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Human papillomavirus (HPV) vaccination for the prevention of cervical cancer and other HPV-related diseases: a network meta-analysis (Protocol)

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TABLE OF CONTENTS

[Intervention Protocol]

Human papillomavirus (HPV) vaccination for the prevention of cervical cancer and other HPV-related diseases: a network meta-analysis

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

We aim to evaluate the safety and efficacy of WHO pre-qualified human papillomavirus (HPV) vaccines given in different dose schedules, in females and males, to prevent cervical cancer and other HPV-related diseases by undertaking a network meta-analysis (NMA). We will rank the different vaccines and dose schedules according to the critical outcomes.

BACKGROUND

Description of the condition

Cervical cancer is the fourth most common cancer and the fourth leading cause of death from cancer amongst females worldwide, with an estimated 570,000 new cases and 311,000 deaths in 2018 (Bray 2018). Cervical cancer is a common cancer in young women and people with a uterine cervix, particularly in the 25 to 45 age group (Bray 2018). The risk of developing cervical cancer by age 65 years ranges from 0.8% in developed countries to 1.5% in developing countries and more than 85% of all cervical cancer deaths occur in low- and middle-income countries (LMIC) (Bray 2018). The large geographical variation in cervical cancer rates and survival correlates with the availability of primary and secondary prevention strategies, as well as the prevalence of high-risk human papillomavirus (hrHPV) infection. However, even in the UK, with a highly organised, regulated and effective screening programme, cervical cancer in females aged 25 to 49 is the fourth-highest cause of cancer death (Cancer Research UK 2020). In England, 4.63 million women are invited for cervical screening in a year (2019 to 2020), in order to identify and treat those at higher risk cervical cancer (NHS Digital 2020a). Of these, nearly 100,000 required further investigation with colposcopy (direct visualisation of the cervix with a microscope) to determine whether treatment is needed for cervical intra-epithelial neoplasia (CIN), a precursor lesion, to prevent cervical cancer (NHS Digital 2020b). This can cause anxiety and distress for many people. Furthermore, treatment for CIN, although relatively minor and straightforward in most cases, may put some people at higher risk of premature birth, thereby having long-term knock-on effects of preventative treatment (Kyrgiou 2017).

Human papillomavirus (HPV) is the most common viral infection of the reproductive tract (WHO 2017). Persistent infection with hrHPV is necessary, but not sufficient, to develop cervical cancer. The majority of people are exposed to hrHPV and, although most HPV infections resolve spontaneously (Insinga 2011), persistent infections can lead to precancerous lesions (e.g. cervical and vulval intraepithelial neoplasia (CIN and VIN)), and cancer of the cervix, vagina, vulva, anus, penis, and head and neck. In 2012, HPV-related cancers accounted for an estimated 4.5% of all cancers worldwide (de Martel 2017). Of these estimated 636,000 HPV-related cancers, 530,000 were cervical cancer, 35,000 anal cancer, 8500 vulval cancer, 13,000 penile cancer, and 37,000 head and neck cancers (de Martel 2017).

Ano-genital warts (AGWs) are caused by non-oncogenic HPV subtypes, with HPV 6 and 11 responsible for 90% of AGWs (Hawkins 2013). AGWs are highly transmissible and difficult to eradicate, with high recurrence rates. The cost of treatment of AGWs in England in 2008 was estimated to be £16.8 million, contributing to 6.6 days of healthy life lost per episode (Desai 2011; Woodhall 2011), and $220 million in the USA in 2004 (Insinga 2005). A systematic review found that annual incidence rates of new and recurrent AGWs, from clinical studies, vary from 160 to 289 per 100,000 (Patel 2013). Incidence is higher in those with immunocompromise, including immunosuppression following organ transplantation and HIV infection, and in men who have sex with men (MSM), with 11.6% of MSM reporting AGWs in a UK-based study (Sonnenberg 2019). Many studies included in the systematic review came from high-income countries. However, one study from Nigeria the incidence of AGWs was 1% in HIV-negative women and 5% in HIV-positive women, demonstrating a significant health burden, especially in LMICs, which can have a profound effect upon quality of life (Dareng 2019).

With the advent of immunisation and screening programmes in developed countries, the majority of invasive cervical cancers could be prevented (Cancer Research UK 2017). In 2018, The World Health Organization (WHO) Director-General made a global call for the elimination of cervical cancer (Adhanom-Ghebreyesus 2018). However, in the absence of organised screening, many people present with symptoms and locally advanced cervical cancer at diagnosis (WHO 2018). Sadly, even in countries with well-organised, freely- available screening programmes, screening cannot prevent all cervical cancers, and are not widely accessible globally. Cervical cancer therefore remains a significant disease. Furthermore, ~20% of HPV-related cancers do not have effective screening methods.

The introduction of primary testing for hrHPV, compared to cervical cytology, improves the sensitivity of screening, albeit at the cost of increased referrals to colposcopy (Koliopoulos 2017). This leads to an increased rate of detection of CIN and is likely to reduce the rate of cervical cancer within a population over time. However, in many of the randomised controlled trials (RCTs) there was follow-up with HPV-testing as one of the outcome measures, outside of screening programmes, so is controlled for in RCTs.

Description of the intervention

HPV vaccines were first licensed in 2006, and by 2016, 55% of high (HIC) and upper-middle-income (UMIC) countries had introduced vaccination programmes, compared to just 14% of lower-middle-income (LMIC) and lower income (LIC) countries, where disease burden of cervical cancer is higher, according to World Bank figures (Gallagher 2018; LaMontagne 2017).

Uptake of HPV vaccination varies widely between countries, ranging from 8% to 98% (83.9% in UK). Reasons for this variation include organisation of immunisation programmes, resistance from healthcare providers, adverse media coverage and concerns about safety (Gallagher 2018).

Four prophylactic HPV vaccines are available and have been pre-qualified by WHO (see Table 1). Each vaccine is directed against two or more hrHPV genotypes. All four vaccines contain L1 proteins of HPV genotypes 16 and 18 (Qiao 2020; WHO 2017), because these cause about 70% of cervical cancers globally. In addition to the pre-qualified vaccines, as of December 2021, there are two vaccines in stage 2 to 3 development, one bivalent vaccine manufactured by Walvax in China, and a quadrivalent vaccine manufactured by the Serum Institute of India (LaMontagne 2017). Two vaccines also contain L1 proteins for HPV 6 and 11 (see Table 1), which are responsible for 90% of AGWs (Hawkins 2013).

