

# BMJ Open Safety, efficacy and immunogenicity of therapeutic vaccines in the treatment of patients with high-grade cervical intraepithelial neoplasia associated with human papillomavirus: a systematic review protocol

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## ABSTRACT

**Introduction** Eighty per cent of the sexually active population will get human papillomavirus (HPV) infection, which is the most prevalent sexually transmitted disease worldwide. Persistence of high-grade HPV infection may evolve to a cervical intraepithelial neoplasia (CIN), and these lesions may be precursors of cervical cancer. However, this progression can be prevented by the administration of therapeutic vaccines which use the main oncoproteins responsible for cancer development in an attempt to trigger a more specific and effective immunological response against this disorder. We aim to evaluate the safety, efficacy and immunogenicity of therapeutic vaccines in the treatment of patients with high-grade CIN 2/3 associated with HPV.

**Methods and analysis** A systematic review of clinical trials will be undertaken. Medline, Excerpta Medica Database, Cochrane Central Register of Controlled Trials, Web of Science, Latin American and Caribbean Health Sciences Literature, Scientific Electronic Library Online and Scopus will be searched, with no restriction regarding publication date. Primary outcomes will include measures related to safety, efficacy and the immunogenicity of the therapeutic vaccines used in these patients. Study selection will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Methodological appraisal of the studies will be assessed by the Cochrane Risk-of-Bias Tool for randomised controlled trials, and the quality evidence of the risk of bias in single studies will be evaluated by Grading of Recommendations Assessment, Development and Evaluation. A narrative synthesis will be done for all included studies. Outcomes will be analysed according to the subgroups of HPV type, CIN grade, route of vaccine administration and vaccine type. Also, if sufficient data are available, a meta-analysis will be conducted. The effect sizes will be generated using Hedges' g score for both fixed and random effect models. I<sup>2</sup> statistics will be used to assess heterogeneity and identify their potential sources.

**Ethics and dissemination** Ethical approval is not required as primary data will not be collected. Findings will

## Strengths and limitations of this study

- This protocol reduces the possibility of duplication, gives transparency to the methods and processes that will be used, reduces possible biases and allows peer review.
- Will offer highest level of evidence for informed clinical decisions from this systematic review of clinical trials about safety, efficacy and immunogenicity of therapeutic vaccines in the treatment of patients with high-grade CIN associated with HPV.
- This systematic review will be the first to evaluate the safety, efficacy and immunogenicity of therapeutic vaccines in the treatment of patients with high-grade cervical intraepithelial neoplasia (CIN 2/3) associated with human papillomavirus (HPV).
- The scarcity of randomised controlled trials undertaken with therapeutic vaccines in the treatment of patients with CIN 2/3 associated with HPV, the publication bias and the methodological quality of the grey literature found may be the main limitations of the study.

be disseminated widely via peer-reviewed publication and in different media, for example, conferences, congresses or symposia.

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## INTRODUCTION

In recent decades, sociocultural changes have influenced human behaviour leading to the emergence of various sexually transmitted diseases, including those caused by human papillomavirus (HPV).<sup>1</sup> HPV is a non-encapsulated DNA virus with approximately 8000 base pairs belonging to the family Papillomaviridae<sup>2</sup> which affects approximately 105 million women at least once in their

lives.<sup>3</sup> HPV is present in 99.7% of cervical intraepithelial neoplasia (CIN)<sup>4</sup> and is closely related to the onset of cervical cancer, and these pathologies are considered to be a public health global problem.<sup>1</sup>

Approximately 80% of the sexually active population is infected with any subtype of HPV.<sup>3</sup> Most lesions regress without treatment within a period of up to 24 months as a result of the immune response, however, occasionally 10% to 30% of infections persist and may progress to high-grade lesions (CIN 2/3).<sup>5</sup>

There are approximately 200 HPV genotypes, and these may be related to low (CIN 1) or high-grade (CIN 2/3) lesions. The main risk factor for the development of CIN is the persistence or relapse of high-risk HPV, especially subtypes 16 and 18 that are present in up to 75% of lesions.<sup>6</sup> These viruses express proteins that promote cell cycle alteration inducing genomic instability in normal cells, inhibiting apoptosis, favouring the formation of mitotic defects and aneuploidy. In addition, they inhibit tumour suppressor genes and modulate the immune system making the tumour cells low immunogenic, which results in immunological tolerance to the tumour and favours the HPV-mediated oncogenicity.<sup>7,8</sup>

