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Serious adverse events associated with HPV vaccination

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Conflicts of interest

The authors of this document have no financial or other conflicts of interest pertaining to Human Papilloma Vaccines.

CONTENTS

EXECUTIVE SUMMARY

A systematic literature review was undertaken to investigate serious adverse events associated with human papillomavirus (HPV) vaccination. The HPV vaccine comes in two types: a bivalent (HPV 16/18, Cervarix™, GlaxoSmithKline) and a quadrivalent (HPV 6/11/16/18, Gardasil® or Silgard, Merck) vaccine.

This review considered all primary and secondary (systematic review, SR) research evidence. Despite a large number of studies that pooled (meta-analysed) primary research evidence, none of these were conducted as formal SRs and so were not included. SRs are characterised by a research question, a comprehensive search for evidence, a protocol for study selection and critical appraisal of the included research, and synthesis of that research. This approach limits the likelihood that the presented results are biased or inaccurate. We found one SR that was eligible, according to our review protocol; however, most of the trials included in this SR had since been updated, and so it was excluded in favour of incorporating the more up-to-date primary research evidence that was available.

There is a considerable amount of randomised controlled trial (RCT) evidence reporting on the safety and efficacy of HPV vaccines. Indeed, the total pool of subjects in this review was over 77 000, and there were several individual trials with large numbers of participants. Although the trials all considered vaccine safety, it was not the primary outcome in the vast majority of cases, and only afforded a small portion of the published reports. Serious adverse events (SAE) were rarely defined.

It is clear that many of the trial investigators interpreted SAEs and the other outcomes - new onset of chronic diseases and medically significant conditions - in very different ways; the reporting rates varied widely across studies. Rates of SAEs were reported as low as <1% and as high as 25% in one comparison. When appraising these studies, using GRADE methodology, the individual outcomes were downgraded for indirectness because of this issue; but the appraisal was also upgraded because the trials were large and had long follow-up times. Thus, on balance, these trials received a high quality rating after being appraised.

Most of the trials assessed whether SAEs were associated with vaccination, but only one trial explained how causality was assessed. The majority of SAEs were deemed to be not vaccine-related. Likewise, most trials reported deaths, but trials that reported causality found no associated between the reported deaths and HPV vaccination.

A number of cohort studies also investigated the association between HPV vaccination and specific adverse events, in particular autoimmune diseases. These studies were generally very well designed and used appropriate methods to minimise confounding. The results from both the trial evidence and from the cohort studies is very consistent in finding that there is no relationship between any serious adverse event and HPV vaccination. The main results are summarised in Table 1.

Table 1: Summary of findings: serious adverse events associated with HPV vaccination

Outcome	Data size and source	Comparison of effects		Certainty of the evidence (GRADE)	Summary
		Vaccine	Control		
Serious adverse events 1 month - 9 yrs follow-up	**Gardasil® versus placebo**: Based on data from 28 671 subjects in 7 RCTs	858.2/100 000	935.8/100 000	⊕⊕⊕⊕ **HIGH** *Downgraded due to serious indirectness; but upgraded due to large numbers in trials*	There is no difference in the rate of serious adverse events between Gardasil® and placebo.
		Absolute event rate difference: Rate per 100 000 (%, 95% CI) -77.6, **(0.08%, 95%CI -0.2%, 0.3%)** Relative difference: RR 0.93 (95% CI 0.72, 1.21)			
	Gardasil® versus control vaccine: Based on data from 3810 subjects in 1 RCT	733.8/100 000	841.2/100 000	⊕⊕⊕⊕ **HIGH** *Downgraded due to serious indirectness; but upgraded due to large numbers in trials*	There is no difference in the rate of serious adverse events between Gardasil® and a control vaccine.
		Absolute event rate difference: Rate per 100 000 (%, 95%CI) -107.4 **(0.11%, 95%CI -0.5%, 0.7%)** Relative difference: RR 0.87 (95% CI 0.43, 1.78)			
	Cervarix™ versus placebo: Based on data from 15 258 subjects in 10 RCTs	1603.4/100 000	1876.2/100 000	⊕⊕⊕⊕ **HIGH** *Downgraded due to serious indirectness; but upgraded due to large numbers in trials*	There is no difference in the rate of serious adverse events between Cervarix™ and placebo.
		Absolute event rate difference: Rate per 100 000 (%, 95%CI) -272.8 **(0.27%, 95%CI -0.15%, 0.7%)** Relative difference: RR 0.87 (95% CI 0.60, 1.25)			
	Cervarix™ versus control: Based on data from 30 843 subjects in 8 RCTs	11 676.8/ 100 000	11 595.7/ 100 000	⊕⊕⊕⊕ **HIGH** *Downgraded due to serious indirectness; but upgraded due to large numbers in trials*	There is no difference in the rate of serious adverse events between Cervarix™ and a control vaccine.
		Absolute event rate difference: Rate per 100 000 (%, 95%CI) 81.1 **(0.1%, 95%CI -0.8%, 1.0%)** Relative difference: RR 1.01 (95% CI 0.95, 1.07)			

Outcome	Data size and source	Comparison of effects		Certainty of the evidence (GRADE)	Summary
		Vaccine	Control		
New onset chronic disease 1 month – 9 yrs follow-up	**Cervarix™ versus placebo**: Based on data from 9511 subjects in 9 RCTs	1240.1/100 000	1306.6/100 000	⊕⊕⊕⊕ **HIGH** *Downgraded due to serious indirectness; but upgraded due to large numbers in trials*	There is no difference in the rate of new onset chronic disease between Cervarix™ and placebo.
		Absolute event rate difference: Rate per 100 000 (%, 95%CI) -66.5 **(0.07%, 95%CI -0.4%, 0.5%)** Relative difference: RR 0.83 (95% CI 0.58, 1.20)			
	Cervarix™ versus control: Based on data from 30 349 subjects in 7 RCTs	4680.8/100 000	5079.9/100 000	⊕⊕⊕⊕ **HIGH** *Upgraded due to large numbers in trials*	There is no difference in the rate of new onset chronic disease between Cervarix™ and a control vaccine.
		Absolute event rate difference: Rate per 100 000 (%, 95%CI) -399.1 **(0.4%, 95%CI -0.9%, 0.9%)** Relative difference: RR 0.93 (95% CI 0.84, 1.03)			
Medically significant conditions 1 month - 9 yrs follow-up	**Cervarix™ versus placebo**: Based on data from 7623 subjects in 6 RCTs	8201.4/100 000	6949.6/100 000	⊕⊕⊕⊕ **HIGH** *Upgraded due to large numbers in the trials*	There is no difference in the rate medically significant conditions between Cervarix™ and placebo.
		Absolute event rate difference: Rate per 100 000 (%, 95%CI) 1251.8 **(1.25%, 95%CI 0.04%, 2.5%)** Relative difference: RR 1.15 (95% CI 0.88, 1.50)			
	Cervarix™ versus control: Based on data from 28 498 subjects in 4 RCTs	29 372.9/ 100 000	30 069.4/ 100 000	⊕⊕⊕⊕ **HIGH** *Upgraded due to large numbers in the trials*	There is no difference in the rate of medically significant conditions between Cervarix™ and a control vaccine.
		Absolute event rate difference: Rate per 100 000 (%, 95%CI) -696.5 **(0.7%, 95%CI -0.4%, 1.8%)** Relative difference: RR 0.98 (95% CI 0.92, 1.05)			
Autoimmune diseases following HPV vaccination	Data from 5 high quality cohort studies	No differences in rates of most autoimmune diseases between those exposed to vaccine and those unexposed. No findings equated to a safety signal.		⊕⊕⊕O **MODERATE** *Upgraded due to study design that mitigated confounding*	There is no difference in the rate of autoimmune diseases between people who have been vaccinated and people who have not.
Venous thrombo-embolism	Data from 2 high quality cohort studies	No difference in the rate of thromboembolism in those exposed to vaccine and those		⊕⊕⊕O **MODERATE** *Upgraded due to study design that*	There is no difference in the rate of venous thromboembolism between

Outcome	Data size and source	Comparison of effects		Certainty of the evidence (GRADE)	Summary
		Vaccine	Control		
		unexposed.		*mitigated confounding*	people who have been vaccinated and people who have not.
Multiple sclerosis and other demyelinating conditions	Data from 2 high quality cohort studies	Exposed	Unexposed	⊕⊕⊕O **MODERATE** *Upgraded due to study design that mitigated confounding*	There is no difference in the rate of MS or other demyelinating diseases between people who have been vaccinated and people who have not.
		MS: between 3.4 and 6.1 / 100 000 person years	Between 2.5 and 21.5/ 100 000 person years		
		IRR between 0.90 (95%CI 0.70, 1.15) and 1.37 (0.74, 3.20)			
		Other: between 1.1 and 7.5 /100 000 person years	Between 1.6 and 16.1/ 100 000 person years		
		IRR between 0.71 (0.38, 2.13) and 1.00 (95%CI 0.80, 1.26)			

* CI = confidence interval; IRR = incidence rate ratio; MS = multiple sclerosis; RCT = randomised controlled trials; RR = relative risk

1 INTRODUCTION

Adelaide Health Technology Assessment (AHTA), University of Adelaide, was contracted by the World Health Organisation (WHO) to provide an independent assessment of serious adverse events associated with vaccination with human papillomavirus (HPV).The aim of this systematic literature review is to provide the best available evidence to inform WHO's guidance on HPV vaccine safety.

1.1 HPV vaccination

Since 2006/7, two vaccines for HPV have been available: a bivalent HPV 16/18 vaccine (Cervarix™, GSK) and a quadrivalent HPV 6/11/16/18 vaccine (Gardasil® or Silgard, Merck) to reduce the risk of cervical cancer. These vaccines protect against two herpes types which are known to cause at least 70% of cervical cancers, and Gardasil® also protects against two other herpes types which cause anogenital warts. Amongst a range of strategies for cervical cancer prevention and control, WHO recommends primary prevention of cervical cancer with HPV vaccination of girls before they become sexually active. HPV vaccination had been introduced into 65 countries by mid-2016, mostly in developed countries but also in an increasing number of middle and low-income countries.

HPV vaccines have been widely researched, with a multitude of randomised controlled trials throughout all regions of the world. Indeed, GlaxoSmithKline published a pooled analysis of their clinical trials up to April 2011 and included 42 completed or ongoing studies in 40 countries, with a total of 31 173 adolescent girls and women receiving the HPV 16/18 vaccine. (1)

Although some systematic reviews have been published, none have brought together all available information on each of the HPV vaccines or focused on serious adverse events. Whilst some reports have pooled data from multiple trials, these reports have not been systematic reviews.

This systematic review, then, considered all the available high-level evidence for the safety of HPV vaccination in relation to specific serious adverse events, described in Chapter 2.

The research questions associated with this review, as set by WHO, were:

> **What is the vaccine attributable serious adverse reaction rate (per 100,000 vaccinees) for serious adverse events after vaccination with HPV vaccines Gardasil® and Cervarix™?**
>
> **What is the relative risk (and confidence intervals) for serious adverse events after vaccination with HPV vaccines Gardasil® and Cervarix™?**

2 METHODS

A systematic literature review was undertaken to identify, appraise and report on relevant studies that investigated outcomes of serious adverse events following vaccination with HPV 16/18 or HPV 6/11/16/18.

2.1 Literature search strategy

A search of PubMed, Embase, Toxline and the Cochrane Library (Cochrane reviews and other studies indexed in the library) was undertaken in November 2016 to identify relevant literature. Search terms included the relevant MeSH and Emtree subheadings for HPV, and the trade names of the vaccines.

2.2 Results of the literature search

The literature search resulted in a total of 3980 papers to consider, once duplicates were removed (using Endnote). The PRISMA flow chart for the literature search is shown in Figure 1.

2.3 Selection criteria

The study selection criteria were pre-specified according to the Population, Intervention, Comparator and Outcomes (PICO) addressed in each study. These PICO criteria are shown in Table 2.

Table 2: PICO criteria for adverse events associated with HPV vaccination

Population	Anyone receiving the HPV vaccine Subgroups: age, sex, vaccine type
Intervention	HPV vaccines: quadrivalent- Gardasil® (Merck/Wyeth) or bivalent- Cervarix™ (GSK)
Comparators	Any comparator vaccine or placebo
Outcomes	Serious adverse events, Grade 3-5, including death, and including but not limited to: 1. Guillain-Barré Syndrome 2. Autoimmune disease (including but not limited to multiple sclerosis, acute demyelinating encephalomyelitis, encephalitis, SLE, demyelinating disease) 3. Primary ovarian failure BUT excluding postural orthostatic tachycardia syndrome (POTS) and chronic regional pain syndrome (CRPS)

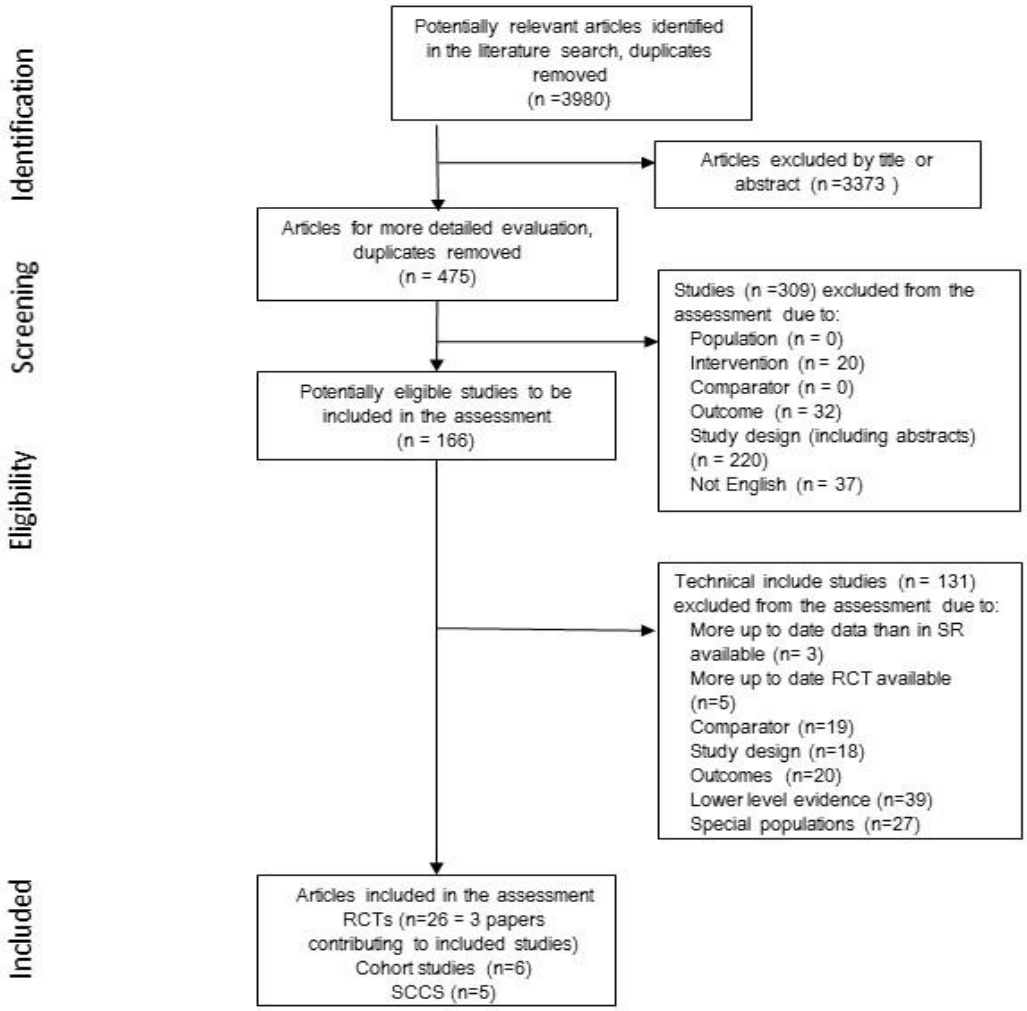

Figure 1: PRISMA flow chart for literature search

For the purposes of this review, all serious adverse events reported by the primary study authors (and included in systematic reviews where these were assessed) were considered. Where studies assessed causality, this was reported. Otherwise, the assessment made no judgements on causality associated with the reported adverse events.

All events named as 'serious adverse events', even when definitions of what was considered 'severe' were not given, were included. POTS and CRPS were not considered in this review as WHO have elected to use the report by the European Medicines Agency (EMA) to inform event rates for these outcomes.

Studies were screened for inclusion in the systematic review using the Rayyan software program and with reference to the pre-defined study selection criteria. Full text articles were then managed via a reference database (Endnote).

Study types that were considered for inclusion in the review were:

- Systematic reviews (SRs) of randomised controlled trials (RCTs) and/or observational studies
- RCTs
- Observational studies, including cohort studies and self-controlled case series

SRs were included if they posed the same question and examined the same long and short term outcomes as required for this current review, and the assessors were satisfied that the SR had adequately considered the risk of bias in the primary studies. If the SRs were deemed irrelevant, for reasons of PICO variation or because bias in the evidence base was not adequately assessed, all primary research (RCTs and observational studies) was considered.

Literature identified as opinion pieces, editorials or other papers without a clear study design and description of method and results were not included. Likewise, many studies that pooled multiple trials, but were not actually SRs, were not included.

2.4 Extraction of data

Information on each included study was extracted into an individual study profile table designed for this review. The study profiles are shown in Appendix B. Data extracted to address individual outcomes were reported in GRADE evidence profile tables that collate the information across the body of evidence, as well as in evidence summary tables presented according to each pre-specified outcome of interest (see Appendix A).

Meta-analyses were conducted where appropriate using Stata software (metan program). Forest plots were produced using a random-effects model and the heterogeneity of the pooled results was assessed using the I-squared statistic.

2.5 Critical appraisal

Each study identified for inclusion in the review was assessed for quality using a validated appraisal (risk of bias) tool:

- For SRs: the Assessing the Methodological Quality of Systematic Reviews, AMSTAR, tool was used (2).

- For RCTs: the Cochrane Collaboration's tool for assessing risk of bias was used. This includes the domains of selection bias, performance bias, detection bias, attrition bias, reporting bias and any other bias not covered elsewhere. For each study, a risk of bias table, detailing the judgement on risk of bias (high, low or unclear) for each domain and providing support for the judgement, was provided. (3)

- For observational studies: The Agency for Healthcare Research and Quality, AHRQ, item bank was used for assessing risk of bias and confounding in observational studies. The tool includes the domains of selection, performance, and attrition bias, and whether confounding variables were taken into account in the design and analysis of the study. (4)

For each identified health outcome (eg serious adverse events), the quality of the evidence contributing to that outcome was assessed using GRADE methodology. The GRADE approach involves considering the within-study risk of bias, directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias for each outcome, resulting in an overall quality of evidence depicted using the ⊕ symbol, with four ⊕ indicating high quality and one, very low quality. (5,6)

Recognising that study types other than RCTs can contribute important data of relevance to population-based immunisation programs, WHO's "Guidance for the development of evidence-based vaccine-related recommendations" provides the following definitions for the GRADE quality ratings, as they apply to studies of vaccines:

- High = Evidence supports a high level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome (level 4, or ⊕⊕⊕⊕).
- Moderate = Evidence supports a moderate level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome (level 3, or ⊕⊕⊕).
- Low = Evidence supports a limited level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome (level 2, or ⊕⊕).
- Very low = Evidence supports a very low level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome (level 1, or ⊕).(2)

3 RESULTS

The studies considered in this assessment fell into six main categories: systematic reviews and meta-analyses, RCTs, cohort studies, case control studies of various type, case series, and reports and surveys. Some of the observational studies used routinely-collected and specialised administrative and surveillance datasets.

A number of SRs, meta-analyses and 'pooled' analyses were identified in the literature search. However, on closer inspection, only one of these studies actually met the criteria for inclusion in the review, in that it used appropriate SR methodology (3). This SR by Lu et al, published in 2011, included six RCTs which were also identified in the search for this assessment. However, more than half of the studies included in this SR have since reported more follow-up data, and because so many trials have been published since the search period for Lu's SR, it was decided to exclude this review and concentrate on the primary studies identified in the search.

Reports from a total of 26 RCTs were included in this assessment. Where multiple reports were published from one trial (for example, from different follow up periods), the latest data from the longest follow up period was included. Most of the RCTs addressed general safety questions and reported SAEs as a group.

A number of relevant cohort studies investigated particular safety concerns of interest; these are addressed in section 3.2.

As there was so much high level evidence from RCTs and cohort studies, the lower levels of evidence (case control studies, case series) were not included in this assessment (pre-specified in the review protocol). However, it should be noted that well designed case-control studies, such as some of those studies identified, may be completely appropriate for investigating rare outcomes.

3.1 Serious adverse events as reported in the randomised controlled trials

In total, there were 26 RCTs included, which covered both vaccine types, and studies compared to both placebo and control vaccines. Studies were conducted in both females and males, and with ages as young as nine years and as old as 45 years. In general, SAEs were not reported for age groups within trials. Follow-up varied from one month post-dose three (ie a seven month study) to up to about nine years. The earliest trials began recruiting in the early 2000s. Trials were conducted around the world, with the largest trials undertaken in multiple centres in up to 18 countries. A summary of the trials is provided in Table 3. The study profiles, including quality appraisal, are available in Appendix B.

Table 3: Summary of RCTs included in assessment

Comparison	Number of trials included	Number of participants	Types of participants	Age range (years)
Cervarix™ versus placebo (4-13)	10	15 258	Females only	10-45
Cervarix™ versus control vaccine (14-21)	8	30 843	Females and males	9-25
Gardasil® versus placebo (22-28)	7	24 776	Females and males	9-45
Gardasil® versus control vaccine (29)	1	3810	Females	24-45

All RCTs contributed *general* data about serious adverse events (SAE); indeed, nearly every trial included in this review claimed to be a 'safety and efficacy' study. However, the focus of the vast majority of studies was on efficacy and immunogenicity, with safety a secondary concern and affording a small portion of the published study report.

Follow-periods for the trials also varied, with a minority of trials only following up their participants to one month after their final dose of vaccine. Studies with less than 12 months follow-up tended to be smaller and single-centre, as opposed to the studies that had longer follow-up and were larger and multi-centred.

The evidence base of RCTs for SAEs was generally of high quality, with most trials having a low risk of bias. This is not surprising, given that nearly all the trials were conducted in conjunction with one of the two companies making the vaccines, and the methods were similar across studies. However, the evidence base was also characterised by a lack of detail in how SAEs were identified and recorded, how and why they were classified as SAEs and which criteria were used for assessing whether the SAE was likely to be related to vaccination. This is demonstrated by the widely varying rates in the same outcomes across trials and between vaccines.

Four major categories of SAE were reported by the trials:

- any SAEs (with some studies making an assessment of likely association with the vaccine of interest)
- medically significant conditions (mostly described as conditions requiring a visit to the emergency room or physician, that were not related to common diseases or for routine health matters; some studies also included adverse events (AEs) that were not related to common diseases)
- new onset of chronic diseases (NOCD), defined as conditions that had not been described in the patient's medical history
- deaths (some studies applied causality).

A limited number of studies also reported on new autoimmune diseases or autoimmune AEs, and new neurological conditions. Most of the studies of females also considered pregnancy outcomes; these are not considered here, although some of the total SAE numbers include adverse pregnancy outcomes.

Each SAE category is addressed below.

3.1.1 Any serious adverse events

All the trials contributed data to this outcome. In many trials, the definition of an SAE was not reported; in a minority of others, it was defined with some or all of the following criteria: an event that resulted in death, was life threatening, needed prolonged admission to hospital, resulted in disability or incapacity, was a congenital abnormality or birth defect in the offspring of the vaccinated subject, or was any other important medical event in the judgement of the investigator. Given that the rate of SAEs varies widely across studies (for example, from as low as 2% to as high as 25% in Cervarix™ versus control studies) it is highly likely that different definitions of SAEs were used in each trial. As very few details about what constituted an SAE were available in most studies, it is not possible to tell if this is the case. Nevertheless, any SAE that was reported in the trials has been included in our analyses.

None of the trial publications described how SAEs were identified or reported, or whether the investigation of SAEs was blinded to treatment allocation. Additionally, for trials with long-term follow-up, denominators were usually the 'total vaccinated cohort'; it is not clear how safety outcomes in participants who were lost to follow-up were monitored. That being said, rates of follow-up in these trials were generally high and equivalent in both arms of the trials, so although using the total vaccinated cohort denominator may slightly underestimate the risk of SAEs, it is unlikely to impact on the comparison between trial arms.

A summary of the findings for all SAEs can be found in Table 4. Although the rates per 100 000 varied considerably between comparisons, as a result of the different criteria for reporting SAEs, no differences in the rate of SAEs between HPV vaccine group and control was found for any comparison.