How the intervention might work

HPV L1 coat proteins self-assemble into virus-like particles (VLP), empty virus particles (capsids), containing no virus DNA (Kirnbauer 1992), which cannot cause an active infection. They work as prophylactic vaccines, which means they prevent an initial infection by HPV, in turn preventing the development of intraepithelial lesions caused by HPV genotypes that are present in the vaccine (Stanley 2006). HPV vaccines are therefore less effective in those already exposed to HPV (Arbyn 2018), hence why they are

offered to adolescents, aiming for immunity prior to onset of sexual activity.

The virus-like particles in the vaccines produce very high levels of antibodies in blood samples. The International Agency for Research on Cancer regards persistent HPV infection with HPV types 16 and 18 as an accurate surrogate marker for the development of precancerous lesions of the cervix and anus (IARC 2014). Persistent infection with hrHPV is the main cause of cervical cancer (Bosch 2002;Jaisamrarn 2013; Munoz 1996), with a well-recognised progression from persistent HPV infection to the development of cervical intraepithelial neoplasia (CIN), although the majority of infections are cleared spontaneously and do not cause persistent infection (Insinga 2011). However, left untreated, almost one in three of those with high-grade CIN (CIN3) will go on to develop cancer over 8 to 15 years (Campbell 1989; McIndoe 1984). It was therefore assumed that prevention of precancerous lesions would also be shown to prevent cancer when sufficient follow-up time has accrued in post-licensure studies. Less is known about the prognostic value of persistent HPV infection in the development of vaginal, vulval and oropharyngeal cancers (IARC 2014).

Initial vaccine schedules used a three-dose regimen. However, data from RCTs and post-licensure studies demonstrated good effectiveness for those who had not received all three doses (D'Addario 2017; Kreimer 2011; Kreimer 2015; Markowitz 2018; Sankaranarayanan 2016). Subsequent studies have used a two and, more recently, a single-dose strategy. Simplified HPV vaccination schedules, with fewer doses, should allow more people to receive the vaccine, especially in resource-poor settings. Preadolescents and adolescents (age 9 to 15 years) produce stronger antibody responses to VLP HPV vaccines than older adolescents and adults (Block 2006; Dobson 2013), even after a single dose (Sankaranarayanan 2016). The likely mechanism for this is more fully explained in a previous Cochrane Review (Bergman 2019).

Why it is important to do this review

Prevention or early detection of cancer is a major priority for health care, especially within the UK, where survival rates for many cancers lag behind European counterparts, largely due to late detection (De Angelis 2014).

In cervical cancer we are fortunate, as the main focus is on prevention, since, unlike many cancers, it can be prevented or detected at a pre-invasive stage. A major priority for healthcare providers, including WHO and Cochrane, is to update and combine data from two separate Cochrane Reviews on HPV vaccination (Arbyn 2018; Bergman 2019), including non-published data, and drawing these together as a network meta-analysis (NMA) to compare different vaccines and vaccination schedules.

The recommended dosing schedules for HPV vaccines have changed from originally being three doses (as assessed in the placebo-controlled trials) to two doses (WHO 2017). Results of RCTs on single-dose vaccination are becoming available and comparative analyses are needed to inform future HPV vaccine strategies. The aim of this NMA is to compare these dose schedules, as well as the different types of HPV vaccine in terms of benefits and harms. This will aid WHO and other decision-makers in recommending vaccine schedules with fewer doses as this will have implications for screening intervals and change cost-effectiveness of immunisation and screening programmes. HPV vaccination, especially in countries where screening programmes are currently unaffordable, has the potential to be transformative.

Evaluating the longer-term harms and benefits of HPV vaccination is extremely important, especially in the face of community concerns about these issues, which can fuel vaccine hesitancy (Karafillakis 2019; Wong 2020). Scares about adverse events can be catastrophic to a vaccination programme. For example, in Denmark and Ireland community scares saw vaccination rates temporarily drop from over 80% to around 50% (Corcoran 2018; Suppli 2018). In Japan, a scare also resulted in a pause in government recommendation of vaccination (Ujiie 2022).

With the global reach of social media, dissemination of information regarding adverse effects of vaccination can be extremely pervasive, as seen with the unfounded claims regarding measles, mumps and rubella (MMR) vaccination (Deer 2004). Criticisms of HPV vaccine trials include inadequate assessment of possible rare conditions (Arana 2017). It is therefore extremely important to evaluate these outcomes more fully, some of which take more time to become apparent, to provide robust data to better inform to provide reliable data to young people, parents, clinicians, policymakers, and others when they are making choices about vaccination.

The previous Cochrane intervention reviews only compared head-to-head studies, whereas a NMA approach explores benefits and harms of different vaccines and dosing schedules, even where these have not been directly compared. Published data only were included in the 2018 review (Arbyn 2018) and this proposed NMA will also include clinical study report data, allaying this criticism of the previous review (Jørgensen 2018). Furthermore, an update of the evidence at this stage is timely, as there is potential for inclusion of longer-term follow-up data from RCTs. Those vaccinated as adolescents have had 10 to 20 years since vaccination, allowing evaluation of the impact on cervical cancer outcomes, as seen in population-level studies (Falcaro 2021; Lei 2020), which would allow evaluation of the use of surrogate outcomes in clinical trials (IARC 2014). The full impact of HPV vaccination on cancer incidence will not be known for many years, since the natural history of anal, vulval, penile and head and neck cancers, caused by hrHPV, is much longer.

A comprehensive examination of rare risks and a better understanding of longer-term benefits of HPV vaccination, such as effects on cancer rates, preterm birth rates and reduced complications due to falling need for treatment of CIN, require large datasets from population-level studies. We aim to evaluate these in a parallel Cochrane Review based on non-RCT data. It is hoped that these reviews will better inform the public debate about the benefits and harms of HPV vaccination and allow better decision-making at an individual level.

OBJECTIVES

We aim to evaluate the safety and efficacy of WHO pre-qualified human papillomavirus (HPV) vaccines given in different dose schedules, in females and males, to prevent cervical cancer and other HPV-related diseases by undertaking a network meta-analysis (NMA). We will rank the different vaccines and dose schedules according to the critical outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs). Long-term follow-up of trial participants will be included if the randomisation is kept intact (i.e. participants are not allocated or exposed to other interventions).

Types of participants

The target population is adolescents, although some studies have included adults, and these will also be considered. Analyses will be stratified by sex (females, males) and age groups (≤ 14 years, 15 to 25 years, and > 25 years).