When the virus is detected, the therapy of choice is the physical removal of the lesion, which is able to eliminate more than 80% of initial lesions. However, viral DNA often remains<sup>9</sup> and may lead to a recurrence of the lesion that may progress to cervical cancer<sup>10</sup> requiring more aggressive treatments, such as chemotherapy and radiotherapy, resulting in the death of 50% of patients.<sup>11</sup> On the other hand, treatments that stimulate the immune response have been shown to eliminate up to 90% of CIN 2 lesions on 24 months.<sup>12</sup> Therefore, new therapeutic strategies that effectively and permanently eliminate the HPV virus are currently needed.<sup>12,13</sup>

The production of therapeutic vaccines focuses on the effectiveness of specific immunological responses against antigens<sup>14,15</sup> to eliminate the established pathology or prevent the patient from being reinfected, neutralising subsequent infections by the same virus. Due to this characteristic, therapeutic vaccines differ significantly from the available prophylactic vaccines, since these later have no therapeutic properties.<sup>16</sup> Moreover, because the risk population continues to be exposed to the virus without having an associated protective factor, therapeutic vaccines have low adherence rates, and therefore the picture of HPV infections that can progress to aggressive pathologies remains unchanged.<sup>17</sup>

Hence, based on the fact that HPV infections are frequent and associated with significant public health morbidity and mortality, it is necessary to develop effective and safe therapeutic vaccines against already established HPV-associated lesions. Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) checklist as guidance,<sup>18</sup> we propose a systematic and reproducible strategy to query the literature about the safety, efficacy and immunogenicity of therapeutic vaccines in the treatment of

patients with high-grade cervical intraepithelial neoplasia (CIN 2/3) associated with HPV.

## RESEARCH AIMS

The main objectives of this systematic review are: (1) to evaluate the efficacy of therapeutic vaccines in patients with high-grade cervical intraepithelial neoplasia, evaluated through histopathological regression of the lesion as well as regression of lesion size or other parameters that the authors considered relevant to assess this variable; (2) to assess the safety of therapeutic vaccines in patients with high-grade cervical intraepithelial neoplasia, reporting possible adverse effects to its administration and (3) to assess the immunogenicity of therapeutic vaccines in patients with high-grade cervical intraepithelial neoplasia by evaluating changes in the immunological profile of individuals who received the treatment compared with those who did not receive it.

## METHODS AND ANALYSIS

### Search strategy

The search strategy will be carried out using resources that enhance methodological transparency and improve the reproducibility of the results and evidence synthesis. The search strategy will be elaborated and implemented prior to study selection, according to the PRISMA-P checklist as guidance.<sup>18</sup> In addition, using the PICOS acronym,<sup>19</sup> we elaborated the guiding question of this review to ensure the systematic search of available literature: 'What are the scientific evidences on the safety, efficacy and immunogenicity of therapeutic vaccines in the treatment of patients with high-grade cervical intraepithelial neoplasia (CIN 2/3) associated with HPV?'

Studies will be retrieved using seven databases: Medical Literature Analysis and Retrieval System Online (MEDLINE; via PubMed), Excerpta Medica Database, Cochrane Central Register of Controlled Trials, Web of Science, Latin American and Caribbean Health Sciences Literature, Scientific Electronic Library Online and Scopus. There will be no restriction regarding publication date. Language restrictions will be applied and only articles in English will be included. Additionally, secondary searches in other sources, such as, Google Scholar and registration sites of clinical trials (eg, ClinicalTrials.gov) will be also carried out. Also, the reference section of the included studies will be hand searched for additional relevant studies. It is noteworthy that two researchers (CAG and LCL-J) will perform the search strategy independently. In addition, the bibliographic software EndNote (<https://www.myendnoteweb.com/>) will be used to store, organise and manage all the references and ensure a systematic and comprehensive search.

