# Cochrane's Editor in Chief responds to a *BMJ Evidence-Based Medicine* article criticizing the Cochrane Review of HPV vaccines

On 27th July 2018, an article was published in the journal *BMJ Evidence-Based Medicine* relating to the recently published Cochrane Review on prophylactic human papillomavirus (HPV) vaccines. The article is based on analyses undertaken at the Nordic Cochrane Centre, and two of the authors are experienced Cochrane researchers: Professors Peter Gøtzsche and Tom Jefferson. It made several criticisms of the Cochrane Review, most notable of which was that the Cochrane Review was incomplete due to missing "nearly half of the eligible trials".

Cochrane takes all criticisms and feedback seriously, seeing this as one mechanism among many to improve the quality of Cochrane Reviews. The organization has 10 long-standing principles that we hold dear, and they include a commitment to quality and the minimization of bias, transparency, and a recognition of the need for our work to be relevant to the needs of evidence users and decision makers. Cochrane aims to create the best current evidence to guide health decisions.

We initiated an investigation in response to the criticisms, working with the review authors and editors and with independent researchers who had not been involved in the original publication. The key findings of our investigation are that:

- The Cochrane Review did not miss "nearly half of the eligible trials". A small number of studies were missed due to the primary focus on peer-reviewed reports in scientific journals, but addition of these data makes little or no difference to the results of the review for the main outcomes;
- The trials comparators were unambiguously, transparently, and accurately described;
- The selection of outcomes for benefits was appropriate and was consistent with World Health Organization guidance;
- The review included published and unpublished data on serious harms, and the findings on mortality were reported transparently and responsibly;
- The review was compliant with Cochrane's current conflict of interest policy;
- Cochrane's media coverage was cautious and balanced, but we recognize that there could be improvements in relation to transparency where external experts are quoted;
- The *BMJ Evidence-Based Medicine* article substantially overstated its criticisms.

**David Tovey**, Editor in Chief, Cochrane

**Karla Soares-Weiser**, Deputy Editor in Chief, Cochrane

Trusted evidence.
Informed decisions.
Better health.

# Contents

# Executive summary

On 27th July 2018, an article was published in the journal *BMJ Evidence-Based Medicine* relating to the recently published Cochrane Review on prophylactic human papillomavirus (HPV) vaccines.[1,2] The article, by Jørgensen et al, is based on analyses undertaken at the Nordic Cochrane Centre, and two of the authors are experienced Cochrane researchers: Professors Peter Gøtzsche and Tom Jefferson. It made several criticisms of the Cochrane Review, most notable of which was that the review was incomplete due to "missing nearly half of the eligible trials".

Cochrane takes all criticisms and feedback seriously, seeing this as one mechanism among many to improve the quality of Cochrane Reviews. The organization has ten long-standing principles that we hold dear, and they include a commitment to quality and the minimization of bias, transparency, and a recognition of the need for our work to be relevant to the needs of evidence users and decision makers. Cochrane aims to create the best current evidence to guide health decisions.

When the Cochrane Review on HPV vaccines was published in May 2018 we were confident that it had been conducted and reported in a manner consistent with the published protocol and with Cochrane's expectations or standards. We believed that the conclusions were an accurate reflection of the results and the analyses. Therefore, we were surprised to see the issues raised by Jørgensen et al, and we initiated an investigation immediately, working with the Cochrane Review authors and editors and with systematic reviewers who had not been involved in the review. Here we present the findings of our investigation, our responses to the most important issues raised by Jørgensen et al, and our plans for the review, including a proposal to incorporate missing data. The *BMJ Evidence-Based Medicine* article reinforces work that forms a key element of Cochrane's Content Strategy in relation to the selection of data sources for reviews.

Following the publication of the criticisms, we contacted two of the authors (Gøtzsche, Jørgensen) requesting details of the list of the 20 "potentially eligible" missing studies they had identified, based on the inclusion criteria of the Cochrane Review. Given the central focus on this issue, we were surprised that this list was not included as an appendix to the article in *BMJ Evidence-Based Medicine*. When we receive this list, we will be able to cross-reference it with the findings of our own investigation.

The key findings of our investigation of the criticisms by Jørgensen and colleagues are that:

- The Cochrane Review did not miss "nearly half of the eligible trials". A small number of studies were missed due to the primary focus on peer-reviewed reports in scientific journals, but addition of these data makes little or no difference to the findings of the review for the main outcomes (see Appendix A);
- The trials comparators were unambiguously, transparently, and accurately described;
- The selection of outcomes for benefits was appropriate and was consistent with World Health Organization guidance;
- The review included published and unpublished data on serious harms, and the findings on mortality were reported transparently and responsibly;
- The review was compliant with Cochrane's current conflict of interest policy;
- Cochrane's media coverage was cautious and balanced, but we recognize that there could be improvements in relation to transparency where external experts are quoted;
- The *BMJ Evidence-Based Medicine* article substantially overstated its criticisms.

We regret that the authors, who are all members and officeholders within Cochrane, did not share their analysis or the conclusions and criticisms contained in the *BMJ Evidence-Based Medicine* article before publication. Having completed our investigation, we conclude that Jørgensen et al made allegations that are not warranted and provided an inaccurate and sensationalized report of their analysis. We believe that there are questions to be asked about the rigour of the peer review and editorial review by *BMJ Evidence-Based Medicine*. We call on BMJ to consider our report and to investigate whether the journal's quality assurance processes were appropriately fulfilled and whether the conclusions of the article are justified and proportionate. This is particularly important given the highly sensitive subject matter and the public health priority of this subject.

# Background to the Cochrane Review

Cervical cancer is the fourth most common cancer in women. Half a million women are diagnosed with cervical cancer each year, and half of these women will die from their disease. Eighty-five percent of those with cervical cancer are in low- and middle-income countries, where screening and therapeutic services are most likely to be challenged.[3] The large majority of these cancers are causally associated with HPV infection. This is not, therefore, an inconsequential academic debate but a serious global public health issue. Like the authors of the *BMJ Evidence-Based Medicine* article, the authors and editors of the Cochrane Review want to paint as accurate a picture of the effects of the HPV vaccines as possible, to inform individual and community-based decisions.

The Cochrane Review authors and editorial team adhered closely to the methods and guidance described in the *Cochrane Handbook for Systematic Reviews of Interventions* and the Methodological Expectations of Cochrane Intervention Reviews (MECIR) standards for conduct and reporting of such reviews. The methods were comprehensively described in the review protocol, which was peer-reviewed and was published in December 2013. The protocol described the 'PICO' (Population, Intervention, Comparison, Outcomes) characteristics for the review and the means of identifying studies and data.