We are planning to evaluate the effect of HPV vaccination in the general population. Immunocompromised people, such as people living with HIV, are a very important risk group for HPV-related disease. Nevertheless, we decided to exclude studies assessing only this group because the development of immunity following vaccination, waning of immunity after vaccination, and the development of HPV-related disease may differ in immunocompromised compared to immunocompetent people (Bergman 2019; Lacey 2019; Zhan 2019).

Types of interventions

Interventions of direct interest

Primary prophylactic administration of HPV vaccines pre-qualified by the WHO (WHO 2021), including Cervarix (bivalent, GlaxoSmithKline), Gardasil (quadrivalent, Merck), Gardasil 9 (nonavalent, Merck), or Cecolin (bivalent, Innovax) HPV vaccines (see Table 1). We will exclude studies assessing non-prophylactic and secondary prevention (i.e.used to prevent recurrence in those treated for HPV-related disease) uses of vaccines.

Specifically, we will investigate the safety and efficacy of:

- vaccination with one of the pre-qualified HPV vaccines compared with saline placebo, adjuvant placebo (aluminium hydroxide or another aluminium compound), no intervention, or a non-HPV control vaccine;
- head-to-head comparisons of vaccination with one of the pre-qualified HPV vaccines compared with one of the other pre-qualified HPV vaccines;
- different number of doses of the pre-qualified HPV vaccines.

Please see Table 2 detailing the nodes in the networks.

We will not assess schedules including more than three doses of HPV vaccine.

We assume that all included interventions are legitimate alternatives and can therefore be considered jointly randomisable, that is, any patient that meets the inclusion criteria will, in principle, be equally likely to be randomised to any of the eligible interventions.

Additional interventions to supplement the analysis

Additional interventions, such as monovalent or plasmid HPV vaccines or HPV vaccines currently in development, will be included in the network to increase the amount of indirect information on the other vaccines (Ades 2013). These interventions will not be used to summarise results.

Types of outcome measures

We will use data with the longest follow-up time reported, unless otherwise stated below.

Outcomes have been classified as critical or important to patients and policymakers. Critical outcomes will be included in the summary of findings tables (see 'Summary of findings and assessment of the certainty of the evidence' section, and Appendix 1).

Whilst we recognise the importance of serious adverse events (those causing death, disability or hospitalisation), we also realise the importance of those adverse events perceived by patients as most prevalent and those adverse events that may prevent uptake. We have therefore conducted surveillance of the social media platforms WebMD and Twitter (Appendix 2). We identified reports of 276 adverse events on WebMD which we analysed by frequency and added pertinent adverse events to our strategy. We also identified 9781 tweets on HPV and found that injury was the top mentioned adverse event (51%), followed by death (23%) as well as similar adverse events to those in WebMD and concern about the HPV vaccine promoting sexual promiscuity.

Primary outcomes

- Invasive cervical, vaginal, vulval, anal, penile, or head and neck cancer rates (critical outcome). The different types of cancer will be analysed separately. In the summary of findings tables for females, cervical cancer rates will be presented separately and the other relevant cancers (vaginal, vulval, anal, head and neck) as a composite outcome. In the summary of findings tables for males, anal cancer will be presented separately, while penile and head and neck cancer rates will be presented as a composite outcome. We recognise that most RCTs are unlikely to report on these outcomes since they require very long-term follow-up due to the natural history of HPV-related cancers. Nevertheless, we include them since they are the ultimate outcomes HPV vaccination is aiming to prevent.
- In females, histologically-confirmed high-grade cervical (CIN2, CIN3, and adenocarcinoma in situ (AIS)), vaginal (VAIN), vulva l (VIN I), or anal intraepithelial neoplasia (AIN), irrespective of HPV genotype, or any lesions associated with the HPV genotypes included in the vaccine (critical outcome). The cervical lesions will be analysed as composite outcomes of grade 2 or worse and grade 3 or worse (i.e. CIN2+ and CIN3+), with separate analyses showing the components of these.
- In males, histologically-confirmed penile (PeIN), or anal (AIN) intraepithelial neoplasia of any grade irrespective of HPV genotype, or any lesions associated with the HPV genotypes included in the vaccine (critical outcome). These lesions will be analysed as a composite outcome, with separate analyses showing the components of these.
- Serious adverse events (that are fatal, life-threatening, result in hospitalisation, persistent or significant disability/incapacity, congenital anomaly/birth defect, or requires intervention to prevent permanent impairment or damage (FDA 2016)) (critical outcome) will be analysed as a composite outcome. A separate analysis for serious adverse events related to the vaccines (as assessed and reported in the studies) will be performed.

Secondary outcomes

- Treatment rates for CIN, AIN, and other HPV-related pre-invasive disease (critical outcome).
- Participation rates in cervical screening.
- Anogenital warts (critical outcome).
- In females, miscarriage and pre-term birth rates, and neonatal outcomes for any pregnancy following vaccination (important outcome).
- Any local adverse events (overall local/injection site adverse events, redness, swelling, pain at the injection site) (important outcome) up to seven days after vaccination.
- Any overall systemic events and general symptoms (important outcome) up to seven days after vaccination.
- Total adverse events (solicited, unsolicited, or both) (important outcome) up to 28 days after vaccination.
- Adverse events that led to discontinuation of the intervention (important outcome).
- Specific adverse events (important outcome): incidence of postural tachycardia syndrome (POTS); chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME); paralysis; complex regional pain syndrome (CRPS) ; premature ovarian failure; Guillain-Barré syndrome; infertility; change in sexual activity. We will only include events that were ascertained in the studies; we will not attempt to retrospectively classify events into these outcome categories.
- All-cause mortality (important outcome). We will tabulate causes of death where this information is available.
- Incident infection with vaccine HPV genotypes (HPV 16 and HPV 18, jointly; HPV 6, HPV 11, HPV 16 and HPV 18 jointly; and HPV 31, HPV 33, HPV 45, HPV 52, and HPV 58 jointly) (important outcome).
- Persistent infection (persisting during at least six months or at least 12 months) with vaccine HPV genotypes (important outcome).

We will also collect information from each trial on methods of adverse events data monitoring and collection based on the CONSORT statement (Ioannidis 2004; Lineberry 2016), including:

- mode of data collection: proactive monitoring, spontaneous reporting, or both;
- timing: whether timeframe of adverse events collection was reported, and if so, what it was;
- attribution methods: who attributed events as adverse and whether they were blinded to the intervention, definitions used;
- intensity of ascertainment;
- harms-related monitoring and stopping rules; and
- frequency-based filter: limiting reporting to adverse events experienced by some minimum percentage of study participants.

