	1096 (100)	1245	(100)	1151 (99.7)	1461	(100)	1338 (100)
	[8]	Tdap, MCV4	13.9	6606	(100)	5292 (100)	1115	(99)	907 (100)	1465	(100)	1059 (99.0)	1702	(100)	1264 (100)
	[9]	Tdap, MCV4	12.6	7370	(100)	7203 (100)	1425	(99.8)	1270 (99.5)	1341	(99.8)	1349 (99.5)	1514	(100)	1610 (100)
HPV2[b]	[10]	Tdap-IPV	14.0	18965	(100)	15608 (99.5)	6902	(100)	6597 (99.5)						
	[11][d]	Tdap, MCV4	13.4	22735	(100)	21856 (100)	8128	(100)	7075 (100)						
	[12]	HepB	22.2	NA		9218 (100)	NA		4727[e] (100)						
	[13]	HepB	11.4	21713	(100)	19820 (99.0)	8839	(100)	8835 (99.5)						
	[14]	HepA-HepB	11.2	26982	(100)	22994 (99.6)	11183	(100)	8671 (99.6)						

Ref = reference number. HPV alone = group that receives only HPV vaccine at one point in time. HPV coadministered = group that receives all study vaccinations at the same point in time. % Seroconversion = percent of population that was seronegative before vaccination who had GMTs > the threshold value one month after administration of the third dose of the HPV vaccine [6–14].

[a] GMT by cLIA in mMU/mL. The threshold required to seroconvert for HPV6 and 16 GMT ≥ 20 mMU/mL and HPV11 GMT ≥ 11 mMU/mL and HPV 18 ≥ 24 mM/mL and for HPV 2 as HPV16 ≥ 8EU/mL and HPV18 ≥ 7EU/mL [6–9].

[b] GMT by ELISA in EU/mL. The threshold required to seroconvert for HPV16 ≥ 8EU/mL and HPV18 ≥ 7EU/mL [10–14].

[c] This study has lower GMTs but an older participant population. Previous studies have demonstrated a decrease in GMT with increasing age.

[d] Results listed in this table are for groups that received HPV vaccines alone and groups that received HPV, Tdap, and MCV at the same visit [11].

HPV4 = quadrivalent HPV vaccine, Gardasil [6–9]. HPV2 = bivalent HPV vaccine, Cervarix [10–14]. Tdap = tetanus, diphtheria, acellular pertussis vaccine, Adacel [9] and Boostrix [8,10]. Tdap-IPV = tetanus, diphtheria, acellular pertussis vaccine combined with inactivated poliovirus vaccine, Repevax [7] and Boostrix-IPV [10]. MCV4 = conjugated meningococcal quadrivalent vaccine, Menveo [8] and Menactra [9,11]. HepB = hepatitis B vaccine, Engerix-B [12,13], Recombivax HB [6]. HepA-HepB = combined hepatitis A and hepatitis B vaccine, Twinrix [14].

criteria, seroconversion or seropositivity for pertussis antibodies varied across studies and responses were often defined based on prevaccination concentrations. Reviewed studies reported noninferior antibody responses against diphtheria, tetanus, hepatitis B, hepatitis A, polio and meningococcal antigens in coadministered groups when compared to individually vaccinated groups.

All studies that evaluated pertussis antibodies demonstrated noninferiority for anti-PT, two studies demonstrated noninferiority for anti-FIM [7,9], and four studies demonstrated noninferiority for anti-PRN and anti-FHA [7,9–11]. One study did not meet noninferiority criteria for some of the pertussis antibodies evaluated (anti-PRN and anti-FHA) [8]; anti-FHA and anti-PRN were considered non-inferior to Tdap alone if the lower limit of the two-sided 95% CI for the ratio of GMCs at 1 month post-vaccination was >0.67. These non-inferiority criteria for anti-PRN and anti-FHA were met for the comparison of the concominant group to the group in which Tdap was given first.

When hepatitis B and HPV vaccines were coadministered, studies reported lower hepatitis B GMTs, however seroconversion rates and seroprotection rates were high and noninferiority criteria were met [6,12–14].

3.3. Safety

Unsolicited symptoms 30 min post vaccination and solicited symptoms at variable intervals were recorded on diary cards (Table 3) [6–14]. Injection site and systemic adverse events, vaccine related events, and deaths were reported with no differences among coadministered and control groups [6–14]. Injection site adverse events, including pain, swelling and bruising, were experienced most frequently, and occurred in all study groups [6–14]. Two studies reported one death each, both following motor vehicle accidents, unrelated to vaccination [6,13].

4. Discussion

This review summarizes available studies on safety and immunogenicity of HPV vaccine coadministered with 5 different vaccines. In all reviewed studies antibody response to HPV vaccine met noninferiority criteria in the coadministered groups. Evaluation of adverse events showed similar profiles in coadministered HPV vaccine groups compared with HPV vaccine groups not coadministered [6–14]. Although studies have not evaluated coadministration with all vaccines, available data suggests HPV vaccine is safe and effective when administered with other vaccines.

