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REVIEW

Efficacy and safety of prophylactic HPV vaccines. A Cochrane review of randomized trials

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ABSTRACT

Introduction: Recently, the evidence on efficacy and safety of prophylactic HPV vaccines derived from randomized trials was published in the Cochrane database of Systematic reviews. A summary of this Cochrane review is presented below.

Areas covered: Only trials involving mono-, bi-, and quadrivalent HPV vaccines were included. Trials evaluating the nonavalent vaccine were excluded since women in the control group received the quadrivalent vaccine. Main efficacy outcomes were: histologically confirmed cervical precancer lesions distinguishing those associated with vaccine HPV types and any cervical precancer. Exposure groups were: women aged: 15–26 or 24–45 years being initially negative for high-risk HPV (hrHPV) or negative for the vaccine types and women unselected by HPV status.

Expert commentary: All evaluated vaccines offered excellent protection against cervical intraepithelial neoplasia of grade 2 or 3 (CIN2 or CIN3) and adenocarcinoma in situ associated with HPV16/18 infection in young women who were not initially infected with hrHPV or HPV16/18. Vaccine efficacy was lower when all women regardless of HPV DNA status at enrollment were included. In young women, HPV vaccination protected also against any cervical precancer but the magnitude of protection was lower than against HPV16/18 associated cervical precancer. Vaccine efficacy was lower in mid-adult (aged 24–45 years) women. No protection against cervical precancer was found in mid-adult women unselected by HPV DNA status at enrollment. Trials were not empowered to address protection against cervical cancer. Occurrence of severe adverse events or adverse pregnancy outcomes was not significantly higher in recipients of HPV vaccines than in women included in the control arms.

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KEYWORDS
Cervical cancer; HPV vaccines; safety; randomized clinical trials; systematic review; meta-analysis

1. Background

The Cochrane Collaboration is an international, independent not-for-profit organization that evaluates interventions for disease prevention, treatment, and rehabilitation by producing systematic reviews of primary research using established methods for summarizing and reporting evidence. On 7 May 2018, our review on efficacy and safety of HPV vaccines was published in the Cochrane Library [1]. That day the Cochrane Collaboration set up a press conference which received wide international coverage [2].

Cervical cancer is etiologically linked with persistent high-risk HPV (hrHPV) infection. A dozen of HPV types is considered as carcinogenic [3]. The worldwide annual incidence is estimated at about 530,000 cases and approximately 70% of them are caused by HPV types 16 or 18 [4,5]. Prophylactic HPV vaccines contain virus-like-particles (VLPs) consisting of the major L1 protein of the capsid. Administration by intramuscular injection triggers production of antibodies that are believed to prevent new type-specific infections and subsequent development of cervical intraepithelial neoplasia (CIN) [6]. CIN of grade 2 (CIN2), and in particular, CIN3 and adenocarcinoma in situ (AIS) are considered as precursor lesions which may develop into invasive squamous or adenocarcinoma of the uterine cervix [3,7–9]. In this paper, we highlighted the main findings of the recently published Cochrane review that addressed two main questions: 1) does the prophylactic HPV vaccines protect against cervical HPV infection and cervical (pre-)cancer? and (2) what are the harms associated with being vaccinated? [1].

2. Methods

We included results from randomized trials published in peer-reviewed journals comparing effects in women who received one to three doses of prophylactic HPV vaccines with those who received the control product. We also included non-peer-reviewed sources (clinicaltrials.gov and www.gsk-clinicalstudyregister.com) reporting on severe adverse effects. The control product was the adjuvant without HPV VLPs or a vaccine protecting against other infectious agents. Standard Cochrane methodology was applied to retrieve references, extract data, and compute pooled relative risks [1]. The current paper is restricted to the following main outcomes: (a) CIN2+, CIN3+, and AIS related to the HPV types included in the vaccine; (b) any CIN2+, CIN3+, and AIS irrespective of HPV types. We separated results for three exposure groups, according to the presence or absence of HPV DNA at enrollment: (a) hrHPV-negative; (b) negative for the HPV vaccine types; (c)

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regardless of HPV status. Randomized trials addressing vaccine efficacy typically enrolled young women (15–26 years) or mid-adult women (24–45 years).