Table 4: Summary of results for the outcome of any Serious Adverse Event

	Number of trials (k) /number of participants (n)	Events n/N in intervention group n/100 000	Events n/N in control group n/100 00	Absolute difference (% difference, 95%CI)	Relative difference (relative risk, 95% CI)	Quality of the evidence (GRADE)
Cervarix™ versus placebo	K=10 N=15 258	125/7796 1603.4	140/7462 1876.2	-272.8/100 000 0.27% (-0.15%, 0.70%)	0.87 (0.60, 1.25)	⊕⊕⊕⊕ **HIGH** *Downgraded due to serious indirectness; but upgraded due to large numbers in trials*
Cervarix™ versus control vaccine	K=8 N=30 843	1805/15 458 11 676.8	1784/15 385 11 595.7	81.1/100 000 0.1% (-0.81%, 1.03%)	1.01 (0.95, 1.07)	⊕⊕⊕⊕ **HIGH** *Downgraded due to serious indirectness; but upgraded due to large numbers in trials*
Gardasil® versus placebo	K=7 N=28 671	109/12 701 858.2	113/12 075 935.8	-77.6/100 000 0.08% (-0.16%, 0.3%)	0.93 (0.72, 1.21)	⊕⊕⊕⊕ **HIGH** *Downgraded due to serious indirectness; but upgraded due to large numbers in trials*
Gardasil® versus control vaccine	K=1 N=3810	14/1908 733.8	16/1902 841.2	-107.4/100 000 0.11% (-0.5%, 0.73%)	0.87 (0.43, 1.78)	⊕⊕⊕⊕ **HIGH** *Downgraded due to serious indirectness; upgraded due to large numbers in trials*

Meta-analyses were conducted of the relative difference (relative risks) for each comparison for which two or more studies were available, and are presented in Figures 1 through 3.

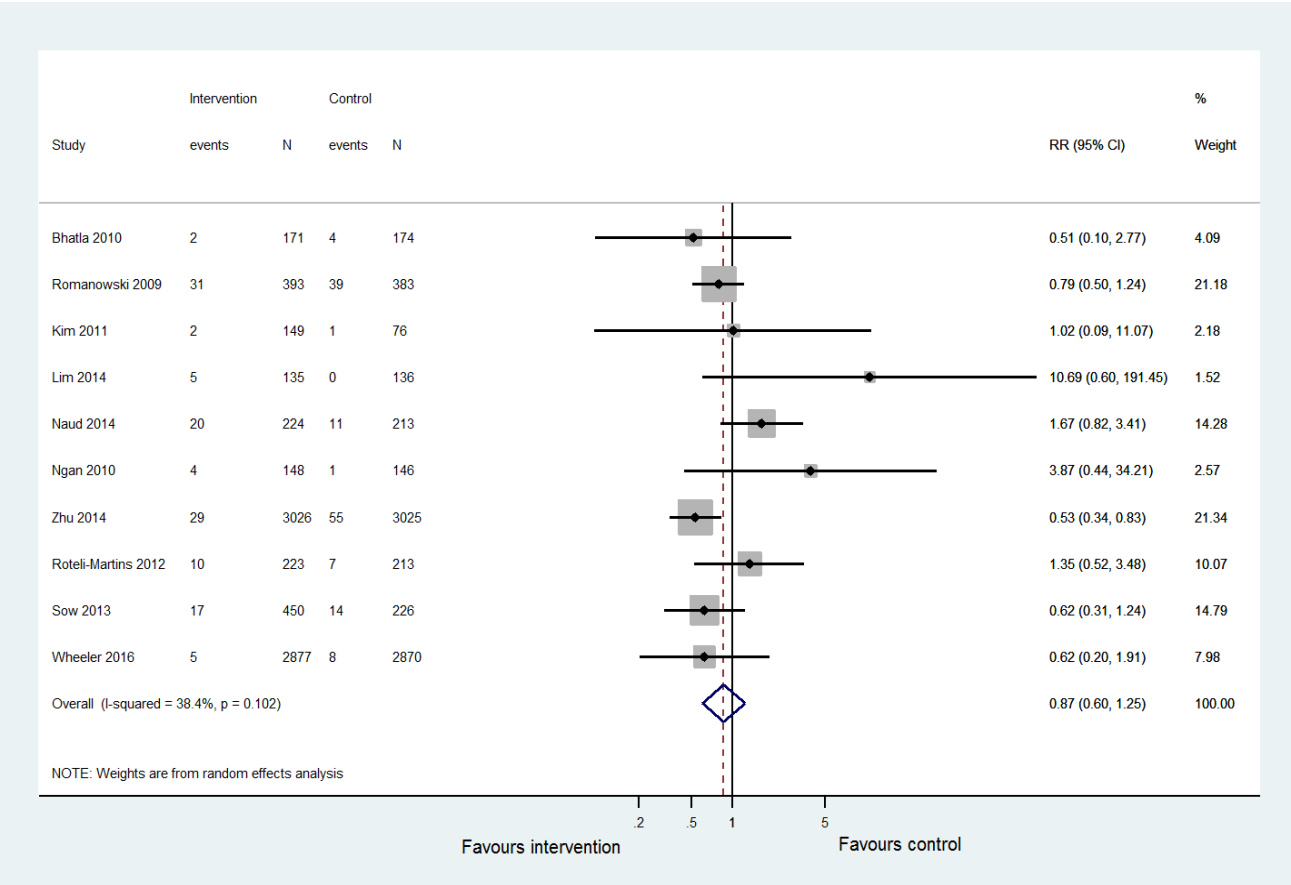

Figure 2: Meta-analysis of studies of SAEs: Cervarix™ versus placebo

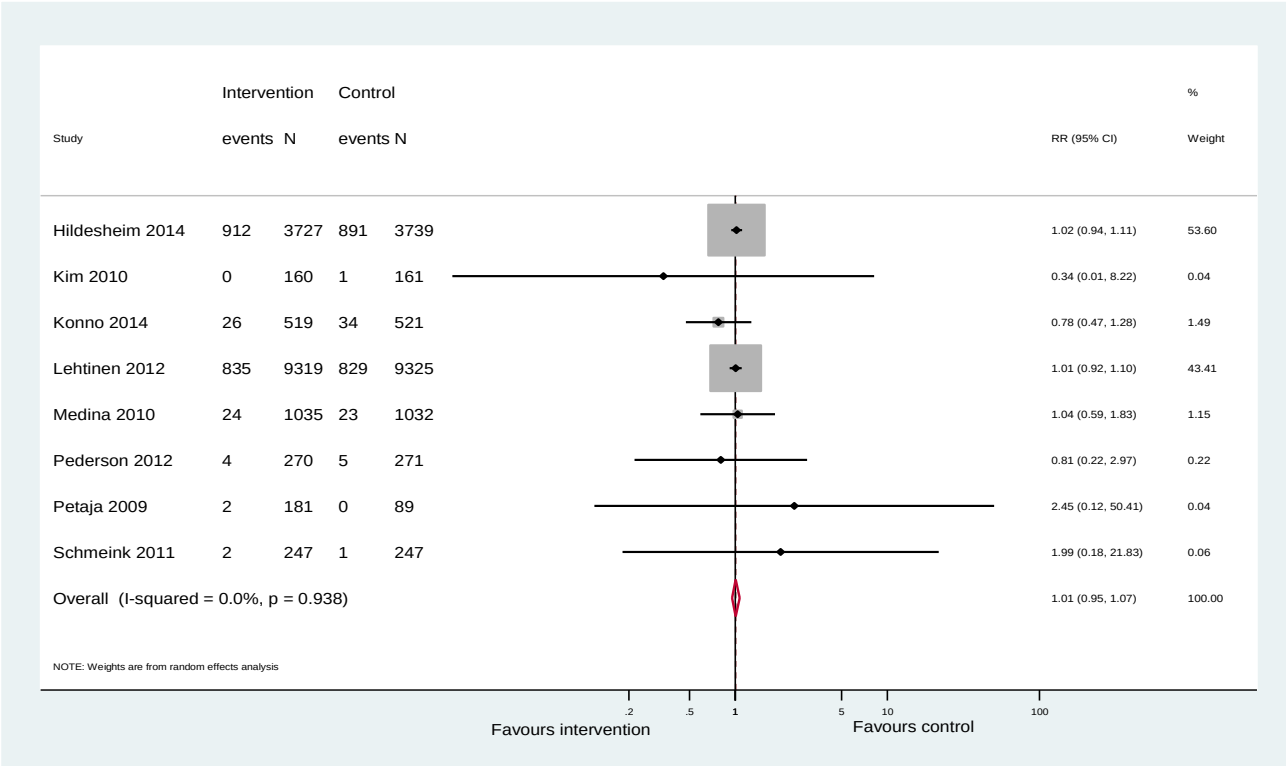

Figure 3: Meta-analysis of studies of SAEs: Cervarix™ versus control vaccine

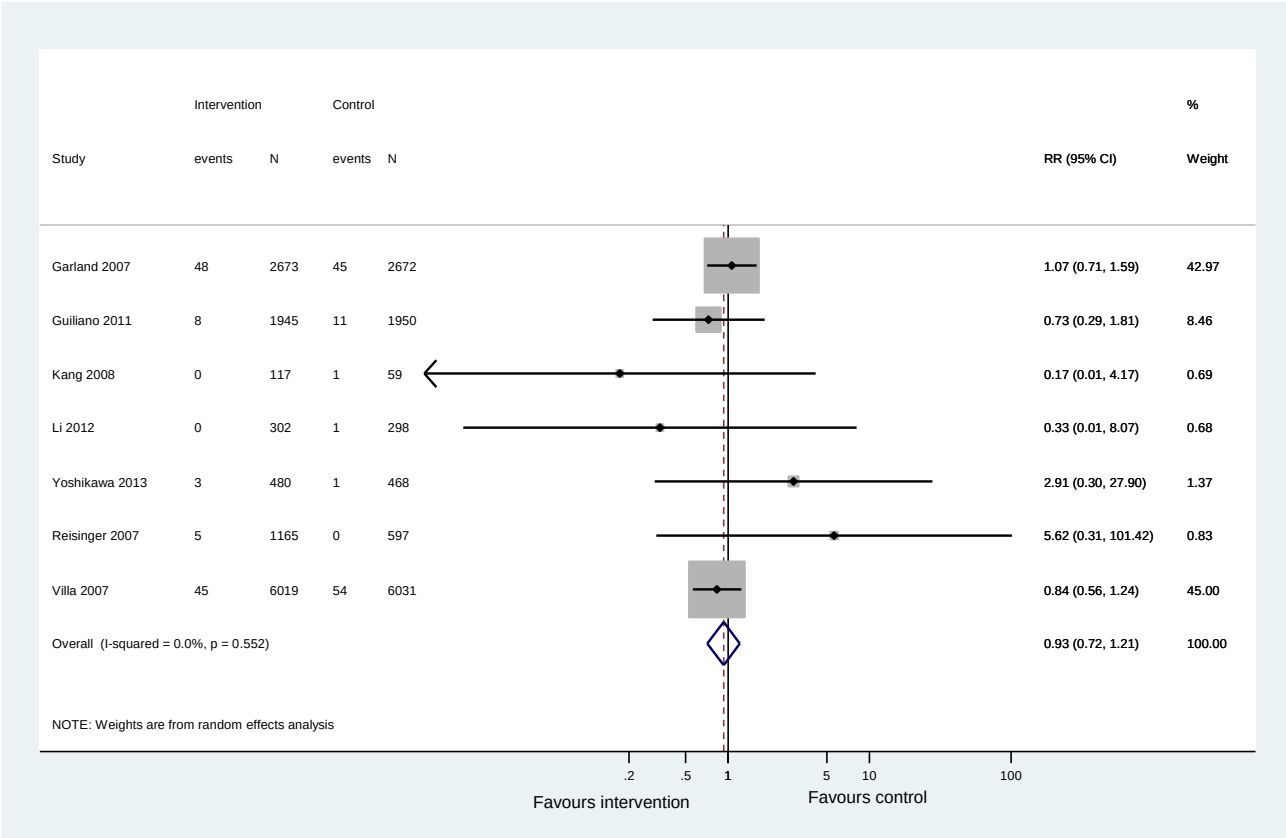

Figure 4: Meta-analysis of studies of SAEs: Gardasil® versus placebo

To examine any difference in the rates of SAEs by gender, each comparison was examined for studies containing only males or only females. Only one small study of Cervarix™ contained only males, so separating this group had little impact on the estimate. Likewise for Gardasil®, only one study contained only males, although this was a larger study and so the estimate for just females was calculated. Four studies contributed to this analysis, and the relative risk was 0.95 (95% CI 0.72, 1.25), barely changing the estimate for all populations (which included one 'males only' study and two mixed-gender studies). Even though the trial with males only was a good size (n=3895), the largest trial in this comparison was three times larger and contained females only, which explains the lack of impact on the estimate when only females are considered. As there were only a small number of trials with males only, they were not considered separately for any other outcome.

SAEs judged to be related to vaccination

In the Cervarix™ versus placebo comparison, seven of the 10 included trials provided data on SAEs that had been judged to be associated with the vaccination. In the HPV vaccine group, six SAEs were judged to be associated with vaccination (0.09%), compared to eight (0.1%) in the placebo group (difference 0.01%, 95% CI -0.11%, 0.13%, p=0.85). Only two of these seven trials reported any vaccine-related SAEs.

In the Cervarix™ versus control vaccine comparison, six of the eight included trials reported on vaccine-related SAEs, with three trials reporting at least one SAE. One trial, which had a much higher

reporting rate of SAEs that most other trials (Hildesheim 2014), reported 53 possible vaccine-related SAEs in the HPV vaccine group compared to 39 in the control group; however, they also noted that all but 12 SAEs (7 in the HPV vaccine group and 5 in the control group) were pregnancy-related. In total, vaccine-related SAEs occurred in 0.4% of the HPV vaccine group and 0.29% in the control group (difference 0.11%, 95% CI -0.03%, 0.25%, p=0.1).

In the Gardasil® studies, two trials reported on this outcome and both studies deemed none of the SAEs to be vaccine-related.

3.1.2 New onset chronic diseases

Only studies investigating Cervarix™ reported on the outcome of new onset chronic diseases (NOCD). Most trials that defined NOCD reported it to be a condition that had not been recorded in the participant's medical history for the trial. A small minority of trials mentioned that assessment of NOCD was undertaken in a blinded manner prior to analysis, and some used a 'predefined list'; most trials gave no details about the methods used to define NOCD. The results are reported in Table 5.

Table 5: Summary of results for the outcome of any new onset chronic disease

	Number of trials (k) /number of participants (n)	**Events n/N in intervention group n/100 000**	**Events n/N in control group n/100 00**	**Absolute difference (%, 95%CI)**	**Relative difference (relative risk, 95% CI)**	**Quality of the evidence (GRADE)**
Cervarix™ versus placebo	K=9 N=9511	61/4919 1240.1	60/4592 1306.6	-66.5/100 000 0.07% (-0.4%, 0.54%)	0.83 (0.58, 1.20)	⊕⊕⊕⊕ **HIGH** *Downgraded due to serious indirectness; but upgraded due to large numbers in trials*
Cervarix™ versus control vaccine	K=7 N=30 349	712/15 211 4680.8	769/15 138 5079.9	-399.1/100 000 0.4% (-0.9%, 0.9%)	0.93 (0.84, 1.03)	⊕⊕⊕⊕ **HIGH** *Downgraded due to serious indirectness; but upgraded due to large numbers in trials*
Gardasil® versus placebo	Outcome not reported					
Gardasil® versus control vaccine	Outcome not reported					

Meta-analysis was undertaken for the two comparisons with data, and those relating to the relative effects are shown in Figures 4 and 5. It can be seen from the forest plots that there is no difference between HPV vaccine and placebo or control vaccine on this outcome.

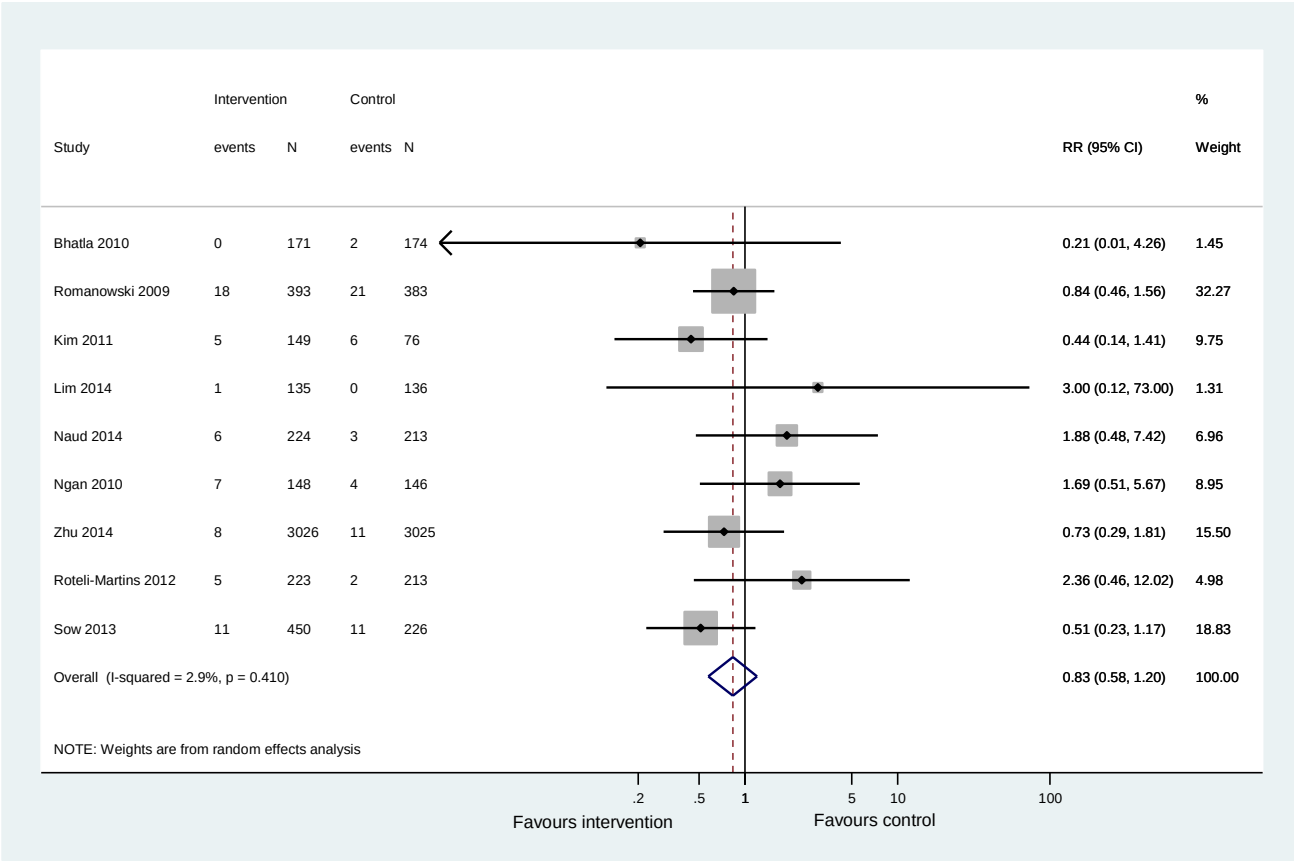

Figure 5: Meta-analysis of studies of NOCD: Cervarix™ versus placebo

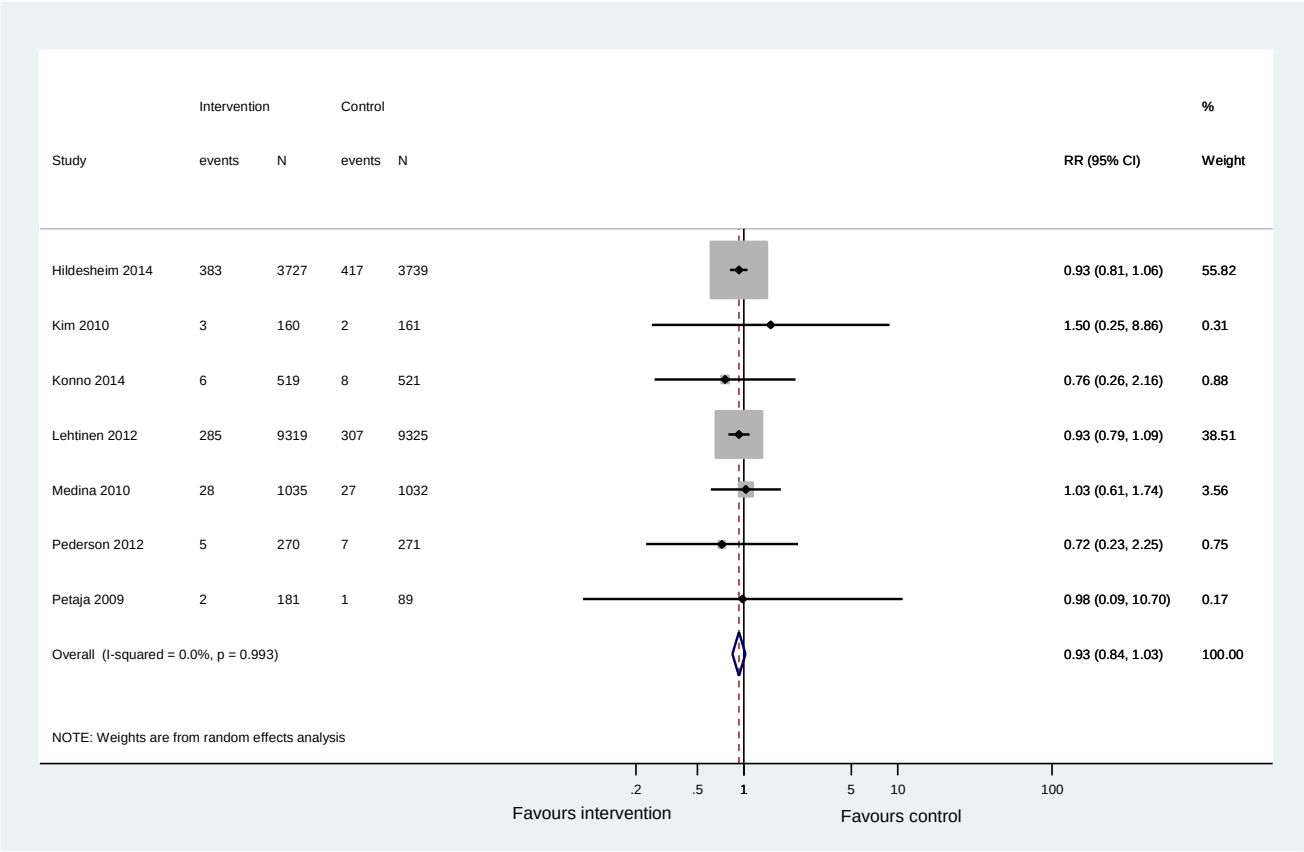

Figure 6: Meta-analysis of studies of NOCD: Cervarix™ versus control vaccine

3.1.3 Medically significant conditions

As with NOCD, only the trials of Cervarix™ included this outcome. Again, this outcome was variously described across trials, although there was some consistency with the description of NOCD, with many trials describing medically significant conditions (MSC) as events prompting emergency department or physician visit, not related to common diseases or visits for routine health issues, and some trials also included SAEs unrelated to common diseases in this definition. There was considerable variation in the reporting rate for this outcome, reflecting the differing definitions. For example, in the Cervarix™ versus control vaccine comparison, one study reported MSC in around 35% of its participants, whereas another trial had rates around 15%. This very high proportion meant the rate per 100 000 in this comparison was much higher than in other comparisons and the meta-analyses showed evidence of moderate heterogeneity of effect. However, no difference was shown between intervention and control arm in any comparison. A summary of results for this outcome is found in Table 6.

