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Mohamed Macki  
*Henry Ford Health System, mmacki2@hfhs.org*

Ali A. Dabaja  
*Henry Ford Health System, adabaja2@hfhs.org*

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Literature review of vaccine-related adverse events reported from HPV vaccination in randomized controlled trials

Mohamed Macki and Ali A. Dabaja

Abstract

Background: The human papilloma virus (HPV) infections were addressed with two FDA-approved HPV vaccines: quadrivalent and bivalent vaccine. The objective of this manuscript is to determine the safety of the HPV vaccine.

Results: A search of PubMed articles for “human papillomavirus vaccine” was used to identify all-type HPV clinical studies prior to October 2014. A refined search of clinical trials, multicenter studies, and randomized studies were screened for only randomized controlled trials comparing HPV vaccine to controls (saline placebo or aluminum derivatives). Studies were limited to the two FDA-approved vaccines. Following PRISMA guidelines, the literature review rendered 13 publications that met inclusion/exclusion criteria. Gender was limited to females in 10 studies and males in 1 study. Two studies included both males and females. Of the 11,189 individuals in 7 publications reporting cumulative, all-type adverse events (AE), the AE incidence of 76.52 % (n = 4544) in the vaccinated group was statistically significantly higher than 67.57 % (n = 3548) in the control group (p < 0.001). The most common AE were injection-site reactions. On the other hand, systemic symptoms did not statistically significantly differ between the vaccination cohort (35.28 %, n = 3351) and the control cohort (36.14 %, n = 3198) (p = 0.223). The pregnancy/perinatal outcomes rendered no statistically significant difference between the vaccine group and control group.

Conclusion: Because the statistically significantly higher incidence of AE in the HPV vaccine group was primarily limited to injection-site reactions, the vaccinations are safe preventative measures in both males and females.

Keywords: Bivalent, HPV, Human papilloma virus, Vaccine, Quadrivalent

Résumé

Contexte: Les infections dues au papillomavirus humain (HPV) ont été prises en compte par deux vaccins HPV approuvés par la FDA (Food and Drug Administration: Agence américaine des Produits Alimentaires et Médicamenteux): les vaccins quadrivalent et bivalent. L’objectif de cet article est de déterminer la sécurité du vaccin HPV.

(Continued on next page)
Background

The human papillomavirus (HPV) is an important preventable cause of sexually-transmitted disease and squamous cell carcinomas. HPV types 16 and 18 have been implicated in cervical, anal, vaginal, and vulvar cancers, while types 6 and 11 cause anogenital warts. Between 2003 and 2004, the overall HPV prevalence was 26.8% [1]. Moreover, the prevalence of HPV infections statistically significantly increased with each year of age from 14 to 24 \((p < \) 0.001) [1]. The National Cancer Institute independently developed the HPV vaccine, which was subsequently sold to Merek & Co and GlaxoSmithKline for randomized controlled trials (RCTs). The HPV vaccine studies were subsequently marketed as a novel intervention to curtail the infection’s oncologic aptitude. Years of clinical trials by the pharmaceutical companies have materialized into two Food and Drug Administration (FDA)-approved HPV vaccine. First, Gardasil or Silgard (Merck & Co) is a human recombinant papillomavirus vaccine- quadrivalent types 6,11,16,18. Second, Cervarix (GlaxoSmithKline) is a bivalent human papillomavirus vaccine- types 16, 18. While the efficacy of both vaccines has been verified in randomized control studies (RCT) [2–4], the safety of these prophylactic interventions has been strongly contested in the outpatient settings.

Methods

The literature review followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Fig. 1) [5]. A search of PubMed articles for "human papillomavirus vaccine" was used to identify all-type HPV clinical studies prior to October 2014. A refined search of clinical trials, multicenter studies, and randomized studies were screened for only randomized controlled trials comparing HPV vaccine to controls (saline placebo or aluminum derivatives). With a compilation of previously published RCTs, we compared adverse effects from the HPV vaccine versus control injection. The primary endpoint was to determine the safety of the HPV vaccine. The literature review outlined in Table 1 includes the primary author, publication year, number study participants, description of the study population, type of adverse events, number of vaccinated and unvaccinated participants for whom adverse events (AE) are reported, and \(P\) value comparison between the two cohorts.

