Assessing the cost-effectiveness of HPV vaccination strategies for adolescent girls and boys in the UK

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Abstract

Background Human papillomavirus (HPV) is the most widespread sexually transmitted infection worldwide. It causes several health consequences, in particular accounting for the majority of cervical cancer cases in women. In the United Kingdom, a vaccination campaign targeting 12-year-old girls started in 2008; this campaign has been successful, with high uptake and reduced HPV prevalence observed in vaccinated cohorts. Recently, attention has focused on vaccinating both sexes, due to HPV-related diseases in males (particularly for high-risk men who have sex with men) and an equity argument over equalising levels of protection.

Methods We constructed an epidemiological model for HPV transmission in the UK, accounting for nine of the most common HPV strains. We complemented this with an economic model to determine the likely health outcomes (healthcare costs and quality-adjusted life years) for individuals from the epidemiological model. We then tested vaccination with the three HPV vaccines currently available, vaccinating either girls alone or both sexes. For each strategy we calculated the threshold price per vaccine dose, i.e. the maximum amount paid for the added health benefits of vaccination to be worth the cost of each vaccine dose. We calculated results at 3.5% discounting, and also 1.5%, to consider the long-term health effects of HPV infection.

Results At 3.5% discounting, continuing to vaccinate girls remains highly cost-effective compared to halting vaccination, with threshold dose prices of £56-£108. Vaccination of girls and boys is less cost-effective (£25-£53). Compared to vaccinating girls only, adding boys to the programme is not cost-effective, with negative threshold prices (-£6 to -£3) due to the costs of administration. All threshold prices increase when using 1.5% discounting, and adding boys becomes cost-effective (£36-£47). These results are contingent on the UK's high vaccine uptake; for lower uptake rates, adding boys (at the same uptake rate) becomes more cost effective.

Conclusions Vaccinating girls is extremely cost-effective compared with no vaccination, vaccinating both sexes is less so. Adding boys to an already successful girls-only programme has a low cost-effectiveness, as males have high protection through herd immunity. If future health effects are weighted more heavily, threshold prices increase and vaccination becomes cost-effective.

Index terms— HPV, sexually transmitted infection, human papillomavirus, epidemiology, modelling, MCMC, cost-effectiveness, vaccination

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Background

Human papillomavirus (HPV) is the world's most common sexually transmitted infection, with the majority of people being infected at some point in their lifetime ([1, 2]). At any time, up to 44% of sexually active women are infected ([3, 4]). Although for most people it is symptomless and they recover from the infection with no adverse effects, for a small proportion the infection may lead to adverse health sequelae. Of the 200 strains known and 120 catalogued thus far ([5, 6]), at least 18 have been labelled 'high-risk' HPV types due to their associations with development of different cancers ([7]); in particular, strains 16 and 18 are associated with the majority of cervical cancers ([8, 9]). The high health and economic burden caused by HPV infection has led to many countries initiating HPV vaccinations campaigns.. Available vaccines include: a bivalent vaccine protecting against HPV-16 and HPV-18 (Cervarix®) and a quadrivalent vaccine, which also protects against HPV-6 and HPV-11 (Gardasil®), both of which are linked to genital warts in both sexes ([10]). A nonavalent vaccine (Gardasil 9®) has recently been approved for administration which, in addition to the aforementioned types, also protects against HPV types 31, 33, 45, 52, and 58. Uptake in different countries has varied considerably since the introduction of HPV vaccination. The United Kingdom (UK), which is the primary focus of this work, has relatively high national uptake rates of around 76-90% ([11]). Australia and Portugal also have relatively high uptake rates (70-80%), while some countries such as the USA, France and New Zealand have low uptake (21-47%) ([12, 13, 14, 15]). Some low and middle income countries such as Rwanda and Bhutan have also successfully set up programmes with extremely high reported uptake rates of 93-99% ([16, 17]).

Vaccinating when young, before sexual debut, is optimal ([18, 19]). Early immunisation programmes targeted young teenage girls, with the focus on reducing incidence of cervical cancer later in life. In 2007, Australia targeted a wider age range of girls / women aged 12-26 as part of a limited catch-up programmes ([20]), and improvements in overall health outcomes have been shown in boys as well as girls due to indirect protection ([21]). In the UK, teenage girls (aged 12-13) have been vaccinated in school since 2008, initially using the bivalent vaccine, replaced by the quadrivalent since 2011 ([22]). National vaccination coverage has been consistently high since vaccination began, in the region of 76-90% ([11, 23]), making the programme one of the most successful globally in combating HPV. A catch-up programme for older girls was also implemented for three years (2008-2011), whereby 13-18 year old girls who missed out due to their age were also offered the vaccine ([24]). Original models ([25, 19]) predicted it would be cost-effective to vaccinate teenage girls, provided the duration of protection was at least ten years, as it would lower the incidence of subsequent health conditions arising from HPV infection, in particular cervical cancer, which is a major health burden ([26]). Recently, the decision was made to reduce the three-dose schedule (two primers plus one booster) to two doses (one primer plus one booster), following immunological evidence for comparable efficacy ([27, 28]) and improved cost-effectiveness ([29]).

In 2011 Giuliano et al. ([30]) questioned whether or not it would be cost-effective to include additional target groups to vaccination programmes, given that the HPV vaccine is efficacious in both sexes. A 2016 meta-analysis by Brisson et al. ([31]) provides an overview of the herd effects of vaccinating girls. Studies have shown some groups to have relatively high prevalence of HPV and significant health effects, including HIV-positive individuals ([32, 33]), and men who have sex with men (MSM) ([34, 35]); the latter benefit less from the herd immunity generated by vaccinating girls than heterosexual men. Modelling has shown (as is intuitive) that increasing targets for vaccination, such as adding boys to a girls-only programme ([18]), and including adults ([36]), leads to further reductions in prevalence. However, in terms of cost-effectiveness, results of health economic analyses of contrasting programmes have generated less clear cut results. Most studies show vaccination of girls is highly cost-effective in many countries despite different cost-effectiveness thresholds for health improvements (e.g.[37, 19, 38]), while the majority of studies that have proposed adding males to a female-only vaccination programme found it was less cost-effective compared to vaccinating only females ([39, 40]) and, in most cases, not cost-effective using standard thresholds of willingness to pay ([41, 42, 24, 43]) . A US study found that it would only be cost-effective if coverage in girls was around 20% ([44]). Research in Australia also showed a limited impact of boys' vaccination on HPV infections and related cancers in males ([45]), although Australia subsequently became the first country to adopt national gender-neutral vaccination of boys as well as girls ([46]); New Zealand also added boys to the national programme in 2016. An analysis of vaccinating MSM in the USA found that it could be cost-effective, although it assumed the current vaccination programme in girls had no effect on HPV

prevalence in MSM ([47]). There thus remain many questions as to the cost-effectiveness of expanding the current girls-only strategy in the UK; we focus on the specific problem of adding teenage boys to the current vaccination programme.

Here we present an analysis of HPV infection and vaccination, to estimate the incremental cost-effectiveness of vaccinating boys as well as girls. The study consists of three parts: firstly, the fitting of parameters associated with HPV transmission, infection and recovery, by use of an epidemiological model incorporating sexual partnerships between individuals, matched to multiple HPV prevalence data sources. Secondly, the simulation of a range of vaccination strategies using the parameters from the above model. Thirdly, an economic analysis of the different strategies, taking into account the potential consequences (including health-related quality of life and cost implications) of HPV infections, to assess the cost-effectiveness of each vaccination strategy. We have not included potential changes to the UK's cervical cancer screening service that might be precipitated by any future reduction in HPV prevalence. In this regard we follow the earlier analysis of female-only vaccination ([19]) and focus on the epidemiological and economic impacts of vaccination.

Methods

Data

HPV prevalence data pre-vaccination

To fit the transmission model to HPV prevalence rates before vaccination programmes were introduced, a variety of data, across a range of countries, was used. In total, results from 13 detailed epidemiological studies were used; information is given in Additional file 3 — Table S1. Data consisted of either prevalence of serum antibodies against HPV types, or HPV DNA presence in the epithelial layer. The sex and age (groups) of individuals in each study were generally known, as well as, in the case of the studies by Nielson et al. ([48]) and Tanton et al. ([49]), sexual activity of individuals, and in the case of the study by King et al. ([35]), sexual orientation. These data were used to infer the infection parameters of our model including type-specific transmission probabilities.

Partnership rates

To model partnership behaviour of individuals, we used data from National Survey of Sexual Attitudes and Lifestyles (NATSAL) 2 and 3 ([50]): UK-wide surveys of sexual behaviour. We fitted distributions to stratified data which allowed us to determine the annual rates of forming new sexual partners where there is unprotected intercourse, as well as the likely ages of these partners. Individuals were stratified by age, sex, sexual preference and previous sexual experience. For all simulations, we used NATSAL-2 distributions up to 2010, and NATSAL-3 distributions simulating forwards from 2010.

Epidemiological model

In the following section we describe the epidemiological model in brief; the transmission framework is explored in more detail in Datta et al. ([50]), and in Additional file 1 — Appendix S1.

We used an individual-based modelling framework, with SIRS-V (Susceptible - Infected - Recovered - Susceptible - Vaccinated) dynamics, thus accounting for both short-duration natural immunity and longer-lasting protection due to vaccination. Populations of 50,000 individuals were generally modelled; this population size was a compromise between stochastic uncertainty and speed of the computationally intensive simulations. We used yearly data from Natsal-2 and Natsal-3 to determine distributions for the rates of new partnerships that involve unprotected sex and could therefore allow the spread of HPV ([50]). Different distributions were defined depending on four personal characteristics: age (years), sex (male/female), sexual orientation (heterosexual/any other) and previous sexual experience (yes/no). Individuals in the population were given a risk-percentile, which determined the values extracted from the distribution of rates, with the distribution defined by the individual's characteristics (e.g. age, sex, etc). This meant that high

risk-percentile individuals consistently had high rates of new partnerships relative to their peers. However, we know that individual behaviour patterns can change (e.g. by starting a long-term relationship); we therefore allowed risk-percentiles to be randomly redrawn with a low age- and sex-dependent probability - this allowed us to capture longer term (5-year and lifetime) behaviour from the NATSAL surveys.

The model was generally run for 100 years, allowing individuals to age, form new partnerships, become infected and recover. When an individual stochastically picked a new partner, the characteristics of the new partner were probabilistically determined by the status of the individual choosing. If the chosen partner was infected with one or more types of HPV, these could be stochastically transferred, with separate transmission probabilities for each type and with asymmetric transmission between the sexes ([51]). Once infected, an individual had a rate of recovery, equal for all types, and may have generated a detectable serological response (separate probabilities for males and females) allowing us to match the model to serological data. After recovery, there was a period of strain-specific natural immunity before the individual became susceptible once more. In total, the model required fifteen HPV-specific parameters to be inferred from the empirical data.