Initially, the existence of controlled descriptors (such as Medical Subject Headings (MeSH) terms, Emtree terms and DeCS—Health Science Descriptors) and their synonyms (keywords) was verified in each database. The

**Table 1** Concepts and search items

Databases	Search items
Medline Embase CENTRAL Cochrane Web of Science Scopus LILACS SciELO	<p>#1 (Cervical Intraepithelial Neoplasia) OR (Neoplasia, Cervical Intraepithelial) OR (Cervical Intraepithelial Neoplasms) OR (Cervical Intraepithelial Neoplasm) OR (Intraepithelial Neoplasm, Cervical) OR (Intraepithelial Neoplasms, Cervical) OR (Neoplasm, Cervical Intraepithelial) OR (Neoplasms, Cervical Intraepithelial) OR (Intraepithelial Neoplasia, Cervical) OR (Cervical Intraepithelial Neoplasia, Grade III) OR (Cervical Intraepithelial Neoplasia Grade II) OR (High Grade Cervical Intraepithelial Neoplasia) OR (CIN) OR (High-grade Cervical Intraepithelial Neoplasia) OR (Cervical Intraepithelial Neoplasia) OR (Precancerous Conditions) OR (Preneoplastic Condition*)</p> <p>#2 (Papillomaviridae) OR (Human papillomavirus) OR (Human Papilloma Viruses) OR (Papilloma Virus, Human) OR (Papilloma Viruses, Human) OR (Virus, Human Papilloma) OR (Viruses, Human Papilloma) OR (HPV, Human Papillomavirus Viruses) OR (Human Papillomavirus Viruses) OR (Human Papillomavirus Virus) OR (Papillomavirus Virus, Human) OR (Papillomavirus Viruses, Human) OR (Virus, Human Papillomavirus) OR (Viruses, Human Papillomavirus)</p> <p>#3 #1 AND #2</p> <p>#4 (Vaccine) OR (Immunomodulatory Therapy) OR (Therapies, Immunomodulatory) OR (Therapy, Immunomodulatory) OR (Vaccines, Neoplasm) OR (Injection, Therapeutic Vaccine) OR (Vaccinotherapy) OR (Therapeutic vaccine) OR (Vaccinotherapy) OR (Vaccine Immunogenicity) OR (Antigenicity, Vaccine) OR (Adjuvant) OR (Vaccination)</p> <p>#5 #3 AND #4</p> <p>#6 (Controlled Trial) OR (Controlled Clinical Trial) OR (Controlled Trials) OR (Random Allocation) OR (Clinical Trial) OR (Clinical Trials) OR (Random*) OR (Prospective Studies) OR (Control) OR (Prospective*)</p> <p>#7 #5 AND #6</p>

CENTRAL, Cochrane Central Register of Controlled Trials; Embase, Excerpta Medica Database; LILACS, Latin American and Caribbean Health Sciences Literature; Medline, Medical Literature Analysis and Retrieval System Online; SciELO, Scientific Electronic Library Online.

search terms were combined using the Boolean operators 'AND' and 'OR'.<sup>20</sup>

Subsequently, the search strategy combining MeSH terms and free-text words that will be used in Medline (via PubMed) and adjusted to the other electronic databases will be as follows in [table 1](#).

### Study selection criteria

A summary of the population (P), interventions (I), comparators (C) and outcomes (O) considered, as well as studies designs (S) included according to PICOS acronym, is provided in [table 2](#).

### Screening and data extraction

Initially the screening of studies will be based on the information contained in their titles and abstracts and will be conducted by two independent investigators (CAG

and LCL-J). When the reviewers disagree, the article will be re-evaluated and, if the disagreement persisted, a third reviewer (GP-S) will make a final decision. Full-paper screening will be conducted by the same independent investigators. Cohen's kappa will be used to measure intercoder agreement in each screening phase.