In the published Cochrane Review, the authors relied predominantly on the published and peer-reviewed reports in scientific journals for most outcomes of interest. Given the importance of an assessment of serious adverse events and mortality, the author team accepted the suggestion of Cochrane editors to extend the search for these outcomes to include unpublished data. This post-protocol change is explained in the appropriate section of the review. In these matters, the author team's decisions were consistent with most reviews that were initiated during the period of the review's gestation, and they were consistent with Cochrane's expectations. The screening of unpublished sources for serious adverse events was a collaborative effort between the author team and the Cochrane Editorial and Methods Department.

# The Cochrane Review did not miss "nearly half of the eligible trials"

The HPV vaccine study index prepared by Jørgensen and colleagues is complex, and we acknowledge the investment that has gone into its preparation.[4] The index contained 298 references, 100 of them duplicate records, and reported 137 unique randomized trials (see Figure 1).

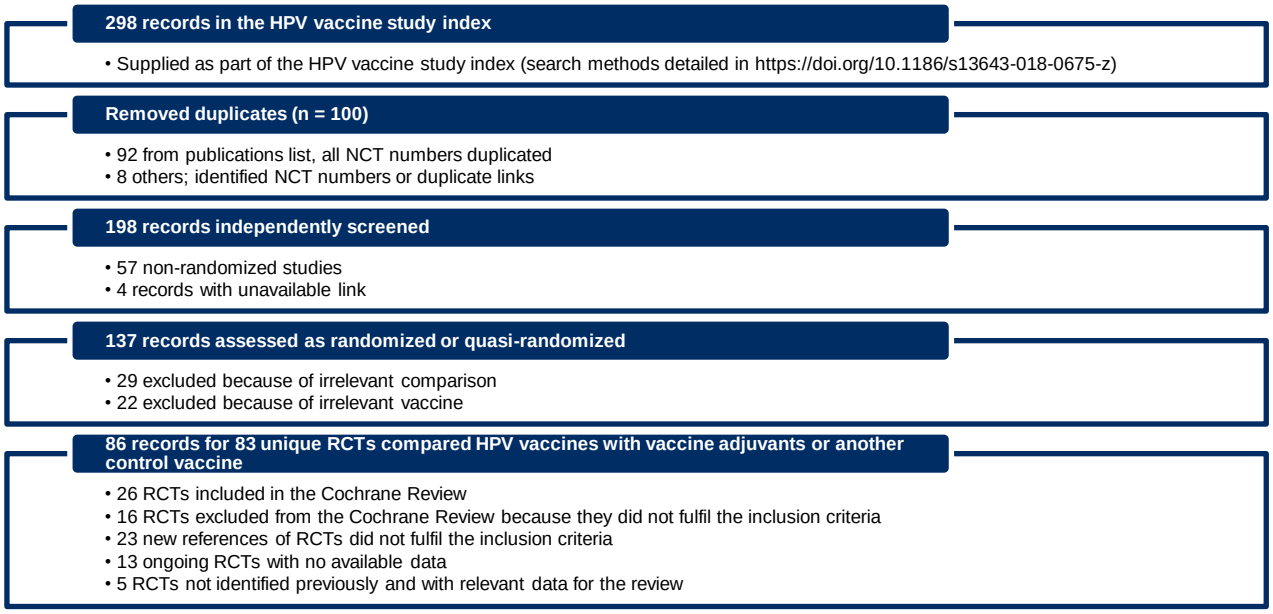


**Figure 1: Flowchart investigating the relationship between the HPV vaccine studies4 index and the Cochrane Review of HPV vaccines2**

As part of our investigation two systematic reviewers independently assessed 137 potentially relevant randomized trials from the index. Of these, 83 trials compared HPV vaccines with vaccine adjuvants or another control vaccine (see Figure 1). The Cochrane Review included 26 trials (73,428 participants) that matched the predetermined study criteria. As a result of our investigations we believe that five eligible completed studies with available data representing 5267 women may have been missed from the Cochrane Review, as a consequence of the search being based on bibliographic databases rather than trials registers. Details of these studies are available in Appendix B. This finding contrasts with the calculation of 20 studies (48,276 women) missed, as suggested by Jørgensen et al in their *BMJ Evidence-Based Medicine* article. Once we have the data from the authors we will seek to understand the difference between these assessments. This might relate to differential understanding of the selection criteria used by the Cochrane authors or to some studies still actively recruiting participants.

The Cochrane Review authors assessed and excluded a phase IV cluster randomized study comparing HPV and hepatitis B vaccines in boys and girls.[5] We have cross-checked the data in women, now published on the GSK Study Register, which includes data on serious adverse events and pregnancy outcomes. Adding these data to the analyses seems to make little or no difference to the results of the Cochrane Review, but the review update process will enable a more formal appraisal of the evidence using the GRADE process. In addition, 13 studies from the HPV index are ongoing and will be assessed for relevance once the results are available (See Appendices C and D).

We do not underestimate the importance of these missing data, but the figure of missed studies amounts to substantially less than "nearly half the eligible trials", and we submit that in making statements such as this, accuracy matters.

We have now had the opportunity to examine what difference the missing data based on the review inclusion criteria make to future iterations of the Cochrane Review (see Appendix A). For transparency, we also analysed the potential impact of adding data on the 9-valent HPV vaccine.

In summary, adding the studies that were missed by limiting the search to published study reports had no impact on the direction of effect for all outcomes reported. A single study comparing the 9-valent vaccine with placebo (924 participants) showed an increase in local adverse events but no impact on systemic or serious adverse events and deaths (see Appendix A). This trial enrolled only women recruited previously in another trial evaluating the quadrivalent vaccine.

We have made the current version of the review freely available, and we will be updating the review urgently to incorporate all the relevant, publicly available data. This was anticipated by the Cochrane Review authors in the 'Implications for research' section of the Cochrane Review and work has already begun.

# The trials comparators were transparently and accurately described

The *BMJ Evidence-Based Medicine* article also raised some concerns about the comparators used in the various trials, which were aluminium based, as described clearly in both the Abstract and Methods sections of the Cochrane Review, and also in the detailed 'Characteristics of included studies' section of the review. For example, under 'Criteria for considering studies for this review' the 'Comparison' is described as: "Administration of placebo containing no active product or only the adjuvant of the HPV vaccine, without L1 VLP, or another non-HPV vaccine".

We recognize that the use of aluminium salts as an adjuvant in vaccines is controversial, and that some groups argue that the controls in the studies should have received water or saline to prevent masking of harms caused by the administration of aluminium salts to both groups in the studies. The Cochrane Review is not an analysis of the possible benefits and harms of aluminium-based adjuvants. Suffice to say that almost all the studies included the use of aluminium salts in the comparator. We consider that this was reported appropriately within the review, but if there are ways of further clarifying this we will be pleased to consider these.