3. Results

3.1. Included trials

We included 26 trials that enrolled almost 74,000 women, followed over a time span of six months in smaller studies to 3–6 years in most of the larger phase-3 studies, with longest follow-up reaching 8–9 years in two extended phase-2 trials [10,11]. One trial evaluated a prototype monovalent HPV16 vaccine [11,12], 18 trials evaluated the bivalent vaccine containing antigens of HPV16/18 (GSK, Rixensart, Belgium) [13–30] and seven trials evaluated the quadrivalent vaccine [31–37] containing antigens of HPV6/11/16/18 (MSD, Whitehouse Station, NJ, USA). Trials assessing the non-avalent vaccine (containing the antigens of HPV6/11/16/18/31/33/45/52/58) were not included in the Cochrane review, since the efficacy was not evaluated against a non-HPV vaccine control group. Ten of the 26 included trials measured efficacy against HPV16/18 infection and associated lesions. None was large enough

Table 1. Summary of the vaccine efficacy estimates, by age group, outcome, and HPV DNA status at enrollment, for women who received at least one dose or three doses of bivalent or quadrivalent HPV vaccine. Table adapted from Arbyn et al., "Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors", Cochr Database Syst Rev 2018, with permission from John Wiley and Sons.

		A	B	C
	Outcome	hr HPV DNA- ≥ 1 dose	HPV16/18 DNA- 3 doses	Regardless of HPV ≥ 1 dose
	Age group 15-26			
	High-grade intraepithelial neoplasia associated with HPV16/18			
1	CIN2+	0.01 (0.00 to 0.05)^{b2q1} [Fig1] ⊕⊕⊕⊕	0.07 (0.03 to 0.15)^{b4q2} [Fig2a] ⊕⊕⊕⊕	0.46 (0.37 to 0.57)^{b1q2} [F3a] ⊕⊕⊕⊕
2	CIN3+	0.01 (0.00 to 0.10)^{b1q1} ⊕⊕⊕⊕	0.07 (0.02 to 0.29)^{b1q2} ⊕⊕⊕⊕	0.55 (0.45 to 0.67)^{b1q1} ⊕⊕⊕⊕
3	AIS+	0.10 (0.01 to 0.82)^{b1q1} ⊕⊕⊕	0.12 (0.02 to 0.70)^{b1q2} ⊕⊕⊕	0.36 (0.17 to 0.78)^{b1q1} ⊕⊕⊕
	Any high-grade intraepithelial neoplasia irrespective of HPV types			
4	CIN2+	0.33 (0.25 to 0.43)^{b4} ⊕⊕⊕⊕ 0.57 (0.44 to 0.76)^{q1} ⊕⊕⊕	0.40 (0.25 to 0.64)^{b2q1} ⊕⊕⊕⊕	0.70 (0.58 to 0.85)^{b2q1} [F4a] ⊕⊕⊕⊕
5	CIN3+	0.08 (0.03 to 0.23)^{b2} ⊕⊕⊕⊕ 0.54 (0.36 to 0.82)^{q1} ⊕⊕⊕	-	0.55 (0.43 to 0.71)^{b2} [Fig4] ⊕⊕⊕⊕ 0.81 (0.69 to 0.96)^{q1} [Fig4] ⊕⊕⊕
6	AIS+	0.10 (0.01 to 0.76)^{b1q1} ⊕⊕⊕	-	0.32 (0.15 to 0.67)^{b1q1} ⊕⊕⊕⊕
	Persistent HPV16/18 infection			
7	6M persisting	0.07 (0.05 to 0.90)^{b1} ⊕⊕⊕	0.06 (0.05 to 0.08)^{b4} ⊕⊕⊕⊕	0.44 (0.38 to 0.51)^{b2} ⊕⊕⊕
	Age group 24-45			
	High-grade intraepithelial neoplasia associated with HPV16/18			
8	CIN2+	-	0.16 (0.04 to 0.74)^{b1q1} [Fig2b] ⊕⊕⊕	0.74 (0.52 to 1.05)^{b1q1} [Fig3b] ⊕⊕⊕
9	CIN3+	-	-	-
10	AIS+	-	-	-
	Any high-grade intraepithelial neoplasia irrespective of HPV types			
11	CIN2+	-	-	1.04 (0.83 to 1.30)^{b1q1} [F4b] ⊕⊕
12	CIN3+	-	-	-
13	AIS+	-	-	-
	Persistent HPV16/18 infection			
14	6M persisting	-	0.11 (0.06 to 0.20)^{b1q1} ⊕⊕⊕⊕	0.57 (0.47 to 0.69)^{b1q1} ⊕⊕⊕⊕