Finally, information from each trial about whether the adverse events were considered to be vaccine-related and how this was determined within each trial (e.g. by trialists or by an independent monitoring board) will be collected.

It should be noted that POTS, CFS/ME and CRPS are diagnoses of exclusion, and global population background rates are not well-established. We will therefore seek to ascertain rates of these and other specific diagnoses, rather than rely on a constellation of symptoms that might or might not be indicative of these rare syndromes.

Search methods for identification of studies

We will attempt to identify all relevant studies regardless of language or publication status (published, unpublished, in press and in progress).

Electronic searches

The Information Specialist at the Cochrane Gynaecological, Neuro-oncology and Orphan Cancers group will design search strategies and run the searches on the core databases:

- MEDLINE Ovid (2000 to current date);
- Embase Ovid (2000 to current date);
- Cochrane Central Register of Controlled Trials (CENTRAL; Year, Issue), in the Cochrane Library.

Due to the timeline of HPV vaccine development, searches earlier than 2000 are not required.

We have presented the MEDLINE search strategy in Appendix 3, which reflects the key concepts of the review. We will adapt the MEDLINE search strategy, as indicated, for other databases.

We will not apply language restrictions to the electronic searches, and we will arrange for translations, as needed. If relevant studies are only reported in abstract form, we will contact the authors for additional information. Where we include them, we will conduct sensitivity analyses to test for their influence on the results.

Searching other resources

We will search the following databases for related systematic reviews and ongoing studies, and check the reference lists of those that are relevant, for additional studies:

- Epistemonikos: https://www.epistemonikos.org;
- ClinicalTrials.gov: http://clinicaltrials.gov;
- WHO International Clinical Trials Registry Platform (ICTRP): www.who.int/clinical-trials-registry-platform;
- HTA Database (Health Technology Assessments Database): www.york.ac.uk/crd/#HTA.

We will use all studies we identify as relevant, as seeds in PubMed, to search for additional studies using the related articles feature. We will also use the relevant studies as seeds in the Science Citation Index ISI Web of Knowledge ResearchGate and Google Scholar, to determine whether articles citing these studies are also relevant.

We will handsearch abstract books of meetings of the International Gynaecological Cancer Society, the European Society of Gynaecological Oncology, International Papillomavirus Meetings, European Research Organisation on Genital Infection and Neoplasia (EUROGIN) and the Society of Gynecologic Oncologists from 2010 to the latest edition, to identify ongoing and unpublished studies. Where necessary, we will contact the main investigators of relevant ongoing studies for further information. We will also contact authors of relevant studies to ask if they know of further data which may or may not have been published.

In addition, we will search vaccine manufacturer websites for relevant clinical study reports (CSR) (GlaxoSmithKline; Merck). We will also screen a list of HPV vaccine studies (Jørgensen 2018), that was constructed through enquiries to HPV vaccine manufacturers and regulators, as well as searches of trial registers and journal publication databases. For each included study, where available, we will identify and screen study governance documents (protocols, trial registration listings and results, manufacturers' clinical study reports) for relevant data and outcomes. We will also apply for access to any missing study governance documents through the European Medicines Agency (EMA).

Data collection and analysis

Results of all searches will be uploaded to DistillerSR to aid sifting and remote teamwork (DistillerSR 2021). RevMan Web will be used for review production, using standard Cochrane methods (RevMan Web 2021).

Selection of studies

Search results will be put through the RCT classifier (Thomas 2021), which uses machine learning to sift out irrelevant studies and automate some aspects of review production. Citations and abstracts will be screened independently, in duplicate by two review authors. A third review author will resolve any disagreements. We will obtain full-text reports for all potentially eligible studies. Two independent review authors will determine the eligibility of studies for inclusion in the review from the full reports according to predefined criteria. A third systematic review author will resolve any disagreements.

Data extraction and management

Two review authors will carry out data extraction independently using pre-tested data extraction forms. Study characteristics and outcome data will be independently extracted, and we will resolve any differences by discussion between the two review authors and referral to the study reports.

We will name studies based on the vaccine, first-named study author, year of publication, and country. Many studies have more than one document associated with them: journal publications (main study reports, reports of long-term follow-up, secondary outcomes and post-hoc analyses), conference abstracts, and study governance documents (protocols, trial registration listings and results, manufacturers' clinical study reports). For each study we will group these documents together and designate one report as the primary reference for the study; the study name will be derived from this particular report. Where available, the CSR will be considered the primary reference. When CSRs are not available for a study, the main peer-reviewed publication reporting on primary outcome/s will be considered the primary reference. For unpublished studies, results reported in trial registries will be considered the primary reference.

If data between the different study documents differ, we will contact study authors to resolve the discrepancy. In cases of pending or absence of a response, we will extract data from the primary reference.

Outcome data

We will collect outcome definitions and time points for each outcome.

For dichotomous outcomes, we will collect the number of participants experiencing an outcome event and the number analysed in each intervention group. Where only rates are reported, we will collect the number of events and the person-years in each intervention group. Where data per group are not available, we will extract any relative effect estimates reported.

For adverse events, we will extract all reports of adverse events from the study documents and categorise these into the outcome categories listed above.

For time-to-event data we will extract hazard ratios (HRs) and standard errors (SEs) or confidence intervals (CIs).

We will use data with the longest follow-up time for the primary analysis.

Study characteristics

From each included study we will extract data on the following study methods, interventions and population characteristics.

- Methods: randomisation (individual or cluster), duration of follow-up, number of study centres, location, inclusion and exclusion criteria, and date of study.
- Participants: number, setting* high- (HIC), upper-middle- (UMIC), lower-middle- (LMIC), or low-income country (LIC) using World Bank classifications (World Bank 2021), age at first dose*, sex*, sexual orientation, sexual history*, HPV serostatus*, morbidities (including HIV, previous HPV disease history, and other genital infections), smoking status*, drug misuse, indicators of socioeconomic status/poverty.
- Interventions: type of vaccine, number of doses and schedule*, comparison group*, co-interventions (e.g. presence of a screening programme in the country*, co-administration of other vaccines).
- Outcomes: primary and secondary outcomes specified and collected, and time points reported.
- Notes: sponsorship/funding for trial* (public/non-profit or industry/private), notable conflicts of interest of trial authors*, trial registry ID numbers.