We used 13 datasets to fit the parameters in the epidemiological model; the datasets used are listed in Additional file 3 — Table S1. All data were either serological data (detecting the presence / absence of antibodies which the individual produced naturally after a previous or current infection), or DNA data (indicative of a current HPV infection). Although serological data were more widely available, the probability of producing antibodies following an infection is not high; probabilities are thought to be around 60% for females ([52]) and 30% for males, although some studies report much lower type-specific rates([53]). These serological probabilities were inferred as part of the model-fitting process. DNA data, on the other hand, was considered more reliable, and we therefore assumed 100% sensitivity and specificity of these data. The model parameters were inferred using a Bayesian Markov Chain Monte Carlo (MCMC) framework and a standard Metropolis-Hastings algorithm. Likelihoods were generated by assuming that the data reflected a binomial sample of the model population.

Simulating vaccination strategies

For predicting the impact of vaccination, we followed the UK's Joint Committee on Vaccination and Immunisation (JCVI) guidelines and used the 'best' parameters from the model fitting (i.e. the mode from the posterior for each fitted parameter). We then estimated future levels of HPV in the population for different vaccination strategies. Although the parameters used for each run were identical, due to the stochastic nature of the simulation, there was considerable variability between runs necessitating multiple simulations (500 runs per vaccination strategy). When simulating future vaccination scenarios, we used available uptake rates to simulate the girls-only vaccination that had occurred in the period 2008-2016 inclusive, using the bivalent vaccine until 2012, and quadrivalent after that ([11, 54]); we also took into account the catch-up campaigns targeting girls aged 13-18 that occurred in 2008-11. (Uptake rates for both the routine and catch-up campaigns are shown in Additional file 4 — Table S2.) For both campaigns, we conservatively assumed that only girls who received all three HPV doses were protected. The three available vaccines, are each assumed to confer complete protection for their target types (16 and 18 for the bivalent vaccine; 6, 11, 16 and 18 for the quadrivalent vaccine; and 6, 11, 16, 18, 31, 33, 45, 52 and 58 for the nonavalent vaccine) but differing levels of cross-protection to any remaining modelled HPV types (Additional file 5 — Table S3). Forward simulations generated lifetime histories of individuals, for use in the economic analysis (see next section). Note that we assumed a two dose schedule (vaccine plus booster) for all future strategies, following evidence that this is likely to be more cost-effective than three doses if vaccine protection is at least 20 years ([29]). We assumed for simplicity that both doses were given simultaneously to individuals, and protection began immediately. Therefore we did not have to explicitly model the first dose.

The following vaccination strategies were simulated into the future, using the bivalent, quadrivalent or nonavalent vaccine. We define 'historical vaccination' as simulating girls-only vaccination for 2008-2016, with uptake rates for the main and catch-up programmes taken from UK data (Additional file 4 — Table S2), and the respective new strategies began at the start of 2017:

1. Halted vaccination: historical vaccination, followed by a halting of all vaccination in 2017;

2. Girls: historical vaccination, followed in 2017 by selecting 85% of 12-year-old females to be vaccinated

at the start of each year (based on predictions from JCVI on future uptake rates);

3. Girls and boys: historical vaccination, followed in 2017 by selecting 85% of 12-year old girls and 85% of 12-year old boys to be vaccinated at the start of each year (this assumed that boys' uptake would be equal to that of girls);

4. Girls and boys equal: historical vaccination, followed in 2017 by selecting 42.5% of 12-year old girls and 42.5% of 12-year old boys at the start of each year to be vaccinated (hence an equal level of vaccination as girls' vaccination (strategy 2));

5. Girls naïve: no historical vaccination, and vaccinating 60% of 12-year old girls from 2008 onwards;

6. Girls and boys naïve: no historical vaccination, and vaccinating 60% of 12-year old girls and 60% of 12-year old boys from 2008 onwards.

Halted vaccination was included, not as a plausible future strategy, but so that the threshold vaccine prices could be compared to a baseline (analogous to starting a new vaccination programme compared to not beginning one). The final three scenarios were designed to provide a scientific understanding of the generic conditions under which a gender-neutral vaccination programme would be cost-effective. Strategy 4 represents countries (like the UK) that have already commenced a girls-only vaccination programme (at varying uptake rates) and are interested in adding boys to the schedule; whilst strategies 5 and 6 represent countries which are yet to begin vaccinating against HPV. In such a way, we showed how impacts changed depending on both the coverage of vaccination in the population and existing herd immunity.

Economic model

The economic model took the form of a continuous time individual patient simulation (Additional file 2 — Appendix S2), using output from the epidemiological model (specifically, times of infection and recovery, with each HPV type, for each individual in the model). The economic model then extrapolated these data to clinical events experienced by each individual over their lifetime (up to a maximum age of 100 years old). The healthcare costs and quality-adjusted life years (QALYs) for each vaccination strategy were compared to a baseline strategy (either no vaccination or girls only) and the incremental cost-effectiveness ratio of each strategy was estimated. We then generated the *threshold vaccine dose price*; that is, the maximum amount the healthcare system is willing to pay given the associated health benefits (currently set at £20,000 per QALY in the UK). Positive prices per vaccine dose below this threshold price will tend to generate positive net health benefits, whilst negative prices per vaccine dose offer no incentive to the manufacturer to provide the vaccine.

The economic evaluation was conducted from a UK National Health Service (NHS) and personal social services perspective with costs presented in pounds sterling (2013-14 prices). The following sections outline the basic clinical, cost and health utility parameters that fed into this economic model.

Clinical parameters

Age- and sex-specific incidences of the six cancer types included in the model (cervical, anal, vaginal, vulvar, penile, oropharyngeal), and cervical intraepithelial neoplasia were taken from 2013 UK cancer registration statistics. Age- and sex-specific incidences of genital warts were taken from a UK Health Protection Agency report ([55]), and age specific incidences of recurrent respiratory papillomatosis from a task force on recurrent respiratory papillomas ([56]).

Proportions of each of these clinical events associated with the HPV types included in the model were extracted from a published meta-analysis ([57]) and a literature review undertaken by Jit and colleagues ([22]) (Additional file 6 — Table S4). It was often not possible to distinguish between events caused by types 6 and 11, so these were modelled as a single risk factor in the economic analysis. The same was true for events caused by types 31, 33, 45, 52 and 58.

Data on disease incidence, proportion of disease associated with HPV, and age- and sex-stratified proportions of people infected with each HPV type pre-vaccination were combined to give annual event rates for the nine diseases included in the model, stratified by age, sex and current and past HPV infection status.

All-cause mortality data were taken from the Office of National Statistics ([58]), as were age-specific one and five year survival data for cervical cancer ([59, 60]). Data for other cancers were not available from the same source. Anal cancer survival rates were taken from an epidemiological study conducted by Jeffreys and colleagues ([61]), and those for other cancers from an Office for National Statistics report on survival rates from less common cancers ([62]). However, since these data were old, the survival rates were adjusted to estimate contemporaneous values, using improvements in cervical cancer survival over the same time period. Mortality rates from recurrent respiratory papillomatosis were taken from a study by Bishai and colleagues ([63]). For oropharyngeal cancer we use the proportion attributable to HPV from ([64]), and allow this proportion to increase up to 80% when sampling from economic parameters, to account for recent data ([65]).

Health utilities

Health utility decrements associated with cases of genital warts ([66]) and recurrent respiratory papillomatosis ([63]) were extracted from the literature. Health utility decrements associated with cancer consisted of two components, a short time loss during treatment, and a long term health utility decrement which persisted for the remainder of the individual's life.

Costs

Costs of recurrent respiratory papillomatosis ([67]), genital warts ([68]), and cervical cancer ([69]) were all taken from the literature and inflated to 2013-14 UK prices. Costs for other cancer types were not available for the UK. Therefore, the relative costs (compared to cervical cancer) for these cancers were estimated from the HPV-ADVISE model ([22]), and these were indexed against the cost of cervical cancer in the model to obtain estimates of cost for other cancer types. The cost of vaccination administration was assumed in the baseline analysis to be £10 per dose (Department of Health, personal communication), and we assumed a two dose schedule (vaccine plus booster) following evidence that this is likely to be more cost-effective than three doses if vaccine protection is at least 20 years ([29]). Given the high level of completion in the UK, we assumed for simplicity that all immunised individuals were given both doses, hence calculating the costs and impact of vaccination was straightforward. If a significant fraction of the population only received one dose, this might skew both the health impacts and the associated costs; however, this is not the case in the UK - in 2017/18, 83.9% received two doses while just 5.2% only received one dose and 10.7% did not receive any vaccine.

The costs and health utility decrements used in the model are summarised in Additional file 7 — Table S5.

Time horizon and discounting

The time horizon of the base case model was 100 years post the point where the different vaccine strategies affected individuals in the model. Thus, people who were born at the start of 2000 were included in the analysis, as were all subsequent newborns.

To comply with the JCVI's guidelines, two criteria were considered. Firstly, that for the most likely set of parameters (modes of posteriors) the mean discounted costs and outcomes should be evaluated against a £20,000 cost-effectiveness threshold value for a QALY ([70]). Secondly, to account for uncertainty, 90% of all posterior parameters should generate cost-effective results at a threshold of £30,000 per QALY. In both cases discounting at a rate of 3.5% per year (for both healthcare costs and QALYs) was used.

As an alternative scenario, we also evaluated the effects of applying a 1.5% discount rate to health impacts; this was in response to the CEMIPP report ([71]) which highlighted that 3.5% discounting was not always appropriate given disparate delays from infection time to health effects, and alternative discounting rates should be considered where appropriate. This is the case for HPV, when there may be many years between vaccination, infection and the onset of life-threatening cancers. 1.5% was chosen in response to the appraisal by the National Institute of Care Excellence, which noted that "A discount rate of 1.5% for costs and benefits may be considered by the Appraisal Committee if it is highly likely that, on the basis of the evidence presented, the long-term health benefits are likely to be achieved" ([70]).

For the uncertainty criterion, we note that a single simulation contains stochasticity due to both parameter uncertainty, and also the finite size of the modelled population and the chance nature of transmission. Our results show that this second form of stochasticity is largely parameter invariant, and therefore we were able to separate these two effects (Supplementary Material). The results shown for the uncertainty analysis therefore reflect only our uncertainty in parameter estimates and not variability between simulations.

Patient Involvement

Patient and public involvement (PPI) in research has become embedded in health research with patients and the public involved as collaborative partners through the research process ([72, 73]). While common in health research, public involvement in mathematical and economic modelling is relatively rare, with few examples of embedded forms of collaborative involvement and a lack of agreed methodology for PPI in modelling.