Level of protection (RR)
Excellent: RR ≤0.10, 1 excluded from CI
Good: RR>0.10 & ≤ 0.20, 1 excluded from CI
Moderate: RR>0.20 & ≤ 0.80, 1 excluded from CI
Weak: RR>0.80 & <1, 1 excluded from CI
No protection: 1 included in CI
Adverse protection: RR>1 and 1 excluded from CI

Quality of evidence*
High ⊕⊕⊕⊕
Moderate ⊕⊕⊕
Low ⊕⊕
Very low ⊕

How to read Table 1. We distinguish seven main endpoints arranged by rows: CIN2+, CIN3+, and AIS associated with HPV16/18 (rows 1–3); any CIN2+, CIN3+, and AIS associated with HPV16/18 (rows 4–6); persistent HPV16/18 infection (row 7). The first seven rows concern young women aged 15–26 years. The next seven rows (8–14) concern mid-adult women aged 14–45 years. We further distinguish 3 exposure groups arranged by columns: women being at baseline hrHPV-negative at baseline, having received at least one dose (col A); women being at baseline negative for HPV16.18 at baseline, having received all 3 doses; women regardless of HPV status at baseline, having received at least one dose.

The index in superscript after the 95% CI corresponds with the number of trials where the bivalent (b) or quadrivalent (q) vaccines were assessed (for instance b1q2: meta-analysis of 3 trials, one with the bivalent and two with the quadrivalent vaccine).

* The quality of evidence, assessed according to GRADE guidelines [38] is based on the quality of studies [39], number of studies, consistency, and precision of estimates. ⊕⊕⊕⊕ means high quality, ⊕ means very low quality.

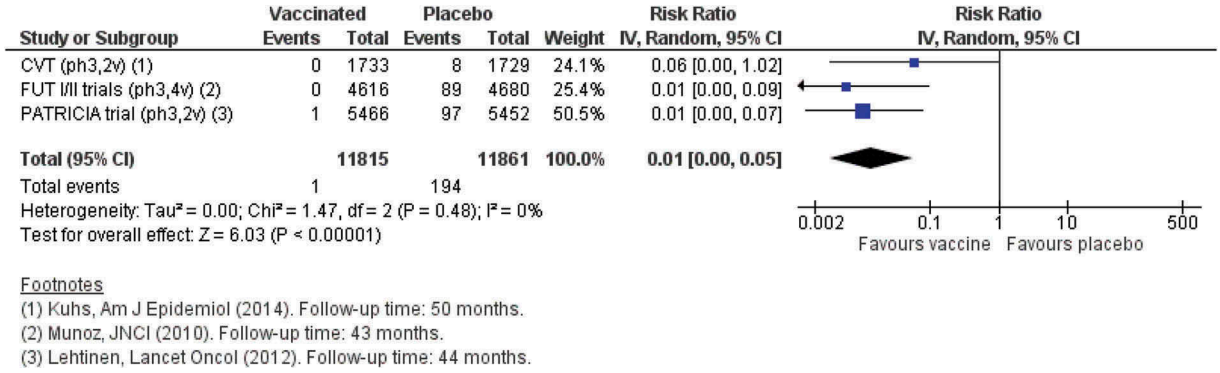

Figure 1. Relative risk to develop CIN2+ associated with HPV16/18 infection in women vaccinated with at least one dose of bivalent or quadrivalent HPV vaccine vs. control women, restricted to women who were hrHPV-negative at enrollment. Name of the trial (2 to 3 years of follow-up) and the name of the HPV vaccine (bivalent = 2v, quadrivalent = 4v) is indicated between brackets after the identification of each trial. Figure reproduced from Arbyn et al., "Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors", Cochr Database Syst Rev 2018, with permission from John Wiley and Sons.