We will consider variables marked with an asterisk (*) as effect modifiers. These will be evaluated in the context of the transitivity assumption by comparing the distribution of the potential effect modifiers across the available direct comparisons in the network (see Subgroup analysis and investigation of heterogeneity). Further, meta-regression and subgroup analyses will be carried out on variables described in the Subgroup analysis and investigation of heterogeneity section. Analyses will be stratified by type of vaccine, number of doses, sex, and age at first dose (see Data synthesis).

Assessment of risk of bias in included studies

We will employ standard Cochrane methodology for assessment of the risk of bias of included studies. This will involve the use of the updated risk of bias 2.0 (RoB 2) tool for assessing risk of bias in randomised trials (Sterne 2019). Two review authors will independently assess the risk of bias for each included study. Any disagreements will be resolved through discussion. When consensus cannot be reached between the two review authors, referral to a senior review author for a final decision will be made.

We will assess the risk of bias for those outcome measures and time points selected for the summary of findings tables. We will assess the effect of assignment to intervention at baseline (the 'intention-to-treat effect'), regardless of whether the interventions were received as intended.

We will assess the risk of bias in the following domains: 1) risk of bias arising from the randomisation process; 2) risk of bias due to deviations from intended interventions; 3) risk of bias due to missing outcome data; 4) risk of bias in measurement of the outcome; 5) risk of bias in selection of the reported result; 6) overall risk of bias based on the assessments in the five domains. For cluster-RCTs, we will also assess and report the risk of bias associated with an additional domain: timing of identification or recruitment of participants in a cluster.

In the RoB 2 tool there are a series of signalling questions within each domain that elicit information relevant to the assessment. The response options to the signalling questions are 'yes,' 'probably yes,' 'probably no,' 'no,' and 'no information'. A risk of bias judgement arising from each domain is generated by an algorithm, based on answers to the signalling questions. Judgements can be 'low risk of bias,' 'some concerns' or 'high risk of bias'. We will consider the overall risk of bias to be low if all domains are at low risk; some concerns if at least one domain is of some concern and no domain is at high risk; and high risk of bias if there is at least one domain considered to be at high risk, or several domains with some concerns (Higgins 2021).

When we assess the risk of bias due to deviations from intended interventions, we will consider screening as a co-intervention that may have an impact on study outcomes if it differs between intervention groups.

Measures of treatment effect

Relative treatment effects

We will estimate the pairwise relative treatment effects of the competing interventions using risk ratios (RRs) with their respective 95% CIs for dichotomous outcomes. Efficacy outcomes will be presented as % vaccine efficacy (VE = (1-RR)*100). We will calculate rate ratios with 95% CIs for dichotomous clinical outcomes reported as incidence rates. HRs will be combined using the generic inverse-variance method. We will assess the robustness of the primary analysis for very rare events (<1%), see Sensitivity analysis.

We will carry out a complete-case analysis (the number analysed) and an intention-to-treat analysis when data are available.

Data that are not usable for analyses, e.g. that were reported only as P values, will be tabulated and reported narratively.

Relative treatment ranking

We will obtain a hierarchy of the competing interventions using the surface under the cumulative ranking curve (SUCRA) and mean ranks. We will obtain a hierarchy of the different interventions according to the critical outcomes.

Unit of analysis issues

Cluster-randomised trials

For trials randomly assigned using clusters (cluster-RCTs), we will extract the intra-cluster correlation coefficient (ICC) when available; we will also record the number of clusters per group, the total size of clusters per group and the unit of randomisation (e.g. household or institution). The statistical methods used to analyse the trial results will be documented, along with details describing whether these methods were adjusted for clustering or for other co-variables.

We will pool cluster-RCT data that have been adjusted for clustering with data from trials that randomly assign individuals (individual-RCTs) using the generic inverse variance random-effects method. When the results of a cluster-RCT have not been adjusted for clustering, we will adjust the data using the clustering effect (ICC) imputed from another study (see chapter 23.1.4 Cochrane Handbook (Higgins 2022). We will perform sensitivity analyses excluding cluster-RCTs.

Dealing with missing data

If data on specific outcomes or population groups are missing, we will attempt to contact study authors or data owners to request this data. We will not impute missing outcome data. Where missing data are substantial (> 5%), we will assess the risk of bias due to missing outcome data in the RoB 2 tool as some concerns, or high risk (Sterne 2019).

Assessment of heterogeneity

We will assess the presence of clinical heterogeneity within each pairwise comparison by comparing the trial and study population characteristics across all eligible trials.

Measures and tests for heterogeneity

For pair-wise analyses, we will inspect forest plots visually to detect heterogeneity. We will report the I^2 values with 95% CIs to indicate statistical heterogeneity. Outcomes with considerable heterogeneity (I^2 > 75%) will not be pooled.

We will assess statistically the presence of heterogeneity in the entire network by calculating I^2. For I^2 we will consider that values over 50% suggest the presence of substantial heterogeneity in the entire network.

Assessment of statistical incoherence

Local approaches for evaluating incoherence

To evaluate the presence of local incoherence we will use the *network* macro for Stata (Stata 2017). We will consider loops/comparisons as potential sources of incoherence in the network based on the SIDE (Separating Indirect from Direct Evidence) approach.

Global approaches for evaluating incoherence

To evaluate coherence in the entire network simultaneously, we will use the *network* macro for Stata to develop incoherence models.

Assessment of reporting biases

To assess the risk of bias in a synthesis when entire studies or particular results within studies are missing selectively, we will carry out the following methods.

- Retrieve protocols and trial registry entries as part of our search and contact study authors of planned studies where results have not been made available for more information.

- Use the ORBIT tool on each included study by recording whether trials planned or measured outcomes but failed to report on them (Kirkham 2018). We will seek further information from study authors to resolve any unexplained discrepancies between protocol or trial registry and report.
- Inspect funnel plots for asymmetry (Page 2021). When interpreting the funnel plots we will bear in mind that asymmetry may be due to non-reporting bias, but could also be due to a real relationship between trial size and effect size (Sterne 2011).
- Undertake network meta-regression to account for small-study effects (Chaimani 2012).

Assessments of reporting biases will be carried out for the critical outcomes.

Data synthesis

Methods for direct treatment comparisons

We will perform standard meta-analyses using a random-effects model in RevMan Web (RevMan Web 2021). Analyses will be stratified by type of vaccine, number of doses, sex, and age at first dose. If age groups are mixed or unknown within a study and cannot be disaggregated, we will place studies in an age group if ≥75% participants qualify for that age group. If the proportions are more equal or unknown, we will analyse the study in a mixed age stratum.