We note that one of the authors of the *BMJ Evidence-Based Medicine* article (Jefferson) published a systematic review in 2004 that found "no evidence" of serious or long-term harms and concluded that further research was not warranted.[6] Despite this, we note that a new Cochrane Review re-examining the safety of aluminium within all vaccines is underway.[7]

# The selection of outcomes for benefits was appropriate

The use of surrogate outcomes in the HPV vaccine trials is, as Jørgensen et al note, "in line with WHO recommendations". This was explained by the authors in the Cochrane Review. Transition from CIN 2 and CIN 3 to cancer is not inevitable if untreated, but it is a clear risk, and for this reason both of these interim states are subject to treatment, which carries its own morbidity. The risk of progression to cancer increases as the lesions progress. Cervical cancer is a malignancy that can be prevented effectively through detection and treatment of the precursor states. Plainly there is no ethical means by which researchers could leave untreated the presence of the precursor states, so that the near complete absence of cervical cancer in any arm of the trials is inevitable. In our judgement it is impossible to see how it could be feasible or ethical to undertake a trial that was large enough and of sufficient duration for cancer outcomes to be reliably demonstrated and where women were denied interventions that are known to prevent cancer.

# The review included published and unpublished data on serious harms, and reported the findings on mortality transparently and responsibly

In making their assessment of serious harms, the Cochrane Review authors identified and included unpublished data, and compared these with data from published trial reports. Jørgensen et al claim that the review authors made an error in their reporting of serious adverse events in relation to the PATRICIA study. This is not the case. We have checked the data presented in the Cochrane Review against the reports on ClinicalTrials.gov and the GSK Study Register, and the figures accurately match the number of women experiencing one or more serious adverse events.

In addition, as Jørgensen et al note, the review authors identified and reported the excess of deaths in the older vaccinated women, in both relative and absolute terms, within the Abstract of the review as well as in the main body of the text. We judged it important to present the data transparently, but also to provide further context to ensure responsible reporting. The assessment by World Health Organization experts and the data on the causes of death provide no clear causal mechanism or link with the vaccine. We judged that readers would find this information useful and that its inclusion was appropriate.

Otherwise the reporting of other harms was, as described in the protocol, limited to the published peer-reviewed reports from randomized controlled trials. This is not unusual for systematic reviews from Cochrane or elsewhere.

In relation to harms more generally, we acknowledge that there is a case for including other forms of evidence. The 'Discussion' section of the Cochrane Review and the accompanying Editorial both noted the importance of national surveillance programmes to identify and report harms.[2,8] This is particularly true when it comes to harms such as autonomic dysfunction syndromes and other syndromes that are not reported (positively or negatively) in most of the journal-published reports, but about which concerns have been raised subsequently from observational reports. This underlines the importance of systematic reviews being used in conjunction with the evidence from national surveillance programmes.

Finally, we believe that this Cochrane Review has raised broader questions for Cochrane in relation to reporting harms. We propose to initiate work aimed at providing updated guidance for author teams on identifying and reporting harms in the current and future data and research environment, as part of our ongoing implementation of Cochrane's content strategy.

# The review was compliant with Cochrane's current conflict of interest policy

Cochrane has had rules in place since 2004 aimed at preventing its reviews from either the fact or perception of inappropriate involvement or influence by commercial organizations. The rules were last updated in 2014. A key feature of Cochrane's approach is that declaration of relevant conflicting interests is essential but may not be sufficient. In specific circumstances individuals are barred from involvement as part of an author team, and the lead author and a majority of any

Cochrane Review author team must not have a relevant conflict. The job of overseeing the implementation of the policy falls to an appointed Funding Arbiter (currently a job share), reporting directly to the Governing Board. The Funding Arbiter, working with a panel of experts, some of who are external to the organization, arbitrates in disputed or borderline cases.

In relation to the HPV vaccines review, Cochrane received comments following the publication of the protocol stating that the intended author team was not compliant with Cochrane's financial conflict of interest policy. The first author had invited a team of HPV vaccination trialists, with the purpose of helping to obtain unpublished data. All these experts had declared their conflicts, but their inclusion made the author team non-compliant with Cochrane's policy. We therefore made changes that ensured the work of the review was undertaken by a team whose members were fully compliant and actively involved in the conduct of the review.

Jørgensen et al also stated that the lead author of the review leads the European Medicine Agency's post-marketing surveillance and linked this to funding from a manufacturer. In fact, Professor Arbyn took the initiative to introduce a surveillance study in his country after having been informed that the European Medicine Agency had approved the Gardasil vaccine, remarking that the post-marketing surveillance conducted in Northern Europe was relevant but should include also non-Nordic countries. Professor Arbyn is not funded by the European Medicine Agency nor by any vaccine manufacturer.

In relation to the sponsorship of the studies, Jørgensen et al stated that the Costa Rica trial was not, as stated in the Cochrane Review, publicly funded but was funded by GlaxoSmithKline. This is not the case, as noted in the conflict of interest declaration in the published report of the study in *JAMA*.[9] This states that the trial was "funded by the NCI (grant N01-CP-11005), with funding support from the National Institutes of Health Office for Research on Women's Health and conducted with support from the Ministry of Health of Costa Rica. Vaccine was provided for our trial by GSK Biologicals, under a Clinical Trials Agreement with the NCI."

## Cochrane's media coverage was cautious and balanced, but we recognize that there could be improvements in relation to transparency where external experts are quoted

Cochrane makes strenuous efforts in its media coverage to present conclusions and implications for practice and research from its reviews in a balanced and measured way. The reference to the Science Media Centre round-up of scientific reaction in the *BMJ Evidence-Based Medicine* article reflects simply a response from representatives of public bodies, sought from an independent organization focussed on the benefits of accurate, evidence-based science coverage in the news media. None of the individuals quoted were sought or contacted by Cochrane. Our press and communications teams acknowledge that the source of any future 'scientific reaction' to published reviews or press coverage could be made more explicit on our organizational websites and other communications, essentially noting that these opinions represent personal perspectives from a range of contributors and do not reflect the views or policies of Cochrane.

# Conclusion: the *BMJ Evidence-Based Medicine* article overstated its criticism

We take very seriously the implications of Cochrane's strapline: 'Trusted evidence. Informed decisions. Better health.'. Our investigation has sought to explore whether in publishing the review of HPV vaccines we had failed to meet the standard implied in that statement of intent. Our conclusion, based on a thorough investigation, is that that the review provides a fair basis for evidence-informed decision making.

Some of the criticisms will inform the next version of this Cochrane Review and the planned review of comparative studies of HPV vaccines.

In our judgement, the criticisms were overstated. For example, the potentially missing studies do not seem to represent anywhere close to "half of the eligible studies". We have analysed the publicly available data from the missing studies, and we believe that including them would make no material difference to the Cochrane Review's results and conclusions (see Appendix A).

We plan to ensure that all relevant studies and associated data are incorporated into an updated version of the review, and we will complete this work urgently. We will also cross-reference the results of our investigation findings against data from the Jørgensen et al to try to understand the discrepancy between the two analyses, and we will seek to identify and report all ongoing studies.