For this analysis, patients and the public were not involved in developing either the research question or the design of the study in relation to the modelling approach, primarily because this is one of the first studies to include PPI in modelling. As such it is exploratory in nature, with our intention to identify the ways in which patients can contribute to modelling. We utilised the development of the HPV model as an opportunity to establish a PPI Reference Group (comprised of public members), to explore the potential for patients or the public to contribute to both the epidemiological and economic modelling components of the study, as part of the wider programme of work.

The Reference Group met regularly at key points in the study, with email contact in between. The wider aim of PPI within the project was to contribute towards conceptual development of PPI in mathematical and economic modelling, through the development of a new framework co-produced with patients and the public. Throughout the project we aimed to identify any impacts of the PPI Reference Group, and these will be disseminated through policy recommendations made by the Department of Health. A separate piece of work on the PPI contribution to the study is currently in progress.

Results

The fitting scheme produced well-defined parameter distributions (see Additional file 8 — Figure S1 and Table S6), and simulating using the distributions provided good agreement between the model and data (see Additional file 9 — Figures S2 and S3). In the following sections the effects of varying vaccination strategy on HPV prevalence, incremental cost-effectiveness and the consequences for threshold vaccine dose prices, are presented.

Epidemiological effects of vaccination strategies

The predicted effect that a range of vaccination strategies would have on the prevalence of HPV is shown in Fig 1.

The eight years of girls-only vaccination (2008-2016) had the effect of reducing HPV prevalence across the entire population (both male and female) from approximately 8% to 6.9%. Assuming that girls-only vaccination continues at 85%, by 2050 prevalence is predicted to drop to around 0.56% (yellow line). Adding boys' uptake at 85% to the girls-only programme from 2017 onwards further reduces prevalence to approximately 0.13% (green line). As an alternative, keeping the number of vaccinations equal to the girls-only programme but splitting them equally between girls and boys (so that uptake is 42.5% in both sexes) leads to a less steep decline in prevalence, falling to around 1.5% by 2047 (blue line). Interestingly, halting vaccination entirely in 2017 leads to a continued fall in prevalence until 2025 (red line), due to the delay between vaccination and girls entering the sexually active population; however, in the longer term prevalence returns to approximately pre-vaccination levels.

As an alternative to the eight years of girls-only vaccination at high uptake, we investigated the effect of a lower uptake HPV vaccination campaign from 2008. Vaccinating just 60% of girls leads to a less marked decline in prevalence, reducing to around 2.5% by 2050 (black solid line); vaccinating 60% of both sexes further reduces the prevalence to 0.31% (black dashed line).

We note that, due to basing pre-2010 individual-level behaviour on Natsal-2 and post-2010 behaviour on Natsal-3 which reported marginally increased sexual behaviour ([74]), we observe slight increases in baseline prevalences from 2010 onwards. This can be seen most easily by contrasting prevalence pre-vaccination with values at 2050 for halted vaccination (7.97% and 8.02% respectively).

These results have two important public-health implications. Firstly the reduction in cases from adding boys to the vaccination program is markedly less that the initial impact of adding girls. Secondly, a gender-neutral campaign vaccinating 60% of the population has comparable impact on infection prevalence as vaccinating 85% of girls (42.5% of the population). Given the heterosexual nature of the majority of the UK population, it is clear that vaccination of girls is generating considerable herd-immunity for boys.

A detailed breakdown in the prevalence of different HPV strains, by age and gender, under alternative vaccination strategies is given in Additional file 11 — Table S7. As might be expected, strains decrease according to the level of protection afforded by the vaccine as in Additional file 5 — Table S3; for example, as strains 6 and 11 are not covered by the bivalent vaccine, prevalences of these strains are comparable between the strategies of halted, girls-only bivalent and gender-neutral bivalent vaccination. If the strain is covered by the vaccine, girls-only vaccination reduces strain prevalence significantly compared to halted vaccination, while adding boys to the girls-only programme has a more limited effect (e.g. for 26-35 year old males, strains 31/33/45/52/58 and the nonavalent vaccine, girls-only vaccination reduces prevalence from 10.2% to 2.05%; gender-neutral vaccination reduces prevalence to 0.658%, a lower incremental benefit).

Cost-effectiveness of vaccination strategies

The mean results of the cost-effectiveness model are shown in Fig 2 and Table 1, with the distribution of threshold prices shown in Additional file 10 — Figure S4. Threshold dose prices for cost-effectiveness, using both 3.5% and 1.5% discounting, with a £20,000 cost-effectiveness threshold value, are shown for all vaccination strategies versus halted vaccination, and for gender-neutral strategies versus girls only. Prices are shown for the cost per dose, assuming a two-dose schedule, and a £10 administration charge for each dose.

Vaccinating girls only or both girls and boys, with any of the vaccines, was always cost-effective compared to not vaccinating, with positive threshold dose prices and positive confidence intervals in all instances. However, vaccinating girls alone was more cost-effective per dose, with a higher threshold price for each vaccine, compared to a gender-neutral strategy. Generally, the nonavalent vaccine was the most effective in preventing disease, followed by the quadrivalent, and finally the bivalent, as would be expected from the level of protection offered, hence a greater threshold price. Incremental to a girls-only vaccination campaign, adding boys gave threshold dose prices very close to, but below, zero, at 3.5%. The results from individual simulations varied widely and 500 replicates were needed to achieve relatively tight confidence intervals around the mean. For the quadrivalent vaccine, the mean dose price was negative (at -£2.92) and, given that the confidence intervals are below zero (from -£3.64 to -£2.18), we can say with 95% confidence that the threshold price is negative. The same arguments apply to both the bivalent and nonavalent vaccines.

At 1.5% discounting all threshold prices increased, but with the same qualitative patterns; for girls-only vaccination compared to halted vaccination threshold prices were £687 – £811 for the three vaccines and gender-neutral vaccination was less cost-effective, with threshold prices of £362 – £429. Incremental to girls only, gender-neutral vaccination had positive threshold prices of £36 – £47. This is due to the lower discount rate adding more weight to economic values placed on health conditions in the future. In general, a lower discounting rate will always make vaccination more cost-effective for infections like HPV, where the health consequences are experienced years or decades after infection.

A detailed breakdown in the reduction in cases of the health sequelae under alternative vaccination strategies is given in Additional file 12 — Table S8. As might be expected, there is a large decrease in cases of health sequelae when vaccinating girls compared to halted vaccination, while adding boys to the girls-only programme yields a much smaller decrease in cases. Incremental cost-effectiveness ratios (ICERs) for alternative vaccination strategies are shown in Additional file 13 — Tables S9 and S10, and Figure S5, at a range of assumed vaccine dose prices. Relative to halted vaccination, girls-only vaccination results in lower ICERs than a gender-neutral programme (Table S9), while ICERs are significantly higher for a gender-neutral programme compared with girls-only vaccination, signalling low cost-effectiveness (Table

S10).

Employing the probabilistic approach as per the JCVI's guidelines, whereby parameters in both the transmission and economic models were sampled from appropriate distributions, and increasing the cost-effectiveness threshold for a QALY to £30,000, the threshold dose prices at the 10th percentile of simulated values (for bivalent, quadrivalent and nonavalent vaccines, and at both 3.5% and 1.5% discount rates) are shown in Table 2, and the cumulative distribution of threshold dose prices are displayed in Fig 3.

It is evident that, while vaccination of girls fulfilled the JCVI criterion of 90% of simulations generating cost-effective results (Fig 3(a)), adding boys to an existing girls-only campaign at 3.5% discounting did not satisfy the condition (Fig 3(b)). For all three vaccines, the 10% boundary in the cumulative distribution for threshold dose price lay below zero - meaning that, by the JCVI guidelines for uncertainty, adding boys is not cost-effective - further supporting the conclusion from the results using the most likely parameters.

Conversely, at 1.5% discounting (Fig 3(c)) all three vaccines had positive values at the 10% boundary (£45 – £67). Hence at 1.5% both criteria for cost-effectiveness are met. We note that the 10% boundary price for the quadrivalent vaccine is higher than for the nonavalent (at both 3.5% and 1.5% discounting). We suggest this is because vaccinating girls only with the nonavalent vaccine induces herd immunity against all 9 HPV types such that the addition of vaccinating boys has limited impact; in contrast, given that the quadrivalent vaccine induces only limited herd immunity against types 31, 33, 45, 52 and 58, including vaccination of boys has a more substantial impact on these types.

Considering the different levels of vaccine uptake in more detail and the resulting herd-immunity provides a richer understanding of the cost-benefit relationship (Fig 4). Two elements contributed to the low threshold dose price previously described. The first is that, as the uptake rate of vaccination in both boys and girls increased, so the threshold dose price decreased; this is because of the herd immunity generated by immunising an increased proportion of girls such that much of the vaccination in boys was effectively "wasted", i.e. the majority of men who were vaccinated as adolescents will not be subsequently exposed to infection. The second is that the high vaccination uptake rates observed so far in the UK, have already generated such high levels of population protection that the impact of vaccinating boys was further reduced (Fig 4, circle markers compared to square markers). Thus, if uptake is expected to be low across a population, then introducing a gender-neutral scheme early is expected to be highly beneficial; for example, at 3.5% discounting and assuming uptake was just 10%, the mean threshold price for adding boys was £112.37 (111.35 - 113.40) without prior vaccination or £78.11 (76.60 - 79.58) if girls had been vaccinated for eight years as assumed elsewhere in this paper.

We note that, using 3.5% discounting (Fig 4(a)), at 85% uptake (dashed vertical line) the cost-effectiveness of gender-neutral vaccination drops below zero for a population with UK vaccination up until present, whereas it is positive for a vaccination-naïve population. As with the previous simulations, decreasing the discounting rate to 1.5% increases all threshold prices (Fig 4(b)), with positive prices up to and including 90% uptake rates.

Discussion

The modelling work performed here combined epidemiological and economic insights with advice from our PPI group, and provides cost-effectiveness results for a variety of vaccination strategies to combat HPV, following standard methodologies (e.g. [26, 75, 19, 76, 77]). Previous studies have predicted that vaccination of girls would be highly cost-effective ([26, 75, 19]), with concomitant decreases in levels of HPV infection (and associated adverse health sequelae) ([9, 10, 78, 79, 80]). The majority of previous economic analyses indicated that adding boys to the girls-only programme is unlikely to be cost-effective (e.g. [26, 81, 45, 24, 43]). The results presented here echo these findings, but provide both a UK-specific context and a broader scientific understanding of the impact of vaccine uptake and economic discounting.

Our fitted epidemiological model provides a good match to the available datasets. The use of likelihood-based techniques and Bayesian MCMC methodology meant that we could account both for inconsistencies between data sets and uncertainty in parameter estimates. In particular, while parameter estimates for the main HPV types (6, 11, 16 and 18) are well defined, there is greater uncertainty surrounding the additional five types in the nonavalent vaccine (31, 33, 45, 52 and 58), reflecting the sparsity of data sources (Additional file 9 — Figures S2 and S3). A lower probability of serological response in men compared to women is in

agreement with a recent meta-analysis on natural immunity ([82]); although that study found immune period difficult to determine due to a lack of knowledge of infection time, our model suggests a period of around 1.4 years.