Methods for indirect and mixed comparisons

We will include RCTs in the NMA providing that populations of included studies are sufficiently similar to satisfy the assumption of joint randomisation and that the interventions connect, creating a network. We have planned for six networks of sufficiently similar populations, for females and males and for age groups (younger adolescents ≤ 14 years, older adolescents 15 to 25 years, and adults > 25 years), see Table 2. For the critical outcomes and latest time points, we will estimate the effects (risk ratios (RRs) or odds ratios (ORs)) of the interventions and their 95% confidence intervals (CIs) using the random-effects model in Stata fitting a multivariate network.

Subgroup analysis and investigation of heterogeneity

We will assess the assumption of transitivity by comparing the distribution of the potential effect modifiers (listed in the Data extraction and management section) across the different pairwise comparisons.

If there is a sufficient number of included studies (highly likely), we will perform meta-regression analyses on the critical efficacy outcomes by using the following effect modifiers to explore their influence as possible sources of incoherence.

- Setting: LIC, MIC, HIC.
- HPV serological status at baseline: HPV seropositive/HPV seronegative.
- History of sexual activity: yes/no.
- Presence of screening programme: yes/no /mixed (for multinational trials).
- Schedule: longer (> 2 months) or shorter (≤ 2 months) duration between doses.
- Type of comparison group: saline placebo, adjuvant placebo, other non-HPV vaccine, no intervention.
- Funding source for trials: public/non-profit or industry/private.
- Study authors' conflicts of interest: yes/no.

Sensitivity analysis

To test the robustness of the data we will carry out several sensitivity analyses for the following critical outcomes.

- Rare events: where events were very rare (i.e. an event rate of < 1% across both trial arms), we will compare the results of the primary analysis calculated with Mantel-Hanzsel risk ratios against those with odds ratio Peto methods (Bradburn 2007).
- Intention-to-treat (ITT) analysis: we are prioritising available case analyses to avoid making assumptions about missing data. We will carry out sensitivity analyses using the ITT denominators.
- Risk of bias: we will exclude studies with overall high risk of bias.
- Trials with abstracts only: we will exclude trials that are only available as abstracts.
- Cluster trials: we will exclude cluster-RCTs.

Summary of findings and assessment of the certainty of the evidence

For pairwise comparisons we will prepare summary of findings tables (Appendix 1) for each comparison for which data are available for the following outcomes that were assessed as critical according to GRADE guidelines (Guyatt 2011):

- for females: invasive cervical cancer; HPV-associated vulval, vaginal, head and neck, or anal cancer; high-grade CIN (CIN3+); HPV-associated VIN, VAIN, or AIN; treatment rates for CIN and other HPV-related pre-invasive disease; anogenital warts; serious adverse events;
- for males: invasive anal cancer; HPV-associated penile or head and neck cancer; histologically-confirmed PeIN or AIN; HPV-associated PeIN or AIN; treatment rates for AIN and other HPV-related pre-invasive disease; anogenital warts; serious adverse events.

For the networks we will prepare summary of findings tables according to a format developed by Yepes-Nuñez (Yepes-Nuñez 2019) for each critical outcome (as above).

We will assess the certainty of evidence in the review through discussion between review authors using the GRADE approach with GRADEpro online software (GRADEpro 2021). We will assess only the primary outcomes reported in the summary of findings tables and appendices using GRADEpro. We will consider the following factors for downgrading the certainty of the evidence: limitations in the study design (overall risk of bias); inconsistency of results (heterogeneity); indirectness of evidence (applicability); imprecision (few events and wide confidence intervals); and publication bias (Guyatt 2011; Puhan 2014).

When certainty of evidence is downgraded, we will detail the reasons in footnotes of the summary of findings tables and summarise these in the 'Quality of the evidence' section. Depending on whether evidence is downgraded or not, we will rate the certainty of the evidence for each outcome as follows.

- High-certainty evidence indicates that we are very confident that the true effect lies close to that of the estimate of the effect (evidence will not be downgraded).
- Moderate-certainty evidence indicates that we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different (evidence will be downgraded one step for any of the factors described above).
- Low-certainty evidence indicates that our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect (evidence will be downgraded two steps for any of the factors described above).
- Very low-certainty evidence indicates that we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect (evidence will be downgraded three steps for any of the factors described above).

Stakeholder engagement

HPV vaccination is a major target for misinformation, especially targeting parents/carers via social media. We aim to provide robust and unbiased evidence for patients, clinicians and policymakers, to enable fully informed decision-making. This Cochrane HPV vaccine NMA is conducted in parallel with a Cochrane Review on long-term population impact of HPV vaccination, mainly from observational studies. These reviews are both high priority for Cochrane and will inform the WHO and national government screening and immunisation strategies at a global level. We are aware that this will subject the review authors to significant scrutiny from communities with concerns about vaccination in general, and HPV vaccination specifically, but we are committed to promoting evidence-based healthcare and improving outcomes for HPV-related disease globally.

An Independent Advisory Group (IAG), including consumers, will advise on review production and content, and respond to community concerns.

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ADDITIONAL TABLES

Table 1. Characteristics of WHO pre-qualified prophylactic HPV vaccines

	Cervarix	Gardasil	Gardasil 9	Cecolin
Manufacturer	GlaxoSmithKline (GSK, Rixensart, Belgium)	Merck, Sharp & Dome (Merck & Co, Whitehouse Station, NJ, USA)	Merck, Sharp & Dome (Merck & Co, Whitehouse Station, NJ, USA)	Xiamen Innovax Biotech Co. Ltd. (Xiamen, Fujian province, China)
Antigens	Bivalent: L1 VLPs of HPV16 (20 µg) and HPV18 (20 µg)	Quadrivalent: L1 VLPs of HPV6 (20 µg), HPV11 (40 µg), HPV16 (40 µg) and HPV18 (20 mg)	Nonavalent: L1 VLPs of HPV6 (30 µg), HPV11 (40 µg), HPV16 (60 µg), HPV18 (40 mg),HPV31 (20 µg), HPV33 (20 µg), HPV45 (20 µg), HPV52 (20 µg)and HPV58 (20 µg)	Bivalent: L1 VLPs of HPV16 (40 µg) and HPV18 (20 µg)

Table 1. Characteristics of WHO pre-qualified prophylactic HPV vaccines *(Continued)*

Vaccination schedule	3 doses: at day 1, month 1, and month 6	3 doses: at day 1, month 2, and month 6	3 doses: at day 1, month 2, and month 6	2 doses: at day 1 and month 6
Adjuvant	AS04: 500 µg aluminium hydroxide, 50 µg 3-deacylated monophosphoryl lipid A (MPL)	225 µg amorphous aluminium hydroxyl-phosphate sulphate	500 µg amorphous aluminium hydroxyl-phosphate sulphate	208 µg aluminium adjuvant
Trade name	Cervarix	Gardasil, Silgard	Gardasil-9	Cecolin
Produced by recombinant technology using	Baculovirus in Trichoplusia in insect cells	Saccharomyces cerevisae (Baker's yeast)	Saccharomyces cerevisae (Baker's yeast)	Escherichia coli

Abbreviations: **HPV:** human papillomavirus; MPL: monophosphoryl lipid; VLP: virus-like particle.