Data will be extracted using previously proposed tools,<sup>21–23</sup> including four domains: (1) identification of the study (article title; journal title; impact factor of the journal; authors; country of the study; language; publication year; host institution of the study (hospital; university; research centre; single institution; multicentre study); conflict of interest and study sponsorship); (2) methodological characteristics (study design; study objective or research question or hypothesis; sample characteristics, eg, sample size, age, race, baseline characteristics; groups

**Table 2** Inclusion and exclusion criteria

PICOS acronym <sup>19</sup>	Inclusion criteria	Exclusion criteria
P—Population	Patients with high-grade CIN 2 and 3 associated with HPV.	Patients with other immunosuppression-associated conditions.
I—Intervention	Use of therapeutic vaccines for the treatment of high-grade CIN 2 and 3 associated with HPV.	
C—Comparison	Usual standard of care without receiving the therapeutic vaccine.	
O—Outcome	The safety, the efficacy and the immunogenicity of the therapeutic vaccines used in patients with high-grade CIN 2 and 3 associated with HPV.	Studies that do not report safety, the efficacy for CIN 2 and 3 and the immunogenicity* of the therapeutic vaccines as primary outcome
S—Study design	Clinical trial.	All the non-primary literature, such as reviews, dissertations, theses, editorials, protocol studies and clinical guidelines.

\*Immunogenicity will be evaluated across the various studies in exploratory way in the blood and in the target tissue (including immune response to vaccine antigen assessment of HPV-specific CD8 and CD4 immune response; or also, via systemic induction of HPV E6 and E7-specific T-cell immune responses and changes of involved lesions and HPV infection status at the uterine cervix), among other parameters (eg, generation of antibodies and release of cytokines).

CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus.

and controls; recruitment methods and study completion rates; stated length of follow-up; validated measures; statistical analyses, adjustments); (3) main findings and implications for clinical practice and (4) conclusions.

In the event that the information in any specific article is unclear or data are missing, the review author will contact the correspondent author of the study. For data extraction, two independent Microsoft Excel spreadsheets will be elaborated by two reviewers (CAG and LCL-J) to summarise the data from the included studies. Then, the spreadsheets will be combined into one. Disagreements will be resolved by a third investigator (GP-d-S).

### Quality assessment

The internal validity and risk of bias for randomised control trials will be assessed with the appraisal tool from the Cochrane Handbook for Systematic Reviews of Interventions V.5.1.0,<sup>24</sup> which assesses the following study-level aspects: (1) randomisation sequence allocation; (2) allocation concealment; (3) blinding; (4) completeness of outcome data and (5) selective outcome reporting; and classifies studies into low, high or unclear risk of bias. In addition, the quality evidence of the risk of bias in single studies, will be evaluated by the Grades of Recommendation, Assessment, Development and Evaluation.<sup>25</sup>

The same two independent reviewers (CAG and LCL-J) will assess the methodological quality of eligible trials as well as will score the selected studies. Disagreements will be resolved by a third reviewer (GP-d-S). The risk of bias for each outcome across individual studies will be summarised as a narrative statement and supported by a risk of bias table. A review-level narrative summary of the risk of bias will also be provided.

### Descriptive analysis and meta-analysis

For studies with a high or unclear risk of bias, defined as high or nuclear risk in 50% or more of the quality assessment outcomes, a narrative description of the risk of bias will be provided. Risk of bias assessments will be incorporated into synthesis by performing sensitivity analysis (ie, limiting to studies at lowest risk of bias in a secondary analysis).

A narrative synthesis will be conducted for all the selected studies, including: (1) characteristics related to the quality of the selected studies as number of dropouts per follow-up, early withdrawal by benefit, intention-to-treat analysis, blindness scheme, allocation secrecy and randomisation; (2) characteristics of the protocol used in studies such as type of intervention and control group, sample size, treatment time, dose and interval of the vaccine administration; (3) study population characteristics, such as, age, staging of disease, association of treatments or surgeries and other relevant information; (4) outcomes, for instance, the changes in immunological parameters, signs of local and systemic toxicity, histopathological regression of the lesion, regression of lesion size or reduction of viral load.

Furthermore, whenever possible, continuous and dichotomous outcomes will be pooled together for meta-analysis purposes. All effect sizes will be transformed into a common metric to make them comparable across studies—the bias-corrected standardised difference in means (Hedges' *g*)—classified as positive when in favour of the intervention and negative when in favour of the control. Heterogeneity will be assessed using  $I^2$ .<sup>26</sup> The presence of publication bias will be evaluated by using a funnel plot and the Duval and Tweedie's trim and fill method.<sup>27</sup> Therefore, we will assess the publication bias if enough studies per outcome are identified.