Vaccination of girls has been observed to lower the population prevalence of HPV ([11, 80]), and our models suggest that in the UK this trend is likely to continue (Fig 1, yellow line). Even if vaccination is stopped, the time-delay between vaccinating young girls and them entering the sexually active population means that prevalence will continue to fall for another nine years before finally returning to pre-vaccination levels of around 9.5% (for any of the nine types modelled here). A girls-only vaccination campaign with 85% uptake with the nonavalent vaccine is expected to reduce population prevalence to around 1% within forty years. This value is further reduced to just 0.2% if boys are also included in the vaccination scheme. Therefore, we find that while introducing vaccination in young girls leads to a reduction in prevalence of around 90%, adding boys to this scheme only provides a limited further reduction in prevalence. Given that the majority of HPV transmission is through heterosexual relationships (so the infection must pass through a male-female-male-female . . . chain), it is clear that completely protecting either sex is sufficient to halt heterosexual transmission. This helps to explain why adding boys to an effective girls-only programme has limited effect. The exception to this is MSM, where there is limited herd-immunity from the girls-only programme, and so vaccination could be expected to be highly effective ([34, 35, 47]). However, a mass (i.e. untargeted) vaccination programme of boys does not target this group.

In general, any additional vaccination will always reduce the prevalence of infection and hence the expected amount of disease; furthermore, greater reductions are naturally predicted for vaccines that provide protection against more HPV types. To understand whether these declines are worth the additional costs of vaccination, requires us to undertake a health economic evaluation comparing health benefits against vaccine-related costs and associated costs. All tested strategies were cost-effective (at the £20,000 cost-effectiveness threshold for a QALY and assuming 3.5% annual discounting) compared to halted vaccination. Girls-only vaccination was highly cost-effective versus halted vaccination, with threshold dose prices of £55.80, £99.64 and £108.05 for the bivalent, quadrivalent and nonavalent vaccines, respectively (Table 1). Gender-neutral vaccination was also cost-effective versus halted vaccination, although at lower threshold dose prices of £25.08, £48.38 and £52.77 for the three respective vaccines. All threshold prices were higher at 1.5% discounting, but the same qualitative pattern observed (Table 1).

Comparing gender-neutral vaccination with girls-only vaccination (that is the cost-effectiveness of adding boys), none of the vaccines had a positive dose threshold price at 3.5% discounting (-£5.67, -£2.92 and -£2.56 for the three vaccines), with confidence intervals that were all below zero (Table 1). Moreover, following UK guidelines for economic evaluations of immunisation programmes, we examined the uncertainty in our predictions. Even removing between-simulation stochasticity, the uncertainty in parameter estimates was such that there is a less than 10% chance that gender-neutral vaccination is cost-effective (compared to girls-only) at a cost-effectiveness threshold value for a QALY as high as £30,000 (Fig 3(b)). In contrast, when comparing all strategies to halted vaccination, the recommended probabilistic threshold is always achieved (Table 2).

At 1.5% discounting all threshold dose prices increase, and gender-neutral vaccination, incremental on girls-only vaccination is cost-effective, with threshold prices of £36.46, £44.70 and £46.88 (Table 1). There is also a greater than 90% chance that gender-neutral vaccination is cost-effective (compared to girls-only) at a cost-effectiveness threshold value of £30,000 per QALY (Fig 3(c)). Recent recommendations from the CEMIPP report ([71]) and the JCVI ([83]) suggest applying a lower discount rate to the health effects of HPV vaccination, given the long time delay between infection and the onset of adverse sequelae.

There is some empirical evidence of cross-protective effects of the bivalent vaccine against warts-causing types 6 and 11 ([10, 84]). Although we have not tested the assumption here, the fact that the quadrivalent and nonavalent vaccines (which offer complete protection against 6 and 11) are not cost-effective for a gender-neutral programme at 3.5% discounting, means that adding these cross-protective effects will not change the conclusions reached.

As vaccine coverage in girls increases, so herd-immunity builds up, making additional vaccination less worthwhile. Hence, with higher uptake rates in girls (and longer historical vaccination of girls), boys' vaccination becomes less cost-effective (Fig 4). This is a critical result, as it shows that in the UK, where uptake in girls has historically been so high ([11, 54]) adding boys is not a cost-effective option. Conversely, in other countries where existing girls-only programmes have lower uptake rates (such as the USA and

France ([13])) adding boys may indeed still be cost-effective. This is due to the higher prevalence of infection remaining in the population, leading to potentially more significant declines in the incidence of adverse health effects such as cervical and oropharyngeal cancer. Similarly, including boys in the vaccination scheme can buffer the programme against fluctuations in level of vaccine uptake ([85]). This impact of uptake in girls, echoes previous findings. Given the significant variation in uptake of the girls' programme between countries ([12]), we would expect to observe a threshold below which gender-neutral vaccination was economically acceptable; however, the reality is more ambiguous. In particular, Australia, New Zealand and Canada have recently added boys to their respective national vaccination programmes, and uptake rates are 71% ([13]), 40-56% ([13, 15]) and 39-89% ([86, 87]) in these respective countries. For New Zealand this contradicts a recent study which found that adding boys would not be cost effective ([43]). Clearly, these health economic arguments are strongly influenced by the vaccine price, with recent reductions in average tender prices favouring the adoption of a gender-neutral programme ([88]).

Girls carry a larger economic burden of HPV-related disease than boys ([89]), due to the relatively high incidence of cervical cancer, so they are always the primary target for vaccination. This is evidenced in Additional file 12 — Table S8, where the incidence of cervical cancer with halted vaccination is higher than all cancers except for oropharyngeal cancer. The addition of boys' vaccination gives small reductions in prevalence of these health effects, in comparison to vaccinating girls alone. Combining the incidence rates in Additional file 12 — Table S8 with the costs and QALY decrements in Additional file 7 — Table S5, we calculate the main cost-saving impact of adding boys is reductions in oropharyngeal cancer and genital warts, with cervical cancer reduction having reduced savings. In low uptake countries, questions remain as to whether it would be more cost-effective to vaccinate boys or to try to increase the coverage in girls, with more studies suggesting the latter ([39]). Recent work, however, has highlighted the increasing importance of other cancers as HPV vaccination programmes lead to declines in cervical cancer cases ([90]).

It is clear from our analysis that mixing patterns are an important factor in the spread of HPV. An aspect not explicitly modelled here was the possibility of disease import from outside the population (i.e. immigration and tourism). This has been considered in some of our work, but unprotected sex with unvaccinated individuals from outside the UK is likely to be a relatively minor component ([91]). It is also likely to be highly non-random in a way in which there is little data to support any assumption.

One limitation of our modelling approach is the decoupling of HPV vaccination from cervical cancer screening – we have implicitly assumed throughout this work that cervical cancer screening will continue in its current form. It is possible that the nature of (and hence costs and consequences of) the cervical cancer screening programme will change in the future. In the near term this is most likely to be caused by evidence showing HPV-based cervical screening is more effective than the current cytology-based programme, and supports increasing the screening intervals from three to five years ([92]). A programmatic change to primary HPV testing for cervical cancer is predicted to reduce cervical cancer incidence ([93]); this has the potential to reduce the estimated cost-effectiveness of HPV vaccination in the UK. On the other hand, screening programmes could change directly as a result of the HPV vaccination programme; it has been estimated that the successful use of the bivalent vaccine could reduce the need for more than three cervical smears per lifetime ([94]). A recent study from Australia concluded that, if continued gender-neutral vaccination was maintained into the future, cases of cervical cancer could reduce from seven cases per 100,000 women to less than four by 2028 ([95]). Overall, while the current cervical screening programme is implicitly accounted for in our study (ignoring any possible fluctuations in screening participation by year/age/vaccination status), we do not account for the impact of future changes to screening technology, interval and compliance. Thus, far more research is needed to inform best policy on the interaction between HPV vaccination and cervical cancer screening. Future changes to the cervical cancer screening programme are beyond the remit of this study, but are an important area of focus for future research.

A key assumption in our models, which may require further study is that vaccination is an independent random process, and in particular is not correlated with sexual behaviour. If this is not appropriate, it may be that the girls who are missing out on vaccination are in the highest risk groups, and may be disproportionately contributing to transmission of HPV. Due to the high prevalence of HPV across both men and women ([96, 97, 98]), this seems unlikely to have a significant effect on the dynamics of infection, although other modelling studies have shown that the correlation does not need to be big to have an impact ([99]). Whilst there is no clear consensus of drivers of vaccine uptake at a community-level ([12]), there is more evidence at the individual level of a relationship between vaccination and risk behaviour ([100, 101]). When

risk is highly clustered to particular groups, for example for hepatitis-B, then the ability to target these groups becomes critical to the decision to vaccinate ([102]). An important follow-up to this work would be to assess the importance of low- and high-risk infection groups, their likelihood of vaccination, the mixing between the two groups, and the effectiveness of vaccination given the relative coverage in the high-risk group.

Conclusions

The generic conclusion from this work is that as coverage in girls increases, there is less incremental benefit from adding boys to the programme, due to existing herd-immunity. In the case of the UK, with the highest reported sustained HPV vaccine uptake rates in girls of any country, it is unlikely that adding boys will be cost-effective within standard economic guidelines which assume a 3.5% economic discounting. However, given the long time-scales associated with HPV infection and resulting disease, it may be more appropriate to adopt a 1.5% discounting, in which case adding boys to the programme becomes cost-effective for all three vaccines considered.

List of abbreviations

HPV: Human papillomavirus; UK: United Kingdom; MSM: men who have sex with men; NATSAL: National Survey of Sexual Attitudes and Lifestyles; SIRS-V: Susceptible - Infected - Recovered - Susceptible - Vaccinated; MCMC: Markov Chain Monte Carlo; JCVI: Joint Committee on Vaccination and Immunisation; QALY: quality-adjusted life year; NHS: National Health Service; PPI: Patient and public involvement; ICER: Incremental cost-effectiveness ratio.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

Data sharing is not applicable to this article as all data used were taken from previously published literature.

Competing interests

The authors declare that they have no competing interests. MU is Chief Investigator or co-applicant on multiple research projects funded by NIHR, and a journal editor for NIHR for which he receives a fee; MU is director and shareholder of Clinvivo Ltd..