Table 6: Summary of results for the outcome of medically significant conditions

	Number of trials (k)/ number of participants (n)	Events n/N in intervention group n/100 000	Events n/N in control group n/100 00	Absolute difference (% difference, 95%CI)	Relative difference (relative risk, 95% CI)	Quality of the evidence (GRADE)
Cervarix™ versus placebo	K=6 N=7623	316/3853 8201.4	262/3770 6949.6	1251.8/100 000 1.25% (0.04%, 2.46%)*	1.15 (0.88, 1.50)	⊕⊕⊕⊕ **HIGH** *Downgraded due to serious indirectness; but upgraded due to large numbers in trials*
Cervarix™ versus control vaccine	K=4 N=28 498	4183/14 241 29 372.9	4287/14 257 30 069.4	-696.5/100 000 0.7% (-0.37%, 1.77%)	0.98 (0.92, 1.05)	⊕⊕⊕⊕ **HIGH** *Downgraded due to serious indirectness; but upgraded due to large numbers in trials*
Gardasil® versus placebo	Outcome not reported					
Gardasil® versus control vaccine	Outcome not reported					

*p=0.04

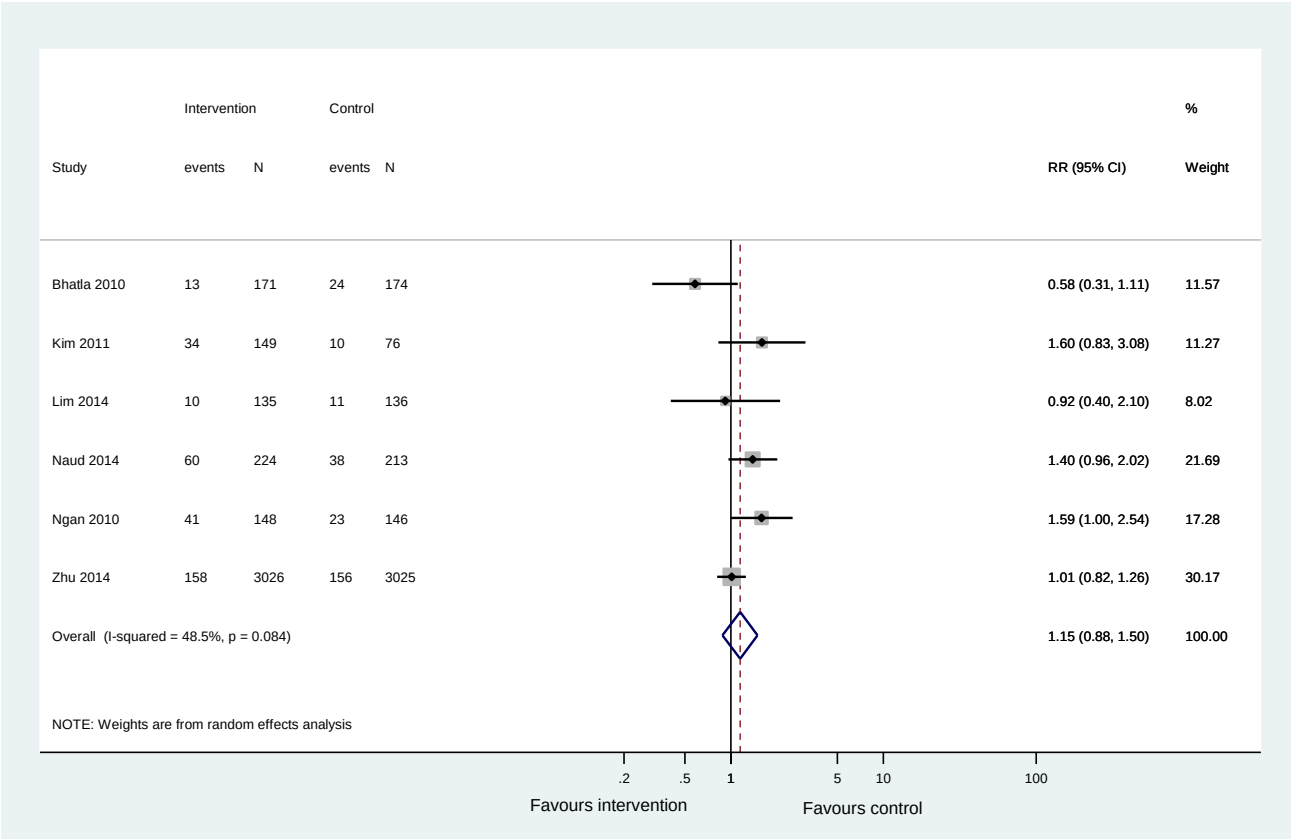

Figure 7: Meta-analysis of studies for MSC: Cervarix™ versus placebo

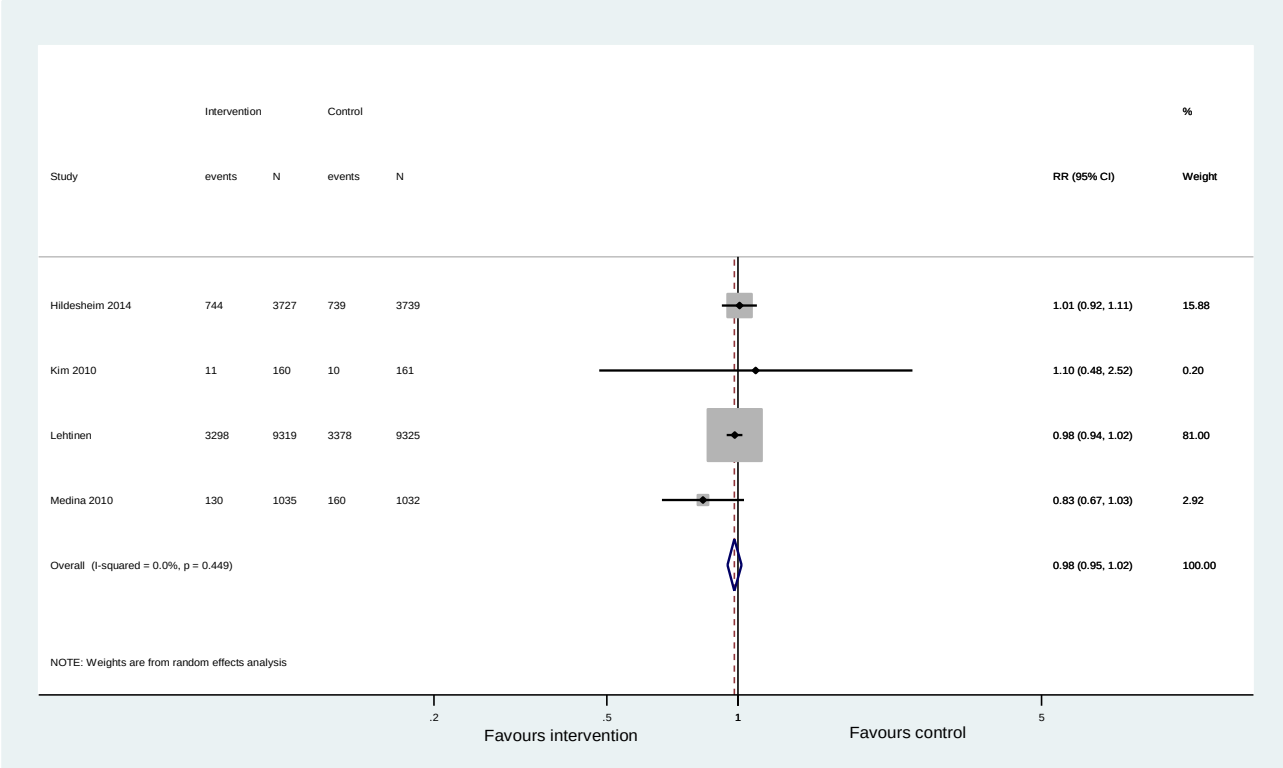

Figure 8: Meta-analysis of studies for MSC: Cervarix™ versus control vaccine

3.1.4 Deaths

Although nearly every trial reported on deaths, and most identified the cause of death for each participant, not every trial assessed causality. In the trials that did report causality, no deaths were judged to be related to vaccination. In the Gardasil® trials, no deaths were considered vaccine-related. In the Cervarix™ trials, two studies reported deaths, did not assess their causality but did report the causes, which were: suicide, car accidents, assault, cancer, Crohn's disease, systemic lupus erythematosus, HIV-related condition and acute myocardial infarction.

3.1.5 Other outcomes from the randomised controlled trials

A limited number of studies also reported on the new onset autoimmune diseases or autoimmune disease adverse events, and their results are presented in Table 7. Again, definitions for this outcome were not given, and the results demonstrate a wide range of reporting rates, as with the other outcomes. There was no difference between Cervarix™ and comparator, with a pooled relative risk of 1.04 (95% CI 0.62, 1.74) for autoimmune disease-related SAEs. Results from the meta-analysis are shown in Figure 9.

Table 7: Summary of results for the outcome of autoimmune diseases

	Number of trials (k)/ number of participants (n)	**Events n/N in intervention group n/100 000**	**Events n/N in control group n/100 00**	**Absolute difference (% difference, 95%CI)**	**Relative difference (relative risk, 95% CI)**	**Quality of the evidence (GRADE)**
Cervarix™ versus placebo	K=3 N=7163	6/3699 162.2	6/3464 173.2	-11.0/100 000 0.01% (-0.21%, 0.24%)	0.78 (0.25, 2.42)	⊕⊕⊕⊕ **HIGH** *Downgraded due to serious indirectness; but upgraded due to large numbers in trials*
Cervarix™ versus control vaccine	K=2 N=8506	25/4246 588.8	22/4260 516.4	72.4/100 000 0.07% (-0.27%, 0.41%)	1.12 (0.63, 2.00)	⊕⊕⊕⊕ **HIGH** *Downgraded due to serious indirectness; but upgraded due to large numbers in trials*
Gardasil® versus placebo	Outcome not reported					
Gardasil® versus control vaccine	Outcome not reported					

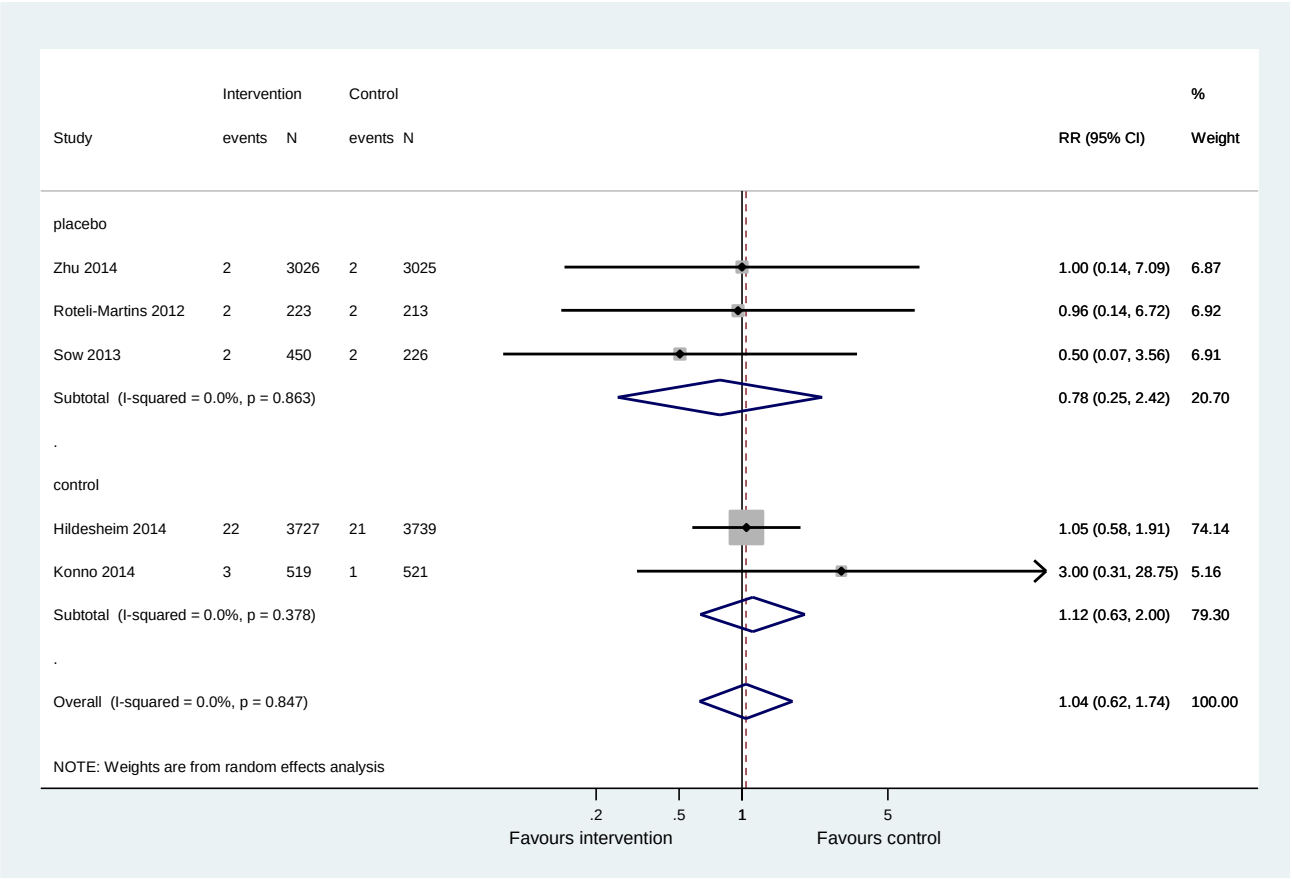

Figure 9: Meta-analysis of studies for autoimmune diseases: Cervarix™ versus comparator (placebo or control vaccine)

3.2 Specific serious adverse events investigated in other study types

As the large body of evidence from the RCTs did not address some of the specific safety concerns about HPV vaccines, different study types were considered to identify any evidence concerning these outcomes.

A total of six good quality cohort studies were identified in this search. As they used different methodologies and reported slightly different outcomes, no meta-analysis was conducted. However, an overall grading of the evidence from these cohort studies for the outcomes of autoimmune diseases, multiple sclerosis and other demyelinating diseases, venous thromboembolism and migraine was applied. Due to the nature of GRADE, outcomes assessed using this tool begin as low quality, as they are observational, even though the studies may be of high quality. However, as detailed in WHO's "Guidance for the development of evidence-based vaccine-related recommendations", designs that mitigate confounding through good quality design can be upgraded. The outcomes from these cohort studies were then all rated as 'Moderate'. Results are presented in Table 8.

Table 8: Selected results from cohort studies investigating specific SAEs associated with HPV vaccination

Outcome	Data size and source	Results		Certainty of the evidence (GRADE)
Autoimmune diseases following HPV vaccination	Data from 5 high quality cohort studies	No differences in rates of most autoimmune diseases between those exposed to vaccine and those unexposed. No findings equated to a safety signal.		⊕⊕⊕O **MODERATE** *Upgraded due to study design that mitigated confounding*
Venous thrombo-embolism	Data from 2 high quality cohort studies	No difference in the rate of thromboembolism in those exposed to vaccine and those unexposed.		⊕⊕⊕O **MODERATE** *Upgraded due to study design that mitigated confounding*
Multiple sclerosis and other demyelinating conditions	Data from 2 high quality cohort studies	Exposed	Unexposed	⊕⊕⊕O **MODERATE** *Upgraded due to study design that mitigated confounding*
		MS: between 3.4 and 6.1/ 100 000 person years	Between 2.5 and 21.5/ 100 000 person years	
		IRR between 0.90 (95%CI 0.70, 1.15) – 1.37 (0.74, 3.20)		
		Other: between 1.1 and 7.54/ 100 000 person years	between 1.6 and 16.14/ 100 000 person years	
		IRR between 0.71 (0.38, 2.13) and 1.00 (95%CI 0.80, 1.26)		

* CI = confidence interval; IRR = incidence rate ratio; MS = multiple sclerosis

All the studies used appropriate methodology and matched their exposed cases (those who had been vaccinated) with unvaccinated controls. In particular, two studies from Scandinavia used the extensive linked administrative datasets available there to study large cohorts of girls for a range of relevant outcomes: 53 predefined outcomes in one study, including a range of autoimmune conditions and venous thromboembolism (VTE)(30), and in the other, multiple sclerosis (MS) and other demyelinating diseases (31). The other cohort studies included one conducted in The Netherlands, also using administrative data about migraine outcomes (32), an American study from a Health Maintenance Organization which investigated Guillain–Barré Syndrome (GBS), stroke, VTE, appendicitis, anaphylaxis, seizure, syncope, and allergic reaction (33), and a study from the UK using

general practice data, which investigated new onset autoimmune disease (34). The study profiles can be found in Appendix 2. The studies and outcomes are discussed below.

The large, high quality cohort study by Arnheim-Dahlstrom et al (30) used linked administrative health data to identify a large cohort of females eligible for HPV vaccination. The study included a cohort of nearly a million girls aged 10 to 17 years, of whom nearly a third had received at least one HPV vaccination (quadrivalent HPV vaccine predominantly used in Scandinavia). Patient registers from hospital inpatients, outpatients and emergency departments were searched for cases of the predefined list of outcomes. Diagnoses made by physicians in general practice were not included in this study; the authors noted that the serious outcomes included would have been seen by paediatricians, which are only available in hospitals in Denmark and Sweden, so it is likely that the majority of cases were captured. The study used an at-risk period of 180 days post vaccination. Twenty-three of the predefined autoimmune outcomes were considered (having five or more exposed cases): Graves' disease, Hashimoto's thyroiditis, other hyperthyroidism, hypothyroidism, coeliac disease, Crohn's disease, ulcerative colitis, pancreatitis, ankylosing spondylitis, Behcet's syndrome, Henoch-Schonlein's purpura, juvenile arthritis, myositis, rheumatoid arthritis, systemic lupus erythematosis, vasculitis (unspecified), idipathic thrombocytopenic purpura, erythema nodosum, localised scleroderma, psoriasis, vitiligo, Raynaud's disease and Type 1 diabetes. There were over two million person years in the unexposed cohort and over 200 000 person years in the exposed cohort. Incidence rates were not significantly increased for 20 of these outcomes, however vaccine exposure was significantly associated with Behcet's syndrome (rate ratio 3.37, 95% CI 1.05, 10.80), Raynaud's disease (1.67, 95% CI 1.14, 2.44) and type 1 diabetes (1.29, 95% CI 1.03, 1.62). The authors investigated the strength of the signal with a predefined analytical strategy, and found the rate ratios in the period starting at day 181 were similar to the rate ratios in the primary risk period, and that the temporal pattern of cases was random. The authors concluded that no consistent evidence for a causal association was found with these three outcomes.

The study also investigated neurological outcomes: Bell's palsy, epilepsy, narcolepsy, optical neuritis, and paralysis, as well as VTE. Rate ratios were not significantly increased in the exposed group for any of the neurological outcomes; indeed, two outcomes (epilepsy and paralysis) the incidence rate ratios were significantly decreased. Likewise for VTE, the rate ratio was not significantly different (IRR 0.86, 95% CI 0.55, 1.36)

This high quality study adjusted their analyses for a range of confounders available to them because of their excellent data repositories: adjustments were made for age, country, calendar year, parental educational level, parental countries of birth and paternal socioeconomic status. The completeness of the registries and the use of the whole eligible cohort minimises possible confounding in this study.

Willame et al (34) also considered new onset autoimmune disease in a study in the UK. This study compared the rates of disease in a cohort of women aged 9-25 years with an age and sex- matched historical cohort (before the introduction of the vaccine), a concurrent age-matched male cohort and an historical age-matched male cohort. The study used data from the Clinical Practice Research

Datalink General Practice Online Database (CRPD GOLD), based on data from general practices, and some linked data to hospital episodes; although the linkage was not complete. The follow-up period was one year. A universal immunisation program for HPV 16/18 had been undertaken in the UK. From the four eligible cohorts identified in the database, 65 000 were randomly chosen for each cohort for follow up, with a total of 259 876 in the final population for main analysis. Predefined autoimmune diseases were identified from the database, with two co-primary endpoints: 1) neuroinflammatory/ophthalmic diseases: multiple sclerosis, transverse myelitis, optic neuritis, Guillain-Barre syndrome, autoimmune uveitis and other demyelinating diseases; 2) other autoimmune diseases: systemic lupus erythematosus, rheumatoid arthritis, juvenile rheumatoid arthritis, Still's disease, psoriatic arthritis, ankylosing spondylitis, idiopathic thrombocytopenic purpura, autoimmune haemolytic anaemia, type 1 diabetes, autoimmune thyroiditis, Crohn's disease, ulcerative colitis and autoimmune hepatitis.

The results showed no cases in the exposed group for the first co-primary endpoint (neuroinflammatory/ophthalmic autoimmune disease). For co-primary endpoint 2, the other autoimmune diseases, the incidence rate in the exposed cohort was 58.73 per 100 000 person years, compared to 41.64 in the historical female cohort (incidence rate ratio (IRR) 1.41, 95% CI 0.86, 2.31), 40.09 per 100 000 in the concurrent male cohort and 23.12 per 100 000 in the historical male cohort (no tests against exposed cohort, however confidence intervals overlap with concurrent cohort; historical cohort significantly different). The number of cases in most categories was small in the exposed cohort, indeed only three diseases had more than 10 cases in the female cohorts: autoimmune thyroiditis, Crohn's disease and type 1 diabetes. Compared to the unexposed historical female cohort, a significant increased risk in the exposed cohort was found for autoimmune thyroiditis, no excess risk was found for Crohn's disease and a protective effect for type 1 diabetes was found. The authors noted that if all suspected cases of autoimmune thyroiditis, rather than confirmed cases, were used in the analysis, the IRR would be no longer significant. The authors indicated that the incidence of autoimmune thyroiditis was still within the expected ranges for the age group. It should be noted that no other potential confounders were considered in this study, and it was funded, designed, conducted, analysed and reported by GlaxoSmithKline, which indicates a source of potential bias.

The cohort study by Scheller et al (31) was also conducted in Denmark and Sweden using a similar design to Arnheim-Dahlstrom. Again, a cohort identified through centralised registries was used to identify women eligible for the HPV vaccination, identifying exposed and unexposed subjects, and then looking for the outcomes of multiple sclerosis (MS) and other demyelinating diseases in patient registers. This study was also of high quality and included 3 983 824 women eligible for the cohort, of whom 789 082 were vaccinated. The study totalled 21 332 622 person-years. The incidence rate per 100 000 years for MS was 6.12 (95% CI 4.86, 7.69) in the exposed cohort, compared with 21.54 (95% CI 20.90, 22.20) in the unexposed cohort, an IRR of 0.90 (95% CI 0.70, 1.15). For other demyelinating diseases, the incidence rate per 100 000 person years in the exposed cohort was 7.54 (6.13, 9.27) compared to 16.14 (15.58, 16.71) in the unexposed cohort, an IRR of 1.00 (0.80, 1.26). The authors

concluded that the data did not support an association between HPV vaccination and MS or other demyelinating diseases.

The study by Gee and colleagues (33) used administrative data from seven managed care organisations in several states in the US to investigate a range of outcomes: anaphylaxis, allergic reactions, appendicitis, Guillain-Barre syndrome (GBS), seizures, first ever seizures, stroke, syncope and VTE. This study was prospective and investigated data weekly for new adverse events. The exposed cohort was formed from females aged 9-26 years and registered at the participating sites who had received at leave one dose of quadrivalent HPV vaccine. The cohort was matched to data from medical encounters in outpatients, emergency departments and hospitals, as well as immunisation data. Outcomes were predefined and well described. The exposed cohort was compared to an historical comparison group not vaccinated with HPV vaccine for the less common outcomes, and a concurrent unexposed group for the more common outcomes. Of all the outcomes investigated, an increased risk of appendicitis in youths was identified; however, analysis of data did not find any temporally-related clusters, and the authors suspected a change in coding at one site may have affected the background rates. One case of GBS was identified and reviewed, and found not to be an incident case. No increased rates were seen for seizures, allergic reactions or syncope. One vaccine-related confirmed case of anaphylaxis in a 26 year old was identified, and resulted in a rate of 1.7 cases per million doses (95% 0.04, 9.3).

The cohort study by Schurink-van't Klooster considered migraine as an adverse outcome (32). All incident cases of migraine in 12-16 year old girls were identified from the Integrated Primary Care Information database, a longitudinal, observational database which contains medical patient records from general practitioners in the Netherlands. Cases were matched to the vaccination record database. Only 22 girls with incident migraine were identified, with half of these vaccinated. Incidence rate ratios for migraine in monthly periods following vaccination ranged between zero and three, with none statistically significant and none related to occurrence of vaccination. This study also embedded a self-controlled case series within this cohort study, using a six-week high risk period post-vaccination as the exposed time. Although a raised relative risk in the high-risk time was observed, it was not statistically significant. The authors concluded that the number of cases was too small to be certain about any relationship between migraine and HPV vaccination.

A study of women vaccinated with HPV4 who were enrolled in two managed care organisations in California also compared rates of various autoimmune and neurological outcomes (35). New conditions were identified through the electronic health records of the organisations. Rates of incident conditions were compared against the rate in unvaccinated women in the same time period. Nearly all the women in the study were aged between nine and 26 years. The at-risk period was 180 days post each vaccination. A sample of cases were reviewed to assess if they were truly new onset. The authors found no significantly elevated incidence rate ratios amongst all the outcomes considered, with the exception of Hashimoto's disease. On investigating this further, no consistent evidence for a safety signal was found.

4 DISCUSSION AND CONCLUSIONS

This comprehensive systematic review containing a large body of high-level evidence is very consistent in finding no difference in the rate of SAEs between people who have received either Cervarix™ or Gardasil® and people who received a placebo or a control vaccine. Good quality cohort studies of specific autoimmune and other SAEs also found no relationship between exposure to HPV vaccination and development of these outcomes.

The major concern with the body of RCT evidence collated is the lack of standard definition of what constitutes an SAE. Most trials did not define the SAEs they collected, how they would collect them or whether the collection of data was blinded to treatment allocation. Only one trial in this review described how they would assess a potential relationship between an SAE and the vaccine. Whilst most trials commented that their SAEs were not related to vaccination, there is no way to know if the criteria used were the same across studies.

The varying definitions of SAEs is reflected in the widely differing rates for SAEs found for this review; this makes applying an average rate of SAEs to the HPV vaccine very difficult. These pooled values should be considered estimates as they may have been affected by the likely different outcome definitions used. The comparison between vaccine and placebo or control vaccine in each analysis is, however, still valid.

REFERENCES

1. Angelo MG, David MP, Zima J, Baril L, Dubin G, Arellano F, et al. Pooled analysis of large and long-term safety data from the human papillomavirus-16/18-AS04-adjuvanted vaccine clinical trial programme. Pharmacoepidemiology and Drug Safety. 2014;23(5):466-79.

2. World Health Organisation. Guidance for the development of evidence-based vaccine-related recommendations. 2015.

3. Lu B, Kumar A, Castellsague X, Giuliano AR. Efficacy and safety of prophylactic vaccines against cervical HPV infection and diseases among women: a systematic review & meta-analysis. BMC Infect Dis. 2011;11:13.

4. Bhatla N, Suri V, Basu P, Shastri S, Datta SK, Bi D, et al. Immunogenicity and safety of human papillomavirus-16/18 AS04-adjuvanted cervical cancer vaccine in healthy Indian women. Journal of Obstetrics and Gynaecology Research. 2010;36(1):123-32.

