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[Intervention Protocol]

Effects of human papillomavirus (HPV) vaccination programmes on community rates of HPV-related disease and harms from vaccination

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ABSTRACT

Objectives

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

We aim to assess population-level effects of human papillomavirus (HPV) vaccination programmes on HPV-related disease and harms from vaccination.

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 world-leading 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 were 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 was 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). 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 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 increase in the rate of detection of CIN and is likely to reduce the rate of cervical cancer within a population over time. However, unless background rates of hrHPV and high-grade CIN also fall, this will increase the treatment rates for CIN.

Description of the intervention

HPV vaccines were first licenced 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).

The uptake of HPV vaccination varies widely between countries: in 2017 coverage rates ranged from 8% to 98% across 82 countries (Brotherton 2018). WHO estimated only 13% global HPV vaccine coverage in 2020, a reduction from 15% in 2019, despite the vaccine being available since 2006 (WHO 2021a). 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 have been pre-qualified by WHO (see Table 1). Each vaccine is directed against two or more high-risk HPV genotypes. All four vaccines contain L1 proteins of HPV genotypes 16 and 18 (Qiao 2020; WHO 2017), because these cause about 70% of cervical cancer 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).

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).

Why it is important to do this review

Prevention or early detection of cancer is a major priority within health care, especially within the UK where survival rates 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. HPV vaccination, especially in countries where screening programmes are currently unaffordable, has the potential to be transformative.

Although conventional Cochrane Reviews of randomised controlled trials (RCTs) have demonstrated effectiveness of HPV vaccination, due to the relatively short time periods of the studies, effective screening and follow-up of those in the studies, outcome measures are surrogate end points, rather than cervical cancer outcomes. As HPV can cause a variety of cancers in both males and females, short-term RCTs are unlikely to capture the population-level benefits of HPV vaccination, especially in un- or under-screened individuals and populations. Additionally, even very large RCTs are unlikely to be able to fully evaluate rare and very rare adverse events, of treatment or non-treatment, including those later events, such as premature delivery of infants due to treatment of CIN, which could otherwise have been avoided (Kyrgiou 2017), and prevention of long-term complications from cancer treatment, such as lymphoedema and late effects of radiotherapy. Furthermore, benefits of vaccination in a population may extend out to non-vaccinated individuals, if vaccination levels are high enough, due to the development of herd immunity, by reducing the prevalence of an infection in a population. Larger, population-level, non-randomised studies (NRS) are therefore better able to inform of the absolute harms and benefits of HPV vaccination, beyond that of selected trial participants. Outcome data on long-term effects of HPV vaccination are now becoming available and recent studies demonstrate improvement in both cervical cancer rates and preterm delivery rates in HPV vaccinated cohorts (Aldhous 2019; Falcaro 2021; Lei 2020). The full impact of HPV vaccination on cancer incidence will not be known for many years, since the natural history of vulval, penile and head and neck cancers, caused by hrHPV, is much longer.

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 more fully evaluate these outcomes, to provide reliable data to young people, parents, clinicians, policymakers, and others when they are making choices about vaccination.

A comprehensive examination of the 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 data from population-level studies. It is hoped that these data will better inform the public debate about the benefits and harms of HPV vaccination and allow better-informed decision-making.

This review will look at NRS of the effects of introducing HPV vaccination at a population-level on rates of HPV-related disease and harms, not just in the individuals vaccinated, thereby more fully informing the harms and benefits of vaccination, which may not be apparent even in large RCT-level datasets. We aim to evaluate RCTs in a parallel Cochrane Review. 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 assess population-level effects of human papillomavirus (HPV) vaccination programmes on HPV-related disease and harms from vaccination.

METHODS

Criteria for considering studies for this review

Types of studies

We will include studies that assess the impact of HPV vaccination on the general population. This includes population-level studies comparing outcomes before and after introduction of HPV vaccine such as pre- versus post-vaccine introduction studies, interrupted time series studies, and controlled before-and-after studies. We will also include individual-level, non-randomised comparative studies such as cohort studies, case-control studies, and self-controlled case series. This will include follow-up of cohorts that were originally included in randomised controlled trials (RCTs). We will not include non-comparative studies, such as single-arm cohorts, case series, or case reports, nor modelling studies, or RCTs. We will include studies that are self-described as the above designs, however the final decision on the design will be made by the review author team. Definitions for the different study designs to be included are provided in Appendix 1.