Funding

The work was supported by the UK Department of Health [grant number 027/0089]. The funder had no role in the study design; in the collection, analysis and interpretation of data; in the writing of the manuscript; and in the decision to submit the article for publication. The views expressed are those of the authors and not necessarily those of the Department of Health. All authors had access to all data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Author's contributions

SD acquired and cleaned the epidemiological data, designed the epidemiological model and the statistical fitting scheme, and drafted and revised the paper. He is guarantor. JP acquired and cleaned the economic data, designed the economic model, and drafted and revised the paper. GFM advised on the epidemiological model design, and revised the draft paper. SP assisted with the economic analysis, and revised the draft paper. SS oversaw PPI elements of the work, and revised the draft paper. MU revised the draft paper. PS assisted with interpreting the Natsal data, and revised the draft paper. MJK oversaw design of the epidemiological model, revised the draft paper, and is PI for the project.

Acknowledgements

We would like to thank colleagues at the Department of Health for their useful suggestions and assistance with various aspects of developing the epidemiological and economic models, in particular Peter Grove and Geoff Wootton. We also extend thanks to the members of the JCVI HPV subcommittee for extremely useful feedback on early iterations of the manuscript, especially Jonathan Crofts and Andrew Earnshaw. Finally, we would also like to extend our thanks to the referees who provided detailed feedback on a previous draft of this manuscript.

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Figures

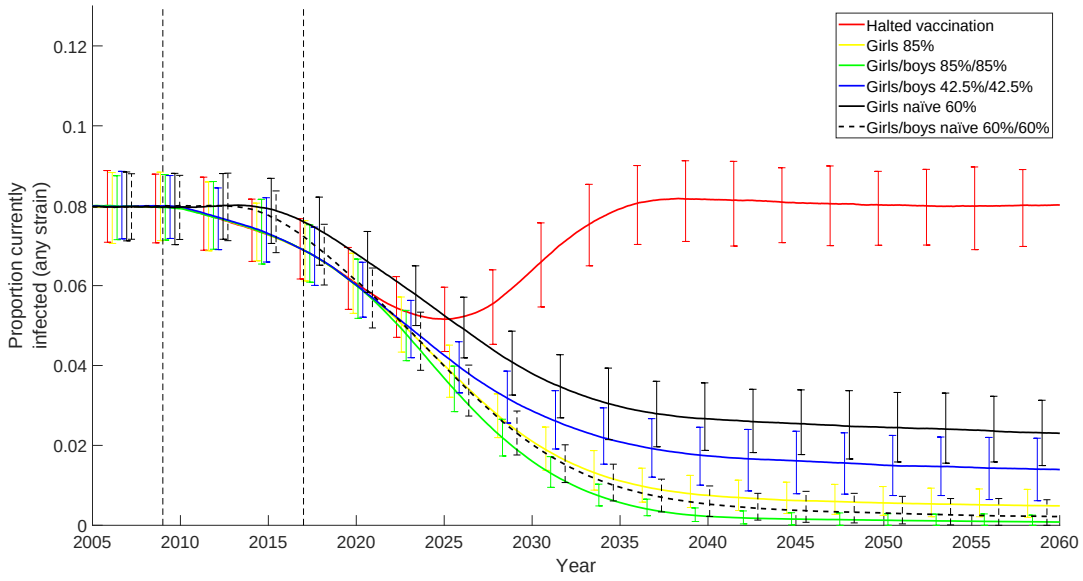

Figure 1: The effects of different vaccination strategies on the prevalence of HPV in the population, over the 30 years following a change in strategy. Strategies tested include: halted vaccination (red), girls only at 85% (yellow), girls/boys at 85%/85% (green), girls/boys at 42.5%/42.5% (blue), girls at 60% from 2008 (black solid), and girls/boys at 60%/60% from 2008 (black dashed). All strategies use the nonavalent vaccine.

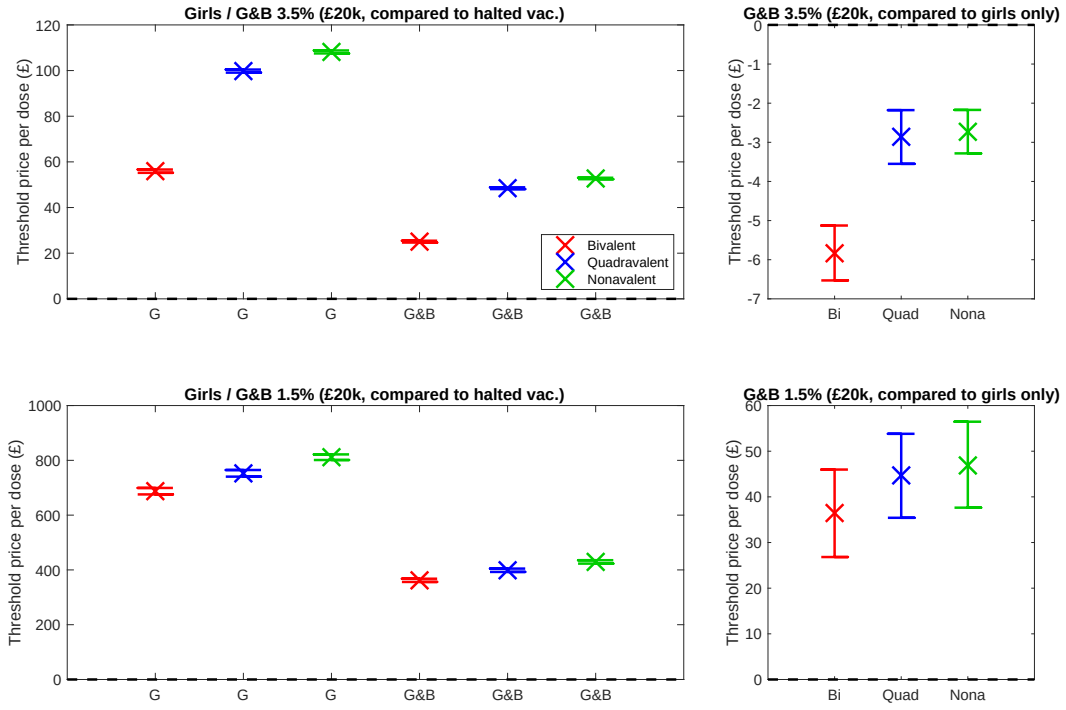

Figure 2: Threshold dose prices for various vaccination strategies, considering a two-dose schedule. All plots assume £20,000 cost-effectiveness threshold for a QALY, modal parameters from posterior used, and a £10 administration charge per dose. Mean values are shown as crosses, with 95% confidence intervals shown by bars. Colours correspond to the three vaccines: bivalent (red), quadrivalent (blue) and nonavalent (green). Top plots assume 3.5% discount rates applied, bottom plots assume 1.5% discount rates applied. Left plot: comparing girls-only and gender-neutral vaccination to halted vaccination. Right plot: comparing vaccination of gender-neutral vaccination to continuing girls-only vaccination. When comparing a strategy to girls-only vaccination the same vaccine is used for correct comparison.

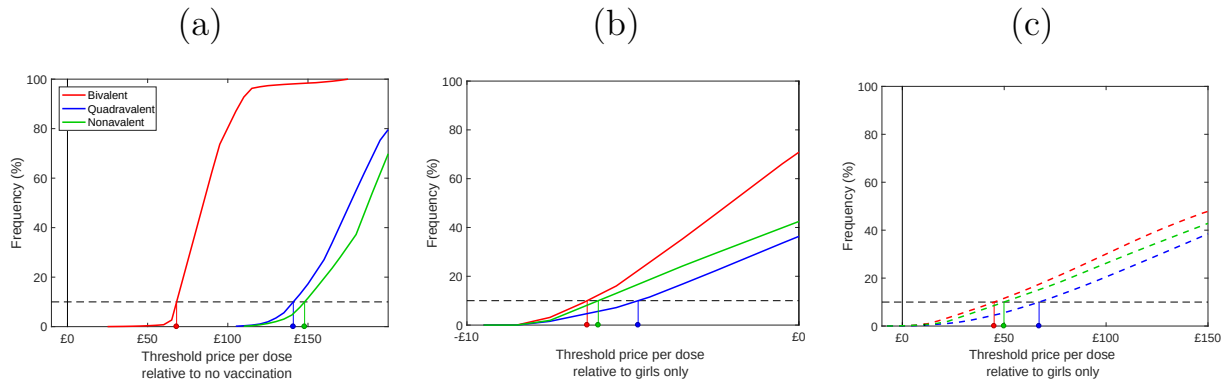

Figure 3: Threshold dose prices for girls-only vaccination compared to halted vaccination (at 3.5% discounting, left plot), and gender-neutral vaccination compared to girls-only vaccination (at 3.5% discounting, middle plot, and at 1.5% discounting, right plot). Coloured lines show different vaccines: bivalent (red), quadrivalent (blue) and nonavalent (green). Threshold dose prices at the 10th percentile of simulated values highlighted by coloured lines from x-axis to curve. Vertical black dashed line indicates £0 threshold price. Results shown for 500 simulations.

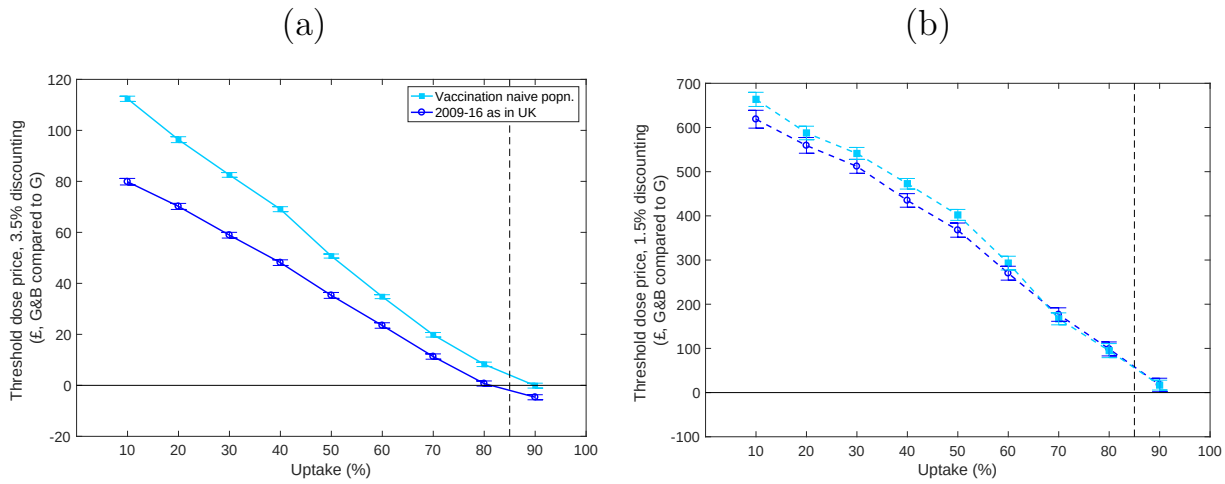

Figure 4: The mean threshold vaccine dose price for gender-neutral vaccination compared to girls-only vaccination, using the quadrivalent vaccine, for (a) 3.5% discounting and (b) 1.5% discounting. Two initial conditions are tested: assuming no vaccination has previously occurred (square markers), or assuming uptake in girls as in the UK historically for 2008-2016 (circle markers). 95% confidence intervals shown for all points. Vertical dashed line highlights 85% uptake, which is the rate assumed for girls-only and gender-neutral vaccination in the future in this paper. 200 simulations carried out for each data point shown.