In addition, we believe that the selection of outcomes was appropriate to guide decision making. We recognize public concerns about the aluminium-based adjuvants but judge that this is better addressed by a separate Cochrane Review. We are not aware of compelling evidence of serious harm caused by the adjuvants.

In summary, we believe that the Cochrane Review represents a robust and accurate summary of the evidence.

Scientific debate is to be welcomed, and differences of opinion between different Cochrane 'voices' is not unexpected. However, public confidence may be undermined, unnecessary anxiety caused, and public health put at risk, if that debate is not undertaken in an appropriate way. This is especially true when such debates take place in public. There is already a formidable and growing anti-vaccination lobby. If the result of this controversy is reduced uptake of the vaccine among young women, this has the potential to lead to women suffering and dying unnecessarily from cervical cancer.

The article in *BMJ Evidence-Based Medicine* highlights issues that go beyond the HPV review and which have been the subject of many discussions. In recent years, evidence synthesis researchers in Cochrane and elsewhere have recognized that reliance on the published reports in scientific journals may introduce bias due to incomplete and selective reporting. In addition, the generally poor reporting of harms in reports from randomized controlled trials has led to the reporting of harms in many systematic reviews being sub-optimal. This has led to an increased interest in searching for and identifying studies, reports and data from different and more diverse sources, including clinical study reports and individual participant data from trials, data from trials registries, and non-randomized studies. This has consequences that reach well beyond Cochrane, as shown by a report by Page et al in 2016 comparing the quality of reporting in Cochrane and non-Cochrane systematic reviews.[10] This study found that 62% of Cochrane Reviews searched trials registers, compared with 20% for non-Cochrane reviews. These additional or expanded searches may add value in selected circumstances, but they all also add substantially to the resources needed to

complete the review and are a challenge to Cochrane's traditional model of reliance on unfunded 'volunteer' authors, who have been the engine of the organization for 25 years.

Therefore, it is true to say that both inside and outside Cochrane, the conduct and reporting of systematic reviews is changing. This is fully reflected in Cochrane's recently approved content strategy, which sets targets and objectives around exploring when and how these additional sources of data should be utilized. This work builds on exploratory work funded by Cochrane and is a key part of our strategy for the future Cochrane Review.

**David Tovey**, Editor in Chief, Cochrane

**Karla Soares-Weiser**, Deputy Editor in Chief, Cochrane

Monday 3rd September 2018

# Acknowledgements

The following people contributed to this report:

**Marc Arbyn**, Epidemiologist, Belgian Cancer Centre (co-author of the Cochrane Review)

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**Lan Xu**, Research Assistant, Belgian Cancer Centre (co-author of the Cochrane Review)

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# Appendix A: Effect of incorporating data extracted from five missing studies on the findings of the Cochrane Review

RR = risk ratio; CI = confidence interval; RCT = randomized controlled trial

### Any HPV vaccine

| Main outcome | Current Cochrane Review | New data incorporated |
|---|---|---|
| Spontaneous abortion/miscarriage (analysis 8.2) | RR 0.88 (95% CI 0.68 to 1.14)<br>$I^2$ = 78% | RR 0.89 (95% CI 0.69 to 1.14)<br>$I^2$ = 76% |

### Bivalent vaccine

| Main outcome | Current Cochrane Review | New data incorporated |
|---|---|---|
| Pain at injection site (analysis 7.2.2) | RR 1.49 (95% CI 1.26 to 1.75)<br>$I^2$ = 98% | RR 1.46 (95% CI 1.26 to 1.68)<br>$I^2$ = 98% |
| Redness at injection site (analysis 7.4.2) | RR 1.80 (95% CI 1.53 to 2.11)<br>$I^2$ = 76% | RR 1.71 (95% CI 1.47 to 2.07)<br>$I^2$ = 76% |
| Swelling at injection site (analysis 7.3.1) | RR 1.62 (95% CI 1.15 to 2.29)<br>$I^2$ = 81% | RR 1.51 (95% CI 1.10 to 2.13)<br>$I^2$ = 95% |
| Serious adverse events (analysis 7.6.2) | RR 1.01 (95% CI 0.96 to 1.07)<br>$I^2$ = 0% | RR 1.01 (95% CI 0.96 to 1.07)<br>$I^2$ = 0% |
| Overall local/injection site adverse events (analysis 7.1.1) | RR 1.29 (95% CI 1.26 to 1.33)<br>$I^2$ = 98% | RR 1.29 (95% CI 1.25 to 1.33)<br>$I^2$ = 95% |
| Overall systemic event and general symptoms (analysis 7.5.1) | RR 1.07 (95% CI 0.97 to 1.19)<br>$I^2$ = 91% | RR 1.06 (95% CI 0.97 to 1.15)<br>$I^2$ = 83% |
| Deaths (analysis 7.7.2) | RR 1.21 (95% CI 0.66 to 2.22) | RR 1.21 (95% CI 0.66 to 2.22) |

| Main outcome | Current Cochrane Review | New data incorporated |
|---|---|---|
| | $I^2$ = 15% | $I^2$ = 15% |

**Quadrivalent vaccine**

| Main outcome | Current Cochrane Review | New data incorporated |
|---|---|---|
| Pain at injection site (analysis 7.2.3) | RR 1.13 (95% CI 1.07 to 1.19)<br>$I^2$= 33% | RR 1.20 (95% CI 1.10 to 1.32)<br>$I^2$ = 74% |
| Redness at injection site (analysis 7.4.1) | RR 1.46 (95% CI 1.32 to 1.63)<br>1 RCT (659/2673; 450/2672) | RR 1.44 (95% CI 1.31 to 1.59)<br>$I^2$ = 0% |
| Swelling at injection site (analysis 7.3.2) | RR 2.79 (95% CI 0.85 to 9.15)<br>$I^2$ = 82% | RR 2.08 (95% CI 1.54 to 2.83)<br>$I^2$ = 64% |
| Serious adverse events (analysis 7.6.3) | RR 0.81 (95% CI 0.65 to 1.02)<br>$I^2$ = 10% | RR 0.83 (95% CI 0.68 to 1.00)<br>$I^2$ = 0% |
| Deaths (analysis 7.7.3) | RR 1.54 (95% CI 0.73 to 3.23)<br>$I^2$ = 0% | RR 1.65 (95% CI 0.80 to 3.38)<br>$I^2$ = 0% |
| CIN2+ associated with HPV 6/11/16/18, at least one dose (analysis 3.2) | RR 0.57 (95% CI 0.38 to 0.86)<br>$I^2$ = 54% | RR 0.54 (95% CI 0.30 to 0.95)<br>$I^2$ = 61% |
| Persistent HPV16/18 infection (12M), at least one dose (analysis 6.4) | RR 0.46 (95% CI 0.40 to 0.54)<br>$I^2$ = 42% | RR 0.41 (95% CI 0.29 to 0.57)<br>$I^2$ = 81% |
| Persistent HPV16/18 infection (6M), at least one dose (analysis 6.2) | RR 0.48 (95% CI 0.41 to 0.57)<br>$I^2$ = 69% | RR 0.48 (95% CI 0.41 to 0.56)<br>$I^2$ = 61% |
| Persistent HPV6/11/16/18 infection (6M), at least one dose (analysis 6.3) | RR 0.52 (95% CI 0.42 to 0.65)<br>1 RCT (110/1856; 211/1857) | RR 0.40 (95% CI 0.19 to 0.81)<br>$I^2$ = 67% |