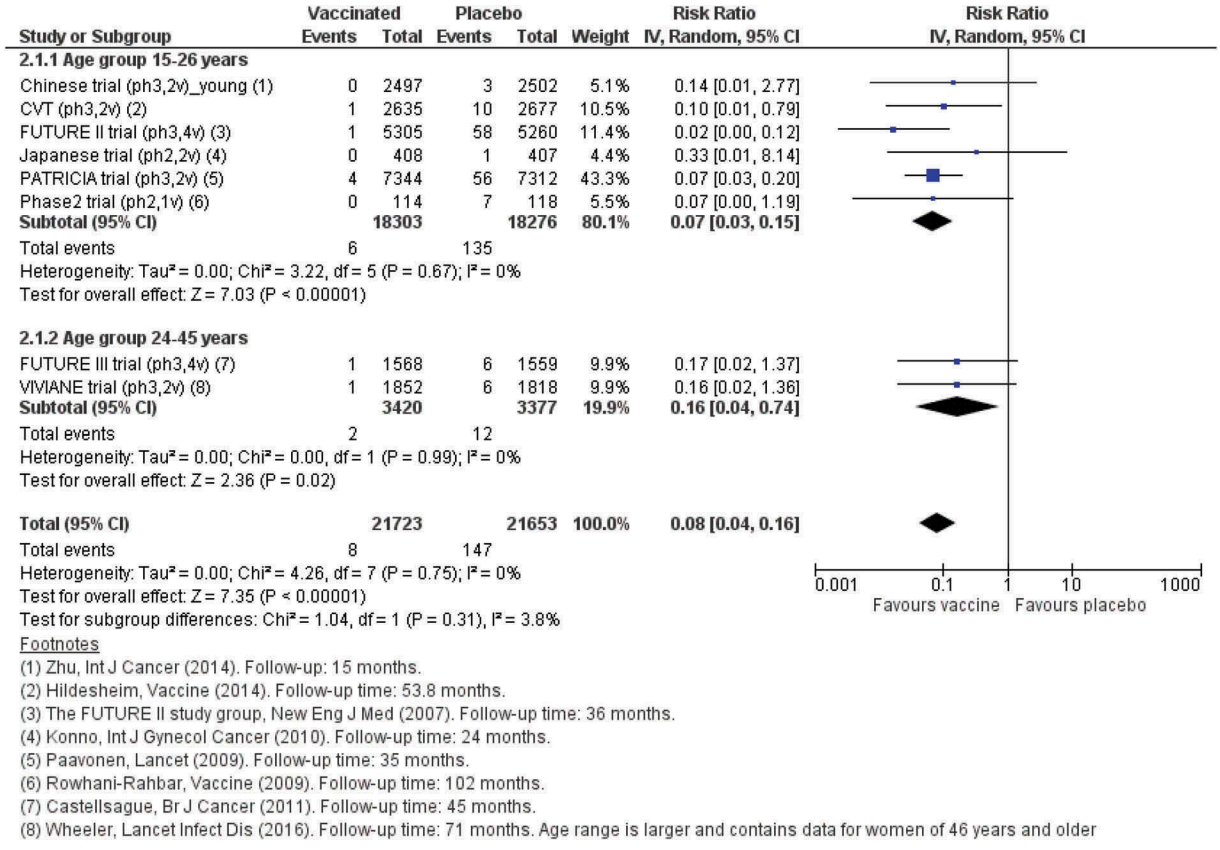

Figure 2. Relative risk to develop CIN2+ associated with HPV16/18 infection in women vaccinated with 3 doses of bivalent or quadrivalent HPV vaccine vs. control women, restricted to women who were hrHPV-negative at enrollment, stratified by age group. Figure reproduced from Arbyn et al., "Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors", Cochr Database Syst Rev 2018, with permission from John Wiley and Sons.

to document protection against cervical cancer. Most studies enrolled young women and only three recruited women of 24 years or older.

3.2. Efficacy in women who were hrHPV-negative or HPV16/18-negative at baseline

Three or at least one dose of HPV vaccine confer excellent protection against 6-month persistent HPV16/18 infection and against CIN2+, CIN3+, and AIS associated with these types in young women who were hrHPV-negative or HPV16/18-negative at enrollment (RR≤ 0.10, Table 1, Figures 1 & 2). Good protection against CIN2+ associated with HPV16/18 was observed also in mid-adult HPV16/18-negative women who received three doses (RR = 0.16, 95% CI 0.04–0.74) but protection was moderate for the group that received at least one dose (RR = 0.30, 95% CI 0.11–0.81).