Tables

Vaccination strategy	£, versus halted vac. (3.5%)	£, versus girls' vac. (3.5%)	£, versus halted vac. (1.5%)	£, versus girls' vac. (1.5%)
Girls, bivalent	55.80 (55.04 – 56.57)	-	687.47 (675.62 – 699.20)	-
Girls, quadrivalent	99.64 (98.90 – 100.37)	-	752.46 (740.51 – 764.72)	-
Girls, nonavalent	108.05 (107.36 – 108.75)	-	811.44 (801.18 – 821.68)	-
Girls & boys, bivalent	25.08 (24.64 – 25.52)	-5.67 (-6.42 – -4.93)	361.99 (356.09 – 367.85)	36.46 (26.82 – 45.98)
Girls & boys, quadrivalent	48.38 (47.95 – 48.80)	-2.92 (-3.64 – -2.18)	398.68 (392.65 – 404.84)	44.70 (35.42 – 53.81)
Girls & boys, nonavalent	52.77 (52.42 - 53.10)	-2.56 (-3.13 - -1.99)	429.26 (422.98 – 435.44)	46.88 (37.63 – 56.46)

Table 1: Threshold dose prices for various vaccination strategies, considering a two-dose schedule. Mean values shown over 500 simulations, with 95% confidence intervals in brackets. All strategies assume a £20,000 cost-effectiveness threshold for a QALY, with both 3.5% and 1.5% discount rates applied, and a £10 administration charge per dose. When comparing a strategy to girls-only vaccination the same vaccine is used for correct comparison.

Vaccination strategy	£, versus halted vac. (3.5%)	£, versus girls' vac. (3.5%)	£, versus halted vac. (1.5%)	£, versus girls' vac. (1.5%)
Girls, bivalent	68.07	-	1024.71	-
Girls, quadrivalent	140.85	-	1121.74	-
Girls, nonavalent	147.90	-	1232.70	-
Girls and boys, bivalent	32.13	–6.38	577.45	45.06
Girls and boys, quadrivalent	74.95	-4.84	654.07	67.12
Girls and boys, nonavalent	81.12	-6.04	676.54	49.89

Table 2: The threshold dose prices at the 10th percentile of simulated epidemiological and economic values (over 500 simulations), using both 3.5% and 1.5% discount rates and an increased cost-effectiveness threshold of £30,000, compared to both halted vaccination and girls-only vaccination, with a £10 administration charge per dose.

Additional Files

Additional file 1 — Appendix S1

A detailed overview of the key assumptions underpinning the epidemiological model employed in the paper.

- We assume SIRS-V (Susceptible - Infected - Recovered - Susceptible - Vaccinated) dynamics - individuals start life susceptible to all HPV types, may become infected with one or more types as sexual partnerships are formed, can transmit infection to others in subsequent partnerships, and then naturally recover from infections after some time. Temporary natural immunity (entering the recovered class) is assumed after clearing an infection, although eventually individuals move from recovered back into the susceptible class. Vaccination moves individuals from any of the S, I or R classes into a vaccinated class, where infection is highly unlikely; after a period of time protection wanes.
- We assume that natural infection confers temporary immunity on an individual, and there is waning of this immunity after some time (a parameter δ is fitted to the data). Following this, full susceptibility returns, and initial infections are no more or less likely than subsequent infections.
- We assume that vaccination effectively treats and immunises infected individuals - an assumption which would impact catch-up vaccination programmes in older cohorts where there may be high prevalence of HPV, but is unlikely to change the results for routine vaccination of 12-13 year olds.
- Nine types of HPV (types 6, 11, 16, 18, 31, 33, 45, 52 and 58) are modelled and the types are assumed to be independent (i.e. having one type does not make infection by another type more or less likely). The impact of this independence assumption is unclear: if there is within-host competition between the types, then immunisation against the common types (6, 11, 16 and 18) may lead to other types dominating, weakening the impact of vaccination; in contrast, if infection with one type leaves individuals more susceptible to other types, this impact will be reversed. In the absence of any data on type interaction, we made the simplest assumption that the types transmit independently.
- We fit the model to recorded prevalence of the nine HPV types using differences in transmission probabilities; an alternative mechanism would be to use differences in infectious period or a mixture of the two. Initially, we attempted to fit both transmission probability and infectious period for each type, but found the inferred values of these two parameters to be highly variable yet highly correlated. Dynamically the impact of these two parameters is indistinguishable (prevalence is largely determined by the basic reproductive ratio which is a product of transmission rate and infectious period). In discussions with HPV clinical experts, it was felt that having type-specific transmission probabilities was more informative, as it was unclear how detectable HPV infection relates to the ability to transmit. Previous work has shown rate of recovery from infection to be an important determinant of type-specific herd effect ([103, 104]), although these studies assumed the same transmission rate across all types. However, the meta-analysis of Rositch et al. ([104]) shows there is huge variability in the duration of infection as measured by the different studies. Furthermore, patterns are not always consistent; Rositch et al. ([104]) have the longest median duration of infection for strain type 31, whereas Lehtinen and Dillner ([103]) have measured this as comparable to other medium duration types (18, 33 and 52). In general, we believe that both the predicted public-health impact and the predicted economic impact of HPV is unaffected by whether we fit to the infectious period or the transmission probability.
- The data used to underpin the epidemiological component of this study, came from a detailed literature search for studies reporting both age- and type-structured prevalence data from the pre-vaccination era. The choice of these datasets was refined and ratified by an independent expert group. By using Bayesian parameter inference, we were able to find model parameters which maximised the likelihood of matching to all data sets, accounting for sample sizes. We note that, while many of these datasets come from outside of the UK, we felt that the benefits of having the additional sample size and information compensated for the lack of UK-specificity. In a similar manner we use both serological and DNA prevalence data, by accounting for seroconversion.

- We simulate using an individual based stochastic model, with the number of individuals generally picked to be 50,000 for simulations. This population size was a compromise between computational efficiency and lack of stochastic variation; larger population sizes produced less variable results but took far longer to simulate. Prior testing of different population sizes confirmed that population sizes of these magnitudes are not influencing our results. Immigration of individuals and tourism (and hence introduction of HPV) are not modelled, as it is difficult to quantify the amount of HPV being introduced to the UK in this manner ([91]).

- Individuals are defined by four factors: age (10-50), sex (male and female), sexual preference (heterosexual or homosexual/bisexual) and the percentile of the distribution of expected partnership rates. This percentile, together with the other three defining factors, is used to determine the rate at which new partnerships are formed.

- Partnership rates and age of partners are taken from the Natsal-2 and -3 datasets (the former until 2010, the latter from 2010 onwards) - this comprises of behaviour and choice of partner dependent on age, sex and sexual preference of individuals ([105, 74]). Although HPV urine tests were carried out on a large sample of individuals in Natsal-3 ((all 16-17 year olds; all 18-24 year olds who reported at least one sexual partner, ever; a random sub-sample of 85% of 25-44 year olds who reported at least one sexual partner, ever; and any remaining 25-44 year old men who reported having sex with another man in the past five years)) ([79]), we chose not to include them as information for our model fit. This was because the reliability of the urine test for assessing HPV prevalence is low compared to either seropositivity and DNA tests from other anatomical sites.

- Individuals who have not yet had a sexual partnership have separate rates of forming their first sexual partnership, which are determined from Natsal.

- As individuals age, their partnership rates change to reflect national patterns; in addition, individuals randomly change their partnership rate percentile to account for dramatic changes in behaviour. In other words, the distribution of partnership rates changes with age from the Natsal data; in addition, as people become a year older, we resample the percentile values for a subsample of the population, so that varying behaviour with age is possible. In such a way we account for switching between having multiple sequencial partnerships and forming a long-term partnership (and vica versa) which occurs within the population.

- We do not directly model the making and breaking of partnerships; instead we assume that the formation of a new partnership is always preceded by the breaking of the old partnership. We assume that new partners are chosen from an independent pool of the population at the partnership rate of the individual, with the infection status of this external pool mirroring the dynamics within the focus population. Thus, we do not explicitly pair up individuals in the population, but rather assume that the different individuals are representative of the wider population, and when a partnership is made, if the chosen partner has any of the HPV types, there is a probability of the partner from the focal population catching the type(s). This is based on evidence that transmission of HPV infection within relationships appears to be fast. This formulation for the dynamics of partner formation and transmission is explored in more detail in Datta et al. ([50]).

- We note that concurrency is not explicitly modelled here, i.e. if person A is in a partnership with person B, then begins a new partnership with person C and is infected with one or more types, these cannot be transmitted to person B. Information from Natsal-3 ([106]) indicates that concurrency is not uncommon and could potentially alter the dynamics. However, results from simpler model structures suggest that once models parameters are inferred to match prevalence data, there is limited impact from concurrency within the population ([107]).

- For sexual partnering behaviour, a parameter (assortativity) is introduced for the likelihood of partnering an individual with a similar partnership rate to one's own (i.e. high partnership rates with other high partnership rate individuals); we fit this by calculating the effect of the assortativity on the HPV prevalence across age groups (i.e. how mixing of different partnership rates increases the spread of HPV).

- We include a parameter for the ratio of outward male transmission to outward female transmission, due to data suggestive that there are noticeable differences between the two sexes ([51]), and use prevalence data available on both sexes to fit this ratio. We find that there is a slightly higher rate of transmission from males compared to transmission from females, although the result is not statistically significant.

- In terms of HPV type dynamics, when a new partnership is established, infecting HPV types are transmitted from the partner in the wider population to the partner from the focal population with independent probabilities (we may therefore get no transmission, transmission of just one infecting type or multiple transference). Intensity of sexual contact or types of sexual act are not modelled, as there is relatively little data available to parameterise the risks associated with this additional heterogeneity.

- With each infection by a strain we assume a probability of seroconversion (i.e. production of antibodies against the HPV strain), which is disaggregated into male and female seroconversion, due to evidence of differing rates ([96], [82]). We fit these two parameters to the serological datasets included in Additional file 3 — Table S1. Note that we assume instant seroconversion in the model, whereas some studies show a delay between DNA presence and antibody production (e.g. 12 months [96]).