5. Kim SC, Song YS, Kim YT, Kim YT, Ryu KS, Gunapalaiah B, et al. Human papillomavirus 16/18 AS04-adjuvanted cervical cancer vaccine: Immunogenicity and safety in 15-25 years old healthy Korean women. Journal of Gynecologic Oncology. 2011;22(2):67-75.

6. Lim BK, Ng KY, Omar J, Omar SZ, Gunapalaiah B, Teoh YL, et al. Immunogenicity and safety of the AS04-adjuvanted human papillomavirus-16/18 cervical cancer vaccine in malaysian women aged 18-35 years: A randomized controlled trial. Medical Journal of Malaysia. 2014;69(1):2-8.

7. Naud PS, Roteli-Martins CM, De Carvalho NS, Teixeira JC, De Borba PC, Sanchez N, et al. Sustained efficacy, immunogenicity, and safety of the HPV-16/18 AS04-adjuvanted vaccine: Final analysis of a long-term follow-up study up to 9.4 years post-vaccination. Human Vaccines and Immunotherapeutics. 2014;10(8):2147-62.

8. Ngan HY, Cheung AN, Tam KF, Chan KK, Tang HW, Bi D, et al. Human papillomavirus-16/18 AS04-adjuvanted cervical cancer vaccine: immunogenicity and safety in healthy Chinese women from Hong Kong. Hong Kong Med J. 2010;16(3):171-9.

9. Romanowski B, de Borba PC, Naud PS, Roteli-Martins CM, De Carvalho NS, Teixeira JC, et al. Sustained efficacy and immunogenicity of the human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine: analysis of a randomised placebo-controlled trial up to 6.4 years. Lancet. 2009;374(9706):1975-85.

10. Roteli-Martins CM, Naud P, De Borba P, Teixeira JC, De Carvalho NS, Zahaf T, et al. Sustained immunogenicity and efficacy of the HPV-16/18 AS04-adjuvanted vaccine: Up to 8.4 years of follow-up. Human Vaccines and Immunotherapeutics. 2012;8(3):381-8.

11. Sow PS, Watson-Jones D, Kiviat N, Changalucha J, Mbaye KD, Brown J, et al. Safety and immunogenicity of human papillomavirus-16/18 AS04-adjuvanted vaccine: A randomized trial in 10-25-year-old HIV-seronegative African girls and young women. Journal of Infectious Diseases. 2013;207(11):1753-63.

12. Wheeler CM, Skinner SR, Del Rosario-Raymundo MR, Garland SM, Chatterjee A, Lazcano-Ponce E, et al. Efficacy, safety, and immunogenicity of the human papillomavirus 16/18 AS04-adjuvanted vaccine in women older than 25 years: 7-year follow-up of the phase 3, double-blind, randomised controlled VIVIANE study. The Lancet Infectious Diseases. 2016;16(10):1154-68.

13. Zhu FC, Chen W, Hu YM, Hong Y, Li J, Zhang X, et al. Efficacy, immunogenicity and safety of the HPV-16/18 AS04-adjuvanted vaccine in healthy Chinese women aged 18'25 years: Results from a randomized controlled trial. International Journal of Cancer. 2014;135(11):2612-22.

14. Hildesheim A, Wacholder S, Catteau G, Struyf F, Dubin G, Herrero R, et al. Efficacy of the HPV-16/18 vaccine: Final according to protocol results from the blinded phase of the randomized Costa Rica HPV-16/18 vaccine trial. Vaccine. 2014;32(39):5087-97.

15. Kim YJ, Kim KT, Kim JH, Cha SD, Kim JW, Bae DS, et al. Vaccination with a human papillomavirus (HPV)-16/18 AS04-adjuvanted cervical cancer vaccine in Korean girls aged 10-14 years. Journal of Korean Medical Science. 2010;25(8):1197-204.

16. Konno R, Yoshikawa H, Okutani M, Quint W, Suryakiran PV, Lin L, et al. Efficacy of the human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical intraepithelial neoplasia and cervical infection in young Japanese women: Open follow-up of a randomized clinical trial up to 4 years post-vaccination. Human Vaccines and Immunotherapeutics. 2014;10(7):1781-94.

17. Lehtinen M, Paavonen J, Wheeler CM, Jaisamrarn U, Garland SM, Castellsagué X, et al. Overall efficacy of HPV-16/18 AS04-adjuvanted vaccine against grade 3 or greater cervical intraepithelial neoplasia: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial. The Lancet Oncology. 2012;13(1):89-99.

18. Medina DM, Valencia A, de Velasquez A, Huang LM, Prymula R, Garcia-Sicilia J, et al. Safety and immunogenicity of the HPV-16/18 AS04-adjuvanted vaccine: a randomized, controlled trial in adolescent girls. J Adolesc Health. 2010;46(5):414-21.

19. Pedersen C, Breindahl M, Aggarwal N, Berglund J, Oroszlán G, Silfverdal SA, et al. Randomized trial: Immunogenicity and safety of coadministered human papillomavirus-16/18 AS04-adjuvanted vaccine and combined hepatitis A and B vaccine in girls. Journal of Adolescent Health. 2012;50(1):38-46.

20. Petaja T, Keranen H, Karppa T, Kawa A, Lantela S, Siitari-Mattila M, et al. Immunogenicity and safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine in healthy boys aged 10-18 years. J Adolesc Health. 2009;44(1):33-40.

21. Schmeink CE, Bekkers RL, Josefsson A, Richardus JH, Berndtsson Blom K, David MP, et al. Co-administration of human papillomavirus-16/18 AS04-adjuvanted vaccine with hepatitis B vaccine: randomized study in healthy girls. Vaccine. 2011;29(49):9276-83.

22. Garland SM, Hernandez-Avila M, Wheeler CM, Perez G, Harper DM, Leodolter S, et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. N Engl J Med. 2007;356(19):1928-43.

23. Giuliano AR, Palefsky JM, Goldstone S, Moreira ED, Jr., Penny ME, Aranda C, et al. Efficacy of quadrivalent HPV vaccine against HPV Infection and disease in males. N Engl J Med. 2011;364(5):401-11.

24. Kang S, Kim KH, Kim JH, Kim YT, Kim YT, Song YS, et al. Safety and immunogenicity of a vaccine targeting human papillomavirus types 6, 11, 16 and 18: a randomized, placebo-controlled trial in 176 Korean subjects. Int J Gynecol Cancer. 2008;18(5):1013-9.

25. Li R, Li Y, Radley D, Liu Y, Huang T, Sings HL, et al. Safety and immunogenicity of a vaccine targeting human papillomavirus types 6, 11, 16 and 18: A randomized, double-blind, placebo-controlled trial in Chinese males and females. Vaccine. 2012;30(28):4284-91.

26. Reisinger KS, Block SL, Lazcano-Ponce E, Samakoses R, Esser MT, Erick J, et al. Safety and persistent immunogenicity of a quadrivalent human papillomavirus types 6, 11, 16, 18 L1 virus-like particle vaccine in preadolescents and adolescents: a randomized controlled trial. Pediatr Infect Dis J. 2007;26(3):201-9.

27. Villa LL, Perez G, Kjaer SK, Paavonen J, Lehtinen M, Muñoz N, et al. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. New England Journal of Medicine. 2007;356(19):1915-27.

28. Yoshikawa H, Ebihara K, Tanaka Y, Noda K. Efficacy of quadrivalent human papillomavirus (types 6, 11, 16 and 18) vaccine (GARDASIL) in Japanese women aged 18-26 years. Cancer science [Internet]. 2013; 104(4):[465-72 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/340/CN-00908340/frame.html

http://onlinelibrary.wiley.com/store/10.1111/cas.12106/asset/cas12106.pdf?v=1&t=iy4284ar&s=9155cdf1836416f284396031b9f4b691ac006925.

29. Castellsagué X, Mũoz N, Pitisuttithum P, Ferris D, Monsonego J, Ault K, et al. End-of-study safety, immunogenicity, and efficacy of quadrivalent HPV (types 6, 11, 16, 18) recombinant vaccine in adult women 24-45 years of age. British Journal of Cancer. 2011;105(1):28-37.

30. Arnheim-Dahlström L, Pasternak B, Svanström H, Sparén P, Hviid A. Autoimmune, neurological, and venous thromboembolic adverse events after immunisation of adolescent girls with quadrivalent human papillomavirus vaccine in Denmark and Sweden: Cohort study. BMJ (Online). 2013;347(f5906).

31. Scheller NM, Svanstrom H, Pasternak B, Arnheim-Dahlstrom L, Sundstrom K, Fink K, et al. Quadrivalent HPV vaccination and risk of multiple sclerosis and other demyelinating diseases of the central nervous system. JAMA. 2015;313(1):54-61.

32. Schurink-Van't Klooster TM, de Ridder MA, Kemmeren JM, van der Lei J, Dekker F, Sturkenboom M, et al. Examining a possible association between human papilloma virus (HPV) vaccination and migraine: results of a cohort study in the Netherlands. Eur J Pediatr. 2015;174(5):641-9.

33. Gee J, Naleway A, Shui I, Baggs J, Yin R, Li R, et al. Monitoring the safety of quadrivalent human papillomavirus vaccine: Findings from the Vaccine Safety Datalink. Vaccine. 2011;29(46):8279-84.

34. Willame C, Rosillon D, Zima J, Angelo MG, Stuurman AL, Vroling H, et al. Risk of new onset autoimmune disease in 9- to 25-year-old women exposed to human papillomavirus-16/18 AS04-adjuvanted vaccine in the United Kingdom. Human Vaccines and Immunotherapeutics. 2016;12(11):2862-71.

35. Chao C, Klein NP, Velicer CM, Sy LS, Slezak JM, Takhar H, et al. Surveillance of autoimmune conditions following routine use of quadrivalent human papillomavirus vaccine. Journal of Internal Medicine. 2012;271(2):193-203.

APPENDIX A BODY OF EVIDENCE PROFILES

	Quality assessment			Effect				GRADE	Importance
Outcome	**Comparison**	**Participants Studies**	**Quality of evidence**	**Intervention results**	**Comparator results**	**Relative**	**Absolute**		
Serious adverse events	Cervarix™ versus placebo	14 268 K=10	Risk of bias: 0 Inconsistency: 0 Indirectness: -1 Imprecision: 0 Other bias: +1	1836.6 / 100 000	1876.2 / 100 000	RR 0.91 (95% CI 0.68, 1.22)	Rate per 100,000 (%, 95%CI) -39.6 **0.04%,** **(-0.4%, 0.5%)**	⊕⊕⊕⊕ **HIGH**	Critical
	Cervarix™ versus control vaccine	30 843 K=8	Risk of bias: 0 Inconsistency: 0 Indirectness: -1 Imprecision: 0 Other bias: +1	11 676.8 / 100 000	11 595.7 / 100 000	RR 1.01 (95% CI 0.95, 1.07)	Rate per 100,000 (%, 95%CI) 81.1 **0.1%,** **(-0.8%, 1.0%)**	⊕⊕⊕⊕ **HIGH**	Critical
	Gardasil® versus placebo	28 671 K=7	Risk of bias: 0 Inconsistency: 0 Indirectness: -1 Imprecision: 0 Other bias: +1	858.2 / 100 000	935.8 / 100 000	RR 0.93 (95% CI 0.72, 1.21)	Rate per 100,000 (%, 95%CI) -77.6 **0.08%** **(-0.2%, 0.3%)**	⊕⊕⊕⊕ **HIGH**	Critical
	Gardasil® versus control vaccine	3810 K=1	Risk of bias: 0 Inconsistency: 0 Indirectness: -1 Imprecision: 0 Other bias: +1	733.8 / 100 000	841.2 / 100 000	RR 0.87 (95% CI 0.43, 1.78)	Rate per 100,000 (%, 95%CI) -107.4 **0.11%** **(-0.5%, 0.7%)**	⊕⊕⊕⊕ **HIGH**	Critical
New onset	Cervarix™	9511	Risk of bias: 0	1240.1 / 100,000	1306.6 / 100,000	RR 0.83	Rate per 100,000	⊕⊕⊕⊕	Important

	Quality assessment			Effect				GRADE	Importance
Outcome	**Comparison**	**Participants Studies**	**Quality of evidence**	**Intervention results**	**Comparator results**	**Relative**	**Absolute**		
chronic disease	versus placebo	K=9	Inconsistency: 0 Indirectness: -1 Imprecision: 0 Other bias: +1			(95% CI 0.58, 1.20)	(%, 95%CI) -66.5 **0.07%** **(-0.4%, 0.5%)**	HIGH	
	Cervarix™ versus control vaccine	30 349 K=7	Risk of bias: 0 Inconsistency: 0 Indirectness: -1 Imprecision: 0 Other bias: +1	4680.8 / 100,000	5079.9 / 100,000	RR 0.93 (95% CI 0.84, 1.03)	Rate per 100,000 (%, 95%CI) -399.1 **0.4%** **(-0.9%, 0.9%)**	⊕⊕⊕⊕ HIGH	Important
Medically significant conditions	Cervarix™ versus placebo	7623 K=6	Risk of bias: 0 Inconsistency: 0 Indirectness: -1 Imprecision: 0 Other bias: +1	8201.4 / 100,000	6949.6 / 100,000	RR 1.15 (95% CI 0.88, 1.50)	Rate per 100,000 (%, 95%CI) 1251.8 **1.25%** **(0.04%, 2.5%)**	⊕⊕⊕⊕ HIGH	Important
	Cervarix™ versus control vaccine	28 498 K=4	Risk of bias: 0 Inconsistency: 0 Indirectness: -1 Imprecision: 0 Other bias: +1	29,372.9 / 100,000	30,069.4 / 100,000	RR 0.98 (95% CI 0.92, 1.05)	Rate per 100,000 (%, 95%CI) -696.5 **0.7%** **(-0.4%, 1.8%)**	⊕⊕⊕⊕ HIGH	Important
Autoimmune diseases	Data from 4 high quality cohort studies		Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Other bias: +1	No differences in rates of most autoimmune diseases between those exposed to vaccine and those unexposed. No findings equated to a safety signal.				⊕⊕⊕O MODERATE	Important
Venous thromboemboli	Data from 2 high quality cohort studies			No difference in the rate of thromboembolism in those exposed to vaccine and those unexposed.				⊕⊕⊕O MODERATE	Important

	Quality assessment			Effect				GRADE	Importance
Outcome	**Comparison**	**Participants Studies**	**Quality of evidence**	**Intervention results**	**Comparator results**	**Relative**	**Absolute**		
sm									
Multiple sclerosis and other de-myelinating conditions	Data from 1 high quality cohort study			MS:				⊕⊕⊕O MODERATE	Important
				6.12 / 100 000 person years	21.54 / 100 000 person years	IRR 0.90 (95%CI 0.70, 1.15)			
				Other demyelinating conditions					
				7.54 / 100,000 person years	16.14 / 100,000 person years	IRR 1.00 (95%CI 0.80, 1.26)			

APPENDIX B STUDY PROFILES

1. STUDY IDENTIFICATION			#001
First author	Bhatla		
Year of publication	2010		
Journal citation	Bhatla, N., et al. (2010). "Immunogenicity and safety of human papillomavirus-16/18 AS04-adjuvanted cervical cancer vaccine in healthy Indian women." Journal of Obstetrics and Gynaecology Research36(1): 123-132.		
Trial number*(where applicable)*	NCT00344032		
2. SETTING			
Region	India (four teaching/tertiary care hospitals)		
Study period	July 2006 to March 2007		
Duration follow-up	1 month post final vaccination		
3. PARTICIPANTS			
Study population/setting	Double blind, placebo controlled RCT in Indian women aged 18-35 years; subjects had to be healthy, not taking other investigational products or steroids, not pregnant or planning pregnancy		
Total enrolled & in each group	**# Total: 354** HPV: 176 Placebo 178		
Gender	Female		
Age metrics	**Age range for inclusion:** 18-35 years	**Metrics: mean age** 28.4 ± 4.91	
Special group?	☐ **Yes** *(please specify):* ☒ **No**		
4. STUDY DESIGN & GROUP SPECIFICATION			
Study design	☐ RCT – Phase 2 ☒ RCT – Phase 3 ☐ Other controlled trial *(please specify)* _____ ☐ Case-control ☐ SCohort ☐ Self-controlled case series ☐ Case series ☐ Case report	☐ Surveillance system – passive ☐ Sentinel surveillance ☐ Linked administrative data ☐ Population study ☐ Other *(please specify)*	
Group(s)	**Vaccine/ adjuvant** HPV 16/18, AS04-adjuvanted 0,1,6 month schedule	**Brand** Cervarix™	**Comparator** Aluminium hydroxide-containing placebo

5. ADVERSE EVENT OUTCOME					
Case definition	☐**N/A**☐**No**		☒**Yes** *(please specify):* SAE classified by MeDRA, new onset chronic disorders, medically significant conditions (AEs requiring emergency room or physician visit unrelated to common diseases or routine visits), pregnancies	☐**Other** *(please specify):*	
AEFI Outcomes	**Case defn**	**Intervention** **n/N**	**Control** **n/N**	**Test**	
	SAEs	2/171	4/174	None deemed related	
	death	0/171	0/174		
	NOCD	0/171	2/174		
	Medically significant AEs	13/171	24/174	None vaccine related	
Method used for rate calculation					

Quality assessment for RCTs- Cochrane Risk of Bias Tool

Domain	Assessment High risk/low risk/unclear	Comment
Random sequence generation	Low risk	Computerised, conducted at remote centre
Allocation concealment	Low risk	Vaccines randomised centrally then sent to study centres, where they were administered according to treatment number
Blinding of participants and researchers	Unclear	States double blind but no description
Blinding of outcomes assessors	Unclear	
Incomplete outcome data	Low risk	Safety data based on total vaccinated cohort; low attrition and equivalent in groups
Selective reporting of outcomes	High risk	Limited data on SAEs available, denominators not reported (have been estimated from other data)
Any other bias	High risk	Funding, design, conduct and analysis of trial all by sponsor (GSK)

Overall assessment of bias: Low risk

1. STUDY IDENTIFICATION		#002
First author	Castellsague	
Year of publication	2011	
Journal citation	Castellsagué, X., et al. (2011). "End-of-study safety, immunogenicity, and efficacy of quadrivalent HPV (types 6, 11, 16, 18) recombinant vaccine in adult women 24-45 years of age." British Journal of Cancer105(1): 28-37.	
Trial number*(where applicable)*	NCT00090220	
2. SETTING		
Region	38 international sites; Columbia, France, Germany, Philippines, Spain, Thailand, US	
Study period	Enrolled 18 June 2004 to 30 April 2005	
Duration follow-up	4 years; mean 3.8 years	
3. PARTICIPANTS		
Study population/setting	Double blind, placebo controlled RCT in women 24-45 years; eligible if not pregnant, not undergone hysterectomy and used contraception for first 7 months of study. Ineligible if history of genital warts or current/past cervical disease, HIV positive or immunosuppressed	
Total enrolled & in each group	**# Total: 3819** HPV: 1911 Placebo: 1908	
Gender	females	
Age metrics	**Age range for inclusion: 24-45 years**	**Metrics: mean age 34.3±6.3 years**
Special group?	☐ **Yes** *(please specify):* ☒ **No**	
4. STUDY DESIGN & GROUP SPECIFICATION		
Study design	☐ RCT – Phase 2 ☒ RCT – Phase 3 ☐ Other controlled trial *(please specify)* _____ ☐ Case-control ☐ S Cohort ☐ Self-controlled case series ☐ Case series ☐ Case report	☐ Surveillance system – passive ☐ Sentinel surveillance ☐ Linked administrative data ☐ Population study ☐ Other *(please specify)*

Group(s)	**Vaccine/ adjuvant**	**Brand**	**Comparator**
	qHPV	Gardasil®	Adjuvant containing placebo

5. ADVERSE EVENT OUTCOME			
Case definition	☐ **N/A** ☒ **No**	☐ **Yes** *(please specify):*	☐ **Other** *(please specify):*

	SAEs not defined in this or original trial paper AEs solicited from participants at visits				
AEFI Outcomes	**Case defn**	**Intervention** **n/N**	**Control** **n/N**	**Test**	
	All SAE	14/1908	16/1902	NR	
	SAE deemed related to vaccination	0/1908	0/1902		
	Deaths	7/1908	1/1902		
	Deaths deemed related to vaccination	0/1908	0/1902		
Method used for rate calculation					

Quality assessment for RCTs- Cochrane Risk of Bias Tool

Domain	Assessment High risk/low risk/unclear	Comment
Random sequence generation	Low risk	Computer generated allocation schedule
Allocation concealment	Low risk	Randomised using an interactive voice response system
Blinding of participants and researchers	Low risk	States blinding but does not describe how
Blinding of outcomes assessors	Low risk	States blinding but does not describe how
Incomplete outcome data	Unclear	Although totals in adverse events appear near to complete, no mention is made of loss to follow up at the four year mark
Selective reporting of outcomes	Unclear	No definition of SAE or predefined outcomes
Any other bias	High risk	Funding, design, conduct, analysis and writing up of trial by sponsor (Merck)

Overall assessment of bias: Low risk

1. STUDY IDENTIFICATION		#003
First author	Garland	
Year of publication	2007	
Journal citation	Garland, S. M., et al. (2007). "Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases." N Engl J Med356(19): 1928-1943.	
Trial number*(where applicable)*	NCT00092521 (FUTURE I)	
2. SETTING		
Region	62 sites in 16 countries in Asia-Pacific, Europe, North, Central and South America	
Study period	Enrolment Jan 2002 to March 2003	
Duration follow-up	48 months; average 3 years	
3. PARTICIPANTS		
Study population/setting	Double blind, placebo controlled RCT, including healthy women with no history of genital warts or abnormal cervical cytology, ≤4 lifetime sexual partners and not pregnant	
Total enrolled & in each group	**# Total: 5455** HPV: 2723 Placebo: 2732	
Gender	Female	
Age metrics	**Age range for inclusion:**16-24 years	**Metrics:** HPV mean age 20.2, placebo mean age 20.3
Special group?	☐**Yes** *(please specify):* ☒**No**	
4. STUDY DESIGN & GROUP SPECIFICATION		
Study design	☐RCT – Phase 2 ☒RCT – Phase 3 ☐Other controlled trial *(please specify)* _____ ☐Case-control ☐S Cohort ☐Self-controlled case series ☐Case series ☐Case report	☐Surveillance system – passive ☐Sentinel surveillance ☐Linked administrative data ☐Population study ☐Other *(please specify)*

Group(s)	Vaccine/ adjuvant	Brand	Comparator
	qHPV/amorphous aluminium hydroxyphosphate sulfate	Gardasil®	Aluminium-containing placebo
5. ADVERSE EVENT OUTCOME			

Case definition	☐**N/A** ☒**No** AEs not defined or pre-specified		☐**Yes** *(please specify):*	☐**Other** *(please specify):*	
AEFI Outcomes	**Case defn**	**Intervention** **n/N**	**Control** **n/N**	**Test- risk difference [95%CI]**	
	Serious AE	48/2673	45/2672	0.1 [-0.3, 0.8]	
	Vaccine related SAE	1/2673	0/2672	0 [-0.1, 0.2]	
	Any death	2/2673	2/2672		
	Vaccine related death	0/2673	0/2672		
	SAEs by organ system				
	Blood and lymphatic system	1/2673	0/2672		
	Hepatobiliary	1/2673	0/2672		
	Infections and infestations	10/2673	2/2672		
	Injury, poisoning, procedural	19/2673	27/2672		
	Musculoskeletal and connective tissue	0/2673	1/2672		
	Nervous system	1/2673	4/2672		
	Pregnancy related	14/2673	11/2672		
	Psychiatric	1/2673	0/2672		
	Renal and urinary	0/2673	1/2672		
	Reproductive system	0/2673	1/2672		
	Respiratory, thoracic and mediastinal	3/2673	1/2672		
	Vascular	1/2673	1/2672		
Method used for rate calculation					

Quality assessment for RCTs- Cochrane Risk of Bias Tool

Domain	Assessment High risk/low risk/unclear	Comment

Random sequence generation	Low risk	Computer generated
Allocation concealment	Low risk	Interactive voice response system
Blinding of participants and researchers	Low risk	Stated double blind but no details
Blinding of outcomes assessors	Unclear	
Incomplete outcome data	Low risk	Relatively low drop-out rate
Selective reporting of outcomes	Low risk	All types of SAEs reported
Any other bias	High risk	Study funded, designed, conducted, analysed and reported by Merck