Types of participants

The target population for vaccination is adolescents, although some countries also vaccinate adults. The general population will be included, and where possible, analyses will be stratified by age at vaccination and sex. If age groups are mixed within a study and cannot be disaggregated, we will place studies in a group if ≥75% participants qualify for that group. If the proportions are more equal or unknown, we will analyse the study in a mixed stratum.

Types of interventions

We will investigate primary prophylactic administration of HPV vaccines pre-qualified by WHO (WHO 2021b), including Cervarix (bivalent, GlaxoSmithKline), Gardasil (quadrivalent, Merck), Gardasil 9 (nonavalent, Merck), or Cecolin, (bivalent, Innovax) HPV vaccine (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.

We will include studies that compare vaccination with any of the HPV vaccines with no vaccination. Partial vaccination schedules compared with no vaccination will be investigated using subgroup analysis.

Types of outcome measures

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 (see 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 potential for HPV vaccination to promote sexual promiscuity.

Any measure of the below outcomes will be eligible for inclusion. While the duration and completeness of follow-up may vary, we will extract all relevant outcomes and time points reported. We will stratify all analyses by outcome time point as immediate term (< 4 weeks); short term (< 1 year); medium term (1 to 5 years); and long term (> 5 years).

Primary outcomes

- Invasive cervical, vaginal, vulval, anal, penile, or head and neck cancer rates.
- In females, histologically-confirmed high-grade cervical (CIN2, CIN3, and adenocarcinoma in situ (AIS)), vaginal, vulva, or anal intraepithelial neoplasia (AIN), irrespective of HPV genotype, or any lesions associated with the HPV genotypes included in the vaccine.
- 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.
- Specific adverse events: 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; indicators of sexual activity. We will also report whether adverse events were monitored systematically and proactively or self-reported spontaneously.

Secondary outcomes

- Participation rates in screening.
- Treatment rates for CIN and other HPV-related pre-invasive disease.
- Anogenital warts.
- In females, miscarriage and pre-term birth rates, and neonatal outcomes.
- All-cause mortality. We will tabulate causes of death where this information is available.
- 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).
- 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).
- Persistent infection (persisting for at least six months or at least 12 months) 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).

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);
- the 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 1, 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 trial 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;
- 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, EUROGIN (EUropean Research Organisation on Genital Infection and Neoplasia) 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 trial authors of relevant studies to ask if they know of further data which may or may not have been published.

We will also search vaccine manufacturer websites for any relevant non-randomised studies (NRS).

Data collection and analysis

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

Selection of studies

Citations and abstracts will be screened independently, in duplicate by Cochrane Crowd and one of our systematic reviewer team members. A third review author will resolve any disagreements. Cochrane Crowd is Cochrane's citizen science platform, hosting citation screening tasks. Evaluations of Crowd accuracy have shown very high levels of sensitivity (99%) and specificity (99%) for RCTs (Noel-Storr 2021). We will develop a learning module and agreement algorithm for the Crowd to screen for NRS. 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.

We will check all studies for potential overlapping populations. Where we consider populations to be overlapping, e.g., if two studies include people in the same region during overlapping time periods, we will only include one study in the meta-analysis if the studies report on the same outcomes. This will be the study with the most comprehensive coverage of the population.

Data extraction and management

Two review authors will carry out data extraction independently using pretested 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. Where there are two or more sources of data with conflicting information, we will note the conflict and attempt to contact study authors for clarification.

Outcome data and confounders

We will collect outcome definitions, source of outcome data, and duration since vaccination for each outcome.

We will collect the number of participants experiencing an outcome event and the number of participants analysed in each group. Where only rates are reported, we will collect the event rate or the number of events and the person-years in each intervention group. Where available, adjusted effect estimates with their respective measure of variance (standard error (SE), standard deviation (SD), or 95% confidence interval (95% CI)) will be extracted. Data will be collected on any confounding factors considered in the analysis and the methods used to control for confounding.

