Review

Systematic review of human papillomavirus vaccine coadministration

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A B S T R A C T

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
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 (mIU/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 presents 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: ≥0.15 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.

<table>
<thead>
<tr>
<th>Ref</th>
<th>Vaccine</th>
<th>Group</th>
<th>Mean age, yrs</th>
<th>HPV GMTs (% Seroconversion)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HPV16</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>alone</td>
</tr>
<tr>
<td>HPV4</td>
<td>[6]</td>
<td>HepB</td>
<td>20.4</td>
<td>2160 (100)</td>
</tr>
<tr>
<td>[7]</td>
<td>Tdap-IPV</td>
<td>12.1</td>
<td>6508 (99.7)</td>
<td>5836 (100)</td>
</tr>
<tr>
<td>[8]</td>
<td>Tdap, MCV4</td>
<td>13.9</td>
<td>6606 (100)</td>
<td>5282 (100)</td>
</tr>
<tr>
<td>[9]</td>
<td>Tdap, MCV4</td>
<td>12.6</td>
<td>7370 (100)</td>
<td>7203 (100)</td>
</tr>
<tr>
<td>HPV2a</td>
<td>[10]</td>
<td>Tdap-IPV</td>
<td>14.0</td>
<td>18965 (100)</td>
</tr>
<tr>
<td>[11]</td>
<td>Tdap-IPV</td>
<td>13.4</td>
<td>22735 (100)</td>
<td>21856 (100)</td>
</tr>
<tr>
<td>[12]</td>
<td>HepB</td>
<td>22.2</td>
<td>NA</td>
<td>9218 (100)</td>
</tr>
<tr>
<td>[13]</td>
<td>HepB</td>
<td>11.4</td>
<td>21713 (100)</td>
<td>19820 (99.0)</td>
</tr>
<tr>
<td>[14]</td>
<td>HepB-HepB</td>
<td>11.2</td>
<td>26882 (100)</td>
<td>22994 (99.6)</td>
</tr>
</tbody>
</table>

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 seroconverting at one point in time. GMT by ELISA in mIU/mL. The threshold required to be seroconverting for HPV6 and 16 GMT ≥ 20 mIU/mL and HPV11 GMT ≥ 11 mIU/mL and HPV18 ≥ 24 mIU/mL and for HPV 2 as HPV16 ≥ 8 EU/mL and HPV18 ≥ 7 EU/mL.[6–9].

This study was lower GMTs but was not described in GMT with increasing age.

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].


4. Discussion

This discussion summarizes available studies on safety and immunogenicity of HPV vaccine administered with 5 different vaccines. In all reviewed studies, antibody levels were similar to those observed in prior vaccination groups. The clinical efficacy of the vaccine against HPV-related diseases was not affected by the coadministration of other vaccines. In addition, no new adverse events were observed in studies with coadministration.

3. Safety

Unsolicited symptoms 30 days post vaccination and solicited events related to events recorded on diary cards (Table 3) [6–14]. Injection site and systemic adverse events were recorded on diary cards and controlled by review of medical records. All studies reported no difference in adverse events between groups. Two studies reported one death each: both following motor vehicle accidents unrelated to vaccination [6,13].
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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Conflict of interest: The authors have no conflicts of interest.

References