All reviewed studies except one demonstrated that the immune response to non-HPV vaccines when coadministered with HPV vaccine was noninferior when compared to vaccines not coadministered with HPV vaccine [6–14]. Of five studies that evaluated pertussis antibodies, four studies reported noninferiority criteria were met to evaluated antibodies [7,9–11]. Only one study, Arguedas et al., found that among the group that received Tdap and MCV4 administered at the same time as HPV vaccine, the anti-PRN and anti-FHA ratio of GMCs did not meet noninferiority criteria [8]. A prior study of Tdap and meningococcal vaccine coadministration found that anti-PRN and anti-PT did not meet non-inferiority criteria, suggesting the finding of pertussis antibody differences reported in Arguedas et al., could be due to meningococcal vaccine rather than HPV vaccine coadministration [17]. The clinical significance of this difference in GMCs, if any, is unclear; serologic correlates of protection for pertussis are unknown [18].

Reviewed studies demonstrated no significant increases in overall reactogenicity including local and systemic adverse events in coadministered groups [6–14]. Studies inconsistently reported differences in specific adverse events such as swelling and pain. For

Table 3
Evaluation of adverse events, human papillomavirus (HPV) vaccine coadministered and HPV vaccine alone.

	Ref	Coadministered vaccine	*N*	HPV vaccine coadministered/HPV vaccine alone						
				% Systemic adverse events	% Injection site adverse events	% Temp ≥100 F	% Myalgia	% Headache	% Pain	% Swelling
HPV4	[6]	HepB	1871	56/61	90/87	19/19	NR	24/27	NR	NR
	[7]	Tdap-IPV	843	49/48	91/89	7/8	NR	27/19[a]	NR	9/5[a]
	[8]	Tdap, MCV4	1404	NR	NR	5/3	8/6	18/16	49/36-47[b]	10/5[c]
	[9]	Tdap, MCV4	1042	44/43	87/86	5/5	NR	NR	82/76	28/28
HPV2	[10]	Tdap-IPV	655	NR	NR	10/6	38/29	38/30	85/85	24/25
	[11]	Tdap, MCV4[d]	1283	NR	NR	~10/10	~48/42	~59/52	~96/95	~50/44
	[13]	HepB	676	NR	NR	5/4	11/10	31/29	89/87	29/24
	[14]	HepA-HepB	779	NR	NR	3/4	21/20	24/26	78/80	32/30

Ref = reference number. NR = not reported.
[a] Study reports small increase in swelling in the coadministered group.
[b] Study reports pain after all three doses and this is presented in the table as a range.
[c] Administration of MCV4 alone and Tdap alone resulted in swelling in 13% of participants similar to the 10% in the coadministered group, suggesting difference in swelling due to MCV4 or Tdap.
[d] Data listed in the tables are for the study group that receives all study vaccines at one visit compared to the study group that receives only the HPV vaccine.
~ = an approximation of values from graphs represented in papers. HPV4 = quadrivalent HPV vaccine, Gardasil [6–9]. HPV2 = bivalent HPV vaccine, Cervarix [10–14].Tdap = tetanus, diphtheria, acellular pertussis vaccine, Adacel [9] and Boostrix [8,10]. Tdap-IPV = tetanus, diphtheria, acellular pertussis vaccine combined with inactivated poliovirus vaccine, Repevax [7] and Boostrix-IPV [10]. MCV4 = conjugated meningococcal quadrivalent vaccine, Menveo [8] and Menactra [9,11]. HepB = hepatitis B vaccine, Engerix-B [12,13], Recombivax HB [6]. HepA-HepB = combined hepatitis A and hepatitis B vaccine, Twinrix [14].

example, four studies reported a 3.8–10% increase in injection site swelling in coadministered groups [7,8,11,13] not reported in four other studies [9,10,12,14], and two studies reported a 6–13% increase in pain in coadministered groups [8,9], not reported in five other studies [10–14]. Conclusions on safety endpoints in all studies were limited for some outcomes by insufficient power to evaluate rare adverse events. Additionally, observation bias due to unblinded study design in eight studies may have contributed to reported differences in injection site adverse events [7–14]. Areas for further research include HPV vaccine coadministration with other vaccines not evaluated in this review, including influenza vaccines and live vaccines such as measles, mumps or rubella vaccines.

5. Conclusion

This review supports coadministration of HPV vaccines with other adolescent vaccines. Optimizing clinical visit time by administration of multiple recommended vaccinations at office visits could improve vaccine coverage by eliminating missed opportunities [5,19]. Coadministration of HPV vaccine with other vaccines including Tdap, meningococcal conjugate, and influenza vaccine could increase HPV vaccine coverage for the first dose to 90% [19]. Given HPV vaccine coverage is below target levels in the United States, this review provides evidence that coadministration is safe and effective.

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