We will preferentially extract outcomes assessed by the most clinically valid measure and effect estimates adjusted for the most confounders.

We will assess whether there was targeted ascertainment of pre-specified participant outcomes, or if the information had to be extracted from routine healthcare administrative or insurance databases, which were not designed specifically for research measurement.

Study characteristics

We will record information on the following study characteristics.

- Methods: study design, study dates, duration of follow-up, source of data.
- Setting: country and location, country income level (high- (HIC), upper-middle- (UMIC), lower-middle- (LMIC), or low-income country (LIC) using World Bank classifications (World Bank 2021).
- Population: sample size, sex, sexual orientation, age at first dose, age at outcome collection, morbidities, and socioeconomic status.
- Intervention: vaccine type, vaccination schedule (doses, interval), start date of vaccination programme, participation rates in vaccination HPV programme, co-interventions (type (primary HPV versus cytological with or without HPV-triage) and participation rates of cervical screening programme in the population).
- Notes: source of funding, conflicts of interest of study authors.

Assessment of risk of bias in included studies

We will assess the risk of bias of all included studies using different tools according to study design. For NRS of interventions, e.g. cohort, case-control, historical control, controlled before-and-after, and interrupted time series studies, we will use the ROBINS-I tool (Sterne 2016; Sterne 2021). In the ROBINS-I tool, the following risks of bias will be assessed: confounding, selection bias, bias in

classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measurement of outcomes, and bias in selection of the reported result. For other study designs, such as self-controlled case series, we will use different methodological quality checklists based on the key sources of bias (Farrington 2004, Petersen 2016).

Two review authors will independently assess the risk of bias of each result included in the summary of findings tables. Any disagreements will be resolved through discussion, and if consensus cannot be reached a third review author will decide. Following assessment of all included studies, reliability and consistency of ratings across the studies will be ensured through discussion among the review team. Any further disagreements will be resolved through discussion within the review team.

As part of the risk of bias assessment, a preliminary specification of important confounders and co-interventions has been made using directed acyclic graphs (Suttorp 2015). These confounders and co-interventions were derived from the adjustment and stratification variables used in analyses of known studies, variables mentioned or used in relevant systematic reviews (Drolet 2019; Markowitz 2018), and variables used in an ongoing living systematic review assessing risk of bias in observational studies on COVID vaccines (COVID NMA 2021).

We consider the most important confounding domains to be as follows.

Time-fixed confounders

- Age
- Sex
- Socioeconomic status
- Ethnicity
- Geographic location
- Preventive health-seeking behaviour

Time-varying confounders

- Calendar time (to reflect changing incidence of virus and time since vaccine introduction)

We consider the most important co-intervention to be presence of a cervical cancer screening programme in the country in which the study was conducted.

The results of the risk of bias assessments will be summarised and will provide an evaluation of the overall methodological quality of the included studies. They will also contribute to GRADE ratings of the certainty of the evidence on an outcome basis.

Measures of treatment effect

Where data permit, we will combine adjusted point estimates using risk ratios (RR), odds ratios (OR), hazard ratios (HR), or relative incidence (RI) and their 95% CIs. We will use the DerSimonian and Laird random-effects method (DerSimonian 1986).

If several adjusted estimates are reported within a study, we will give preference to the estimate that adjusts for the most important confounders that we have pre-specified for the review.

Unit of analysis issues

Unit of analysis issues are not expected. We will analyse partial and full vaccination separately.

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 these 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 ROBINS-I tool as moderate or serious risk (Sterne 2016).

Assessment of heterogeneity

Clinical and methodological heterogeneity

We will not pool data from different study designs. Analyses will be stratified by study design, type of vaccine, age at first dose and sex. If these characteristics are mixed or unknown within a study and cannot be disaggregated, we will analyse such studies in a mixed group. Potential sources of heterogeneity will be described, and the certainty of the evidence downgraded according to GRADE criteria, where appropriate.