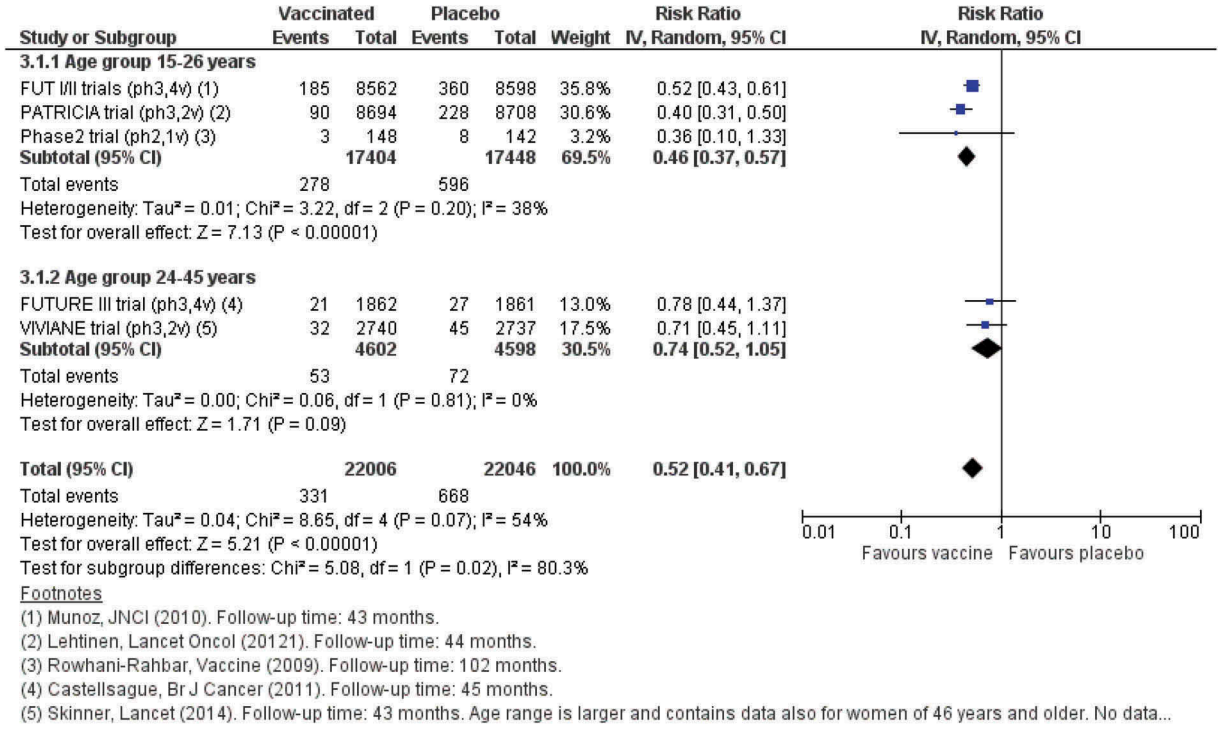

Figure 3. Relative risk to develop CIN2+ associated with HPV16/18 infection in women vaccinated with at least one dose of bivalent or quadrivalent HPV vaccine vs. control women, including all women regardless of HPV DNA status at enrollment, stratified by age group.
Figure reproduced from Arbyn M, et al. "Prophylactic efficacy of HPV-vaccines against cervical cancer and its precursors", Cochr Database Syst Rev 2018, with permission from John Wiley and Sons.

When the protection against any high-grade lesions irrespective of HPV types is considered, we observe a lower but still significant protection. However, the efficacy against any CIN2+ and any CIN3+ was better with the bivalent vaccine. Protection against any high-grade lesions was not documented for mid-adult women.