Both solicited and unsolicited adverse events were included in the review. AE were determined by the article investigator as possibly, probably, or definitely related to the vaccine. AE were categorized according to the discrete time intervals during which the unintended outcome occurred. HPV vaccine was typically administered in a 3-dose schedule. The number of adverse events was expressed as a proportion of subjects, rather than the proportion of doses.

Inclusion/Exclusion criteria

Only randomized controlled trials were included in the present article. Vaccination groups were limited to the two FDA-approved HPV vaccinations: (1) quadrivalent HPV-6,11,16,18 L1 virus-like particle (VLP) vaccine; (2) HPV-16,18 Adjuvant System (AS) 04 vaccine. Vaccines are composed of either quadrivalent or bivalent antigens plus either an amorphous aluminum hydroxyphosphate sulfate (AAHS) adjuvant or aluminum hydroxide \([\text{Al(OH)}_3]\). Control cohorts were limited to solutions containing either (A) saline placebo; or (B) identical components to those in the...
vaccine, with the exception of the HPV antigens. Twelve articles included AAHS or Al(OH)₃ placebo [2, 3, 6–15]; however, Reisinger et al. utilized a saline placebo [16]. RCTs with hepatitis A and/or hepatitis B vaccine controls were excluded [17–29]. Control groups without injections were also removed from the literature review insomuch as the study design would interfere with the blinded schema and become susceptible to a reporting bias/ information bias [30]. Randomized controlled trials without mention of adverse events and/or non-clinical RCTs were excluded from the literature review. Repeat studies, ad hoc subgroup analysis, and pooled analyses were similarly excluded [4, 31–38]. Lastly, AE expressed as a percentage of doses, rather than a percentage of study participants, were not included in Table 1 [13].

Results

The PRISMA flow diagram detailing the selection process is presented in Fig. 1. The most common reason for exclusion was non-randomized, clinical-controlled trials (n = 230). Of the 86 RCTs, the most prevalent exclusion criteria was non-clinical studies/ studies without mention of AE (n = 29), followed by HPV RCTs with vaccines other than the quadrivalent HPV-6,11,16,18 L1 VLP or HPV-16/18 AS04 vaccine (n = 18). Non-placebo control group, e.g., Hepatitis A or Hepatitis B vaccine (n = 13). Repeat articles (n = 9). Control group without a placebo injection (n = 1).