Table 2. Nodes in the network*

Grouped intervention	**Subgrouped by dose**
bi valent Cervarix	1 dose
	2 doses
	3 doses
quadri valent Gardasil	1 dose
	2 doses
	3 doses
nona valent Gardasil-9	1 dose
	2 doses
	3 doses
bi valent Cecolin	1 dose
	2 doses
	3 doses
Control groups	
Injection control**: Adjuvant placebo; Saline placebo; Non-HPV control vaccine (active control, e.g., HBV, HAV)	
No intervention control	

*The nodes presented in Table 1 are for the following 6 networks:
- Network 1: Safety and efficacy of HPV vaccines in females ≤ 14 years
- Network 2: Safety and efficacy of HPV vaccines in females 15-25 years
- Network 3: Safety and efficacy of HPV vaccines in females > 25 years

- Network 4: Safety and efficacy of HPV vaccines in males ≤ 14 years
- Network 5: Safety and efficacy of HPV vaccines in males 15-25 years
- Network 6: Safety and efficacy of HPV vaccines in males > 25 years

**The components of injection control (saline, adjuvant, other vaccine) will be analysed in a meta-regression, see Subgroup analysis and investigation of heterogeneity.

APPENDICES

Appendix 1. Template summary of findings tables

Template summary of findings: Safety and efficacy of prophylactic HPV vaccination in females

Outcome Follow-up	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)** **N° of participants & studies**	**Certainty of the evidence (GRADE)**
	Assumed risk with placebo	**Corresponding risk with HPV vaccine**		
Invasive cervical cancer Follow-up: longest time point reported	[n] per 1000	[n] per 1000 ([n] to [n])	RR [estimate] [n] participants in [n] RCTs	[LEVEL OF CERTAINTY][footnotes]
HPV-associated vulval, vaginal, head and neck, or anal cancer Follow-up: longest time point reported	[n] per 1000	[n] per 1000 ([n] to [n])	RR [estimate] [n] participants in [n] RCTs	[LEVEL OF CERTAINTY][footnotes]
Histologically confirmed high grade cervical lesions (CIN3 +), irrespective of HPV genotype Follow-up: longest time point reported	[n] per 1000	[n] per 1000 ([n] to [n])	RR [estimate] [n] participants in [n] RCTs	[LEVEL OF CERTAINTY][footnotes]
HPV-associated vulval (VIN), vaginal (VAIN), or anal intraepithelial neoplasia (AIN) Follow-up: longest time point reported	[n] per 1000	[n] per 1000 ([n] to [n])	RR [estimate] [n] participants in [n] RCTs	[LEVEL OF CERTAINTY][footnotes]
Treatment rates for CIN and other HPV-related pre-invasive disease Follow-up: longest time point reported	[n] per 1000	[n] per 1000 ([n] to [n])	RR [estimate] [n] participants in [n] RCTs	[LEVEL OF CERTAINTY][footnotes]
Anogenital warts Follow-up: longest time point reported	[n] per 1000	[n] per 1000 ([n] to [n])	RR [estimate] [n] participants in [n] RCTs	[LEVEL OF CERTAINTY][footnotes]
Serious adverse events Follow-up: longest timepoint reported	[n] per 1000	[n] per 1000 ([n] to [n])	RR [estimate] [n] participants in [n] RCTs	[LEVEL OF CERTAINTY][footnotes]

[footnotes: explaining reasons for downgrading the evidence]

Template summary of findings: Safety and efficacy of prophylactic HPV vaccination in males

Outcome Follow-up	Illustrative comparative risks* (95% CI)		Relative effect (95% CI) N° of participants & studies	Certainty of the evidence (GRADE)
	Assumed risk with placebo	Corresponding risk with HPV vaccine		
Invasive anal cancer Follow-up: longest timepoint reported	[n] per 1000	[n] per 1000 ([n] to [n])	RR [estimate] [n] participants in [n] RCTs	[LEVEL OF CERTAINTY][footnotes]
HPV-associated penile or head and neck cancer Follow-up: longest time point reported	[n] per 1000	[n] per 1000 ([n] to [n])	RR [estimate] [n] participants in [n] RCTs	[LEVEL OF CERTAINTY][footnotes]
Histologically-confirmed penile (PeIN) or anal (AIN) intraepithelial neoplasia, irrespective of HPV genotype Follow-up: longest time point reported	[n] per 1000	[n] per 1000 ([n] to [n])	RR [estimate] [n] participants in [n] RCTs	[LEVEL OF CERTAINTY][footnotes]
HPV-associated penile (PeIN) or anal (AIN) intraepithelial neoplasia Follow-up: longest time point reported	[n] per 1000	[n] per 1000 ([n] to [n])	RR [estimate] [n] participants in [n] RCTs	[LEVEL OF CERTAINTY][footnotes]
Treatment rates for AIN and other HPV-related pre-invasive disease Follow-up: longest time point reported	[n] per 1000	[n] per 1000 ([n] to [n])	RR [estimate] [n] participants in [n] RCTs	[LEVEL OF CERTAINTY][footnotes]
Anogenital warts Follow-up: longest time point reported	[n] per 1000	[n] per 1000 ([n] to [n])	RR [estimate] [n] participants in [n] RCTs	[LEVEL OF CERTAINTY][footnotes]
Serious adverse events Follow-up: longest time point reported	[n] per 1000	[n] per 1000 ([n] to [n])	RR [estimate] [n] participants in [n] RCTs	[LEVEL OF CERTAINTY][footnotes]

[footnotes: explaining reasons for downgrading the evidence]

Appendix 2. Social media analysis of adverse events following HPV vaccination

We sought to identify adverse events that were potentially related to HPV vaccination that were commonly mentioned in social media.

Firstly, all of the reviews on WebMD (www.webmd.com) of HPV vaccines were screened to identify mentions of adverse events. Each mention of a personal experience was coded where possible to MedDRA preferred terms.