3.3. Efficacy of all women regardless of baseline HPV DNA status

In young women, regardless whether HPV was present or not, HPV vaccines protect against 6-month persisting HPV16/18 infection and against CIN2+ (Figure 3a), CIN3+, and AIS associated with HPV16/18 (RR between 0.36 and 0.55). The efficacy

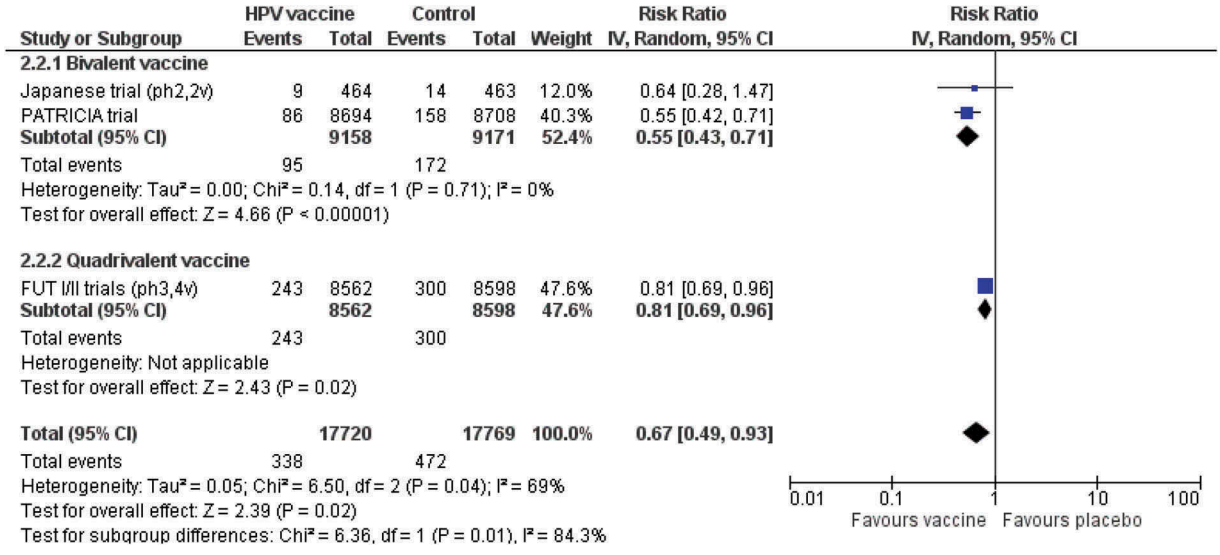

Figure 4. Relative risk to develop any CIN3+ irrespective of infection with HPV types in young women vaccinated with at least one dose of bivalent or quadrivalent HPV vaccine vs. control women, including all women regardless of HPV DNA status at enrollment, stratified by vaccine brand.
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against any CIN3+ differed by vaccine valency: RR 0.55 (95% CI 0.43–0.71) and 0.81 (95% CI 0.69–0.96) for the bi- and quadrivalent vaccine, respectively (Figure 4).

Vaccination of mid-adult women reduced 6-month persistent HPV16/18 infection. However, risks of CIN2+ associated with HPV16/18 or any CIN2+ were not different in vaccinated and control arms (unity included in 95% CI around RR).

3.4. Adverse events

Short-term local adverse events were noted more frequently among receivers of HPV vaccine compared to those who received the control product (RRs 1.18 to 1.73). The risks of overall systemic events and serious adverse events were similar in the HPV vaccine arms as in the control arms (RR 1.02, 95% CI 0.98–1.07 and 0.98, 95% CI 0.92 to 1.05, respectively). Pooled estimates derived from data published in peer-reviewed journals matched very well with those from publically accessible registries. The mortality ratio (deaths occurring in the vaccine versus the control arm) was 1.29 (95% CI 0.85–1.98). The level of certainty about a relation between death and vaccination was judged as low. This judgment was motivated by the broad confidence interval and the heterogeneity by age group (no excess in risk in vaccinated young women [RR = 0.98, 95% CI 0.59] vs. higher risk in vaccinated mid-adult women [RR = 2.36, 1.10–5.03]). No pattern in the cause or timing of deaths has been established among mid-adult women. It should be noted that women in the control received aluminium adjuvants and sometimes other non-HPV vaccines.

3.5. Pregnancy outcomes

In vaccinated women who became pregnant around the period of vaccination, we did not find significantly increased risks of miscarriage (RR 0.88, 95% CI 0.68–1.14), termination of pregnancy (RR 0.90, 95% CI 0.80–1.02), stillbirths (RR 1.12, 95% CI 0.68–1.83) or congenital abnormalities (RR 1.22 95% CI 0.88–1.69).