Statistical analysis

Demographic information was described using summary statistics. The percent of subjects who experienced an AE in the vaccine group were compared to the placebo counterparts with Chi-squared (χ²) tests. Stata (version 12.0, College Station, TX, USA) and GraphPad Software were used for statistical interpretations of the raw data. Statistical significance was set a p ≤ 0.05.
| Author, Year | Study population | Inclusion criteria | Adverse events | Vaccine group (%) | Control group (%) | P  |
|-------------|-----------------|--------------------|----------------|-------------------|------------------|----|
| Harper et al. 2004 [6] | N = 1113 women from 32 study sites in North America and Brazil. | 15–25 years ≤5 lifetime sexual partners No abnormal Pap test No external condylomata HPV 16/18 seronegative | 7-day period Injection-site symptoms Pain Swelling Redness General symptoms Fatigue Gastrointestinal Headache Itching Rash Fever | N = 531 Gardasil N = 538 Al(OH)3 | 499 (93.97) 496 (93.41) 182 (34.27) 189 (35.59) 458 (56.25) 308 (58.00) 178 (33.52) 331 (62.34) 130 (24.48) 60 (11.30) | 472 (87.73) 469 (87.17) 113 (21.00) 131 (24.35) 462 (85.87) 289 (53.72) 172 (31.97) 331 (62.34) 109 (20.26) 88 (16.57) | <0.001 <0.001 <0.001 <0.001 0.860 0.175 0.602 0.706 0.106 0.552 0.172 |
| Villa et al. 2005 [7] | N = 277 women from Brazil, Europe, and USA | 16–23 years Non-pregnant No abnormal Pap smears ≤4 lifetime sex partners | Vaccine-associated adverse events Injection-site Systemic Vaccine-related serious adverse events Discontinued vaccination due to hypoaesthesia | N = 272 Gardasil N = 274 AAHS | 243 (89.34) 234 (86.03) 104 (38.24) 0 | 225 (82.12) 212 (77.37) 90 (32.85) 0 | 0.016 0.009 0.188 1.000 0.319 |
| Reisinger et al. 2007 [16] | N = 1781 children from 47 sites in 10 countries in North America, Latin America, Europe, and Asia, enrolled from December 2002 to September 2004 | 9–15 years old Sexually naive Intact uterus No gross purulent cervicitis No genital warts No abnormal Pap smear No cervical intraepithelial neoplasia ≤4 lifetime sex partners Non-pregnant | Injection-site event Erythema Pain Swelling Systemic Vaccine-related serious adverse events Discontinued vaccination due to hypoaesthesia | N = 1165 Gardasil N = 584 Saline | 2320 (86.79) 659 (24.65) 237 (20.34) 694 (25.96) 0 | 2068 (77.40) 413 (15.46) 77 (13.18) 260 (44.52) 1 | <0.001 <0.001 <0.001 <0.001 0.448 0.638 |
| Merck V501-013 FUTURE I Study Garland et al. 2007 [2] | N = 5455 women at 62 study sites in 16 countries, enrolled from January 2002 to March 2003 | 16–24 year old Non-pregnant No history of genital warts No abnormal cervical cytology testing ≤4 lifetime sex partners Effective contraception | Injection-site event Erythema Pain Pruritus Swelling | N = 2673 Gardasil N = 2672 AAHS | 2320 (86.79) 659 (24.65) 2281 (85.33) 109 (4.70) 694 (25.96) | 2068 (77.40) 450 (16.84) 2014 (75.37) 80 (2.99) 413 (15.46) | <0.001 <0.001 <0.001 <0.001 <0.001 |
| Study | Participants | Age/Status | Protocol Details | 15-day period | Entire study period |
|-------|--------------|------------|------------------|---------------|---------------------|
| Merck V501-015 FUTURE II Study, 2007 [3] | N = 12,167 women in 13 countries, enrolled from June 2002 to March 2003 | 15–26 year old | Non-pregnant | Injection-related systemic event | 1561 (43.43) |
| | | | No abnormal Papainocloa smear | Pyrexia | 361 (13.51) |
| | | | ≤4 lifetime sex partners | Effective contraception | 1085 (40.61) |
| | | | 15-day period | Discontinuation for vaccine-related event | 2 (0.07) |
| | | | | Death | 2 (0.07) |
| | | | | Vaccine-related serious event | 1 (0.03) |
| Bhatla et al. 2010 [9] | N = 330 women at four teaching/tertiary care hospitals across India, enrolled from July 2006 to March 2007 | 18–35 year old | Non-pregnant | Injection-site event | 378 (84.38) |
| | | | No investigational products/steroids | Pain | 372 (83.04) |
| | | | | Systemic event | 275 (61.38) |
| | | | | 15-day period | Discontinuation for serious injection-related event | 2 (1.2) |
| | | | | Death | 0 |
| Bhatla et al. 2010 [9] | N = 330 women at four teaching/tertiary care hospitals across India, enrolled from July 2006 to March 2007 | 18–35 year old | Non-pregnant | Injection-related event | 7 (0.12) |
| | | | No investigational products/steroids | Death | 0 |
| | | | | Vaccine-related adverse events | 3 (0.05) |
| | | | | Discontinuation for serious injection-related event | 0 |
| | | | | Injection-related event | 2 (0.03) |