| Main outcome | Current Cochrane Review | New data incorporated |
|---|---|---|
| Overall local/injection site adverse events (analysis 7.1.2) | RR 1.14 (95% CI 1.12 to 1.16)<br><br>$I^2$ = 54% | RR 1.14 (95% CI 1.12 to 1.16)<br><br>$I^2$ = 68% |
| Overall systemic event and general symptoms (analysis 7.5.2) | RR 1.01 (95% CI 0.98 to 1.04)<br><br>$I^2$ = 0% | RR 1.01 (95% CI 0.98 to 1.04)<br><br>$I^2$ = 0% |

**9-valent vaccine**

| Main outcome | Current Cochrane Review | New data incorporated |
|---|---|---|
| Pain at injection site (analysis 7.2.2) | Not included | RR 2.37 (95% CI 2.05 to 2.75)<br><br>1 RCT (549/608; 116/305) |
| Redness at injection site (analysis 7.4.2) | | RR 4.96 (95% CI 3.39 to 7.24)<br><br>1 RCT (257/608; 26/305) |
| Swelling at injection site (analysis 7.3.1) | | RR 8.31 (95% CI 5.27 to 13.10)<br><br>1 RCT (298/608; 18/305) |
| Serious adverse events (analysis 7.6.2) | | RR 0.50 (95% CI 0.10 to 2.47)<br><br>1 RCT (3/608; 3/305) |
| Deaths (analysis 7.7.2) | | Not estimable<br><br>1 RCT (0/608; 0/305) |
| Overall systemic event and general symptoms (analysis 7.5.3) | | RR 1.07 (95% CI 0.95 to 1.21)<br><br>1 RCT (363/608; 170/305) |
| Overall local/injection site adverse events (analysis 7.1.3) | | RR 2.07 (95% CI 1.82 to 2.36)<br><br>1 RCT (554/608; 134/305) |

# Appendix B: Characteristics of the additional studies identified in the HPV vaccine study index that met the inclusion criteria of the Cochrane Review

**NCT01627561**

| | |
|---|---|
| **Methods** | Phase III, randomized, controlled, single-blind, multicentre study |
| **Participants** | Participants: 148 healthy girls (74 in each group) enrolled in 7 study centres from 3 countries (Colombia, Mexico, Panama).<br><br>Age range: 4 to 6 years.<br><br>Inclusion criteria: healthy girls who had previously received 4 doses of a DTP (diphtheria, tetanus, poliomyelitis)-containing vaccine (3 doses in 1st year of life and 4th dose in 2nd year of life) and only 1 dose of the measles-mumps-rubella (MMR) vaccine, in their 2nd year of life.<br><br>Exclusion criteria: previous vaccination against HPV; any other confirmed or suspected immunosuppressive condition; other illness. |
| **Interventions** | Vaccine: AS04-HPV-16/18 vaccine - 2-dose schedule at 0 and 6 months.<br><br>Comparator: 1 dose of MMR (Priorix, GSK) vaccine at 0 months and 1 dose of the diphtheria-tetanus-acellular-pertussis (DTPa; Infanrix, GSK) vaccine at 6 months. |
| **Outcomes** | Safety and immunogenicity outcomes |
| **Notes** | Main report: Lin 2018<br><br>Last report average follow-up time: serious adverse events to 6 months after second vaccination. Immunogenicity to 12 months after baseline in last report (follow up at 18, 24, and 36 months planned). |

**Risk of bias**

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| **Random sequence generation (selection bias)** | Low risk | Treatment allocation at the investigator site was performed using a central randomization system on Internet. |

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| **Allocation concealment (selection bias)** | Low risk | Treatment allocation at the investigator site was performed using a central randomization system on Internet. |
| **Blinding of participants and personnel (performance bias)** | High risk | The study was single-blind up to 6 months after the completion of the vaccination course |
| **Blinding of outcome assessment (detection bias)** | Unclear risk | Not described in the paper. |
| **Incomplete outcome data (attrition bias)** | Low risk | Outcomes assessed in the total vaccinated cohort. None of the girls in the HPV group were withdrawn up to the M12 visit. Three girls from the control group were withdrawn from the study. Reasons for exclusions were presented. |
| **Selective reporting (reporting bias)** | Low risk | All outcomes (safety and immunogenicity) are presented, in line with trial registration and results in registry. |

**NCT00834106**

| | |
|---|---|
| **Methods** | Phase III, randomized, placebo-controlled, double-blind study |
| **Participants** | Participants: 3006 healthy females (1503 in each group) were enrolled at 6 trial centres in China.<br><br>Age range: 20 to 45 years.<br><br>Inclusion criteria: healthy women who have used effective contraception for 2 weeks prior to starting in the study and do not have a temperature within 24 hours before the first injection.<br><br>Exclusion criteria: prior history of genital warts; more than 4 lifetime sexual partners; have undergone hysterectomy; have active cervical disease or history of cervical disease. |
| **Interventions** | Vaccine: quadrivalent HPV (types 6, 11, 16, 18) recombinant vaccine at 0, 2, and 6 months.<br><br>Control: saline injection containing aluminium diluent at 0, 2, and 6 months. |

| | |
|---|---|
| **Outcomes** | Safety outcomes (adverse events and pregnancy outcomes) and efficacy outcomes (HPV-related persistent infection and vaccine type-specific genital diseases). |
| **Notes** | Main report: Merck Sharp & Dohme 2017 confidential report.<br><br>Last report average follow-up time: 92% of participants were followed to 30 months, 86.6% to 90 months. |

### Risk of bias

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| **Random sequence generation (selection bias)** | Unclear risk | Not reported |
| **Allocation concealment (selection bias)** | Unclear risk | Not reported |
| **Blinding of participants and personnel (performance bias)** | Unclear risk | Stated as double-blind, but details not reported. |
| **Blinding of outcome assessment (detection bias)** | Unclear risk | Stated as double-blind, but details not reported. |
| **Incomplete outcome data (attrition bias)** | Low risk | Low attrition: 92% of participants were followed to 30 months, 86.6% to 90 months. |
| **Selective reporting (reporting bias)** | Low risk | All outcomes (safety and efficacy) are reported, in line with trial registration. |