- We model the waning of vaccine-induced immunity as a sigmoidal function, centred at 20 years such that protection against vaccine types is high leading up to 20 years, but then wanes, and is close to zero by 25 years. This assumption comes from the latest HPV vaccination data and the expert opinion of immunologists on the JCVI panel. This applies to all three vaccines modelled (bivalent, quadrivalent and nonavalent). We assume that the nonavalent vaccine protects against all nine types equally, and efficacy is regardless of prior or current infections. As for cross-protection, we use values from ([108]) to inform our model, with numbers as in Table S3. (Values from ([22]) were also considered, but the type-specific detail in the former article made it the more appropriate). All cross-protection wanes at the same rate as for the vaccine types (almost total for 20 years, before dropping off sigmoidally to zero by 25 years). Alternative patterns of waning immunity are possible and have been assumed in other work; for example, the simplest assumption of exponentially decaying immunity will decrease the impact of immunisation, due to the proportion of individuals who lose protection between vaccination and becoming sexually active.

- We assumed the same levels of induced protection by the vaccine in both boys and girls, and the same rate of waning immunity. We also assume that a 2-dose schedule (at 0 and 12 months) is equally protective as a 3-dose schedule (at 0, 6 and 12 months); see Additional file 5 — Table S3.

Additional file 2 — Appendix S2

Economic model assumptions.

In the following section we provide a detailed overview of the economic model employed in the paper.

- Economic costs are based on the results of individual-level discrete event simulations, in which the lifetime health consequencies (related to HPV infection) are modelled for 100,000 individuals over the simulated time horizon.
- Individuals have a maximum age of 100 years old, but have death rates which are age-dependent and are based on the latest UK estimates.
- HPV associated events included in the economic model are genital warts, recurrent respiratory papillomatosis, and six types of cancer (CIN/cervical, vaginal, vulvar, anal, penile and oropharyngeal). Each of these has associated economic and health costs.
- An individual's risk of developing one of these events, at any point in time, is determined by their age, current HPV infection status and which HPV types they have been infected with in the past. However, the risk of disease is assumed independent of number of previous HPV infections with the same type, time since infection (provided they are not currently infected), and age of initial infection. Changes to these basic assumptions are likely to increase the cost-effectiveness of vaccination, as both infection times and hence disease event times are pushed later into an individual's lifetime.
- HPV infections are assumed to change only the probabilities of initially developing each of the different health sequelae, and not the speed with which that sequela progresses once it has developed, nor the final outcome of the sequela.
- The effects on event probabilities by types 6 and 11 are modelled jointly rather than separately, and the same for HPV-16 and 18. This is because most studies that report the proportion of various cancer types associated with HPV infection report jointly for the two types, rather than separately.
- There are no direct costs or health-related quality of life losses associated with HPV infection itself; only through the events it later causes.
- The costs associated with sequelae of HPV infection are all taken from UK studies, as we expect these to be country-specific.

Additional file 3 — Table S1

A summary of the datasets used to fit the HPV transmission model to for pre-vaccination populations.

No.	Data	Country	Data type	Sex (number)	Age groups	Types included
1	Desai et al., 2011 ([96])	England	Sero+	M (2400), F (2400)	10-49 separate	6, 11, 16, 18
2	Introcaso et al., 2014 ([109])	USA (NHANES 2003-2006)	Sero+	M (3673), F (3956)	14-19, 20-24, 25-29, 30-39, 40-49	6, 11, 16, 18
3	Hariri et al., 2008 ([110])	USA (NHANES III)	Sero+	M (2644), F (3455)	12-19, 20-29, 30-39, 40-49	11
4	Stone et al., 2002 ([111])	USA (NHANES III)	Sero+	M (2752), F (3580)	12-19, 20-29, 30-39, 40-49	16
5	Jit et al., 2007 ([112])	England	Sero+	F (1483)	10-29 separate	6, 11, 16, 18
6	Ryding et al., 2008 ([81])	Sweden	Sero+	M (1383), F (1709)	11-19 separate, 20-22, 23-26	16
7	Castro et al., 2014 ([113])	Chile	Sero+	F (268)	15-20, 21-30, 31-40, 41-50	16, 18, 45
8	Sargent et al., 2008 ([114])	England (ARTISTIC)	DNA	F (18860)	20-29, 30-39, 40-49	16, 18, 31, 33, 45, 52, 58
9	Tanton et al., 2017 ([49])	England (Natsal-3)	DNA	sex. active F (3282)	16-29	6, 11, 16, 18, 31, 33, 45, 52, 58
10	Giuliano et al., 2008 ([115])	USA	DNA	M (290)	18-44	6, 11, 16, 18, 31, 33, 45, 52, 58
11	Kavanagh et al., 2008 ([116])	Scotland	DNA	F (2062)	20-21	16, 18, 31, 33, 45, 52, 58
12	Nielson et al., 2007 ([48])	USA	DNA	sex. active M (463)	18-40	6, 11, 16, 18, 31, 45, 52
13	King et al., 2015 ([35])	England	DNA	MSM (511)	18-40	6, 11, 16, 18, 31, 33, 45, 52, 58

Table S1: A summary of the datasets used to fit the HPV transmission model to for pre-vaccination populations.

Additional file 4 — Table S2

Vaccine uptake in the UK, 2008-2016.

Year	Vaccine	Routine uptake (%)	13	14	15	16	17
2008-09	Bivalent	80.9	0	0	0	0	47.4
2009-10	Bivalent	77.5	0	68.5	68.6	41.7	38.9
2010-11	Bivalent	83.8	4.5	0.3	7.2	2.2	6.4
2011-12	Quadrivalent	87.0	0	0	0	0	0
2012-13	Quadrivalent	85.8	0	0	0	0	0
2013-14	Quadrivalent	88.1	0	0	0	0	0
2014-15	Quadrivalent	87.5	0	0	0	0	0
2015-16	Quadrivalent	85.1	0	0	0	0	0

Table S2: HPV vaccine uptake of girls in the UK over the period 2008-2016, for both the routine campaign (targeting 12-13 year old girls) and the catch-up campaign (targeting those between 13 and 18 years old). Numbers are taken from ([11]) and ([54]), and references therein.

Additional file 5 — Table S3

Efficacy of the three HPV vaccines against different HPV types.

Vaccine	6	11	16	18	31	33	45	52	58
Bivalent	0	0	100	100	77.1	43.1	79.0	18.9	0.0
Quadrivalent	100	100	100	100	46.2	28.7	7.8	18.4	5.5
Nonavalent	100	100	100	100	100	100	100	100	100

Table S3: Level of protection (%) of the three vaccines against the nine HPV types in the model. Values taken from ([108]).

Additional file 6 — Table S4

Clinical parameter values and sources.

Disease type	% caused by 9 types	6/11	16	18	31/33/45/52/58
Cervical cancer	95.7	0	62.3	18.6	19.1
Anal cancer	84.3	3.6	82.5	5.8	8.1
Vulvar cancer	41.7	4.8	73.5	10.0	11.7
Vaginal cancer	41.7	5.8	69.7	9.9	14.6
Penile cancer	46.9	9.6	68.3	15.4	6.7
Oropharyngeal cancer	31.0	6.7	87.0	2.6	3.8
CIN (grades 2/3)	63.2	0	75.2	9.9	14.8
Genital warts	90	100	0	0	0
RRP	90	100	0	0	0

Table S4: Proportions of the various adverse health effects caused by the nine HPV types. The first column shows percentages of health effects caused by the nine HPV types included in the model; subsequent columns allocate proportions of these percentages to individual types and type groups. All values are taken from reviews by ([57]) and ([22]), except for oropharyngeal cancer ([64]).

Additional file 7 — Table S5

Costs and health utility decrements

Parameter	Value	Source
Cost - cervical cancer	£16,527	([69])
Cost - anal cancer	£10,610	([22])
Cost - vulvar/vaginal cancer	£12,446	([22])
Cost - penile cancer	£11,120	([22])
Cost - oropharyngeal cancer	£16,731	([22])
Cost - CIN (grades 2/3)	£385.63	([117])
Cost - genital warts	£281.57	([68])
Cost - RRP	£3,036.01	([67])
Utility decrement (cervical cancer treatment)	0.198	([118])
Utility decrement (anal cancer treatment)	0.355	([118])
Utility decrement (vulvar cancer treatment)	0.223	([118])
Utility decrement (vaginal cancer treatment)	0.223	([118])
Utility decrement (penile cancer treatment)	0.202	([118])
Utility decrement (oropharyngeal cancer treatment)	0.174	([119])
Utility decrement - CIN	0.0261	([120])
Utility decrement - GW episode	0.018	([66])
Utility decrement - RRP episode	1.302	([63])
Permanent utility decrement - cancer recovery	0.0305	([121])
Risk of death - RRP	0.021	([63])

Table S5: Costs and health utility decrements for adverse health effects in the model. Note that costs have been inflated to 2013-14 UK prices.

Additional file 8 — Figure S1 and Table S6

Parameter distributions.

Following the fitting scheme described in the Methods section, the parameter distributions are shown in Fig S1 and Table S6, comparing to literature estimates where possible.

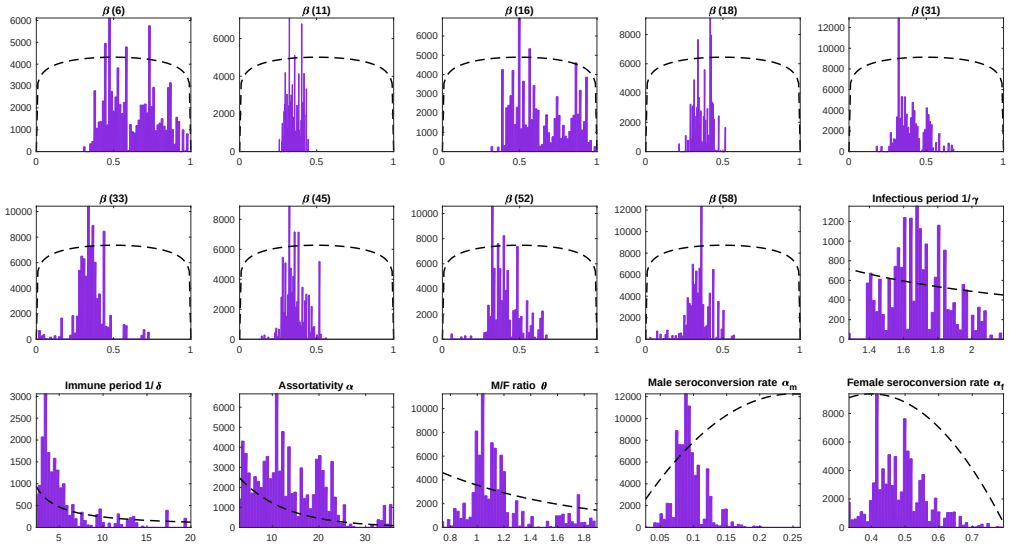

Figure S1: The parameter distributions for the parameters in the model. Purple histograms are the frequency of parameter values, and black dashed lines are prior distributions. From top to bottom, left to right: plots 1-9 show probabilities β of transmitting each type of HPV upon a new partnership being formed; plots 10 and 11 show infectious period $1/\gamma$ and immune period $1/\delta$; plot 12 shows assortativity α; plot 13 shows male-to-female ratio of transmission θ; plots 14 and 15 show male seroconversion σ_M, and female seroconversion σ_F. Note that plots 10 and 11 are inverted and displayed as time periods rather than rates, for ease of intuition.