Overall assessment of bias: Low risk

1. STUDY IDENTIFICATION			#004
First author	Giuliano		
Year of publication	2011		
Journal citation	Giuliano, A. R., et al. (2011). "Efficacy of quadrivalent HPV vaccine against HPV Infection and disease in males." N Engl J Med364(5): 401-411. Also: Moreira, E. D., Jr., et al. (2011). "Safety and reactogenicity of a quadrivalent human papillomavirus (types 6, 11, 16, 18) L1 viral-like-particle vaccine in older adolescents and young adults." Hum Vaccin 7(7): 768-775.		
Trial number*(where applicable)*	NCT00090285		
2. SETTING			
Region	71 sites in 18 countries		
Study period	Enrolled between 3 Sep 2004 to 29 Aug 2008		
Duration follow-up	Median 2.9 years after first dose		
3. PARTICIPANTS			
Study population/setting	Double blind, placebo controlled RCT of males; if heterosexual, eligible if aged 16-23 years and 1-5 lifetime female sexual partners; if had sex with male partners, eligible if aged 16-26 years and 1-5 lifetime male or female partners. Ineligible if had clinically detectable anogenital warts or lesions suggestive of other STI, or with history of such findings		
Total enrolled & in each group	**# Total: 4065** HPV: 2032 Placebo: 2033		
Gender	Males		
Age metrics	**Age range for inclusion:16-26 years**	**Metrics:**	
Special group?	☐ **Yes** *(please specify):* ☒ **No**		
4. STUDY DESIGN & GROUP SPECIFICATION			
Study design	☐ RCT – Phase 2 ☒ RCT – Phase 3 ☐ Other controlled trial *(please specify)* _____ ☐ Case-control ☐ S Cohort ☐ Self-controlled case series ☐ Case series ☐ Case report	☐ Surveillance system – passive ☐ Sentinel surveillance ☐ Linked administrative data ☐ Population study ☐ Other *(please specify)*	
Group(s)	**Vaccine/ adjuvant**	**Brand**	**Comparator**

	qHPV/ amorphous aluminium hydroxyphosphate sulfate adjuvant	Gardasil® or Silgard (both Merck)	Amorphous aluminium hydroxyphosphate sulfate containing placebo

5. ADVERSE EVENT OUTCOME					
Case definition	☐**N/A** ☒**No** SAEs recorded if investigators believed them to be associated with the vaccine or study procedure; no other details provided	☐**Yes** *(please specify):*		☐**Other** *(please specify):*	
AEFI Outcomes	**Case defn**	**Intervention** **n/N**	**Control** **n/N**	**Test** **Difference in risk [95%CI]**	
	SAEs	8/1945	11/1950	-0.2 [-0.7, 0.3] p=0.49	
	Vaccine related SAEs	0/1945	0/1950	0.0 [-0.2, 0.2] p=1	
	Deaths	3/1945	10/1950	-0.4 [-0.8, 0.01] p=0.052	
	Vaccine related deaths	0/1945	0/1950	0	
Method used for rate calculation					

Quality assessment for RCTs- Cochrane Risk of Bias Tool

Domain	Assessment High risk/low risk/unclear	Comment
Random sequence generation	Unclear	Method not reported in main article or supplementary appendix
Allocation concealment	Unclear	As above
Blinding of participants and researchers	Unclear	As above
Blinding of outcomes assessors	Unclear	As above
Incomplete outcome data	Low	Low attrition, similar between groups
Selective reporting of outcomes	Unclear	Vaccine-relatedness judged by investigators; no criteria detailed
Any other bias	High risk	Trial supported by sponsor (Merck) and Merck employees are authors

Overall assessment of bias: Unclear

1. STUDY IDENTIFICATION		#005
First author	Romanowski	
Year of publication	2004/2006/2009	
Journal citation	Harper, D. M., et al. (2004). "Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: A randomised controlled trial." Lancet364(9447): 1757-1765. Harper, D. M., et al. (2006). "Sustained efficacy up to 4·5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomised control trial." Lancet367(9518): 1247-1255. Romanowski, B., et al. (2009). "Sustained efficacy and immunogenicity of the human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine: analysis of a randomised placebo-controlled trial up to 6.4 years." Lancet374(9706): 1975-1985.	
Trial number*(where applicable)*	NCT00120848	
2. SETTING		
Region	US, Canada, Brazil, 27 sites	
Study period	Original trial dates not reported: early 2000s. Follow up study took place between Nov 2003 to Aug 2007	
Duration follow-up	Up to 6.4 years post first vaccine dose	
3. PARTICIPANTS		
Study population/setting	Double blind, placebo controlled RCT: eligible women were healthy, had no more than six lifetime sexual partners, no history of abnormal pap test or treatment of cervix, HPV-DNA negative to 14 high risk HPV types. Subgroup of original RCT who received all 3 doses and for whom treatment allocation remained double blinded.	
Total enrolled & in each group	**# Total: 1113** HPV: 560 Placebo: 553 For safety analysis at follow up: HPV: 373, Placebo: 371	
Gender	Females	
Age metrics	**Age range for inclusion:**15-25 years	**Metrics:** Follow-up phase. HPV mean age 23.2 years, placebo mean age 23.2 years
Special group?	☐ **Yes** *(please specify):* ☒ **No**	
4. STUDY DESIGN & GROUP SPECIFICATION		
Study design	☐ RCT – Phase 2 ☒ RCT – Phase 3 ☐ Other controlled trial *(please specify)* _____ ☐ Case-control	☐ Surveillance system – passive ☐ Sentinel surveillance ☐ Linked administrative data ☐ Population study

	☐S Cohort ☐Other *(please specify)* ☐Self-controlled case series ☐Case series ☐Case report		
Group(s)	**Vaccine/ adjuvant** bHPV/ AS04 adjuvant containing aluminium hydroxide and 3-deacylated monophosphoryl lipid A	**Brand** GlaxoSmithKline	**Comparator** Aluminium hydroxide-containing placebo

5. ADVERSE EVENT OUTCOME

Case definition	☐**N/A** ☐**No**	☒**Yes** *(please specify):* New onset of chronic disease defined according to MeDRA; serious adverse event defined as event that resulted in death, was life threatening, needed prolonged admission to hospital, resulted in disability or incapacity, was a congential abnormality or birth defect in offspring, or other important medical event in judgement of investigator.	☐**Other** *(please specify):*

AEFI Outcomes	**Case defn**	**Intervention n/N**	**Control n/N**	**Test**	
	SAE	31/393	39/383		
	Vaccine related SAE	0/393	0/383		
	deaths	0/393	0/383		
	NOCD	18/393	21/383		
Method used for rate calculation					

Quality assessment for RCTs- Cochrane Risk of Bias Tool

Domain	Assessment High risk/low risk/unclear	Comment
Random sequence generation	Low risk	Computerised randomisation system
Allocation concealment	Low risk	Centralised internet randomisation centre
Blinding of participants and researchers	Low risk	
Blinding of outcomes assessors	Unclear	Various laboratories reporting results. Blinding not mentioned
Incomplete outcome data	Unclear	High drop out in extended months follow up

		Unclear how adverse events were actually followed up if women dropped out
Selective reporting of outcomes	Low risk	SAEs defined but not detailed; criteria for vaccine relatedness not reported
Any other bias	High risk	Funding, clinical support, analysis by trial sponsor (GSK)

Overall assessment of bias: Low risk

1. STUDY IDENTIFICATION		#006
First author	Hildesheim	
Year of publication	2014	
Journal citation	Hildesheim, A., et al. (2014). "Efficacy of the HPV-16/18 vaccine: Final according to protocol results from the blinded phase of the randomized Costa Rica HPV-16/18 vaccine trial." Vaccine32(39): 5087-5097. Information for quality assessment came from Herrero et al, 2008	
Trial number*(where applicable)*	NCT00128661	
2. SETTING		
Region	Coast Rica	
Study period	Enrolled June 2004 to December 2005	
Duration follow-up	Total 4 years	
3. PARTICIPANTS		
Study population/setting	Double blind RCT: healthy women randomised to bHPV or HepA vaccine	
Total enrolled & in each group	**# Total: 7466** HPV: 3727, HepA: 3739	
Gender	Female	
Age metrics	**Age range for inclusion:18-25 years**	**Metrics:**
Special group?	☐ **Yes** *(please specify):* ☒ **No**	
4. STUDY DESIGN & GROUP SPECIFICATION		
Study design	☐ RCT – Phase 2 ☒ RCT – Phase 3 ☐ Other controlled trial *(please specify)* _____ ☐ Case-control ☐ S Cohort ☐ Self-controlled case series ☐ Case series ☐ Case report ☐ Surveillance system – passive ☐ Sentinel surveillance ☐ Linked administrative data ☐ Population study ☐ Other *(please specify)*	
Group(s)	**Vaccine/ adjuvant** HPV 16/18/AS04-adjuvanted	**Brand** Cervarix™ / **Comparator** Hepatitis A vaccine
5. ADVERSE EVENT OUTCOME		

Case definition	☐**N/A**☐**No**		☒**Yes** *(please specify):* Not prespecified, but all AEs compared with pre-defined list of potential chronic diseases derived from MeDRA	☐**Other** *(please specify):*
AEFI Outcomes	**Case defn**	**Intervention** **n/N**	**Control** **n/N**	**Test**
	Any SAE	912/3727	891/3739	
	SAE possibly related to vaccination	53/3727 Not related to pregnancy; 7/3727	39/3739 Not related to pregnancy; 5/3739	All but 12 related to pregnancy
	NOCD	383/3727	417/3739	
	Autoimmune adverse events	22/3727	21/3739	
	Neurological adverse events	626/3727	591/3739	
	Deaths	8/3727	7/3739	4 suicides, 3 car accidents, 2 physical assault, 2 cancer, 1 Crohns disease, 1 systemic lupus erythematosus, 1 HIV related, 1 acute myocardial infarction
	Medically significant conditions (grade 3 severe AE)	744/3727	739/3739	
Method used for rate calculation				

Quality assessment for RCTs- Cochrane Risk of Bias Tool

Domain	Assessment High risk/low risk/unclear	Comment
Random sequence generation	Low risk	Random numbers for vaccines produced at central data management centre; delivered to manufacturing plant.
Allocation concealment	Low risk	Pre-numbered vials, in sequential order, sent to study sites and dispensed in sequential order. All numbering off-site.
Blinding of participants and researchers	Low risk	Stated double blind but no details
Blinding of outcomes assessors	Unclear	
Incomplete outcome data	Unclear	Denominator for safety is total vaccinated cohort, but follow up at four years not

		reported and unclear how those who are lost to follow up are monitored for AE
Selective reporting of outcomes	Low risk	Very comprehensive safety outcomes; predefined list of NOCD associated with vaccine
Any other bias	Low risk	Study externally funded; vaccine provided by GSK under clinical trials agreement with National Cancer Institute. GSK had some input into trial design, conduct, analysis and reporting.

Overall assessment of bias: Low risk

1. STUDY IDENTIFICATION		#007
First author	Kang	
Year of publication	2008	
Journal citation	Kang, S., et al. (2008). "Safety and immunogenicity of a vaccine targeting human papillomavirus types 6, 11, 16 and 18: a randomized, placebo-controlled trial in 176 Korean subjects." Int J Gynecol Cancer18(5): 1013-1019.	
Trial number*(where applicable)*	NCT00157950	
2. SETTING		
Region	Ten sites in Korea	
Study period	Enrolled between October 2005 and May 2006	
Duration follow-up	I month after last dose	
3. PARTICIPANTS		
Study population/setting	Double blind, placebo controlled RCT. Eligible subjects were not pregnant, didn't have a fever at vaccination, no sexual experience and no plans for it (9-15 year olds) and less than four sexual partners and required to use contraception for study period (16-23 year olds)	
Total enrolled & in each group	**# Total: 176** HPV: 117 Placebo: 59	
Gender	Female	
Age metrics	**Age range for inclusion:**9-23 years	**Metrics: mean age** 16.6 years
Special group?	☐**Yes** *(please specify):* ☒**No**	

4. STUDY DESIGN & GROUP SPECIFICATION		
Study design	☐RCT – Phase 2 ☒RCT – Phase 3 ☐Other controlled trial *(please specify)* _____ ☐Case-control ☐S Cohort ☐Self-controlled case series ☐Case series ☐Case report	☐Surveillance system – passive ☐Sentinel surveillance ☐Linked administrative data ☐Population study ☐Other *(please specify)*

Group(s)	**Vaccine/ adjuvant**	**Brand**	**Comparator**
	qHPV/amorphous aluminium hydroxyphosphate sulfate adjuvant	Gardasil®	Amorphous aluminium hydroxyphosphate sulfate adjuvant-containing placebo

5. ADVERSE EVENT OUTCOME

Case definition	☐**N/A** ☒**No** Outcomes not prespecified or defined; criteria for vaccine relatedness not reported		☐**Yes** *(please specify):*	☐**Other** *(please specify):*	
AEFI Outcomes	**Case defn**	**Intervention** **n/N**	**Control** **n/N**	**Test**	
	SAE	0/117	1/59		
	Vaccine-related SAE	0/117	0/59		
Method used for rate calculation					

Quality assessment for RCTs- Cochrane Risk of Bias Tool

Domain	Assessment High risk/low risk/unclear	Comment
Random sequence generation	Unclear	Not enough detail about any method to judge quality
Allocation concealment	Unclear	
Blinding of participants and researchers	Unclear	
Blinding of outcomes assessors	Unclear	
Incomplete outcome data	Low risk	Short follow up
Selective reporting of outcomes	Unclear	
Any other bias	Unclear	Merck funded study; no further details about input

Overall assessment of bias: Unclear

1. STUDY IDENTIFICATION		#008
First author	Kim	
Year of publication	2011	
Journal citation	Kim, S. C., et al. (2011). "Human papillomavirus 16/18 AS04-adjuvanted cervical cancer vaccine: Immunogenicity and safety in 15-25 years old healthy Korean women." Journal of Gynecologic Oncology22(2): 67-75.	
Trial number*(where applicable)*	NCT00485732	
2. SETTING		
Region	Korea	
Study period	June 2007-March 2008	
Duration follow-up	1 year post third dose	
3. PARTICIPANTS		
Study population/setting	Double blind, placebo controlled RCT: women had to be not pregnant at each vaccination, and women with history of chronic diseases such as autoimmune diseases or cancer were ineligible	
Total enrolled & in each group	**# Total: 225** HPV: 149 Placebo: 76	
Gender	Female	
Age metrics	**Age range for inclusion:** 15-25 years	**Metrics:** Mean age 22 ± 2.37 years
Special group?	☐ **Yes** *(please specify):* ☒ **No**	
4. STUDY DESIGN & GROUP SPECIFICATION		
Study design	☐ RCT – Phase 2 ☒ RCT – Phase 3 ☐ Other controlled trial *(please specify)* _____ ☐ Case-control ☐ S Cohort ☐ Self-controlled case series ☐ Case series ☐ Case report ☐ Surveillance system – passive ☐ Sentinel surveillance ☐ Linked administrative data ☐ Population study ☐ Other *(please specify)*	
Group(s)	**Vaccine/ adjuvant** HPV16/18/ AS04 adjuvant	**Brand** GSK **Comparator** Placebo containing aluminium hydroxide
5. ADVERSE EVENT OUTCOME		

Case definition	☐**N/A**☐**No**		☒**Yes** *(please specify):* SAEs, new onset chronic disease (such as autoimmune diseases, asthma, type 1 diabetes – considered NOCD if hadn't been recorded in previous medical history of vaccination), medically significant conditions (prompting an emergency room or physician visit that is unrelated to common diseases or routine visits, or SAEs unrelated to common diseases) Criteria for vaccine relatedess not specified	☐**Other** *(please specify):*	
AEFI Outcomes	**Case defn**	**Intervention** **n/N**	**Control** **n/N**	**Test**	
	SAE	2/149	1/76		
	Vaccine related SAE	0/149	0/76		
	Medically significant condition	22.8% 34/149	13.2% 10/76		
	NOCD	5/149	6/76		
Method used for rate calculation					

Quality assessment for RCTs- Cochrane Risk of Bias Tool

Domain	Assessment High risk/low risk/unclear	Comment
Random sequence generation	Low risk	Randomisation done centrally using computer program
Allocation concealment	Low risk	Internet based randomisation system
Blinding of participants and researchers	Low risk	Participants and study personnel blinded but no other details
Blinding of outcomes assessors	Unclear	
Incomplete outcome data	Low risk	Total vaccinated cohort used; short follow up
Selective reporting of outcomes	Low risk	
Any other bias	High risk	Funding, design, conduct, analysis and reporting of trial by GSK

Overall assessment of bias: Low risk

1. STUDY IDENTIFICATION		#009
First author	Kim	
Year of publication	2010	
Journal citation	Kim, Y. J., et al. (2010). "Vaccination with a human papillomavirus (HPV)-16/18 AS04-adjuvanted cervical cancer vaccine in Korean girls aged 10-14 years." Journal of Korean Medical Science25(8): 1197-1204.	
Trial number*(where applicable)*	NCT00290277	
2. SETTING		
Region	Korea	
Study period	Enrolled November 2005 to August 2006	
Duration follow-up	1 month post third dose	
3. PARTICIPANTS		
Study population/setting	Described as observer-blind RCT: healthy girls not pregnant or planning to become pregnant and not breastfeeding; needed to be using contraception if sexually active. Pregnancy tests undertaken before each vaccination.	
Total enrolled & in each group	**# Total: 321** HPV: 160 Control (HepA): 161	
Gender	Female	
Age metrics	**Age range for inclusion:**10-14 years	**Metrics:** Mean age 11.9 ± 1.41 years
Special group?	☐**Yes** *(please specify):* ☒**No**	
4. STUDY DESIGN & GROUP SPECIFICATION		
Study design	☐RCT – Phase 2 ☒RCT – Phase 3 ☐Other controlled trial *(please specify)* _____ ☐Case-control ☐S Cohort ☐Self-controlled case series ☐Case series ☐Case report	☐Surveillance system – passive ☐Sentinel surveillance ☐Linked administrative data ☐Population study ☐Other *(please specify)*

Group(s)	Vaccine/ adjuvant	Brand	Comparator
	HPV 16/18/ AS04 adjuvant	Cervarix™	Hepatitis A vaccine (Havrix)

5. ADVERSE EVENT OUTCOME

Case definition	☐**N/A**☐**No**	☒**Yes** *(please specify):* Medically significant conditions defined as conditions that needed emergency room or physician visits not related to common diseases or routine visits, or SAEs not related to common diseases SAEs, new onset chronic diseases not defined.		☐**Other** *(please specify):*	
AEFI Outcomes	**Case defn**	**Intervention** **n/N**	**Control** **n/N**	**Test**	
	SAE	0/160	1/161		
	Vaccine related SAE	0	0		
	NOCD	3/160	2/161		
	Medically significant conditions	6.9% 11/160	6.2% 10/161		
Method used for rate calculation					

Quality assessment for RCTs- Cochrane Risk of Bias Tool

Domain	Assessment High risk/low risk/unclear	Comment
Random sequence generation	Low risk	Internet –based randomisation system
Allocation concealment	Low risk	
Blinding of participants and researchers	High risk	Appearance of vaccines was different
Blinding of outcomes assessors	Unclear	
Incomplete outcome data	Low risk	Total vaccinated cohort, short follow up
Selective reporting of outcomes	Unclear	SAEs not prespecified
Any other bias	High risk	Funding, design, conduct, analysis and reporting of trial by GSK

Overall assessment of bias: Low risk

1. STUDY IDENTIFICATION		#010
First author	Konno	
Year of publication	2014	
Journal citation	Konno, R., et al. (2014). "Efficacy of the human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical intraepithelial neoplasia and cervical infection in young Japanese women: Open follow-up of a randomized clinical trial up to 4 years post-vaccination." Human Vaccines and Immunotherapeutics10(7): 1781-1794. Also used Konno 2009 for trial information	
Trial number*(where applicable)*	NCT00929526, original trial NCT00316693	
2. SETTING		
Region	Japan	
Study period	Extended follow up period enrolled June 2009 to February 2011; original recruitment April to October 2006	
Duration follow-up	48 months from initial trial	
3. PARTICIPANTS		
Study population/setting	Extension study to RCT that enrolled women in original trial; eligible women were those who received at least one dose of a vaccine in original trial, normal or low grade cytology at baseline, not pregnant or recently terminated pregnancy.	
Total enrolled & in each group	**# Total: 752** (1040 eligible from initial trial - 288 did not participate, reasons not detailed) Safety outcomes based on total number vaccinated in original trial HPV: 519 Control: 521	
Gender	Female	
Age metrics	**Age range for inclusion:** 20-25 years	**Metrics:**
Special group?	☐ **Yes** *(please specify):* ☒ **No**	
4. STUDY DESIGN & GROUP SPECIFICATION		
Study design	☒ RCT – Phase 2 ☐ RCT – Phase 3 ☐ Other controlled trial *(please specify)* _____ ☐ Case-control ☐ S Cohort ☐ Self-controlled case series ☐ Case series ☐ Case report	☐ Surveillance system – passive ☐ Sentinel surveillance ☐ Linked administrative data ☐ Population study ☐ Other *(please specify)*

Group(s)	Vaccine/ adjuvant	Brand	Comparator
	HPV 16/18/AS04 adjuvant		Hepatitis A vaccine (Aimmugen™, Kaketsuken)

5. ADVERSE EVENT OUTCOME			
Case definition	☐**N/A**☐**No**	☒**Yes** *(please specify):* SAEs, new onset chronic diseases, medically significant conditions (SAE or adverse events prompting emergency room or physician visit other than those related to common diseases), pregnancy outcomes	☐**Other** *(please specify):*

AEFI Outcomes	**Case defn**	**Intervention n/N**	**Control n/N**	**Test**	
	SAE	26/519	34/521		
	Vaccine related SAE	1/519	0/521		
	Deaths	1/519	0/521	suicide	
	NOCD	6/519	8/521		
	New onset autoimmune disease	3/519	1/521		
Method used for rate calculation					

Quality assessment for RCTs- Cochrane Risk of Bias Tool

Domain	Assessment High risk/low risk/unclear	Comment
Random sequence generation	Unclear	Randomisation procedures not detailed
Allocation concealment	Unclear	
Blinding of participants and researchers	Unclear	Called double blind but not described
Blinding of outcomes assessors	Unclear	
Incomplete outcome data	High risk	Large number of women not included in extended follow up and reasons not given
Selective reporting of outcomes	Unclear	
Any other bias	High risk	Trial funded and coordinated by GSK

Overall assessment of bias: Unclear - not enough information to adequately assess

1. STUDY IDENTIFICATION			#011
First author	Lehtinen		
Year of publication	2012		
Journal citation	Data on trial also from: Paavonen 2007		
Trial number*(where applicable)*	NCT00122681 (PATRICIA)		
2. SETTING			
Region	14 countries in Asia Pacific, Europe, Latin America, North America		
Study period	Enrolled in trial May 2005- June 2005		
Duration follow-up	4 years		
3. PARTICIPANTS			
Study population/setting	Double blind RCT: healthy women 15-25 years with no more than six lifetime sexual partners, who agreed to adequate contraception over the vaccination period and had an intact cervix. Excluded if pregnant or breastfeeding, history of colposcopy, or chronic or autoimmune disease or immunodeficiency		
Total enrolled & in each group	**# Total: 18,729** 18,644 in total vaccinated cohort HPV: 9319 Control: 9325		
Gender	Female		
Age metrics	**Age range for inclusion: 15-25 years**	**Metrics:** HPV: 20.0 ± 3.1 years; Control: 20.0 ± 3.1 years	
Special group?	☐ **Yes** *(please specify):* ☒ **No**		
4. STUDY DESIGN & GROUP SPECIFICATION			
Study design	☐ RCT – Phase 2 ☒ RCT – Phase 3 ☐ Other controlled trial *(please specify)* _____ ☐ Case-control ☐ S Cohort ☐ Self-controlled case series ☐ Case series ☐ Case report	☐ Surveillance system – passive ☐ Sentinel surveillance ☐ Linked administrative data ☐ Population study ☐ Other *(please specify)*	
Group(s)	**Vaccine/ adjuvant**	**Brand**	**Comparator**

	HPV 16/18/ 50 µg 3-O-desacyl-4-monophosphoryl lipid A and 0·5mg aluminium hydroxide	GSK	Investigational Hepatitis A vaccine, based on Havrix (GSK)

5. ADVERSE EVENT OUTCOME

Case definition	☐**N/A**☐**No**	☒**Yes** *(please specify):* Serious adverse events, new onset chronic disease including new onset autoimmune disease, medically significant conditions (adverse events prompting either emergency room visits or physician visits that are not related to common diseases, eg. sinusitis and pharyngitis), pregnancy and pregnancy outcomes Criteria for relatedness to vaccination not reported	☐**Other** *(please specify):*

AEFI Outcomes	**Case defn**	**Intervention n/N**	**Control n/N**	**Test**	
	SAE	835/9319	829/9325		
	Vaccine related SAE	10/9319	5/9325		
	Medically significant condition	3298/9319	3378/9325		
	NOCD – predefined list of potential NOCD was reviewed by independent monitoring committee; clinical database was searched based on this list; considered NOCD if had not been recorded in previous medical history or if symptoms characteristic of NOCD	285/9319	307/9325		
	Death	10/9319	13/9325		
	Vaccine related death	0/9319	0/9325		

Method used for rate calculation	

Quality assessment for RCTs- Cochrane Risk of Bias Tool

Domain	Assessment High risk/low risk/unclear	Comment
Random sequence generation	Low risk	Internet based centralised randomisation system
Allocation concealment	Low risk	Central randomisation
Blinding of participants and researchers	Low risk	Vaccines identical in appearance and provided to study in prefilled syringes
Blinding of outcomes assessors	Unclear	No details for most SAE outcomes
Incomplete outcome data	Unclear	Although safety based on total cohort, large drop outs occurred in trial; unclear how safety data were collected once participant had dropped out
Selective reporting of outcomes	Low risk	
Any other bias	High risk	GSK funded and coordinated study