Statistical heterogeneity

When pooling of studies is feasible (at least two studies included), forest plots will be visually inspected for potential outlying studies and variability in the estimated effects across studies. Statistical heterogeneity will be assessed using the I^2 statistic. This statistic quantifies the percentage of inconsistency in the treatment effects across studies beyond simple chance.

Assessment of reporting biases

For all included studies we will search for published or online study protocols or statistical analysis plans. The presence or absence of these will be recorded in the study characteristics tables and addressed by the risk of bias tools. Where studies do not explicitly report on outcomes we will not consider them at risk of selective reporting, unless there is evidence that they were planned and omitted from the report.

Data synthesis

The inclusion of various study designs in this review that use different estimation methods and statistical models means that we will calculate different measures of effect and interpret these separately. We will carry out quantitative and qualitative data syntheses separately for effectiveness and safety (harms).

We will group studies for quantitative analysis according to study design (see Types of studies and Appendix 1) and outcome. All analyses will be stratified by age at vaccination, sex, type of vaccine, and outcome time point. We will analyse all outcomes according to time from first vaccination, considering short term to be less than 12 months, medium term from 12 months to 5 years, and long term for follow-up longer than 5 years. If a study reports multiple time points within these categories, we will prioritise the longest time point for meta-analysis. Where necessary, we will contact corresponding authors of included studies to request their data using the same data stratifications (e.g. by age group or HPV type) to allow comparison between studies and pooling.

To account for confounding, if both adjusted and unadjusted estimates are reported within a study, we will give preference to the estimate that adjusted for the most important confounders for the review. Where data permit, we will combine adjusted point estimates in the first instance using the generic inverse variance method. If adjusted point estimates are not available, we will combine unadjusted estimates using the DerSimonian and Laird random-effects model (DerSimonian 1986).

We will check all observational studies for potential overlapping populations, based on the location, study dates, and source of the population and outcome data. Where we consider studies to be overlapping, we only included one study in the meta-analysis. This will be the study with the lowest risk of bias, the largest sample size, or that covered the longest time period.

We will use RR and its CI as measures of effect for cohort studies and population-level studies. We will use the OR and its CI for case-control studies. For self-controlled case series studies we will calculate a RI and its CI. Where necessary, we will transform effect estimates according to the recommendations in the Cochrane Handbook (Higgins 2022).

When meta-analysis is not possible or appropriate, we will use 'Synthesis without meta-analysis' (SWiM) methodology (Campbell 2020).

Subgroup analysis and investigation of heterogeneity

We will carry out subgroup analyses by time since vaccination programme introduction and partial versus full schedule.

Sensitivity analysis

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

- Risk of bias: we will exclude studies with overall critical or high risk of bias.
- Performing meta-analysis using the Hartung-Knapp-Sidik-Jonkman method (IntHout 2014).
- Studies reported only as abstracts: we will exclude studies that are only reported as abstracts.

Summary of findings and assessment of the certainty of the evidence

We will prepare summary of findings tables (Schünemann 2021) for HPV vaccination compared with no vaccination, stratified by sex and study design. 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) for the following outcomes.

- In females, invasive cervical, vaginal, vulval, anal, or head and neck cancer rates; histologically-confirmed high grade cervical (CIN3 and adenocarcinoma in situ (AIS)), vaginal, vulva, or anal intraepithelial neoplasia (AIN), irrespective of HPV genotype.
- In males, invasive anal, penile, or head and neck cancer rates; histologically-confirmed penile (PeIN), or anal (AIN) intraepithelial neoplasia of any grade irrespective of HPV genotype.
- For all populations: anogenital warts, severe adverse events.

We will create separate summary tables for specific adverse event outcomes, recording the number and type of studies evaluating each adverse event, number of participants analysed, and the estimates of effect comparing vaccination with no vaccination.

NRS will start as high-certainty evidence, and 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). In addition, evidence can be upgraded if the pooled estimates revealed a large magnitude of effect or a dose-response gradient is apparent (Schünemann 2019).