### Patient and public involvement, ethics and dissemination

Patients were not directly involved in the design of this study. Because this is a protocol for a systematic review and no participant recruitment will take place, their involvement on the recruitment and dissemination of findings to participants was not applicable. Additionally, any amendments to this protocol will be documented with reference to saved searches and analysis methods, which will be recorded in bibliographic databases (Ovid), EndNote and Excel templates for data collection and synthesis.

The results of the review will be disseminated via peer-reviewed publication as well as in different media, for example, conferences, congresses or symposia.

### DISCUSSION

One of the strengths of the proposed study is to apply a reproducible and transparent procedure for systematic review of the literature. In this protocol, we clearly describe the types of studies, participants, interventions and outcomes that will be included, as well as the data sources, search strategy, data extraction methods (including quality assessment) and methods of combining data.<sup>28</sup> By publishing the research protocol, we reinforce the clarity of the strategy and minimise the risk of bias, namely selective outcome reporting.<sup>25</sup> Second, we will focus solely on the impact of the safety, efficacy and immunogenicity of therapeutic vaccines in the treatment of patients with high-grade cervical intraepithelial neoplasia (CIN 2/3) associated with HPV. These results shall provide high-level information to inform, support and customise decisions from the oncology clinicians.

Potential limitations of this study include the heterogeneity of measures and outcomes evaluated and the potentially reduced number of studies in subgroup analyses, which may negatively influence the statistical power in data synthesis.

It is noteworthy that although prophylactic vaccines against HPV are safe and provide protective immunity against viruses that cause high-grade cancers,<sup>3 29 30</sup> the adherence to these vaccines is low, impairing an effective prevention against the development of this disease as well as cervical cancer. Low adherence to the vaccination also allows the spread of sexually transmitted diseases associated with this pathogen, constituting a serious global

problem for public health. Once the disease is already in activity, prophylactic vaccines are no longer effective, and therefore effective and safe therapeutic vaccines that also activate a memory immune response by promoting the regression of precancerous lesions are needed, thus reducing mortality, morbidity, time and cost of treatment in these patients. In this sense, the present study will provide relevant evidence on the efficacy, safety and immunogenicity of therapeutic vaccines used in the treatment of patients with high-grade cervical intraepithelial neoplasia to address the gap in the literature on this new therapy to women's health.

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**Contributors** CAG, LCL-J and GP-d-S conceptualised and designed the protocol, drafted the initial manuscript and reviewed the manuscript. CAG and LCL-J defined the concepts and search items, data extraction process as well as methodological appraisal of the studies. FKN and AZ planned the data extraction and statistical analysis. PCMM and GP-d-S provided critical insights. All authors have approved and contributed to the final written manuscript.