276 adverse events were mentioned and annotated. The most common adverse events were injection site pain, headaches, and missed periods.

WebMD adverse event mentions (rank order of frequency)	Adverse event
1	injection site pain
2	headache
3	missing periods
4	dizziness
5	fatigue
6	nausea
7	myalgia
8	fever
9	malaise
10	pain
11	syncope
12	abdominal pain
13	influenza-like illness
14	alopecia
15	cramping
16	dyspnoea
17	rash
18	tremor
19	vomiting
20	anxiety
21	arthralgia
22	chest pain
23	cough
24	diarrhoea

(Continued)

25	infertility
26	syncope (recurrent)
27	tingling
28	aluminium toxicity
29	back pain
30	death
31	dehydration
32	hives
33	hypoaesthesia
34	insomnia
35	migraine
36	shoulder pain
37	swollen glands
38	seizure
39	auto-immune disease

We also investigated an analysis of "Tweets" on Twitter (twitter.com). Recent news events with the release of the results of a clinical trial and activity on Twitter related to the COVID-19 vaccines meant that recent posts suffered from a lot of noise. Many posts mentioning adverse events were also doing so to promote an anti-HPV vaccination stance rather than personal experience, with accounts dedicated to promoting HPV side effect information (@HPVSideEffects) and reference to the vaccine as 'Human Paralysis inducing Vaccine'. Refusal of the vaccine was also stated to be related to parents not wanting to promote sexual activity in their children.

We were able to uncover 46 recent adverse events experience mentions.

WebMD adverse event mentions (rank order of frequency)	**Adverse event**
1	death
2	auto-immune disease
3	chronic fatigue syndrome
4	inability to walk
5	infertility

(Continued)

6	myalgic encephalomyelitis
7	paralysed
8	seizures/epilepsy
9	tremors
10	aluminium toxicity
11	anxiety
12	chronic kidney disease
13	encephalitis
14	epilepsy
15	Epstein Barr
16	functional neurologic disorder
17	Hashimoto's disease
18	heart problem
19	missing periods
20	myocarditis
21	nervous breakdown
22	pain
23	Postural orthostatic tachycardia syndrome
24	stuttering
25	syncope
26	Systemic lupus erythematosus
27	weakness
28	Amyotrophic lateral sclerosis

Appendix 3. Medline Search Strategy

1. exp Papillomavirus Vaccines/
2. gardasil*.mp.
3. cervarix*.mp.
4. ((human papilloma virus* or human papiloma virus*) adj (vaccin* or immuni*)).tw.
5. ((human papillomavirus* or human papilomavirus*) adj (vaccin* or immuni*)).tw.
6. (HPV* adj3 (vaccin* or immuni*)).tw.
7. 1 or 2 or 3 or 4 or 5 or 6
8. randomized controlled trial.pt.

9. controlled clinical trial.pt.
10. randomized.ab.
11. placebo.ab.
12. drug therapy.fs.
13. randomly.ab.
14. trial.ti.
15. groups.ab.
16. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17. (animals not (humans and animals)).sh.
18. 16 not 17
19. 7 and 18

CONTRIBUTIONS OF AUTHORS

JM conceived and designed the review. HB, NH, and JM drafted the protocol, with input and approval from all the other authors.

DECLARATIONS OF INTEREST

Henschke N, Bergman H, Villanueva G, Loke YK, Morrison J, Golder S, Crosbie EJ, Kyrgiou M, Dwan K.

- **Nicholas Henschke:** reports contracts to update a systematic review on immunogenicity, efficacy and effectiveness on different schedules of rotavirus vaccines in 2018 and 2019 from the World Health Organization, Initiative for Vaccine Research; payment to institution. NH has been employed since 2016 by Cochrane Response, an evidence consultancy initiative from Cochrane, Cochrane Response was commissioned by WHO to perform reviews and by Cochrane CET to perform tasks on this review. NH reports payment for travel costs to present findings of systematic review at WHO SAGE working group meeting on HPV immunization in September 2018 and June 2019 from the World Health Organization, Initiative for Vaccine Research; payment to institution.
- **Hanna Bergman:** reports contracts to update a systematic review on immunogenicity, efficacy and effectiveness on different schedules of rotavirus vaccines in 2018 and 2019 from the World Health Organization, Initiative for Vaccine Research; payment to institution. HB reports payment for travel costs to present findings of systematic review at WHO SAGE working group meeting on HPV immunization in September 2018 and June 2019 from the World Health Organization, Initiative for Vaccine Research; personal payment. HB will be paid to carry out this review as part of an ongoing consultancy contract with Cochrane Response; personal payment.
- **Gemma Villanueva**: reports being an employee of Cochrane Response since 2017. Cochrane Response was commissioned by NIHR to perform parts of this systematic review.
- **Yoon Kong Loke**: reports grant funding from the NIHR; payment to institution.
- **Jo Morrison:** reports NIHR grant to support performing this review (academic support to perform review from non-conflicted source); personal payment. JM is the Co-Chair of BGCS guidelines subgroup; unpaid position (this has no COI with this review rather the review informs the guidelines). JM has published opinions inTwitter, Cochrane editorial about controversy of previous version of HPV vaccine reviews (has tweeted results of the previous versions of HPV vaccine reviews). JM is a consultant gynaecologist in Somerset NHS FT, JM treats patients with HPV-related conditions, including cervical and vulval cancer and pre-cancer. Clinical expertise informed by the results of the studies included in the previous HPV vaccine reviews and is a member of the NHS Cervical Screening Research Advisory Committee (unpaid). JM was a Co-Ed in Cochrane at time of previous versions of HPV vaccine reviews.
- **Su P Golder:** declared that they have no conflict of interest.
- **Emma J Crosbie:** declared that they have no conflict of interest.
- **Maria Kyrgiou: Maria Kyrgiou:** reports NIHR EME grant to support the NOVEL trial (trial assessing value of vaccine in women having conisation for CIN), MSD is only providing the vaccine for this trial; the NIHR EM grant payment is to the institution. MK is an author of the article 'Human papillomavirus vaccination: The ESGO-EFC position paper of the European society of Gynaecologic Oncology and the European Federation for colposcopy' (Joura EA, Kyrgiou M, Bosch FX, Kesic V, Niemenen P, Redman CW, Gultekin M. Eur J Cancer. 2019 Jul;116:21-26. doi: 10.1016/j.ejca.2019.04.032. Epub 2019 Jun 1. PMID: 31163338). MK works as consultant in the Imperial Healthcare NHS Trust.

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