### NCT00411749

| | |
|---|---|
| **Methods** | Phase II randomized, double-blind, controlled trial |
| **Participants** | Participants: 107 pre-adolescent females (82 in the vaccine arm and 25 in the placebo arm) enrolled in 8 sites in Japan.<br><br>Age range: 9 to 17 years.<br><br>Inclusion criteria: virginal female subject aged 9 to 17 years.<br><br>Exclusion criteria: male subject. |
| **Interventions** | Vaccine: HPV6/11/16/18 vaccine (Gardasil) recombinant vaccine (V501), 0.5 mL injection in 3-dose regimen (at day 1, month 2, and month 6).<br><br>Placebo: unspecified placebo vaccination 0.5 mL injection in 3-dose regimen (at day 1, month 2, and month 6). |

| | |
|---|---|
| **Outcomes** | Immunogenicity, safety, and tolerability outcomes. |
| **Notes** | Immunogenicity evaluated at month 7 (1 month after last dose) and month 30 (24 months after last dose). Adverse event data were collected from the entire period of the study (to month 7). Other non-serious adverse events data were collected from day 1 to day 15 following vaccination.<br><br>There is a plan to share individual participant data:<br><br>http://www.merck.com/clinical-trials/pdf/Merck%20Procedure%20on%20Clinical%20Trial%20Data%20Access%20Final_Updated%20July_9_2014.pdf<br><br>http://engagezone.msd.com/ds_documentation.php |

### Risk of bias

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| **Random sequence generation (selection bias)** | Unclear risk | Not described in the NCT record. |
| **Allocation concealment (selection bias)** | Unclear risk | Not described in the NCT record. |
| **Blinding of participants and personnel (performance bias)** | Low risk | The participants and investigator were blinded to the allocated trial arm. |
| **Blinding of outcome assessment (detection bias)** | Unclear risk | Not described in the NCT record |
| **Incomplete outcome data (attrition bias)** | Low risk | The per-protocol immunogenicity population includes all subjects who were not general protocol violators, received all 3 vaccinations within acceptable day ranges, were seronegative at day 1 for the relevant HPV type, and a month 7 serum sample collected within an acceptable time range.<br><br>Vaccine: completed at 24 months after vaccination series (month 30). Subjects were followed until month 30.<br><br>Placebo: Completed at 1 month after vaccination series (month 7). Subjects were followed until month 7. |
| **Selective reporting (reporting bias)** | Low risk | All outcomes (immunogenicity, safety and tolerability) were presented. |

### NCT01489527

| | |
|---|---|
| **Methods** | Phase II randomized, double-blind, controlled trial |
| **Participants** | Participants: 406 females (205 in the vaccine arm and 201 in the placebo arm) enrolled in the Western Cape, South Africa.<br><br>Age range: 16 to 24 years.<br><br>Inclusion criteria: HIV-negative women aged 16 to 24 years of age who reported: having vaginal intercourse; had never had Pap testing or had only normal results; had no autoimmune disease requiring steroid use; never had a splenectomy; not currently enrolled in an HIV prevention trial; no IV drug or crystal methylamphetamine use in the past 6 months.<br><br>Exclusion criteria: women who have a history of severe allergic reaction, have a known allergy to any vaccine component (e.g., aluminium, yeast, or benzonase), are currently immuno-compromised, have received a marketed HPV vaccine, or are pregnant and lactating. |
| **Interventions** | Vaccine: HPV6/11/16/18 vaccine (Gardasil) in 3 dosing regimen (at day 1, month 2, and month 6)<br><br>Placebo: saline placebo vaccination in 3 dosing regimen (at day 1, month 2, and month 6) |
| **Outcomes** | Efficacy (prevention of HIV infection and prevalence of sexually transmitted infections, including HPV genotypes), compliance (through the 3-dose vaccination series), and safety outcomes. |
| **Notes** | Four of the 406 participants randomized had a false HIV-negative test result, reducing the participants to 202 in the Gardasil arm and 200 in the placebo arm.<br><br>Main reports: Giuliano 2015 and Sudenga 2017.<br><br>Findings may not be generalizable to all South African women.<br><br>The EVRI trial had a short duration with limited follow-up time (up to 7 months), so clinical efficacy in reducing HIV acquisition cannot be assessed. |

### Risk of bias

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| **Random sequence generation (selection bias)** | Unclear risk | Not described in the papers. |

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| **Allocation concealment (selection bias)** | Unclear risk | Not described in the papers. |
| **Blinding of participants and personnel (performance bias)** | Low risk | The participants, care providers, and investigator were blinded to the allocated trial arm. |
| **Blinding of outcome assessment (detection bias)** | Low risk | All staff and study investigators were blinded to participants' vaccine status except the pharmacist dispensing the vaccine. |
| **Incomplete outcome data (attrition bias)** | Low risk | Among randomized participants, 91% completed the 3-dose vaccination series, with pregnancy being the predominant reason for trial discontinuation. |
| **Selective reporting (reporting bias)** | Low risk | All outcomes (efficacy, compliance and safety) were presented. |

**NCT01356823**

| | |
|---|---|
| **Methods** | Phase II randomized, double-blind, controlled trial |
| **Participants** | Participants: 1600 females (400 in the 30 μg vaccine arm, 400 in the 60 μg vaccine arm, 400 in the 90 μg vaccine arm, and 400 in the control arm) enrolled in Dongtai County, Jiangsu Province, China.<br><br>Age range: 18 to 25 years.<br><br>Inclusion criteria: Healthy female 18 to 25 years of age, not pregnant and having no plan for pregnancy.<br><br>Exclusion criteria: Pregnant or breastfeeding or having plan for pregnancy during the whole study (months 0 to 7); previous vaccination against HPV; severe allergic history or other immunodeficiency; using chemotherapy or other immunosuppressive agents. |
| **Interventions** | Vaccine: 30 μg of HPV16/18 bivalent vaccine at 0, 1, 6 months for 3 doses.<br><br>Vaccine: 60 μg of HPV16/18 bivalent vaccine at 0, 1, 6 months for 3 doses.<br><br>Vaccine: 90 μg of HPV16/18 bivalent vaccine at 0, 1, 6 months for 3 doses. |

| | |
|---|---|
| | Control: 10 μg of hepatitis B vaccine at 0, 1, 6 months for 3 doses. |
| **Outcomes** | Immunogenicity and safety outcomes. |
| **Notes** | Main report: Wu 2015.<br><br>Last report average follow-up time: 7 months. |

### Risk of bias

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| **Random sequence generation (selection bias)** | Low risk | Randomization schedule was computer generated. |
| **Allocation concealment (selection bias)** | Low risk | The individuals involved in the randomization and masking did not participate in any other part of the trial. |
| **Blinding of participants and personnel (performance bias)** | Low risk | All the participants and investigators were masked to the treatment allocation. |
| **Blinding of outcome assessment (detection bias)** | Low risk | All the participants and investigators were masked to the treatment allocation. |
| **Incomplete outcome data (attrition bias)** | Low risk | 91.4% of the enrolled participants received all the 3 doses per protocol; the rates of drop-out were similar among the 4 groups. None of the recorded reasons for drop-out was associated with adverse events. |
| **Selective reporting (reporting bias)** | Low risk | All outcomes (safety and immunogenicity) are presented, in line with trial registry. |