| | | | | Death | 0 |
| | | | | Serious injection-related event | 0 |
| | | | | Serious injection-related adverse events | 7 (0.12) |
| Muñoz et al. 2009 [8] | N = 3819 women from 38 international sites in Colombia, France, Germany, Philippines, Spain, Thailand, and USA | 24–45 year old | Intact uterus | Injection-site event | 1875 (82.84) |
| | | | No genital warts or cervical disease | Pain | 1758 (76.71) |
| | | | | Systemic event | 1389 (73.65) |
| | | | | 15-day period | Discontinuation for serious injection-related event | 7 (0.12) |
| | | | | Death | 0 |
| | | | | Vaccine-related serious event | 3 (0.05) |
| | | | | Discontinuation for serious injection-related event | 0 |
| | | | | Injection-related event | 2 (0.03) |
| | | | | Death | 0 |
| | | | | Serious injection-related event | 0 |
| | | | | Serious injection-related adverse events | 0 |
| | | | | Serious vaccine-related adverse events | 7 (0.12) |
| Ngan et al. 2010 [10] | N = 300 women at a single center in Hong Kong | 18–35 year old | Non-pregnant | Pain, all-type | 137 (80.12) |
| | | | No chronic disease | Grade 3 Pain | 105 (60.34) |
| | | | Non-pregnant/breastfeeding | Redness, any size | 7 (4.02) |
| | | | | >50 mm | 1 (0.58) |
| | | | | >50 mm | 9 (5.12) |
| | | | | >50 mm | 1 (0.58) |
| | | | | Grade 3 solicited general symptoms | 1 (0.58) |
| | | | | Medically significant adverse event | 1 (0.58) |
| | | | | Medically significant conditions | 1 (0.58) |
| | | | | New onset chronic disease | 1 (0.58) |
| | | | | Abdominal pain, IBS, dizziness, headache | 3 (2.07) |
| | | | | Pelvic inflammatory disease | 0 (0.69) |
| | | | | Medically significant conditions | 42 (2.90) |
| | | | | New onset chronic disease | 7 (4.83) |
| Study                        | Participants                                                                 | HPV vaccination details                                    | Randomized Controlled Trials                                                                 |
|------------------------------|------------------------------------------------------------------------------|------------------------------------------------------------|------------------------------------------------------------------------------------------------|
| Levin et al. 2010 [11]       | *N* = 126 children HIV-seropositive children                                 | 7–12 years old HIV with CD4 ≥ 15% ≥ 3 months HAART if CD4 < 25% | Table 1 Literature review of vaccine-related adverse events reported from HPV vaccination in randomized controlled trials (Continued) |
| V501-20 Giuliano et al. 2011 | *N* = 4065 males from 71 sites in 18 countries                               | 16–26 years old 1–5 male or female sexual partners No anogenital lesions | Vaccine-related events Injection-site Systemic Vaccine-related serious events Death Discontinuation for vaccine-related adverse event* |
| Sow et al. 2013 [13]         | *N* = 676 women in 2 centers in sub-Saharan Africa (Senegal and Tanzania) from October 2007 to July 2010 | 10–25 years old HIV seronegative Not pregnant ≤ 6 lifetime sexual partners | Grade 3 injection-site pain Serious adverse event* Medically significant condition New onset chronic disease New onset autoimmune disease Deaths Premature births- infant death |
| Yoshikawa et al. 2013 [14]   | *N* = 1030 Japanese women, multicenter                                       | 18–26 years old Not pregnant No previous abnormal Pap smears ≤ 4 males sex partners Effective contraception | Days 1–15 All-type adverse event Injection-site adverse event Systemic adverse event Serious adverse event Discontinuation for vaccine-related adverse event* Death |
| Denny et al. 2013 [15]       | *N* = 150 women at a single center in Khayelitsha, Cape Town, Republic of South Africa. | 18–25 years old ≤ 6 lifetime sexual partners Non-pregnant Intact cervix | 30-day period Unsolicited adverse event Headache Upper respiratory tract infection Lobar Pneumonia (Grade 3) Bacterial Pneumonia (Grade 3) Death |
| Time Period | Medically Significant Adverse Event | Discontinuation for Vaccine-Related Adverse Event |
|------------|------------------------------------|-----------------------------------------------|
| Up to 7 months | 18 (29.51)/5 (16.67) | 21 (35.59) | 0.477/0.063 |
| 7–12 months | N = HIV54 (+)/24 (-) | N = 52 HIV(+) | |
| Medically Significant Adverse Event | 6 (11.11)/2 (8.33) | 5 (9.62) | 0.801/0.857 |
| Discontinuation for Vaccine-Related Adverse Event | 0/0 | 0 | 1.000 |