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#### REFERENCES

- Medeiros LR, Ethur AB, Hilgert JB, *et al.* Vertical transmission of the human papillomavirus: a systematic quantitative review. *Cad Saude Publica* 2005;21:1006–15.
- Wright Jr TC. Natural History of HPV infections. *J Fam Practice* 2009;58:S3–S7.
- Crosbie EJ, Einstein MH, Franceschi S, *et al.* Human papillomavirus and cervical cancer. *Lancet* 2013;382:889–99.
- D'Souza G, Dempsey A. The role of HPV in head and neck cancer and review of the HPV vaccine. *Prev Med* 2011;53(Suppl 1):S5–S11.
- McCredie MR, Sharples KJ, Paul C, *et al.* Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study. *Lancet Oncol* 2008;9:425–34.
- Kyrgiou M, Athanasiou A, Paraskevidi M, *et al.* Adverse obstetric outcomes after local treatment for cervical preinvasive and early invasive disease according to cone depth: systematic review and meta-analysis. *BMJ* 2016;354:1–15.
- Narisawa-Saito M, Kiyono T. Basic mechanisms of high-risk human papillomavirus-induced carcinogenesis: roles of E6 and E7 proteins. *Cancer Sci* 2007;98:1505–11.
- Tindle RW. Immune evasion in human papillomavirus-associated cervical cancer. *Nat Rev Cancer* 2002;2:59–64.
- Martin-Hirsch PPL, Paraskevidis E, Bryant A, *et al.* Surgery for cervical intraepithelial neoplasia. *Cochrane database Syst Rev* 2014;6:1–93.
- Corona Gutierrez CM, Tinoco A, Navarro T, *et al.* Therapeutic vaccination with MVA E2 can eliminate precancerous lesions (CIN 1, CIN 2, and CIN 3) associated with infection by oncogenic human papillomavirus. *Hum Gene Ther* 2004;15:421–31.
- Lacey CJ, Woodhall SC, Wikstrom A, *et al.* 2012 European guideline for the management of anogenital warts. *J Eur Acad Dermatol Venereol* 2013;27:e263–e70.
- Discacciati MG, de Souza CA, d'Ottaviano MG, *et al.* Outcome of expectant management of cervical intraepithelial neoplasia grade 2 in women followed for 12 months. *Eur J Obstet Gynecol Reprod Biol* 2011;155:204–8.
- Siegel RL, Miller KD, Jemal A, *et al.* Cancer statistics, 2019. *CA Cancer J Clin* 2019;69:7–34.
- Bagarazzi ML, Yan J, Morrow MP, *et al.* Immunotherapy against HPV16/18 generates potent TH1 and cytotoxic cellular immune responses. *Sci Transl Med* 2012;4:1–33.
- Dunn GP, Bruce AT, Ikeda H, *et al.* Cancer immunoediting: from immunosurveillance to tumor escape. *Nat Immunol* 2002;3:991–8.
- Kash N, Lee MA, Kolipara R, *et al.* Safety and efficacy data on vaccines and immunization to human papillomavirus. *J Clin Med* 2015;4:614–33.
- Saúde BMda. Secretaria de Vigilância em Saúde. Departamento de Vigilância Epidemiológica. Coordenação Geral do Programa Nacional de Imunizações. Informe Técnico sobre a Vacina Papilomavirus Humano-HPV na Atenção Básica. Brasília: Ministério da Saúde, 2014.
- Moher D, Shamseer L, Clarke M, *et al.* Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.
- Chapter 5: Defining the review question and developing criteria for including studies. In: Higgins JPT, Green S, eds. *Cochrane Handbook of Systematic Reviews. Version 5.0.1: The Cochrane Collaboration*, 2008. (Accessed 5 Feb 2013).
- Lefebvre C, Manheimer E, Glanville J. Searching for studies. In: Higgins JPT, Greene S, eds. *Cochrane Handbook for Systematic Reviews of Interventions, Version 5.0*, 2008.
- Lopes-Júnior LC, Bomfim EO, Nascimento LC, *et al.* Non-pharmacological interventions to manage fatigue and psychological stress in children and adolescents with cancer: an integrative review. *Eur J Cancer Care* 2016;25:921–35.
- Lopes-Júnior LC, Rosa M, Lima RAG. Psychological and psychiatric outcomes following PICU admission: a systematic review of cohort studies. *Pediatr Crit Care Med* 2018;19:e58–e67.
- Lopes-Júnior LC, Cruz LA, Leopoldo VC, *et al.* Effectiveness of Traditional Chinese Acupuncture versus Sham Acupuncture: a Systematic Review. *Rev Lat Am Enferm* 2016;24:e2762.
- Higgins JPT, Green S. *Cochrane Handbook for Systematic Reviews of Interventions. 5.1.0 edition. Cochrane Collaboration*. Chichester, UK: John Wiley & Sons, 2016.
- Guyatt GH, Oxman AD, Vist GE, *et al.* GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924–6.
- Egger M, Davey Smith G, Schneider M, *et al.* Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.
- Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 2000;56:455–63.
- Silagy CA, Middleton P, Hopewell S. Publishing protocols of systematic reviews: comparing what was done to what was planned. *JAMA* 2002;287:2831–4.
- Dunne EF, Unger ER, Sternberg M, *et al.* Prevalence of HPV infection among females in the United States. *JAMA* 2007;297:813–9.
- Herrero R, González P, Markowitz LE. Present status of human papillomavirus vaccine development and implementation. *Lancet Oncol* 2015;16:e206–16.