### Additional 9-valent study

#### NCT01047345

| | |
|---|---|
| **Methods** | Phase III randomized, double-blind, controlled trial |
| **Participants** | Participants: 924 women (618 in the vaccine arm and 306 in the placebo arm) enrolled in 32 study sites in 8 countries.<br><br>Age range: 12 to 26 years. |

| | |
|---|---|
| | Inclusion criteria: women who had previously received a 3-dose regimen of the quadrivalent vaccine; generally healthy.<br><br>Exclusion criteria: history of abnormal Pap test results; pregnancy; known allergy to any vaccine component; thrombocytopenia; immunosuppression/previous immunosuppressive therapy. |
| **Interventions** | Vaccine: 9-valent vaccine at 0, 2, and 6 months<br><br>Placebo: saline placebo |
| **Outcomes** | Safety and immunogenicity outcomes |
| **Notes** | Main reports: Garland 2015<br><br>Last report average follow-up time: 7 months (1 month after third dose) |

### Risk of bias

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| **Random sequence generation (selection bias)** | Low risk | Not clearly stated how the sequence was generated, however, an Interactive Voice Response System was used to allocate participants and assign clinical material, therefore we have assumed that an adequate method of sequence generation was used. |
| **Allocation concealment (selection bias)** | Low risk | "An Interactive Voice Response System was used to allocate study subjects." |
| **Blinding of participants and personnel (performance bias)** | Low risk | The vaccine and saline placebo were visually distinguishable, therefore they were "prepared and administered by designated unblinded study personnel not otherwise involved in the care and management of the study participants". Otherwise, investigators, study site personnel, and laboratory personnel were blinded. |
| **Blinding of outcome assessment (detection bias)** | Low risk | "clinical, statistical, and data management teams were blinded to vaccination group" |
| **Incomplete outcome data (attrition bias)** | Low risk | Safety data were reported on the total vaccinated cohort; immunogenicity data on the PP cohort. Reasons for exclusion were noted and balanced |

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| | | between the vaccine arm and the control arm. |
| **Selective reporting (reporting bias)** | Low risk | All outcomes (safety and immunogenicity) were presented. |

# Appendix C: Five studies awaiting classification (not recruiting, but no results available) potentially relevant for the current Cochrane Review

**ISRCTN32729817**

| | |
|---|---|
| Methods | Randomized, partially blind, 2 x 2 factorial trial |
| Participants | 1000 male and female participants with first or repeat episode of clinically diagnosed anogenital warts |
| Interventions | Intervention: imiquimod cream plus quadrivalent HPV vaccine<br><br>Intervention: podophyllotoxin cream plus quadrivalent HPV vaccine<br><br>Control: imiquimod cream plus saline placebo injection<br><br>Control: podophyllotoxin cream plus saline placebo injection |
| Outcomes | Clinical (genital warts), safety |
| Notes | Trial end date: 31 March 2017 |

**NCT02199691**

| | |
|---|---|
| Methods | Phase II, randomized trial |
| Participants | 1715 participants aged 10 to 17 years |
| Interventions | Intervention: MenACYW conjugate vaccine, Tdap vaccine (Adacel), and HPV vaccine (Gardasil)<br><br>Intervention: Tdap vaccine (Adacel) and HPV vaccine (Gardasil)<br><br>Control: MenACYW conjugate vaccine<br><br>Control: Menveo vaccine |
| Outcomes | Immunogenicity and safety |
| Notes | Recruitment completed: 9 February 2018 |

**NCT02564237**

| | |
|---|---|
| Methods | Phase I, randomized, observer-blind, comparator-controlled trial |
| Participants | 39 male and female participants aged 18 to 50 years |

| | |
|---|---|
| Interventions | Intervention: Three 0.5 mL doses of comparator (Hepatitis B vaccine, Hepatitis A vaccine, or HPV vaccine) will be administered on days 0, 30, and 180. Participants will indicate which vaccine they wish to receive.<br><br>Control: Three 0.6 mL doses (600 µg protein) of group A streptococcal vaccine (StreptAnova) will be administered on days 0, 30, and 180. |
| Outcomes | Immunogenicity and safety |
| Notes | Recruitment completed: 19 January 2017<br><br>Estimated completion date: December 2017. |

**NCT02740790**

| | |
|---|---|
| Methods | Phase II, randomized, blinded, placebo-controlled trial |
| Participants | 1200 females aged between 9 and 45 years |
| Interventions | Intervention: 300 women 9 to 17 years of age receiving HPV bivalent (types 16 and 18) vaccine (yeast); 3 doses at 0, 2, and 6 months.<br><br>Control: 300 women 9 to 17 years of age receiving placebo control; 3 doses at 0, 2, and 6 months.<br><br>Intervention: 120 women 18 to 26 years of age receiving HPV bivalent (types 16 and 18) vaccine (yeast); 3 doses at 0, 2, and 6 months<br><br>Control: 120 women 18 to 26 years of age receiving placebo control; 3 doses at 0, 2, and 6 months<br><br>Intervention: 180 women 27 to 45 years of age receiving HPV bivalent (type 16 and 18) vaccine (yeast); 3 doses at 0, 2, and 6 months<br><br>Control: 180 women 27 to 45 years of age receiving placebo control; 3 doses at 0, 2, and 6 months |
| Outcomes | Immunogenicity and safety |
| Notes | Recruitment completed: 8 March 2017<br><br>Estimated study completion date: December 2017 |

**NCT03085381**

| | |
|---|---|
| Methods | Phase I, randomized, double-blind, placebo-controlled trial |
| Participants | 90 female participants aged 9 to 45 years |
| Interventions | Intervention: quadrivalent HPV (types 6, 11, 16, 18) recombinant vaccine (*Hansenula polymorpha*); 3 doses at 0, 2, and 6 months<br><br>Control: placebo; 3 doses at 0, 2, and 6 months |

| | |
|---|---|
| Outcomes | Safety |
| Notes | Recruitment completed: 21 March 2017<br><br>Estimated study completion date: December 2017 |

# Appendix D: Eight ongoing studies (actively recruiting, no results available) potentially relevant for the current Cochrane Review