Statistically significant values are in bold.

*Number of adverse events expressed as a function of the number of doses, rather than the number of patients, were excluded. These adverse events included malaria, headache, dysmenorrhea, abdominal pain, vertigo, cough, nasopharyngitis.

Amorphous aluminum hydroxyphosphate sulfate (AAHS) adjuvant; aluminum hydroxide \([\text{Al(OH)}_3]\)

Bronchospasm 1 day after the third dose

Serious adverse events in the vaccine group were gastroenteritis, headache, hypertension, injection-site pain, and decrease in joint movement at the injection site

Serious adverse events in both the vaccinated and control groups were likely due to malaria infection, unrelated to the vaccine

Elective discontinuation in the vaccine group was due to spontaneous abortion, unrelated to the vaccine

Elective discontinuation in the vaccine group was due to vaccine-related malaise and headache

Elective discontinuation in the vaccine group was due to vaccine-related pyrexia
the exception of a Chinese trial by Ngan et al. and a Japanese trial by Yoshikawa et al. [10, 14]. Similarly, all trials were multi-center studies, with the exception of a single-institutional RCT in Hong Kong [10]. The most common study inclusion criteria were ≤4–6 lifetime sexual partners, no abnormal Papanicolaou smears, non-pregnant, and no cervical infections/ anogenital warts. Women were encouraged to utilize effective contraception. Two studies specifically focused on Human Immunodeficiency Virus (HIV)-seropositive participants [11, 15].

Of the 11,189 individuals in 7 publications reporting cumulative, all-type adverse events [7, 8, 11, 12, 14–16], the AE incidence of 76.52 % ($n = 4544$) in the vaccinated group was statistically significantly higher than 67.57 % ($n = 3548$) in the placebo group ($p < 0.001$). The most common AE were injection-site reactions. In fact, of the 18,348 participants in 9 reporting articles [2, 3, 6–8, 11, 12, 14, 16], the 77.43 % of vaccinated subjects ($n = 7355$) who experienced all-type injection-site reactions was statistically significantly higher than the 67.70 % of control subjects ($n = 5991$) ($p < 0.001$). The most common injection-site reactions were pain, induration, and erythema. On the other hand, systemic symptoms did not statistically significantly differ between the vaccination cohort (35.28 %, $n = 3351$) and the placebo cohort (36.14 %, $n = 3198$) ($p = 0.223$). The most common systemic symptoms included fatigue, headache, and fever. Ten articles ($n = 30,398$) reported serious adverse events [2, 3, 6–9, 12–14, 16]. The incidence of 0.15 % ($n = 23$) in the vaccination division did not statistically significantly differ from 0.14 % ($n = 20$) in the control counterparts ($p = 0.774$). Of the 23 subjects experiencing serious AE, 17 (73.91 %) were attributable to malaria infection, unrelated to the vaccine, in the sub-Saharan Africa study by Sow et al. [13]. Serious AE in the remaining 6 vaccinated subjects included bronchospasm, acute pancreatitis, lymph node tuberculosis, gastroenteritis, headache, and hypertension. Only 4 patients (0.03 %) in the vaccine unit [6, 12] and 7 patients (0.06 %) in the control unit [6, 7, 12, 14] discontinued the study due to adverse events ($p = 0.367$). Of the four elective terminations in the vaccine group, three men cited vaccine-related malaise, headache, and pyrexia in the publications by Giuliano et al. [12, 39] and Yoshikawa et al. [14], whereas one woman experienced a spontaneous abortion in the publication by Harper et al. [6], thought to be unrelated to the vaccine. Twelve and seventeen individuals died in the vaccine and control groups, respectively. Causes of death in the vaccine cohort included pneumonia and sepsis, overdose of an illicit drug, motor vehicle accident (6 persons), pulmonary embolism, infective thrombosis, homicide, and suicide, none of which were linked with the vaccine [2, 3, 12].