Overall assessment of bias: Low risk

1. STUDY IDENTIFICATION		#012
First author	Li	
Year of publication	2012	
Journal citation	Li, R., et al. (2012). "Safety and immunogenicity of a vaccine targeting human papillomavirus types 6, 11, 16 and 18: A randomized, double-blind, placebo-controlled trial in Chinese males and females." Vaccine30(28): 4284-4291.	
Trial number*(where applicable)*	NCT00496626	
2. SETTING		
Region	China	
Study period	Enrolled July 2008 to August 2008	
Duration follow-up	1 month post last vaccine dose	
3. PARTICIPANTS		
Study population/setting	Double blind, placebo controlled RCT: healthy males and females, females ineligible if pregnant or history of abnormal Pap test or biopsy showing CIN or worse. All ineligible if any immune-related disorders, or more than four lifetime sexual partners.	
Total enrolled & in each group	**# Total: 600 (100 male, 500 female)** HPV: 302 Placebo: 298	
Gender	Male/female	
Age metrics	**Age range for inclusion:**9-45 years	**Metrics: mean age** 24.6 years
Special group?	☐ **Yes** *(please specify):* ☒ **No**	
4. STUDY DESIGN & GROUP SPECIFICATION		
Study design	☐ RCT – Phase 2 ☒ RCT – Phase 3 ☐ Other controlled trial *(please specify)* _____ ☐ Case-control ☐ S Cohort ☐ Self-controlled case series ☐ Case series ☐ Case report ☐ Surveillance system – passive ☐ Sentinel surveillance ☐ Linked administrative data ☐ Population study ☐ Other *(please specify)*	

Group(s)	**Vaccine/ adjuvant**	**Brand**	**Comparator**
	qHPV/amorphous aluminium hydroxyphosphate sulfate adjuvant	Gardasil®	Aluminium-containing placebo
5. ADVERSE EVENT OUTCOME			

Case definition	☐**N/A** ☒**No** **'**New medical condition or health concerns and serious AEs' not otherwise described**.** Criteria for vaccine relatedness not defined.		☐**Yes** *(please specify):*	☐**Other** *(please specify):*	
AEFI Outcomes	**Case defn**	**Intervention** **n/N**	**Control** **n/N**	**Test**	
	SAE	0/302	1/298		
	Vaccine related SAE	0/302	0/298		
Method used for rate calculation					

Quality assessment for RCTs- Cochrane Risk of Bias Tool

Domain	Assessment High risk/low risk/unclear	Comment
Random sequence generation	Unclear	Randomisation not described
Allocation concealment	Unclear	
Blinding of participants and researchers	Unclear	Called double blind but no details provided
Blinding of outcomes assessors	Unclear	
Incomplete outcome data	Low risk	Short follow up time, very low drop-out rate
Selective reporting of outcomes	Unclear	Poor safety reporting for SAE
Any other bias	High risk	Funding, design, conduct, analysis and reporting by sponsor (Merck)

Overall assessment of bias: Unclear

1. STUDY IDENTIFICATION		#013
First author	Lim	
Year of publication	2014	
Journal citation	Lim, B. K., et al. (2014). "Immunogenicity and safety of the AS04-adjuvanted human papillomavirus-16/18 cervical cancer vaccine in malaysian women aged 18-35 years: A randomized controlled trial." Medical Journal of Malaysia69(1): 2-8.	
Trial number*(where applicable)*	NCT00345878	
2. SETTING		
Region	Malaysia	
Study period	Sept 2006 to Dec 2007	
Duration follow-up	1 month	
3. PARTICIPANTS		
Study population/setting	Double blind, placebo controlled RCT: healthy women in Malaysia who were not pregnant with no history of chronic immunosuppressant use or chronic conditions like cancer or autoimmune disease.	
Total enrolled & in each group	**# Total: 271** HPV: 135 Placebo 136	
Gender	Females	
Age metrics	**Age range for inclusion:**18-35 years	**Metrics:** 24.9 ± 4.02 years
Special group?	☐ **Yes** *(please specify):* ☒ **No**	
4. STUDY DESIGN & GROUP SPECIFICATION		
Study design	☐ RCT – Phase 2 ☒ RCT – Phase 3 ☐ Other controlled trial *(please specify)* _____ ☐ Case-control ☐ S Cohort ☐ Self-controlled case series ☐ Case series ☐ Case report ☐ Surveillance system – passive ☐ Sentinel surveillance ☐ Linked administrative data ☐ Population study ☐ Other *(please specify)*	

Group(s)	**Vaccine/ adjuvant**	**Brand**	**Comparator**
	HPV 16/18/ AS04 adjuvant	Cervarix™	Aluminium hydroxide-containing placebo

5. ADVERSE EVENT OUTCOME					
Case definition	☐**N/A**☐**No**		☒**Yes** *(please specify):* SAEs, NOCD (defined as condition that had not been recorded in participant's history), medically significant conditions (AEs needing emergency or physician visit not related to common diseases and not routine visits, or SAEs unrelated to common diseases) Causality judged by investigators	☐**Other** *(please specify):*	
AEFI Outcomes	**Case defn**	**Intervention** **n/N**	**Control** **n/N**	**Test**	
	SAE	5/135	3/136		
	Vaccine related SAE	0/135	0/136		
	NOCD	1/135	0/136		
	At least one medically significant AE	10/135	11/136		
Method used for rate calculation					

Quality assessment for RCTs- Cochrane Risk of Bias Tool

Domain	Assessment High risk/low risk/unclear	Comment
Random sequence generation	Low risk	Centrally performed using computer program
Allocation concealment	Low risk	Internet-based randomisation system
Blinding of participants and researchers	Low risk	Blinding stated by not described
Blinding of outcomes assessors	Unclear	
Incomplete outcome data	Low risk	Low drop outs, short follow up time
Selective reporting of outcomes	Low risk	
Any other bias	High risk	Funding, design, conduct, analysis and reporting of trial by GSK.

Overall assessment of bias: Low risk

1. STUDY IDENTIFICATION			#014
First author	Medina		
Year of publication	2010		
Journal citation	Medina, D. M., et al. (2010). "Safety and immunogenicity of the HPV-16/18 AS04-adjuvanted vaccine: a randomized, controlled trial in adolescent girls." J Adolesc Health46(5): 414-421.		
Trial number*(where applicable)*	NCT00196924		
2. SETTING			
Region	Australia, Colombia, Czech Republic, France, Germany, Honduras, Korea, Norway, Panama, Spain, Sweden, Taiwan		
Study period	June 2004 to August 2005		
Duration follow-up	1 month post third dose; up to month 12 for safety outcomes		
3. PARTICIPANTS			
Study population/setting	Observer blind RCT: healthy girls without immunodeficiency, acute or chronic neurologic, hepatic or renal abnormality or history of chronic conditions requiring treatment. No exclusions based on HPV status, Pap smear history or sexual activity.		
Total enrolled & in each group	**# Total: 2067** HPV: 1035 Control: 1032		
Gender	Female		
Age metrics	**Age range for inclusion:** 10-14 years	**Metrics:** Mean age at first vaccination 12.1 years	
Special group?	☐ **Yes** *(please specify):* ☒ **No**		
4. STUDY DESIGN & GROUP SPECIFICATION			
Study design	☐ RCT – Phase 2 ☒ RCT – Phase 3 ☐ Other controlled trial *(please specify)* _____ ☐ Case-control ☐ S Cohort ☐ Self-controlled case series ☐ Case series ☐ Case report	☐ Surveillance system – passive ☐ Sentinel surveillance ☐ Linked administrative data ☐ Population study ☐ Other *(please specify)*	
Group(s)	**Vaccine/ adjuvant** HPV 16/18/ AS04 adjuvant	**Brand** GSK	**Comparator** Hepatitis A vaccine (GSK)
5. ADVERSE EVENT OUTCOME			

Case definition	☐**N/A**☐**No**		☒**Yes** *(please specify):* SAEs, NOCDs (identified in a blinded manner before analysis), MSCs (events prompting emergency or physician visit not related to common disease). Investigators assessed likely causality of solicited general and unsolicited AEs. Criteria not defined.	☐**Other** *(please specify):*	
AEFI Outcomes	**Case defn**	**Intervention** **n/N**	**Control** **n/N**	**Test**	
	SAE up to month 7	11/1035	13/1032		
	Vaccine – related SAE up to month 7	0/1035	1/1032		
	SAE months 7-12	13/1014	10/1009		
	Vaccine related SAE 7-12 months	0/1014	0/1009		
	NOCD up to month 7	25/1035	21/1032		
	NOCD 7-12 months	3/1014	6/1009		
	MSC 30 days post vaccination	130/1035	160/1032		
	MSC 7-12 months	36/1014	35/1009		
Method used for rate calculation					

Quality assessment for RCTs- Cochrane Risk of Bias Tool

Domain	Assessment High risk/low risk/unclear	Comment
Random sequence generation	Low risk	'Randomisation algorithm', so assume computer generated
Allocation concealment	Unclear	No details
Blinding of participants and researchers	Unclear	Study vaccines differed in appearance so staff who administered them knew which vaccine they were administering- they were not further involved in the study however chance of unblinding in their interaction with subject

Blinding of outcomes assessors	Unclear	'NOCDs identified in blinded manner' but no other information available
Incomplete outcome data	Low risk	High follow up rate and relatively short follow up time
Selective reporting of outcomes	Low risk	
Any other bias	High risk	Study funded, data analysed, and report partially written by GSK

Overall assessment of bias: Unclear

1. STUDY IDENTIFICATION			#015
First author	Naud		
Year of publication	2014		
Journal citation	Naud, P. S., Roteli-Martins, C. M. et al (2014). 'Sustained efficacy, immunogenicity, and safety of the HPV-16/18 AS04-adjuvanted vaccine: Final analysis of a long-term follow-up study up to 9.4 years post-vaccination'. Human Vaccines and Immunotherapeutics, 10 (8), 2147-62.		
Trial number*(where applicable)*	NCT00518336 (follow up study from NCT00689741)		
2. SETTING			
Region	Brazil (subset of original trial which was conducted in US, Canada, Brazil)		
Study period	Original study recruited 2001		
Duration follow-up	Total follow up 113 months (9.4 years); mean 107 months (8.9 years)		
3. PARTICIPANTS			
Study population/setting	Long term follow up of subset of women from Brazil who participated in original double blind, placebo controlled trial. Eligible women were HPV 16 and 18 seronegative, HPV DNA-negative in cervix for 14 HPV types and normal cervical cytology. Results only reported for follow up between 77 and 113 months.		
Total enrolled & in each group	**# Total: 437** HPV: 224 Placebo: 213		
Gender	Female		
Age metrics	**Age range for inclusion:**15-25 years in original trial	**Metrics:** Original trial mean age 19.9 years, follow up entry 23.5 years	
Special group?	☐**Yes** *(please specify):* ☒**No**		
4. STUDY DESIGN & GROUP SPECIFICATION			
Study design	☐RCT – Phase 2 ☒RCT – Phase 3 ☐Other controlled trial *(please specify)* _____ ☐Case-control ☐S Cohort ☐Self-controlled case series ☐Case series ☐Case report	☐Surveillance system – passive ☐Sentinel surveillance ☐Linked administrative data ☐Population study ☐Other *(please specify)*	
Group(s)	**Vaccine/ adjuvant** bHPV/ AS04 adjuvanted	**Brand** Cervarix™ (GSK)	**Comparator** Placebo containing aluminium hydroxide
5. ADVERSE EVENT OUTCOME			

Case definition	☐**N/A**☐**No**		☒**Yes** *(please specify):* SAEs, medically significant AEs (prompting emergency room or physician visit not related to common diseases) and NOCDs	☐**Other** *(please specify):*	
AEFI Outcomes	**Case defn**	**Intervention** **n/N**	**Control** **n/N**	**Test**	
	Medically significant AE	60/224	38/213		
	SAEs Included 7pregnancy related (HPV) and 3 (placebo)	20/224	11/213	**note outcomes measured from month 77-113***	
	NOCD	6/224	3/213		
Method used for rate calculation					

Quality assessment for RCTs- Cochrane Risk of Bias Tool

Domain	Assessment High risk/low risk/unclear	Comment
Random sequence generation	Low risk	Computerised randomisation system
Allocation concealment	Low risk	Centralised internet randomisation centre
Blinding of participants and researchers	Low risk	
Blinding of outcomes assessors	Unclear	Various laboratories reporting results. Blinding not mentioned
Incomplete outcome data	Low risk	Subset of women with high retention rates from original studies; relatively low loss to follow up
Selective reporting of outcomes	Unclear	Outcomes not specified; criteria for vaccine relatedness not reported
Any other bias	High risk	Trial funded, designed, run, analysed and written by sponsor, GSK

Overall assessment of bias: Low risk

1. STUDY IDENTIFICATION			#016
First author	Ngan		
Year of publication	2010		
Journal citation	Ngan, H. Y., Cheung, A. N. et al (2010). 'Human papillomavirus-16/18 AS04-adjuvanted cervical cancer vaccine: immunogenicity and safety in healthy Chinese women from Hong Kong'. Hong Kong Med J, 16 (3), 171-9.		
Trial number*(where applicable)*	NCT00306241		
2. SETTING			
Region	Hong Kong		
Study period	Enrolled March 2006 to June 2007		
Duration follow-up	1 month post third dose		
3. PARTICIPANTS			
Study population/setting	Double blind, placebo controlled RCT: healthy women, who had not received an AS04 adjuvant or HPV vaccine, who were pregnant or planning to become pregnant or having a chronic disease were excluded.		
Total enrolled & in each group	**# Total: 300** HPV: 150, Placebo: 150		
Gender	Female		
Age metrics	**Age range for inclusion:** 18-35 years	**Metrics:**	
Special group?	☐ **Yes** *(please specify):* ☒ **No**		
4. STUDY DESIGN & GROUP SPECIFICATION			
Study design	☐ RCT – Phase 2 ☐ RCT – Phase 3 ☐ Other controlled trial *(please specify)* _____ ☐ Case-control ☐ S Cohort ☐ Self-controlled case series ☐ Case series ☐ Case report ☐ Surveillance system – passive ☐ Sentinel surveillance ☐ Linked administrative data ☐ Population study ☐ Other *(please specify)*		
Group(s)	**Vaccine/ adjuvant** HPV 16/18 / AS04 adjuvant	**Brand** Cervarix™ (GSK)	**Comparator** Aluminium hydroxide-containing placebo
5. ADVERSE EVENT OUTCOME			

Case definition	☐**N/A**☐**No**		☒**Yes** *(please specify):* SAEs, medically significant conditions (events that prompted emergency room or physician visit unrelated to common diseases or routine visits), new onset chronic diseases (based on a review of subject's pre-vaccination medical history)	☐**Other** *(please specify):*	
AEFI Outcomes	**Case defn**	**Intervention** **n/N**	**Control** **n/N**	**Test**	
	SAE	4/148	1/146		
	Vaccine related SAE	0/148	0/146		
	MSC	28% 41/148	16% 23/146		
	NOCD Paper reports NOCD based on "GSK assessment"	5% 7/148	3% 4/146		
Method used for rate calculation					

Quality assessment for RCTs- Cochrane Risk of Bias Tool

Domain	Assessment High risk/low risk/unclear	Comment
Random sequence generation	Low risk	List of treatment numbers generated using computer program
Allocation concealment	Low risk	Central randomisation system on the internet
Blinding of participants and researchers	Low risk	Double blind stated but no other details
Blinding of outcomes assessors	Unclear	
Incomplete outcome data	Unclear	Safety denominators not defined in results, only in study flow, and not on TVC
Selective reporting of outcomes	Unclear	
Any other bias	High risk	Funding, design, conduct and analysis of study by sponsor (GSK)

Overall assessment of bias: Unclear

1. STUDY IDENTIFICATION		#017
First author	Pedersen	
Year of publication	2012	
Journal citation	Pedersen, C., Breindahl, M. et al (2012). 'Randomized trial: Immunogenicity and safety of coadministered human papillomavirus-16/18 AS04-adjuvanted vaccine and combined hepatitis A and B vaccine in girls'. Journal of Adolescent Health, 50 (1), 38-46.	
Trial number*(where applicable)*	NCT00578227	
2. SETTING		
Region	21 International sites in Canada, Denmark, Hungary and Sweden	
Study period	December 2007 to December 2008	
Duration follow-up	12 months	
3. PARTICIPANTS		
Study population/setting	Three-arm RCT (randomisation 1:1:1) in healthy girls aged 9-15 years; participants had to have negative pregnancy test at the time of each vaccination and to be of non-child-bearing potential, or of childbearing potential, to be abstinent from sexual activity or using contraceptive precautions Exclusion criteria included a history of hepatitis A or B infection, known exposure to hepatitis A or B within 6 weeks before vaccination, previous administration of HPV, hepatitis A or hepatitis B vaccines or planned administration of HPV, hepatitis A, hepatitis B or non-routine vaccines not foreseen by the study protocol	
Total enrolled & in each group	**# Total: 814** HPV+HAB: 272 HPV: 270, HAB: 271	
Gender	Female	
Age metrics	**Age range for inclusion:** 9-15 years	**Metrics: Mean age** 11 years
Special group?	☐ **Yes** *(please specify):* ☒ **No**	
4. STUDY DESIGN & GROUP SPECIFICATION		
Study design	☐ RCT – Phase 2 ☒ RCT – Phase 3 ☐ Other controlled trial *(please specify)* _____ ☐ Case-control ☐ S Cohort ☐ Self-controlled case series ☐ Case series ☐ Case report	☐ Surveillance system – passive ☐ Sentinel surveillance ☐ Linked administrative data ☐ Population study ☐ Other *(please specify)*

Group(s)	Vaccine/ adjuvant	Brand	Comparator
	HPV-16/18 AS04-adjuvanted vaccine	GlaxoSmithKline	HAB vaccine HPV-16/18 vaccine coadministered with HAB vaccine

5. ADVERSE EVENT OUTCOME					
Case definition	☐**N/A** ☒**No**		☐**Yes** *(please specify):*	☐**Other** *(please specify):*	
AEFI Outcomes	**Case defn**	**Intervention** **HPV** **n/N**	**Control 1** **HAB** **n/N**	**Control 2** **HPV+HAB** **n/N**	**Test**
	All SAEs (investigators considered none were vaccine related without further information provided)	4/270	5/271	2/272	No
	All NOCDs not considered SAEs by investigators	5/270	7/271	4/272	No
Method used for rate calculation	NA				

Quality assessment for RCTs- Cochrane Risk of Bias Tool

Domain	Assessment High risk/low risk/unclear	Comment
Random sequence generation	Low	Internet-based randomisation system
Allocation concealment	Low	Centralised, internet-based
Blinding of participants and researchers	Unclear	Not reported
Blinding of outcomes assessors	Unclear	Specifies blinding for serological assessment only
Incomplete outcome data	Unclear	No denominators reported for SAE outcomes (can only be assumed based on number of subjects enrolled)
Selective reporting of outcomes	Unclear	SAE definition not reported, predefined safety outcomes not reported
Any other risk of bias	High	Industry sponsored trial

Overall assessment of bias: Unclear

1. STUDY IDENTIFICATION		#018
First author	Petaja	
Year of publication	2009	
Journal citation	Petaja, T., Keranen, H. et al (2009). 'Immunogenicity and safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine in healthy boys aged 10-18 years'. J Adolesc Health, 44 (1), 33-40.	
Trial number*(where applicable)*	NCT00309166	
2. SETTING		
Region	Seven study sites in Finland	
Study period	April 2006 to January 2007	
Duration follow-up	7 months	
3. PARTICIPANTS		
Study population/setting	Double-blind parallel-group RCT (randomisation 2:1) in healthy males aged 9-18 years; individuals were excluded from enrolment if they had used an investigational drug or vaccine within 30 days, chronic immune-modifying drugs within 6 months, immunoglobulins or blood products within 3 months, or planned to use any of these during the study period, had previously received an HPV vaccine, or had previously been vaccinated against HBV), had a known clinical history of HBV infection, or known exposure to HBV within the previous 6 weeks, or had any confirmed or suspected immunosuppressive or immune-deficient condition including HIV infection	
Total enrolled & in each group	**# Total: 270** HPV: 181 HBV: 89	
Gender	Male	
Age metrics	**Age range for inclusion:** 9-18 years	**Metrics: Mean age** 14.4 years
Special group?	☐ **Yes** *(please specify):* ☒ **No**	
4. STUDY DESIGN & GROUP SPECIFICATION		
Study design	☒ RCT – Phase 2 ☐ RCT – Phase 3 ☐ Other controlled trial *(please specify)* _____ ☐ Case-control ☐ S Cohort ☐ Self-controlled case series ☐ Case series ☐ Case report	☐ Surveillance system – passive ☐ Sentinel surveillance ☐ Linked administrative data ☐ Population study ☐ Other *(please specify)*

Group(s)	**Vaccine/ adjuvant**	**Brand**	**Comparator**
	HPV-16/18 AS04-adjuvanted vaccine	Cervarix™	HBV vaccine (Energix-B)
5. ADVERSE EVENT OUTCOME			

<table>
<tr><td>Case definition</td><td colspan="2">☐N/A☐No</td><td colspan="2">☒Yes (please specify):

SAE defined as any untoward medical occurrence that resulted in death, was life-threatening, required hospitalisation, resulted in disability or incapacity, was an important medical event or was a congenital anomaly/birth defect in the offspring of a study subject

NOCDs, e.g. diabetes mellitus, autoimmune diseases, asthma, allergies, etc.

Medically significant conditions were defined as non-serious AEs prompting either emergency room or physician visits for physical examination or vaccination, or SAEs not related to common diseases (common diseases included upper respiratory infections, sinusitis, pharyngitis, gastroenteritis, urinary tract infections and injury</td><td>☐Other (please specify):</td></tr>
<tr><td rowspan="3">AEFI Outcomes</td><td>Case defn</td><td>Intervention

n/N</td><td>Control

n/N</td><td>Test</td><td></td></tr>
<tr><td>All SAEs

All new onset chronic conditions</td><td>2/181

One SAE believed to have been related to a Crohn’s disease diagnosis prior to the first vaccine dose and one case of epilepsy related to a family history

Both events were non-fatal

2/181 (Crohn’s, atopic dermatitis)</td><td>0

1/89 (asthma)</td><td>NA</td><td></td></tr>
<tr><td>Method used for rate calculation</td><td colspan="4">NA</td></tr>
</table>

Quality assessment for RCTs- Cochrane Risk of Bias Tool

Domain	Assessment High risk/low risk/unclear	Comment
Random sequence generation	Low	Block randomisation
Allocation concealment	Low	Automated
Blinding of participants and researchers	Low	All personnel but administering nurse were blinded
Blinding of outcomes assessors	Low	Outcomes assessors were blinded
Incomplete outcome data	Unclear	No denominators reported for SAE outcomes (can only be assumed based on number of subjects enrolled)
Selective reporting of outcomes	Low	SAE definition provided *a priori*
Any other risk of bias	High	Industry sponsored trial

Overall assessment of bias: Low risk

1. STUDY IDENTIFICATION		#019
First author	Reisinger	
Year of publication	2007	
Journal citation	Reisinger, K. S., Block, S. L. et al (2007). 'Safety and persistent immunogenicity of a quadrivalent human papillomavirus types 6, 11, 16, 18 L1 virus-like particle vaccine in preadolescents and adolescents: a randomized controlled trial'. Pediatr Infect Dis J, 26 (3), 201-9	
Trial number*(where applicable)*	NCT00092547	
2. SETTING		
Region	47 study sites in 10 countries in North America, Latin America, Europe and Asia	
Study period	October 2003 to march 2004	
Duration follow-up	18 months	
3. PARTICIPANTS		
Study population/setting	1781 sexually naïve children aged 9-15 years	
Total enrolled & in each group	**# Total: 1781** HPV: 1184 Placebo: 597	
Gender	Male and female	
Age metrics	**Age range for inclusion:** 9-15 years	**Metrics:** Mean age 11.9 ± 1.9 years
Special group?	☐ **Yes** *(please specify):* ☒ **No**	

4. STUDY DESIGN & GROUP SPECIFICATION			
Study design	☐ RCT – Phase 2 ☒ RCT – Phase 3 (assumed) ☐ Other controlled trial *(please specify)* _____ ☐ Case-control ☐ S Cohort ☐ Self-controlled case series ☐ Case series ☐ Case report	☐ Surveillance system – passive ☐ Sentinel surveillance ☐ Linked administrative data ☐ Population study ☐ Other *(please specify)*	
Group(s)	**Vaccine/ adjuvant** Quadrivalent HPV-6/11/16/18 vaccine	**Brand** Gardisil/Silgard	**Comparator** Non-aluminium placebo
5. ADVERSE EVENT OUTCOME			

Case definition	☐**N/A**☒**No**		☐**Yes** *(please specify):*	☐**Other** *(please specify):*	
AEFI Outcomes	**Case defn**	**Intervention** **n/N**	**Control** **n/N**	**Test**	
	All SAEs (none considered vaccine related according to study investigators)	5/1165 (0.4%)	0	No	
Method used for rate calculation	NA				