4. Expert commentary

The randomized trials demonstrated excellent protection against cervical cancer precursors associated with the HPV vaccine types among young women who were not infected at baseline with these types or with hrHPV types in general (see Figure 1). These findings provide the evidence to consider girls or young women before onset of sexual activity as first target of routine vaccination programmes. However, less studies reported outcomes in this hrHPV) DNA negative population. More trials documented outcomes in women who were at baseline negative for the HPV types included in the vaccine (see Figure 2) that are the target for the typical per-protocol outcome analyses.

Protection was lower when young women, who were already exposed to HPV, were also included. The findings in this larger group (often called the intention-to-treat population), reflect the expected effectiveness for catch-vaccination in young women aged 15–26 years. No differences in efficacy against HPV16/18 associated lesions between vaccine brands were found.

Since other hrHPV types also cause cervical precancer, protection induced by an HPV16/18 vaccine against any CIN2+, CIN3+, or AIS is as expected lower than against HPV16/18 associated lesions. The potential impact of immunization with bi- or multivalent vaccines has been estimated using weighted pooled prevalence of HPV types in cervical cancer and its precursors and the derived population risks attributed to HPV types [40–42]. How HPV vaccination, with this or that vaccine, will change the burden of cervical (pre-) cancer, will be the target of careful surveillance consisting in linking HPV vaccination data with screening and pathology/cancer registries [43,44].

Our Cochrane review has revealed remarkable differences in protection against any CIN2+ and CIN3+ between the bi- and quadrivalent vaccines in both the restricted hrHPV-negative group and in the larger group regardless of initial HPV status. Moreover, the review demonstrated for the first time that the evaluated HPV vaccines significantly reduce the risk of AIS associated with HPV16/18 and any AIS. Another first finding was that less than three doses protected against precancer associated with HPV16/18 infection in young women. For all endpoints and exposure groups, for which data were available, vaccine efficacy was lower in older women.

The Cochrane review could not provide the evidence that HPV vaccines protect against invasive cervical cancer. A WHO expert committee had advised that high-grade CIN and AIS or worse was a sufficient endpoint for HPV vaccination trials, given the knowledge of the natural history of HPV infection and CIN derived from cervical cancer screening studies, and given the excessive resources and long duration of studies required to prove vaccine efficacy for this outcome [45]. Neither occurrence of rare adverse events nor certain adverse pregnancy outcomes associated with HPV vaccination could be excluded with a high level of certainty. Therefore, health authorities must organize pharmacovigilance activities and long-term surveillance joining vaccine and morbidity registries to complete observations from the trials. Reviews performed on observational good-quality follow-up data on HPV vaccines did not raise safety concerns up to now [46–48]. Pooling of effectiveness and safety from population-wide linkage studies should be priority for future systematic reviews.

5. Five-year view

In collaboration with colleagues of the Cochrane editor's office and other systematic reviewers we aim to update and complete the Cochrane review and cover: (a) safety and efficacy of the nonavalent HPV vaccine as well as other newly developed HPV vaccines; (b) assessment of protection of HPV vaccines against genital warts and HPV infection in other anatomical locations and associated (pre-)cancer lesions (vaginal, vulvar, penile, anal, oropharyngeal); (c) complete gaps in information by exploring data from the grey literature and requesting data from principle investigators. Moreover, we want to stimulate

international collaboration in order to concentrate resources and avoid inefficient multiplication of efforts.

Key issues

- Bivalent and quadrivalent HPV vaccines induce excellent protection against persistent HPV16/18 infection and associated precursor lesions in young females (not older than 25 years) who are not infected with high-risk HPV. Teenagers should, therefore, be the first target of HPV vaccination campaigns.
- Vaccine efficacy estimates are lower when also females already infected with HPV are included.
- Vaccine efficacy decreases by age. No protection against any CIN2+/AIS was found in the group of older women (aged 24 or older) unselected by HPV DNA status at enrollment.
- Similar rates of serious adverse events were observed in the experimental and control arms of randomized trials.
- Careful population-wide surveillance of HPV vaccine effectiveness (targeting also incidence of HPV-related cancers) and safety (including also rare conditions such as neurologic and auto-immune syndromes) should be set up by linking vaccination, cervical cancer screening, and morbidity registries.

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Declaration of interest

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Reviewer disclosures

A reviewer on this manuscript has disclosed authorship of many papers in this field.

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