Ngan et al. and Sow et al. reported new-onset chronic disease/ autoimmune disease following injection with drug vs control [10, 13]. Of the 966 enrollees in the two studies, the rate of 3.36 % in the vaccine randomization did not statistically significantly differ from 4.85 % in the control randomization ($p = 0.246$). Lastly, while effective contraception and non-pregnancy represented key selection criteria for most RCTs in the present literature review, pregnancy was reported in the follow up period. Birth complications included one spontaneous abortion, nine elective abortions, and one death of a premature infant in the vaccination cohort in comparison to one spontaneous abortion, one miscarriage, one ectopic pregnancy, three elective abortions, and one death of a premature infant in the control cohort. None of these experiences were liked with the injections. The pregnancy/ perinatal outcomes from the Females United to Unilaterally Reduce Endo/Ectocervical Disease (FUTURE) I (Merck V501-013), FUTURE II (Merck V501-015), Merck V501-016, and Merck V501-018 RCTs were combined in the Appendix in the FUTURE II study (Merck V501-016, 018 did not meet selection criteria in this literature review) [38]. In brief, no statistically significant difference was observed between the vaccine group and control group.

**Discussion**

In 1796, an English physician, Edward Jenner, performed the first vaccination by inoculating an 8-year-old boy with pus from a cowpox lesion [40]. Despite the growing safety concerns for his experimental design of a smallpox vaccine, Dr. Jenner published his conclusions in a landmark text in the annals of medicine: *Inquiry into the Causes and Effects of the Variolae Vaccine* [41]. Since the development of Dr. Jenner’s time-honored work, vaccine production over the ensuing centuries have ushered in a new era of preventive medicine; nevertheless, safety concerns for vaccination of children and young adults still remains the greatest barrier to these scientific advancements. A testament to this belief today, the most recent FDA-approved vaccines, Gardasil/Silgard and Cervarix, have met significant resistance owing to the fear of unknown side-effects. In this literature review, we compared adverse effects from the HPV vaccine versus control injection from a compilation of published randomized controlled trials. The primary endpoint of this study was to determine the safety of the HPV vaccine.