When the 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 population level effect review is conducted in parallel with a Cochrane network meta-analysis of randomised controlled trials. These reviews are both high priority for Cochrane and will inform the WHO and national government screening and immunisation strategies at national and global levels. 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 health care 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)
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*

HPV: human papillomavirus; **VLP:** virus-like particles.

APPENDICES

Appendix 1. Medline Search Strategy

1. exp Papillomavirus Vaccines/
2. gardasil*.mp.
3. (cervarix* or cecolin*).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. ae.fs.
9. safe*.ti,ab.
10. de.fs.
11. adverse.ti,ab.
12. co.fs.
13. side effect*.ti,ab.
14. complication*.ti,ab.
15. ci.fs.
16. tolerated.ti,ab.
17. tolerance.ti,ab.
18. harm*.ti,ab.
19. toxicity.ti,ab.
20. risk.ti.
21. Pregnancy complications/dt
22. Clinical trial phase IV.pt.
23. Drug hypersensitivity/
24. Tolerability.ti,ab.
25. to.fs.
26. toxicology/
27. Drug induced.ti,ab.
28. Negative effects.ti,ab.
29. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30. exp cohort studies/ or exp epidemiologic studies/ or exp clinical trial/ or exp evaluation studies as topic/ or exp statistics as topic/
31. (control and (group* or study)).mp.
32. (time and factors).mp.
33. Program.mp.
34. survey*.mp.
35. ci.mp.
36. cohort.mp.
37. (comparative stud* or prospective* or retrospective* or longitudinal*).mp.
38. evaluation studies.mp.
39. 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38
40. (animals/ not humans/) or comment/ or editorial/ or exp review/ or meta analysis/ or consensus/ or exp guideline/
41. case report.mp.
42. 40 or 41
43. 39 not 42
44. 7 and 29
45. 43 and 44

Appendix 2. Social Media Analysis of HPV Vaccine Adverse Events

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 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.

There were 276 adverse events 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
25	infertility
26	syncope (recurrent)

(Continued)

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. 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
6	myalgic encephalomyelitis
7	paralysed

(Continued)

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. Study design definitions

Population level studies

Pre- versus post-vaccine introduction studies: a type of ecologic study that focuses on the comparison of groups, rather than individuals. Studies compare the frequency of an outcome between pre-vaccination and post-vaccination periods among the general population and should use the same population source and recruitment methods before and after vaccination. These types of studies are often considered to evaluate the 'impact' of vaccine introduction.

Interrupted time-series study (ITS): a study that uses observations at multiple time points before and after an intervention (the ‘interruption’). The design attempts to detect whether the intervention, in this case HPV vaccine introduction, has had an effect significantly greater than any underlying trend over time (Reeves 2022).

Controlled before-and-after study (CBA): a study in which observations are made before and after the implementation of an intervention, both in a group that receives the intervention and in a control group that does not.

Individual level studies

Prospective cohort study/retrospective cohort study: an epidemiological study where groups of individuals are identified who vary in their exposure to an intervention or hazard and are followed to assess outcomes. Association between exposure and outcome are then estimated. Cohort studies are best performed prospectively (prospective cohort study) but can also be undertaken retrospectively (retrospective cohort study) if suitable data records are available. We will consider non-randomised comparative studies e.g. comparisons of a vaccinated group with an unvaccinated group as a type of cohort study.

Case-control study: an epidemiological study usually used to investigate the causes of disease. Study participants who have experienced an adverse outcome or disease are compared with participants who have not. Any differences in the presence or absence of hypothesised risk factors are noted.

Self-controlled cases series study (SCCS): uses individuals as their own controls. The ages at vaccination are regarded as fixed, and the age at the time of an adverse event is the random variable of interest within a predetermined observation period (Farrington 2004; Petersen 2016).

CONTRIBUTIONS OF AUTHORS

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

DECLARATIONS OF INTEREST

- **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. 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. NH will be paid to carry out this review as part of an ongoing consultancy contract with Cochrane Response.
- **Hanna Bergman**: reports contracts to update a systematic review on safety, 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.
- **Su P Golder:** declared that they have no conflict of interest.
- **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 on Twitter, 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.
- **Emma J Crosbie:** declared that they have no conflict of interest.
- **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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