Quality assessment for RCTs- Cochrane Risk of Bias Tool

Domain	Assessment High risk/low risk/unclear	Comment
Random sequence generation	Low	Computer-generated blocking factor of 6
Allocation concealment	Low	An interactive voice response system was used to allocate study subjects and to assign allocation numbers
Blinding of participants and researchers	Low	All but personnel administering the vaccine were blinded
Blinding of outcomes assessors	Low	Independent safety monitor not employed by the sponsor
Incomplete outcome data	Low	Low attrition, similar in both groups
Selective reporting of outcomes	Unclear	SAE definition not reported, included SAEs not predefined
Any other risk of bias	High	Industry sponsored trial

Overall assessment of bias: Low risk

1. STUDY IDENTIFICATION		#020
First author	Roteli-Martins	
Year of publication	2012	
Journal citation	Roteli-Martins, C. M., Naud, P. et al (2012). 'Sustained immunogenicity and efficacy of the HPV-16/18 AS04-adjuvanted vaccine: Up to 8.4 years of follow-up'. Human Vaccines and Immunotherapeutics, 8 (3), 390-7.	
Trial number*(where applicable)*	NCT00518336	
2. SETTING		
Region	Brazil	
Study period	NR	
Duration follow-up	8.4 years	
3. PARTICIPANTS		
Study population/setting	Women aged 15–45 years with normal cervical cytology, HPV-16/18 seronegative by ELISA, DNA-negative for 14 oncogenic HPV types by PCR, received either the HPV-16/18 vaccine or placebo	
Total enrolled & in each group	**# Total: 436** HPV: 223 Placebo: 213	
Gender	Female	
Age metrics	**Age range for inclusion:** 15-45 years	**Metrics:** Mean age 26.5 years
Special group?	☐ **Yes** *(please specify):* ☒ **No**	
4. STUDY DESIGN & GROUP SPECIFICATION		
Study design	☐ RCT – Phase 2 ☒ RCT – Phase 3 ☐ Other controlled trial *(please specify)* _____ ☐ Case-control ☐ S Cohort ☐ Self-controlled case series ☐ Case series ☐ Case report ☐ Surveillance system – passive ☐ Sentinel surveillance ☐ Linked administrative data ☐ Population study ☐ Other *(please specify)*	

Group(s)	**Vaccine/ adjuvant**	**Brand**	**Comparator**
	HPV-16/18 AS04-adjuvanted vaccine	Cervarix™	Placebo

5. ADVERSE EVENT OUTCOME

Case definition	☐**N/A**☒**No**		☒**Yes** *(please specify):*	☐**Other** *(please specify):*	
AEFI Outcomes	**Case defn**	**Intervention** **n/N (% [95% CI])**	**Control** **n/N (% [95% CI])**	**Test**	
	All SAEs (investigators commented that none were attributable to the vaccine)	10/223 (4.5% [2.2, 8.1])	7/213 (3.3 [1.3, 6.7])	p-value NR	
	All new onset chronic diseases (investigators did not comment on whether vaccine related)	5/223 (2.2 [0.7, 5.2])	2/213 (0.9 [0.1, 3.4])	p-value NR	
	All new onset autoimmune diseases (investigators did not comment on whether vaccine related)	2/223 (0.9 [NR])	2/213 (0.9 [NR])	p-value NR	
Method used for rate calculation	NA				

Quality assessment for RCTs- Cochrane Risk of Bias Tool

Domain	Assessment High risk/low risk/unclear	Comment
Random sequence generation	Unclear	Randomisation method not described
Allocation concealment	Unclear	Method not reported
Blinding of participants and researchers	Low	Double-blinded RCT
Blinding of outcomes assessors	Low	Double-blinded RCT
Incomplete outcome data	Low	Reporting indicates safety outcomes based on entire vaccinated cohort
Selective reporting of outcomes	Unclear	SAE definitions and inclusions not pre-specified
Any other risk of bias	High	Industry sponsored trial

Overall assessment of bias: Unclear

1. STUDY IDENTIFICATION		#021
First author	Schmeink	
Year of publication	2011	
Journal citation	Schmeink, C. E., Bekkers, R. L. et al (2011). 'Co-administration of human papillomavirus-16/18 AS04-adjuvanted vaccine with hepatitis B vaccine: randomized study in healthy girls'. Vaccine, 29 (49), 9276-83.	
Trial number*(where applicable)*	NCT00652938	
2. SETTING		
Region	Seven centres in Sweden and The Netherlands	
Study period	April 2008 to January 2010	
Duration follow-up	12 months	
3. PARTICIPANTS		
Study population/setting	Open-label RCT including healthy girls aged 9–15 years at the time of first vaccination Girls had to have a negative pregnancy test at the time of each vaccination and if of child-bearing potential, to be abstinent from sexual activity or using adequate contraceptive precautions Girls with a history of hepatitis B infection or with known exposure to hepatitis B within 6 weeks prior to vaccination were excluded Previous vaccination against HPV or hepatitis B, or planned administration of HPV or hepatitis B vaccines not foreseen by the study protocol, was forbidden	
Total enrolled & in each group	**# Total: 741** HPV+HBV: 247 HPV: 247 HBV: 247	
Gender	Female	
Age metrics	**Age range for inclusion:** 9-15 years	**Metrics:** Mean age HPV+HBV 11.4 ± 2.17, HPV 11.3˚±˚2.14, HBV 11.4 ± 2.17
Special group?	☐ **Yes** *(please specify):* ☒ **No**	
4. STUDY DESIGN & GROUP SPECIFICATION		
Study design	☐ RCT – Phase 2 ☒ RCT – Phase 3 ☐ Other controlled trial *(please specify)* _____ ☐ Case-control ☐ S Cohort ☐ Self-controlled case series ☐ Case series ☐ Case report	☐ Surveillance system – passive ☐ Sentinel surveillance ☐ Linked administrative data ☐ Population study ☐ Other *(please specify)*

Group(s)	Vaccine/ adjuvant	Brand	Comparator
	HPV-16/18 AS04-adjuvanted vaccine	Cervarix™	HBV vaccine Coadministered HPV and HBV vaccines

5. ADVERSE EVENT OUTCOME					
Case definition	☐**N/A** ☒**No**		☐**Yes** *(please specify):*	☐**Other** *(please specify):*	
AEFI Outcomes	**Case defn**	**Intervention** **n/N**	**Control 1** **HBV** **n/N**	**Control 2** **HPV+HBV** **n/N**	**Test**
	Non-fatal SAEs (all considered to be unrelated to vaccination by study authors)	2/247 (0.8%)	1/247 (0.4%)	2/247 (0.8%)	NA
	Fatal SAEs (unrelated to vaccine – traumatic brain injury following train accident)	0	0	1/247 (0.4%)	NA
Method used for rate calculation	NA				

Quality assessment for RCTs- Cochrane Risk of Bias Tool

Domain	Assessment High risk/low risk/unclear	Comment
Random sequence generation	Low	Randomisation list was computer-generated
Allocation concealment	High	Open study
Blinding of participants and researchers	High	Open study
Blinding of outcomes assessors	High	Open study
Incomplete outcome data	Low	Reporting indicates safety outcomes based on entire vaccinated cohort
Selective reporting of outcomes	Unclear	SAE definitions and inclusions not pre-specified
Any other risk of bias	High	Industry sponsored trial

Overall assessment of bias: High risk

1. STUDY IDENTIFICATION		#022
First author	Sow	
Year of publication	2013	
Journal citation	Sow, P. S., Watson-Jones, D. et al (2013). 'Safety and immunogenicity of human papillomavirus-16/18 AS04-adjuvanted vaccine: A randomized trial in 10-25-year-old HIV-seronegative African girls and young women'. Journal of Infectious Diseases, 207 (11), 1753-63.	
Trial number*(where applicable)*	NCT00481767	
2. SETTING		
Region	2 centres in sub-Saharan Africa (Senegal and Tanzania)	
Study period	October 2007 to July 2010	
Duration follow-up	12 months	
3. PARTICIPANTS		
Study population/setting	Healthy African girls and young women seronegative for HIV were stratified by age (10–14 or 15–25 years) and randomized (2:1) to receive either HPV-16/18 AS04-adjuvanted vaccine or placebo at 0, 1, and 6 months	
Total enrolled & in each group	**# Total: 676** HPV: 450 Placebo: 226	
Gender	Female	
Age metrics	**Age range for inclusion:** 10-25 years	**Metrics:** Mean age 16.9 ± 4.36 years
Special group?	☐ **Yes** *(please specify):* ☒ **No**	
4. STUDY DESIGN & GROUP SPECIFICATION		
Study design	☐ RCT – Phase 2 ☒ RCT – Phase 3 ☐ Other controlled trial *(please specify)* _____ ☐ Case-control ☐ S Cohort ☐ Self-controlled case series ☐ Case series ☐ Case report	☐ Surveillance system – passive ☐ Sentinel surveillance ☐ Linked administrative data ☐ Population study ☐ Other *(please specify)*

Group(s)	**Vaccine/ adjuvant**	**Brand**	**Comparator**
	HPV-16/18 AS04-adjuvanted vaccine	Cervarix™	Placebo

5. ADVERSE EVENT OUTCOME

Case definition	☐**N/A**☒**No**		☐**Yes** *(please specify):*	☐**Other** *(please specify):*	
AEFI Outcomes	**Case defn**	**Intervention** **n/N (% [95%CI])**	**Control** **n/N (% [95%CI])**	**Test**	
	All SAEs (none considered vaccine-related by investigators)	17 (3.8 [2.2, 6.0])	14 (6.2 [3.4, 10.2])	NA	
	New onset chronic diseases	11 (2.4 [1.2, 4.3])	11 (4.9 [2.5, 8.5])	NA	
	New onset autoimmune disease	2 (0.4 [0.1, 1.6])	2 (0.9 [0.1, 3.2])	NA	
Method used for rate calculation	NA				

Quality assessment for RCTs- Cochrane Risk of Bias Tool

Domain	Assessment High risk/low risk/unclear	Comment
Random sequence generation	Low	Computer-generated randomisation
Allocation concealment	Low	Internet-based randomisation blocking scheme
Blinding of participants and researchers	Low	Double-blind trial
Blinding of outcomes assessors	Low	Double-blind trial
Incomplete outcome data	Low	Reporting indicates safety outcomes based on entire vaccinated cohort
Selective reporting of outcomes	Unclear	SAE definitions and inclusions not pre-specified
Any other risk of bias	High	Industry sponsored trial

Overall assessment of bias: Low

1. STUDY IDENTIFICATION		#023
First author	Villa	
Year of publication	2007	
Journal citation	Villa, L. L., Perez, G. et al (2007). 'Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions'. New England Journal of Medicine, 356 (19), 1915-27.	
Trial number*(where applicable)*	NCT00092534	
2. SETTING		
Region	90 sites across 13 countries representing North America, South America, Europe and Asia	
Study period	June 2002 to May 2003	
Duration follow-up	3 years	
3. PARTICIPANTS		
Study population/setting	12,167 women aged 15-26 years randomised to receive three doses of either HPV-6/11/16/18 vaccine or placebo, administered at day 1, month 2, and month 6	
Total enrolled & in each group	**# Total: 12,167** HPV: 6087, placebo: 6080	
Gender	Female	
Age metrics	**Age range for inclusion:** 15-26 years	**Metrics:** HPV group mean age 20.0 ±2.2 years, placebo group mean age 19.9 ± 2.1
Special group?	☐ **Yes** *(please specify):* ☒ **No**	
4. STUDY DESIGN & GROUP SPECIFICATION		
Study design	☐ RCT – Phase 2 ☒ RCT – Phase 3 ☐ Other controlled trial *(please specify)* _____ ☐ Case-control ☐ S Cohort ☐ Self-controlled case series ☐ Case series ☐ Case report	☐ Surveillance system – passive ☐ Sentinel surveillance ☐ Linked administrative data ☐ Population study ☐ Other *(please specify)*

Group(s)	**Vaccine/ adjuvant**	**Brand**	**Comparator**
	HPV-6/11/16/18 vaccine	Gardasil®	Aluminium-based placebo

5. ADVERSE EVENT OUTCOME			
Case definition	☐ **N/A** ☒ **No**	☐ **Yes** *(please specify):*	☐ **Other** *(please specify):*

AEFI Outcomes	**Case defn**	**Intervention** **n/N**	**Control** **n/N**	**Test** **Risk difference [95%CI]**	
	All SAEs	45/6019 (0.7%)	54/6031 (0.9%)	-0.1 [-0.5, 0.2]	
	Injection related SAEs	3/6019 (<0.1%)	2 (<0.1%)	0 [-0.1, 0.1]	
	Any SAEs leading to discontinuation	7/6019 (0.1%)	6/6031 (0.1%)	0 [-0.1, 0.2]	
	Injection-related SAEs leading to discontinuation	0/6019	1/6031 (<0.1%)	0 [-0.1, 0.1]	
	Death	7/6019 (0.1%)	5/6031 (0.1%)	0 [-0.1, 0.1]	
Method used for rate calculation	95%CIs unadjusted for multiplicity				

Quality assessment for RCTs- Cochrane Risk of Bias Tool

Domain	Assessment High risk/low risk/unclear	Comment
Random sequence generation	Low	Computer-generated randomized allocation schedule using permuted blocks of size six
Allocation concealment	Low	Interactive voice response system assigned a separate block of 18 allocation numbers to each study site upon allocation of the first subject at that site Block of 18 numbers was used to allocate subjects to one of three lots of vaccine, or placebo
Blinding of participants and researchers	Low	Double-blinded trial
Blinding of outcomes assessors	Low	End-point assignment was based on blinded consensus diagnosis
Incomplete outcome data	Low	Low attrition, similar in both groups
Selective reporting of outcomes	Unclear	SAE definitions and inclusions not pre-specified
Any other risk of bias	High	Industry sponsored trial

Overall assessment of bias: Low risk

1. STUDY IDENTIFICATION		#024
First author	Wheeler	
Year of publication	2016	
Journal citation	Wheeler, C. M., Skinner, S. R. et al (2016). 'Efficacy, safety, and immunogenicity of the human papillomavirus 16/18 AS04-adjuvanted vaccine in women older than 25 years: 7-year follow-up of the phase 3, double-blind, randomised controlled VIVIANE study'. The Lancet Infectious Diseases, 16 (10), 1154-68.	
Trial number*(where applicable)*	NCT00294047	
2. SETTING		
Region	Four regions: Asia Pacific - Australia, the Philippines, Singapore, Thailand Europe - The Netherlands, Portugal, Russia, United Kingdom North America - Canada, USA, Mexico South America - Peru	
Study period	16 Feb 2006 to 29 Jan 2014	
Duration follow-up	7 years	
3. PARTICIPANTS		
Study population/setting	Healthy women older than 25 years were enrolled (age stratified: 26-35 years, 36-45 years, and ≥46 years) 1:1 randomisation to either HPV or placebo	
Total enrolled & in each group	**# Total: 5747** HPV: 2877 Placebo: 2870	
Gender	Female	
Age metrics	**Age range for inclusion: >25 years**	**Metrics: 37 years**
Special group?	☐ **Yes** *(please specify):* ☒ **No**	
4. STUDY DESIGN & GROUP SPECIFICATION		
Study design	☐ RCT – Phase 2 ☒ RCT – Phase 3 ☐ Other controlled trial *(please specify)* _____ ☐ Case-control ☐ S Cohort ☐ Self-controlled case series ☐ Case series ☐ Case report	☐ Surveillance system – passive ☐ Sentinel surveillance ☐ Linked administrative data ☐ Population study ☐ Other *(please specify)*

Group(s)	Vaccine/ adjuvant	Brand	Comparator
	HPV16/18 AS04-adjuvanted vaccine	Cervarix™	Aluminium-based placebo

5. ADVERSE EVENT OUTCOME					
Case definition	☐**N/A** ☒**No**	☐**Yes** *(please specify):*		☐**Other** *(please specify):*	
AEFI Outcomes	**Case defn**	**Intervention n/N**	**Control n/N**	**Test**	
	All SAEs possibly related to the study vaccine	5/2877 (0.2%)	8/2870 (0.3%)	NA	
	Deaths (considered by investigator to be unrelated to study vaccination)	13/2877 (0.5%)	5/2870 (0.2%)	NA	
Method used for rate calculation	NA				

Quality assessment for RCTs- Cochrane Risk of Bias Tool

Domain	Assessment High risk/low risk/unclear	Comment
Random sequence generation	Low	Random numbers generated with a standard SAS program
Allocation concealment	Low	Treatment allocation undertaken with a central randomisation call-in system on the internet
Blinding of participants and researchers	Low	All personnel and participants blinded
Blinding of outcomes assessors	Low	Blinding of treatment allocation for investigators, staff on site, and sponsor personnel up to the end of the study
Incomplete outcome data	Low	~15% attrition in both groups
Selective reporting of outcomes	Unclear	SAE definitions and inclusions not pre-specified
Any other risk of bias	High	Industry sponsored trial

Overall assessment of bias: Low risk

1. STUDY IDENTIFICATION			#025
First author	Yoshikawa		
Year of publication	2013		
Journal citation	Yoshikawa, H., et al. (2013) Efficacy of quadrivalent human papillomavirus (types 6, 11, 16 and 18) vaccine (GARDASIL®) in Japanese women aged 18-26 years. Cancer science104, 465-472		
Trial number*(where applicable)*	NCT00378560		
2. SETTING			
Region	Japan		
Study period	NR		
Duration follow-up	Up to month 30		
3. PARTICIPANTS			
Study population/setting	Double blind, placebo controlled RCT of women: eligible if not pregnant, had no previous abnormal pap smear and had a lifetime history of four or fewer male sex partners.		
Total enrolled & in each group	**# Total: 1030** HPV: 509 Placebo: 512		
Gender	Female		
Age metrics	**Age range for inclusion:** 18-26	**Metrics:** HPV mean age 22.7 ± 2.1 Placebo mean age 22.9 ± 2.1	
Special group?	☐ **Yes** *(please specify):* ☒ **No**		
4. STUDY DESIGN & GROUP SPECIFICATION			
Study design	☒ RCT – Phase 2 ☐ RCT – Phase 3 ☐ Other controlled trial *(please specify)* _____ ☐ Case-control ☐ S Cohort ☐ Self-controlled case series ☐ Case series ☐ Case report	☐ Surveillance system – passive ☐ Sentinel surveillance ☐ Linked administrative data ☐ Population study ☐ Other *(please specify)*	
Group(s)	**Vaccine/ adjuvant** HPV 6/11/16/18 / amorphous aluminium hyroxyphophate sulfate adjuvant	**Brand** Gardasil® (Merck)	**Comparator** Amorphous aluminium hyroxyphophate sulfate-containing placebo
5. ADVERSE EVENT OUTCOME			

Case definition	☐**N/A** ☒**No** No details about SAEs or how collected, or how investigator determined if related to vaccine		☒**Yes** *(please specify):*	☐**Other** *(please specify):*	
AEFI Outcomes	**Case defn**	**Intervention** **n/N**	**Control** **n/N**	**Test**	
	SAE	3/480	1/468		
	Vaccine related SAE	0/480	0/468		
	Death	0/480	0/468		
Method used for rate calculation					

Quality assessment for RCTs- Cochrane Risk of Bias Tool

Domain	Assessment High risk/low risk/unclear	Comment
Random sequence generation	Unclear	Doesn't state how randomisation was actually done
Allocation concealment	Low risk	Appears vaccines were randomised and kept centrally
Blinding of participants and researchers	Low risk	Stated double blind, no other details
Blinding of outcomes assessors	Unclear	No details on how SAE were collected
Incomplete outcome data	Unclear	Some dropouts from denominator for safety analysis but no explanation of why
Selective reporting of outcomes	High risk	SAEs not described or pre-specified; no details on how investigators determined if SAE was vaccine related
Any other bias	High risk	Funding source not disclosed but two authors are employees of Merck.

Overall assessment of bias: Unclear

1. STUDY IDENTIFICATION		#026
First author	Zhu	
Year of publication	2014	
Journal citation	Zhu, F. C., et al. (2014). "Efficacy, immunogenicity and safety of the HPV-16/18 AS04-adjuvanted vaccine in healthy Chinese women aged 18'25 years: Results from a randomized controlled trial." International Journal of Cancer135(11): 2612-2622.	
Trial number*(where applicable)*	NCT00779766	
2. SETTING		
Region	China	
Study period	October 2008 to April 2011	
Duration follow-up	Mean 21 months after first vaccination	
3. PARTICIPANTS		
Study population/setting	Double blind placebo controlled RCT: healthy women with intact cervix. Ineligible if pregnant or breastfeeding, a virgin, had immunosuppressive or immunodeficient condition, history of colposcopy or allergy to vaccine component.	
Total enrolled & in each group	**# Total: 6051** HPV: 3026 Placebo: 3025	
Gender	Female	
Age metrics	**Age range for inclusion:** 18-25 years	**Metrics:**
Special group?	☐ **Yes** *(please specify):* ☒ **No**	
4. STUDY DESIGN & GROUP SPECIFICATION		
Study design	☐ RCT – Phase 2 ☒ RCT – Phase 3 ☐ Other controlled trial *(please specify)* _____ ☐ Case-control ☐ S Cohort ☐ Self-controlled case series ☐ Case series ☐ Case report ☐ Surveillance system – passive ☐ Sentinel surveillance ☐ Linked administrative data ☐ Population study ☐ Other *(please specify)*	

Group(s)	**Vaccine/ adjuvant**	**Brand**	**Comparator**
	HPV 16/18/ AS04 adjuvant	Cervarix™ (GSK)	Alumimium hydroxide-containing placebo

5. ADVERSE EVENT OUTCOME					
Case definition	☐**N/A** ☒**No** SAEs not defined, no criteria for vaccine relatedness		☐**Yes** *(please specify):*	☐**Other** *(please specify):*	
AEFI Outcomes	**Case defn**	**Intervention** **n/N**	**Control** **n/N**	**Test**	
	SAE	29/3026	55/3025		
	MSC	158/3026	156/3025		
	NOCD	8/3026	11/3025		
	New onset autoimmune diseases	2/3026	2/3025		
Method used for rate calculation					

Quality assessment for RCTs- Cochrane Risk of Bias Tool

Domain	Assessment High risk/low risk/unclear	Comment
Random sequence generation	Low risk	No details but internet-based system so assume computer randomisation
Allocation concealment	Low risk	Central internet based randomisation system
Blinding of participants and researchers	Low risk	Blinding stated but no details
Blinding of outcomes assessors	Unclear	No details about how SAEs were recorded or followed up
Incomplete outcome data	Low risk	Follow up rate high, although how safety followed in TVC is not described
Selective reporting of outcomes	Unclear	Limited details provided
Any other bias	High risk	Trial funded, designed, conducted, analysed and reported by GSK

Overall assessment of bias: Low risk

1. STUDY IDENTIFICATION		#027
First author	Arnheim-Dahlstrom	
Year of publication	2013	
Journal citation	Arnheim-Dahlström, L., et al. (2013). "Autoimmune, neurological, and venous thromboembolic adverse events after immunisation of adolescent girls with quadrivalent human papillomavirus vaccine in Denmark and Sweden: Cohort study." BMJ (Online) **347**(f5906).	
Trial number *(where applicable)*		
2. SETTING		
Region	Denmark and Sweden	
Study period	1 October 2006 until 31 Dec 2010 (or from 10th birthday if after start date, and 18th birthday if before end date)	
Duration follow-up	Varied by age. Censored if received bHPV, died, disappeared from registers, emigrated, turned 18 or at adverse event.	
3. PARTICIPANTS		
Study population/setting	Cohort study of girls in Denmark and Sweden; entire cohort of girls the correct age was identified, and matched to vaccination databases (exposure) and predetermined outcomes using patient registers	
Total enrolled & in each group	**# Total:** 997 585 girls; 296 826 had received at least one dose qHPV vaccine; only 160 986 received third dose; 2 797 701 person years of follow up	
Gender	Females only	
Age metrics	**Age range for inclusion: 10-17 years**	**Metrics:**
Special group?	☐ **Yes** *(please specify):*	☒**No**

4. STUDY DESIGN & GROUP SPECIFICATION

Study design

- ☐ RCT – Phase 2
- ☐ RCT – Phase 3
- ☐ Other controlled trial *(please specify)* _____
- ☐ Case-control
- ☒ Cohort
- ☐ Self-controlled case series
- ☐ Case series
- ☐ Case report
- ☐ Surveillance system – passive
- ☐ Sentinel surveillance
- ☒ Linked administrative data
- ☐ Population study
- ☐ Other *(please specify)*

Group(s)	Vaccine/ adjuvant	Brand	Comparator
	qHPV		na

5. ADVERSE EVENT OUTCOME

Case definition			
	☐ **N/A** ☐ **No**	☒ **Yes** *(please specify):* Predefined adverse events: 53 specific outcomes, with ICD codes, occurring within 180 days of vaccine exposure (90 days for venous thromboembolism)	☒ **Other** *(please specify):*

AEFI Outcomes	Case defn	Event	Lowest rate ratio	Highest rate ratio	Rate
	Autoimmune disorders	thyroid	0.90 (0.71, 1.14)	1.12 (0.82, 1.52)	
		gastrointestinal	0.71 (0.49, 1.03)	1.19 (0.60, 2.35)	
		Musculoskeletal/systemic	0.89 (0.52, 1.52)	3.37 (1.05, 10.80)	
		haematological	1.18 (0.65, 2.17)		
		dermatological	1.01 (0.80, 1.28)	1.13 (0.73, 1.74)	

		Miscellaneous: raynaud's disease Type 1 diabetes	1.67 (1.14, 2.44) 1.29 (1.03, 1.62)		
	Neurological		0.56 (0.35, 0.90)	1.02 (0.72, 1.43)	
	Venous thromboembolism		0.86 (0.55, 1.36)		
Method used for rate calculation	Rate ratios adjusted for country, age in two year intervals, calendar year, parental country of birth, parental education and paternal socioeconomic status Three outcomes showed a statistically significantly increased rate ratio with exposure: Behcet's syndrome, Raynaud's disease and Type 1 diabetes. Two outcoems showed a statistically significantly decreasted rate ratio with exposure: epilepsy and paralysis.				