In the present literature review, the vaccine was well-tolerated without undue AE. All-type AE and injection-related AE were the only two parameters with a significantly higher rate in the HPV vaccinated subjects, whereas systemic events, serious AE, and death did not differ. The vaccine cohort (76.52 %) carried an approximately 10 % higher rate of all-type adverse events in comparison to the control cohort (67.57 %) ($p < 0.001$). These results
corroborate a sub-analysis by Moreira et al. [39], who reviewed AE in the 4065 males enrolled in the HPV RCT, V501-20 published by Giuliano et al. [12]. The 1945 males randomized to the Gardasil unit experienced a statistically significantly higher rate of all-type AE (63.86 %) versus AAHS adjuvants (58.15 %) (p < 0.001). In fact of the 7 publications reporting all-type adverse events, 5 found a significant difference between the two cohorts [7, 8, 12, 14, 16]. The remaining two articles reporting no difference were limited by a cohort size of less than 100 persons [11, 15]. The most common AE was injection-site reactions, such as pain, erythema, and induration. In the present literature review, all-type injection-site reactions were statistically significantly higher in the vaccine arm (77.43 %) than the control arm (67.70 %) (p < 0.001). However, true injection-site hypersensitivity reactions occur infrequently, according a retrospective review of 380,000 doses of Gardasil administered to 12–26 year-old females in Victoria and South Australia [42]. In that study, only 35 females had suspected hypersensitivity reactions. Moreover, Kang et al. concluded that “only three of the 25 evaluated schoolgirls had probable hypersensitivity to the quadrivalent human papillomavirus vaccine [42].” Several authors contend that the causes of the general injection-site reactions, and the hypersensitivity experiences specifically, are not completely attributable to the antigenic components of the vaccine, but rather due in part to the aluminum additives [39, 42]. In the RCT by Reisinger et al. (Table 1), the placebo group was given saline injections, from which only half of participants experienced injection-site reactions [16]. By comparison, the frequency of injection-site reactions averages at 68.95 % in control arms with Al(OH)3 or AAHS and 77.43 % in the vaccinated arm, per the set literature review. Such a gradient effect suggests that the aluminum products contribute to the reactogenicity of the vaccine [39].

Systemic events did not differ in the vaccine division (35.28 %) versus the control division (36.14 %) (p = 0.223); furthermore, most reported symptoms were mild or moderate in intensity. Fatigue, headache, and pyrexia were most commonly documented throughout the follow up period. Delayed in onset, these experiences likely reflect the innate innate immunologic response followed by a sustained, adaptive response. Yoshikawa et al. did detect a statistically significant difference of all-type adverse events between the vaccine arm and control arm (p < 0.001) (Table 1) [14]. The most common AE was injection-site adverse event, among which pain was the most frequent symptom. Systemic AE were the next most common event, although no statistically significant difference was detected between the vaccine and control cohorts (p = 0.260). Greater than 90 % of those systemic AEs were of “moderate intensity,” without any specification.

Serious AE in the present study did not statistically significantly differ between the vaccine (0.15 %) and control (0.14 %) groups (p = 0.774) in the present literature review. Commensurate with our findings, Roumbout et al. reported no difference in serious AE in a systematic review of six HPV trials (Peto odds ratio 1.00; 95 % CI 0.87–1.14). Death between the two arms did not differ (Peto odds ratio 0.91; 95 % CI 0.39–2.14) [43]. In the aforementioned review by Roumbout et al. as well as the present review, motor vehicle accidents were the most common cause of death. No mortalities were associated with the vaccine.

Conclusion
Following PRISMA guidelines, the literature review rendered 13 randomized controlled trials comparing HPV vaccine to control. Of the 11,189 individuals in 7 publications reporting cumulative, all-type adverse events, the vaccinated group was statistically significantly higher than the control group, although the most common AE were injection-site reactions. On the other hand, systemic symptoms did not statistically significantly differ. The pregnancy/ perinatal outcomes rendered no statistically significant difference between the vaccine group and control group. Thus, the vaccinations are safe preventative measures for both males and females.

Abbreviations
[Al(OH)3]: Aluminum hydroxide; AAHS: Amorphous aluminum hydroxyphosphate sulfate; AE: Adverse events; AS: Adjuvant System; FDA: Food and Drug Administration; FUTURE: Females United to Unilaterally Reduce Endo/Ectocervical Disease; HIV: Human Immunodeficiency Virus; HPV: Human papilloma virus; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCTs: Randomized controlled trials; VLP: Virus-like particle.

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Availability of data and materials
The data supporting the findings in this manuscript can be obtained by e-mail the corresponding author, Ali Dabaja, MD.

Authors’ contributions
MM contributed to gathering the data and writing/ assembling the manuscript. AAD contributed to interpreting the data. Both authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

Consent for publication
This manuscript does not contain any individual person’s data in any form (including individual details, images or videos).
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