### EudraCT 2007-006651-39

| | |
|---|---|
| Study name | A phase IV, randomized, open-label, controlled, post-licensure study to evaluate the safety of GlaxoSmithKline Biologicals' HPV-16/18 L1 VLP AS04 vaccine (Cervarix®) when administered intramuscularly according to a 0, 1, 6-month schedule in females aged 18-25 years. |
| Methods | Phase IV, randomized, open-label, controlled trial |
| Participants | 100,000 female participants aged 18 to 25 years |
| Interventions | Intervention: Cervarix<br><br>Control: hepatitis A vaccine (Havrix) |
| Outcomes | Safety |
| Starting date | 20 January 2009 (date entered into EudraCT database) |
| Contact information | Sponsor: GlaxoSmithKline Biologicals |
| Notes | Trial status is ongoing; no further details |

### NCT01735006

| | |
|---|---|
| Study name | Efficacy and Immunogenicity Study of Recombinant Human Papillomavirus Bivalent (Type 16/18) Vaccine |
| Methods | Phase III, multicentre, randomized, double-blind trial |
| Participants | 7372 female participants aged 18 to 45 years |
| Interventions | Intervention: novel recombinant HPV16/18 bivalent vaccine manufactured by Xiamen Innovax Biotech; 3 doses at months 0, 1, and 6.<br><br>Control: hepatitis E vaccine (Hecolin); 3 doses at months 0, 1, and 6 |
| Outcomes | Safety, immunogenicity and efficacy (persistent HPV16/18 infection and histological lesions of CIN 1+, 2+ and 3+, VIN1+ and 2+, VaIN1+ and 2+) |
| Starting date | 22 November 2012 |
| Contact information | Jun Zhang, Xiamen University |
| Notes | As of 19 July 2018: recruitment status is active, not recruiting |

### NCT01824537

| | |
|---|---|
| **Study name** | Transmission Reduction and Prevention With HPV Vaccination Study (TRAP-HPV) |
| **Methods** | Phase IV, randomized, double-blind, placebo-controlled trial |
| **Participants** | 1000 participants (500 couples), aged 18 to 45 years |
| **Interventions** | Intervention: 9-valent HPV vaccine (Gardasil9, Merck); 3 doses at months 0, 2, and 6.<br><br>Control: Hepatitis A vaccine (Havrix); 2 doses at months 0 and 6, and 1 dose of saline placebo at month 2. |
| **Outcomes** | Immunogenicity (HPV DNA positivity) |
| **Starting date** | September 2013 |
| **Contact information** | Allita Rodrigues (allita.rodrigues@mcgill.ca) |
| **Notes** | Recruitment status (as of 4 May 2018): recruiting |

**NCT02405520**

| | |
|---|---|
| Study name | Safety and Immunogenicity Study of the Recombinant Human Papillomavirus Virus Type 6/11 Bivalent Vaccine |
| Methods | Phase I, randomized, double-blind, placebo-controlled trial |
| Participants | 144 female participants aged between 18 and 55 years |
| Interventions | Intervention: low dosage of HPV6/11 bivalent vaccine at 0, 1, 6 months for 3 doses.<br><br>Intervention: medium dosage of HPV6/11 bivalent vaccine at 0, 1, 6 months for 3 doses.<br><br>Intervention: high dosage of HPV6/11 bivalent vaccine at 0, 1, 6 months for 3 doses.<br><br>Control: aluminium adjuvant at 0, 1, 6 months for 3 doses. |
| Outcomes | Immunogenicity and safety |
| Starting date | March 2015 |
| Contact information | Jun Zhang, Xiamen University |
| Notes | As of August 6, 2018: recruitment status is active, not recruiting |

**NCT02710851**

| | |
|---|---|
| Study name | Immunogenicity Study of the Recombinant Human Papillomavirus Virus Type 6/11 Bivalent Vaccine |
| Methods | Phase II, randomized, double-blind, placebo-controlled trial |
| Participants | 640 male and female participants aged 18-55 years |
| Interventions | Intervention: low dosage HPV bivalent vaccine with virus-like particles type 6 and 11 at 1:1 ratio; 3 doses at 0, 1, 6 months.<br><br>Intervention: low dosage HPV bivalent vaccine with virus-like particles type 6 and 11 at 1:2 ratio; 3 doses at 0, 1, 6 months.<br><br>Intervention: high dosage HPV bivalent vaccine with virus-like particles type 6 and 11 at 1:1 ratio; 3 doses at 0, 1, 6 months.<br><br>Control: hepatitis E vaccine (Hecolin) for 3 doses at 0, 1, 6 months. |
| Outcomes | Immunogenicity and safety |
| Starting date | March 2016 |
| Contact information | Jun Zhang, Xiamen University |
| Notes | As of 6 August 2018: recruitment status is active, not recruiting |

**NCT02733068**

| | |
|---|---|
| Study name | A Phase III Study of Human Papillomavirus (HPV)-16/18 Vaccine |
| Methods | Phase III, randomized, double-blind, placebo-controlled trial |
| Participants | 12000 female participants aged 18 to 30 years |
| Interventions | Intervention: HPV16/18 vaccine; 3-dose schedule (0, 2, 6 months)<br><br>Control: HPV16/18 placebo; 3-dose schedule (0, 2, 6 months) |
| Outcomes | Cervical intraepithelial neoplasia grade 2 or more (CIN 2+); persistent infection of HPV type 16 and/or 18; safety |
| Starting date | November 2014 |
| Contact information | Zhaojun Mo, Guangxi Center for Disease Prevention and Control, China |
| Notes | As of 11 April 2016: recruitment status is active, not recruiting. |

**NCT02750202**

| | |
|---|---|
| Study name | Effectiveness Study of Human Papilloma Virus (HPV) Vaccines to Prevent Recurrence of Genital Warts (TheraVACCS) |
| Methods | Phase III, randomized, single-blind, placebo-controlled trial |
| Participants | 75 female participants aged >16 years |
| Interventions | Intervention: quadrivalent HPV vaccine (Gardasil, Merck); 3 doses at month 0, 2, 6<br><br>Control: hepatitis B vaccine; 3 doses at month 0, 2, 6 |
| Outcomes | Clinical (genital warts, surgical treatment of warts or other cervical disease), immunogenicity |
| Starting date | July 2016 |
| Contact information | Greta G Dreyer (Greta.Dreyer@up.ac.za) |
| Notes | As of 26 April 2016, recruitment status is not yet recruiting |

**NCT03296397**

| | |
|---|---|
| Study name | Efficacy of Quadrivalent HPV Vaccine to Prevent Relapses of Genital Warts After Initial Therapeutic Response (CONDYVAC) |
| Methods | Phase III, randomized, double-blind, placebo-controlled trial |
| Participants | 300 male and female participants completely cured from external genital warts |
| Interventions | Intervention: quadrivalent HPV vaccine (Gardasil); 3 doses at 0, 2, 6 months<br><br>Control: placebo; 3 doses at 0, 2, 6 months |
| Outcomes | Clinical (relapse free survival), safety |
| Starting date | 15 November 2017 |
| Contact information | Sebastien Fouere, Assistance Publique - Hôpitaux de Paris |
| Notes | Recruitment status (as of 27 February 2018): recruiting |