Quality assessment for observational studies: AHRQ RTI item bank

Domain	result	comment
Selection bias: do exclusion/ inclusion criteria vary across groups	na	
Recruitment strategy	Na	
Selection of comparison group appropriate	Yes	All participants chosen from same pool regardless of their exposure
Important variations from protocol	na	
Blinded outcomes assessment	na	Used administrative data sets to identify exposure and outcomes
Valid and reliable methods	yes	Prespecified and confirmed with ICD classification
Length of follow up same	yes	
Impact of loss to follow up assessed	Na	Administrative data sets used
Important primary otucomes missing	no	
Important harms missing	na	
Results believable	yes	
Attempt to balance allocation between groups	na	
Important confounding taken into account	yes	Results adjusted for relevant confounders; all eligible girls followed so confounding unlikely
OVERALL QUALITY RATING	Low risk of bias	

1. STUDY IDENTIFICATION					#028
First author	Scheller				
Year of publication	2015				
Journal citation	Scheller, N. M., et al. (2015). "Quadrivalent HPV vaccination and risk of multiple sclerosis and other demyelinating diseases of the central nervous system." JAMA **313**(1): 54-61.				
Trial number*(where applicable)*					
2. SETTING					
Region	Denmark and Sweden				
Study period	Oct 2006- Jul 2013				
Duration follow-up	21 332 622 person years				
3. PARTICIPANTS					
Study population/setting	Cohort study-compared exposed time (up two years after vaccination) with unexposed time (time before vaccination or any time if not vaccinated). Outcomes of MS and other demyelinating diseases identified through patient registers (physician assigned diagnoses from hospital inpatient and outpatient departments), defined by ICD10				
Total enrolled & in each group	**# Total:** 3 983 824 eligible for inclusion in the cohort; 789082 were vaccinated;				
Gender	females				
Age metrics	**Age range for inclusion:** 10-44 years			**Metrics:** mean age at entry 25.5 years, mean age at vaccination 18.5 years (Denmark), 15.3 years (Sweden)	
Special group?	☐**Yes** *(please specify):* ☒**No**				
4. STUDY DESIGN & GROUP SPECIFICATION					
Study design	☐RCT – Phase 2 ☐RCT – Phase 3 ☐Other controlled trial *(please specify)* _____ ☐Case-control ☒Cohort ☐Self-controlled case series ☐Case series ☐Case report ☐Surveillance system – passive ☐Sentinel surveillance ☒Linked administrative data ☐Population study ☐Other *(please specify)*				
Group(s)	**Vaccine/ adjuvant** qHPV		**Brand**	**Comparator** Time unvaccinated	
5. ADVERSE EVENT OUTCOME					
Case definition	☐**N/A**☐**No**		☒**Yes** *(please specify):* MS and other demyelinating diseases (optic neuritis, neuromyelitis optica, transverse myelitis, acute disseminated encephalomyelitis, other central demyelinating diseases). Defined by ICD10	☐**Other** *(please specify):*	
AEFI Outcomes	**Case defn**	**Unvaccinated Cases/person years Incidence rate/ 100 000 person years (95% CI)**	**Vaccinated Cases/person years Incidence rate/ 100 000 person years (95% CI)**	**Adjusted RR (95% CI)**	
	MS	4208/19 532 311 21.54 (20.90-22.20)	73/1 193 703 6.12 (4.86-7.69)	0.90 (0.70-1.15)	
	Other demyelinating diseases	2154/19 546 190 16.14 (15.58- 16.71)	90/1 193 591 7.54 (6.13- 9.27)	1.00 (0.80-1.26)	

Method used for rate calculation	

Quality assessment for observational studies: AHRQ RTI item bank

Domain	result	comment
Selection bias: do exclusion/ inclusion criteria vary across groups	NA	Administrative data
Recruitment strategy	NA	
Selection of comparison group appropriate	Yes	Compared to time before vaccination or not vaccinated
Important variations from protocol	na	
Blinded outcomes assessment	na	
Valid and reliable methods	Yes	Complete registers and ICD coded outcomes
Length of follow up same	yes	
Impact of loss to follow up assessed	Na	
Important primary outcomes missing	NA	Focused on MS and demyelinating diseases
Important harms missing	na	
Results believable	Yes	Excellent population registers and physician-diagnosed outcomes
Attempt to balance allocation between groups	na	
Important confounding taken into account	unclear	No confounders adjusted for, however population based study so may expect confounders equally distributed
OVERALL QUALITY RATING	**low risk of bias**	

1. STUDY IDENTIFICATION					#029
First author	Schurink				
Year of publication	2015				
Journal citation	Schurink-Van't Klooster, T. M., et al. (2015). "Examining a possible association between human papilloma virus (HPV) vaccination and migraine: results of a cohort study in the Netherlands." Eur J Pediatr **174**(5): 641-649.				
Trial number*(where applicable)*					
2. SETTING					
Region	Netherlands				
Study period	1 Jan 2007- 31 Dec 2010; incident migraine recorded in 2009/10				
Duration follow-up					
3. PARTICIPANTS					
Study population/setting	Incident migraine as identified from general practice database covering about 9% of Dutch population. Divided into certain and uncertain migraine based on medical records. All patients identified with migraine were compared on exposure to HPV vaccine				
Total enrolled & in each group	**# Total:** 22 girls with incident migraine out of 2005 eligible for the vaccination.				
Gender	females				
Age metrics	**Age range for inclusion: 12-16** years			**Metrics:**	
Special group?	☐**Yes** *(please specify):* ☒**No**				
4. STUDY DESIGN & GROUP SPECIFICATION					
Study design	☐RCT – Phase 2 ☐RCT – Phase 3 ☐Other controlled trial *(please specify)* _____ ☐Case-control ☒Cohort ☐Self-controlled case series ☐Case series ☐Case report ☐Surveillance system – passive ☐Sentinel surveillance ☐Linked administrative data ☐Population study ☐Other *(please specify)*				
Group(s)	**Vaccine/ adjuvant** bHPV		**Brand** Cervarix		**Comparator**
5. ADVERSE EVENT OUTCOME					
Case definition	☐**N/A**☐**No**		☒**Yes** *(please specify):* Migraine according to database-specific code, or migrai* in free text of records		☐**Other** *(please specify):*
AEFI Outcomes	**Case defn**	**IRR (estimated from figure, no data provided)**			
	Migraine: month 1	1.5 (not significant)			
	Month 2	0 (not significant)			
	Month 7	0 (not significant)			
	Month 24	0 (not significant)			
Method used for rate calculation	No analysis Investigators considered none of the SAE to be related to study vaccination				

Domain	result	comment
Selection bias: do exclusion/ inclusion criteria vary across groups	No	All chosen from same dataset
Recruitment strategy	NA	
Selection of comparison group appropriate	Yes	All chosen from same dataset
Important variations from protocol	na	
Blinded outcomes assessment	na	
Valid and reliable methods	Yes	
Length of follow up same	yes	
Impact of loss to follow up assessed	Na	
Important primary outcomes missing	NA	
Important harms missing	na	
Results believable	Yes	
Attempt to balance allocation between groups	na	
Important confounding taken into account	no	No confounders adjusted for
OVERALL QUALITY RATING	**low risk of bias**	

1. STUDY IDENTIFICATION			#030
First author	Willame		
Year of publication	2016		
Journal citation	Willame, C., et al. (2016). "Risk of new onset autoimmune disease in 9- to 25-year-old women exposed to human papillomavirus-16/18 AS04-adjuvanted vaccine in the United Kingdom." Human Vaccines and Immunotherapeutics **12**(11): 2862-2871.		
Trial number*(where applicable)*			
2. SETTING			
Region	UK		
Study period	1 Sept 2008- 31 Aug 2010; historical cohorts 1 Sept 2005-31 Aug 2007		
Duration follow-up			
3. PARTICIPANTS			
Study population/setting	Cohort study of girls with new onset autoimmune disease, comparing those exposed to HPV with historical age and sex matched cohort, and concurrent and historical male cohorts. Data from Clinical Practice Research Datalink General Practice Online Databse (CPRD GOLD)		
Total enrolled & in each group	**# Total:** **Exposed cohort: 64 964;** **Unexposed cohorts: historical female cohort: 64 973; concurrent male cohort: 64 974; historical male cohort: 64 965..**		
Gender	Females only in cases		
Age metrics	**Age range for inclusion:9-25 years**	**Metrics:**	
Special group?	☐**Yes** *(please specify):* ☒**No**		
4. STUDY DESIGN & GROUP SPECIFICATION			
Study design	☐RCT – Phase 2 ☐RCT – Phase 3 ☐Other controlled trial *(please specify)* _____ ☐Case-control ☒Cohort ☐Self-controlled case series ☐Case series ☐Case report ☐Surveillance system – passive ☐Sentinel surveillance ☒Linked administrative data ☐Population study ☐Other *(please specify)*		
Group(s)	**Vaccine/ adjuvant** HPV 16/18	**Brand**	**Comparator** na
5. ADVERSE EVENT OUTCOME			
Case definition	☐**N/A**☐**No**	☒**Yes** *(please specify):* Predefined autoimmune disease: 1) neuroinflammatory/ ophthalmic diseases: multiple sclerosis, tranverse myelitis, optic neuritis, Guillain-Barre syndrome, autoimmune uveitis , other demyelinating diseases 2) other AD: SLE, rheumatoid arthritis, juvenile RA, Still's disease, psoriatic arthritis, ankylosing spondylitis, idiopathic	☒**Other** *(please specify):*

			thrombocytopenic purpura, autoimmune haemolytic anaemia, type 1 diabetes, autoimmune thyroiditis, Crohn's disease, ulcerative colitis, autoimmune hepatitis. Risk period 1 year after vaccination		
AEFI Outcomes	**Case defn**	**Incidence rate /100 000 person years (95% CI) Exposed cohort**	**Incidence rate /100 000 person years (95% CI) Historic female cohort**	**Incidence rate /100 000 person years (95% CI) Concurrent male cohort**	**Incidence rate /100 000 person years (95% CI) Historic male cohort**
	Neuroinflammatory /ophthalmic AD: confirmed cases	0 (0.0-5.70)	1.54 (0.04-8.59)	1.54 (0.04-8.59)	1.54 (0.04-8.59)
	Other AD: confirmed cases	58.73 (51.56-80.61)	41.64 (27.44-60.58)	40.09 (26.19-58.74)	23.12(12.94-38.14)
	In diseases with more than 10 cases in female cohorts:				
	Autoimmune thryroiditis	23.18(12.98-38.24)	6.17(1.68-15.8)	0 (0-5.69)	0 (0-5.69)
	Crohn's disease	9.27(3.40-20.18)	7.71(2.50-18.00)	6.17(1.68-15.79)	1.54(0.04-8.59)
	Type 1 diabetes	12.36(5.34-24.36)	24.68(14.10-40.07)	30.84(18.84-47.62)	12.33(5.35-24.30)
Method used for rate calculation					

Quality assessment for observational studies: AHRQ RTI item bank

Domain	result	comment
Selection bias: do exclusion/ inclusion criteria vary across groups	na	
Recruitment strategy	Na	
Selection of comparison group appropriate	Yes	historical cohort used to ensure unexposed
Important variations from protocol	na	
Blinded outcomes assessment	na	Used administrative data sets to identify exposure and outcomes
Valid and reliable methods	yes	Prespecified and confirmed with ICD classification
Length of follow up same	yes	
Impact of loss to follow up assessed	Na	Administrative data sets used
Important primary otucomes missing	no	
Important harms missing	na	
Results believable	yes	
Attempt to balance allocation between groups	na	
Important confounding taken into account	unclear	Confounding not described
OVERALL QUALITY RATING	Low risk of bias	

Note: study funded, designed and conducted by GSK

1. STUDY IDENTIFICATION		#031
First author	Gee	
Year of publication	2011	
Journal citation	Gee, J., et al. (2011). "Monitoring the safety of quadrivalent human papillomavirus vaccine: Findings from the Vaccine Safety Datalink." Vaccine **29**(46): 8279-8284.	
Trial number*(where applicable)*		
2. SETTING		
Region	7 managed care organisations in several states in the US	
Study period	August 2006- October 2009	
Duration follow-up		
3. PARTICIPANTS		
Study population/setting	Females in correct age range identified from records at participating sites formed the cohort, paired with information from standardised datafiles from outpatient visits, emergency dept visits and hospital settings. Historical comparison group from same sites for less common outcomes; Nationwide data used for Guillain Barre; concurrent unexposed (to HPV) comparison group for more common outcomes. Vaccine safety data from Vaccine Safety Datalink	
Total enrolled & in each group	**# Total:**	
Gender	Females only	
Age metrics	**Age range for inclusion:9-26 years**	**Metrics:**
Special group?	☐**Yes** *(please specify):* ☒**No**	

4. STUDY DESIGN & GROUP SPECIFICATION			
Study design	☐RCT – Phase 2 ☐RCT – Phase 3 ☐Other controlled trial *(please specify)* _____ ☐Case-control ☒Cohort ☐Self-controlled case series ☐Case series ☐Case report		☐Surveillance system – passive ☐Sentinel surveillance ☒Linked administrative data ☐Population study ☐Other *(please specify)*
Group(s)	**Vaccine/ adjuvant** qHPV	**Brand**	**Comparator** na

5. ADVERSE EVENT OUTCOME			
Case definition	☐**N/A**☐**No**	☒**Yes** *(please specify):* Predefined adverse events, defined by ICD9: anaphylaxis, allergic reactions, appendicitis, Guillain-Barre syndrome, seizures, first ever seizures, stroke, syncope, venous thromboembolism Youth: 9-17 years Adults:18-26 years	☐**Other** *(please specify):*

AEFI Outcomes	**Case defn**	**Comparator data**	**Observed events/doses administered**	**Expected events**	**Relative risk**
	GBS	Historical comparison group	Youth:0/416942 Adults:1/183616	Youth:0.80 Adults:0.48	*0.00* 2.10
	Appendicitis	Historical comparison group	Youth:50/203890 Adults:33/139746	Youth:32.8 Adults:25.03	1.52* 1.32
	stroke	Historical comparison group	Youth:0/416942 Adults:2/112619	Youth: 1.35 Adults: 1.50	0 1.33
	Venous	Historical comparison	Youth:8/292302	Youth: 4.04	1.98

	thromboembolism	group	Adults:11/176194	Adults: 15.00	0.73
			Exposed cases	**unexposed cases**	
	Seizure	Concurrent comparison group	Youth:47 Adults:22	Youth: 23 Adults: 37	1.02 1.13
	syncope	Concurrent comparison group	Youth:610 Adults:170	Youth: 202 Adults: 95	0.86 0.54
	Allergic reactions	Concurrent comparison group	Youth:54 Adults:37	Youth: 29 Adults: 8	0.77 1.48
Method used for rate calculation	Data analysed using weekly sequential analysis. Historical comparison group: log likelihood ration test statistic at each time peridod used to determine if elevated risks were statistically significant and a signal generated. Concurrent comparison group: exact sequential analysis used to compare exposed to unexposed matched on age, site and vaccination date; this determined exact p-value required for a signal. All statistical signals and elevated RR were followed up including data quality checks, evaluation of clustering after vaccination; adjustment of other possible confounders.				

Quality assessment for observational studies: AHRQ RTI item bank

Domain	result	comment
Selection bias: do exclusion/ inclusion criteria vary across groups	na	
Recruitment strategy	Na	
Selection of comparison group appropriate	Yes	Two control group: 1 historical and one concurrent
Important variations from protocol	na	
Blinded outcomes assessment	na	Used administrative data sets to identify exposure and outcomes
Valid and reliable methods	yes	Prespecified and confirmed with ICD classification
Length of follow up same	yes	
Impact of loss to follow up assessed	Na	Administrative data sets used
Important primary outcomes missing	no	
Important harms missing	na	
Results believable	yes	
Attempt to balance allocation between groups	na	
Important confounding taken into account	yes	Results adjusted for relevant confounders; all eligible girls followed so confounding unlikely
OVERALL QUALITY RATING	**Low risk of bias**	

APPENDIX C CRITICAL APPRAISAL CHECKLISTS TO DETERMINE RISK OF BIAS

Table 9 Methodological checklist: systematic reviews (AMSTAR; 2)

Reference:	
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of the review. *Note: Need to refer to a protocol, ethics approval, or pre-determined/a priori published research objective to score a "yes"*	Yes No Can't answer Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus process for disagreements should in place. *Note: 2 people do study selection, 2 people do data extraction, consensus process or one person checks the other's work.*	Yes No Can't answer Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and Medline). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialised registers, or experts in the particular field of study, and by reviewing the references of the studies found. *Note: If at least 2 sources + one supplementary strategy used, select "Yes" (Cochrane register/Central counts as 2 sources; a grey literature search counts as supplementary)*	Yes No Can't answer Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc. *Note: If review indicates that there was a search for "grey literature" or "unpublished literature", indicate "yes". SIGLE database, dissertations, conference proceedings, and trial registers are all considered grey for this purpose. If searching a source that contains both grey and non-grey, must specify that they were searching for grey/unpublished lit.*	Yes No Can't answer Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided. *Note: Acceptable if the excluded studies are referenced. If there is an electronic link to the list but the link is dead, select "no".*	Yes No Can't answer Not applicable
6. Where the characteristics of the included studies provided? In an aggregated form such as a table, data from original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	Yes No Can't answer Not applicable

Note: Acceptable if not in table format as long as they are described as above.	
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g. for effectiveness studies if the author(s) chose to include only randomised, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant. *Note: Can include use of a quality scoring tool or checklist, e.g. Jadad scale, risk of bias, sensitivity analysis, etc. or description of quality items, with some kind of result for EACH study ("low", or "high" is fine, as long as it is clear which studies scored "low" and which scored "high"; a summary score/range for all studies is not acceptable).*	Yes No Can't answer Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigour and scientific quality should be considered in the analysis and the conclusions of the review, and explicity stated in formulating recommendations. *Note: Might say something such as "the results should be interpreted with caution due to poor quality of included studies". Cannot score "yes" for this question if scored "no" for question 7.*	Yes No Can't answer Not applicable
9. Were the methods used to combine the findings of the studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their heterogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?). *Note: Indicate "yes" if they mention or describe heterogeneity, i.e. if they explain that they cannot pool because of heterogeneity/ variability between interventions.*	Yes No Can't answer Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g. funnel plot, other available test (e.g. Egger regression test, Hedges-Olken). *Note: If no test values or funnel plot indicated, score "no". Score "yes" if mentions that publication bias could not be assessed because there were fewer than 10 included studies.*	Yes No Can't answer Not applicable
11. Was the conflict of interest included? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies. *Note: To get a "yes", must indicate source of funding or support for the systematic review AND for each of the included studies.*	Yes No Can't answer Not applicable

Additional notes (in italics) made by Michelle Weir, Julia Worswick, and Carolyn Wayne based on conversations with Bev Shea and/or Jeremy Grimshaw in June and October 2008 and July and September 2010. Available from http://amstar.ca/docs/AMSTARguideline.pdf

Table 10 Methodology checklist: Cochrane risk of bias tool (3)

RANDOM SEQUENCE GENERATION **Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence.**	
Criteria for a judgement of 'Low risk' of bias.	The investigators describe a random component in the sequence generation process such as: Referring to a random number table; Using a computer random number generator; Coin tossing; Shuffling cards or envelopes; Throwing dice; Drawing of lots; Minimization*. *Minimization may be implemented without a random element, and this is considered to be equivalent to being random.
Criteria for the judgement of 'High risk' of bias.	The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example: Sequence generated by odd or even date of birth; Sequence generated by some rule based on date (or day) of admission; Sequence generated by some rule based on hospital or clinic record number. Other non-random approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgement or some method of non-random categorization of participants, for example: Allocation by judgement of the clinician; Allocation by preference of the participant; Allocation based on the results of a laboratory test or a series of tests; Allocation by availability of the intervention.
Criteria for the judgement of 'Unclear risk' of bias.	Insufficient information about the sequence generation process to permit judgement of 'Low risk' or 'High risk'.
ALLOCATION CONCEALMENT **Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.**	
Criteria for a judgement of 'Low risk' of bias.	Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: Central allocation (including telephone, web-based and pharmacy-controlled randomization); Sequentially numbered drug containers of identical appearance; Sequentially numbered, opaque, sealed envelopes.
Criteria for the judgement of 'High risk' of bias.	Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: Using an open random allocation schedule (e.g. a list of random numbers); Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or nonopaque or not sequentially numbered); Alternation or rotation; Date of birth; Case record number; Any other explicitly unconcealed procedure.
Criteria for the judgement of 'Unclear risk' of bias.	Insufficient information to permit judgement of 'Low risk' or 'High risk'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement – for example if

	the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.
BLINDING OF PARTICIPANTS AND PERSONNEL **Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.**	
Criteria for a judgement of 'Low risk' of bias.	Any one of the following: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
Criteria for the judgement of 'High risk' of bias.	Any one of the following: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
Criteria for the judgement of 'Unclear risk' of bias.	Any one of the following: Insufficient information to permit judgement of 'Low risk' or 'High risk'; The study did not address this outcome.
BLINDING OF OUTCOME ASSESSMENT **Detection bias due to knowledge of the allocated interventions by outcome assessors.**	
Criteria for a judgement of 'Low risk' of bias.	Any one of the following: No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
Criteria for the judgement of 'High risk' of bias.	Any one of the following: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
Criteria for the judgement of 'Unclear risk' of bias.	Any one of the following: Insufficient information to permit judgement of 'Low risk' or 'High risk'; The study did not address this outcome.
INCOMPLETE OUTCOME DATA **Attrition bias due to amount, nature or handling of incomplete outcome data.**	
Criteria for a judgement of 'Low risk' of bias.	Any one of the following: No missing outcome data; Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; Missing data have been imputed using appropriate methods.
Criteria for the judgement of 'High risk'	Any one of the following: Reason for missing outcome data likely to be related to true outcome, with

of bias.	either imbalance in numbers or reasons for missing data across intervention groups; For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomization; Potentially inappropriate application of simple imputation.
Criteria for the judgement of 'Unclear risk' of bias.	Any one of the following: Insufficient reporting of attrition/exclusions to permit judgement of 'Low risk' or 'High risk' (e.g. number randomized not stated, no reasons for missing data provided); The study did not address this outcome.
SELECTIVE REPORTING **Reporting bias due to selective outcome reporting.**	
Criteria for a judgement of 'Low risk' of bias.	Any of the following: The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
Criteria for the judgement of 'High risk' of bias.	Any one of the following: Not all of the study's pre-specified primary outcomes have been reported; One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; The study report fails to include results for a key outcome that would be expected to have been reported for such a study.
Criteria for the judgement of 'Unclear risk' of bias.	Insufficient information to permit judgement of 'Low risk' or 'High risk'. It is likely that the majority of studies will fall into this category.
OTHER BIAS **Bias due to problems not covered elsewhere in the table.**	
Criteria for a judgement of 'Low risk' of bias.	The study appears to be free of other sources of bias.
Criteria for the judgement of 'High risk' of bias.	There is at least one important risk of bias. For example, the study: Had a potential source of bias related to the specific study design used; or Has been claimed to have been fraudulent; or Had some other problem.
Criteria for the judgement of 'Unclear risk' of bias.	There may be a risk of bias, but there is either: Insufficient information to assess whether an important risk of bias exists; or Insufficient rationale or evidence that an identified problem will introduce bias.

Methodology checklist: observational studies (AHRQ item bank; 4)

Q1: Do the inclusion/exclusion criteria vary across the comparison groups of the study*?*

Q2: Does the strategy for recruiting participants into the study differ across groups?

Q3: Is the selection of the comparison group inappropriate, after taking into account feasibility and ethical considerations?

Q4: Does the study fail to account for important variations in the execution of the study from the proposed protocol?

Q5: Was the outcome assessor not blinded to the intervention or exposure status of participants?

Q6: Were valid and reliable measures, implemented consistently across all study participants used to assess inclusion/exclusion criteria, intervention/exposure outcomes, participant health benefits and harms, and confounding?

Q7: Was the length of follow-up different across study groups?

Q8: In cases of high loss to follow-up (or differential loss to follow-up), was the impact assessed (e.g., through sensitivity analysis or other adjustment method)?

Q9: Are any important primary outcomes missing from the results?

Q10: Are any important harms or adverse events that may be a consequence of the intervention/exposure missing from the results?

Q11: Are results believable taking study limitations into consideration?

Q12: Any attempt to balance the allocation between the groups or match groups (e.g., through stratification, matching, propensity scores).

Q13: Were important confounding variables not taken into account in the design and/or analysis (e.g., through matching, stratification, interaction terms, multivariate analysis, or other statistical adjustment such as instrumental variables)?