Most parameters were well-behaved, and had tight Gaussian-shaped histograms. As expected, types with higher prevalence in the datasets (HPV-6 and 16) had a higher probabilities of transmission upon a partnership being formed than other types. Mean infectious and immune periods were, respectively, approximately 1.7 and 1.4 years. The infectious periods were consistent with those seen in empirical studies ([4]), while there remain questions about the duration (and even existence) of naturally gained immunity ([122], [82]). There was insufficient information in the data to inform the assortativity and male-to-female ratio of transmission, and hence the posteriors for these had less tight histograms. Interestingly, the predicted rates for seroconversion for men and women were lower than the conventional estimates of 30% for men and 65% for women ([96]), with the peaks at roughly 10% for males and 50% for females. This means that the partnership rates taken from Natsal-2 (used for fitting to pre-vaccination prevalences) implied a higher rate of new partnerships, meaning that individuals must have seroconverted at a lower rate to produce the seroprevalence patterns seen in the data. Nevertheless, a higher seroconversion rate was still observed in women.

Parameter	Value	Literature value	Source
Transmission β_6 (strain 6)	0.635 (0.390 - 0.932)	-	-
Transmission β_{11} (strain 11)	0.355 (0.281 - 0.437)	-	-
Transmission β_{16} (strain 16)	0.647 (0.395 - 0.945)	-	-
Transmission β_{18} (strain 18)	0.375 (0.276 - 0.475)	-	-
Transmission β_{31} (strain 31)	0.407 (0.279 - 0.619)	-	-
Transmission β_{33} (strain 33)	0.362 (0.175 - 0.594)	-	-
Transmission β_{45} (strain 45)	0.367 (0.263 - 0.519)	-	-
Transmission β_{52} (strain 52)	0.421 (0.297 - 0.648)	-	-
Transmission β_{58} (strain 58)	0.352 (0.146 - 0.595)	-	-
Infectious period $1/\gamma$ (years)	1.66 (1.57 - 2.00)	0.556 - 1.92	([103])
Immune period $1/\delta$ (years)	1.37 (0.296 - 8,86)	Unknown	([122, 82])
Assortativity α	13.9 (4.04 - 34.2)	-	-
Male:Female ratio θ	1.17 (0.854 - 1.80)	0.593 (0.493 - 0.689)	([51])
Male seroconversion σ_M	9.65% (5.8% - 15%)	29.3% (27.3% - 31.4%)	([96])
Female seroconversion σ_F	48.9% (34.7% - 65.4%)	64.5% (60% - 69%)	([96])

Table S6: Parameter values with credible intervals, from the distributions in Figure S1. Literature values included where possible.

Additional file 9 — Figures S2 and S3

Comparing HPV prevalence between the model and data.

Plots showing the trends in HPV prevalence in the model are plotted alongside the various data used in Fig S2 and Fig S3.

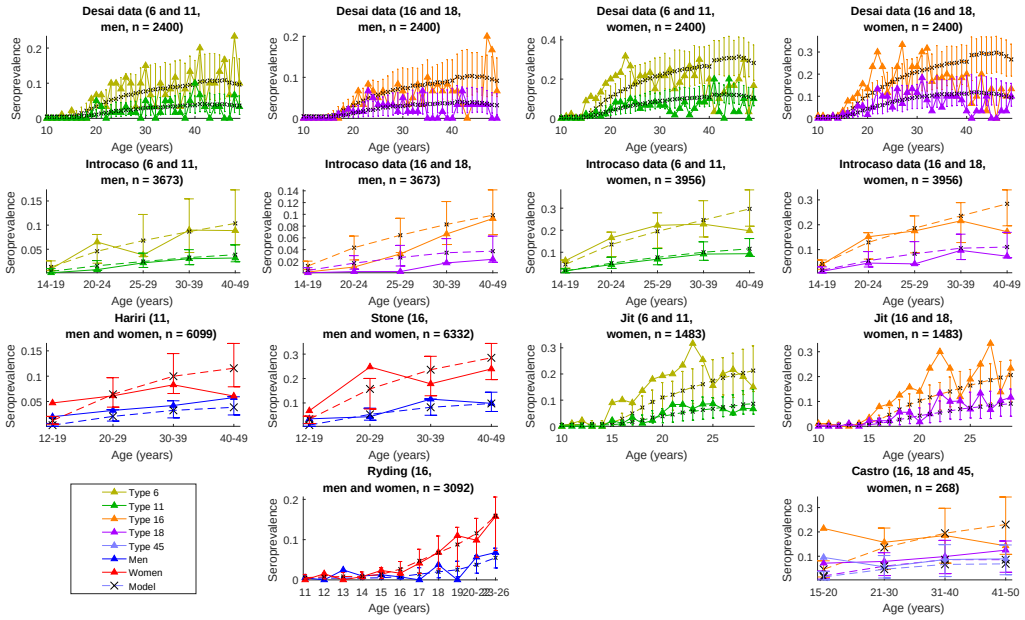

Figure S2: Fitting the epidemiological model to serological data. Seven of the thirteen datasets are serology-based (see Additional file 1 — Appendix S1). Data are shown as solid lines with triangle markers; model means are shown as dashed lines with cross markers, with 95% prediction intervals.

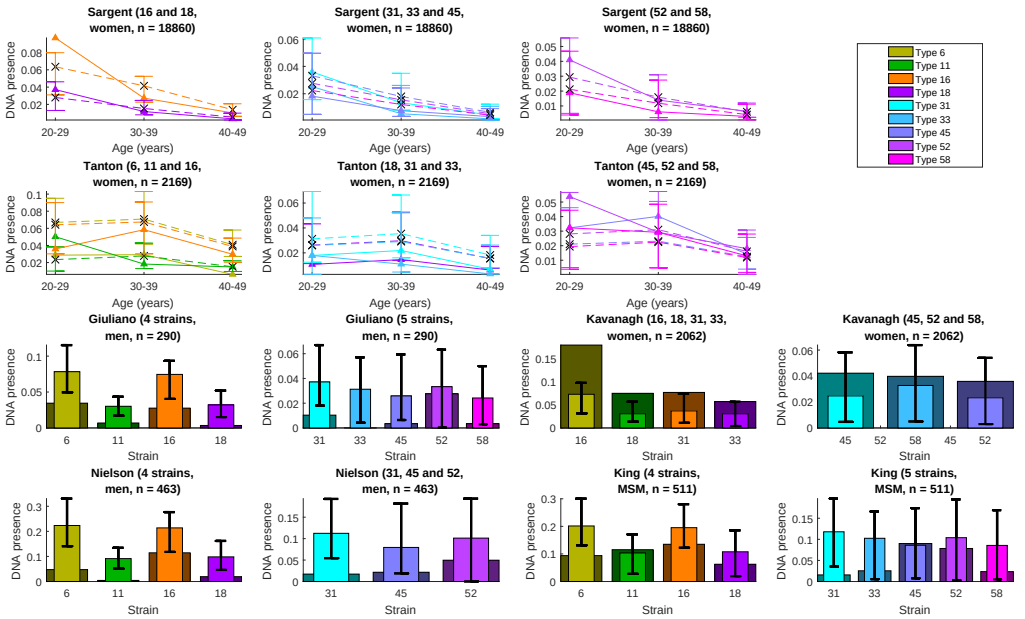

Figure S3: Fitting the epidemiological model to DNA data. Six out of the thirteen datasets are DNA-based (see Additional file 1 — Appendix S1). Data are shown as solid lines with triangle markers, or dark wider bars, as appropriate; model means are shown as dashed lines with cross markers, or lighter narrower bars, with 95% prediction intervals.

Additional file 10 — Figure S4

The mean threshold price per dose, under different vaccination strategies, for the base case scenario, at both 3.5% and 1.5% discount rate.

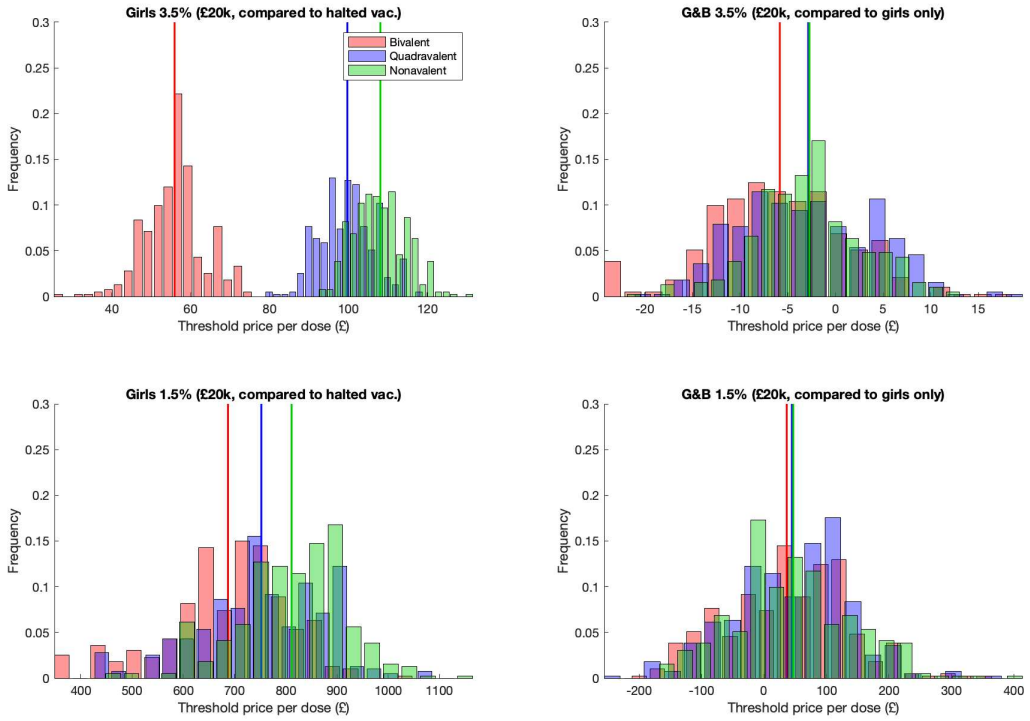

Figure S4: Distribution of threshold dose prices for various vaccination strategies, considering a two-dose schedule. All plots assume £20,000 cost-effectiveness threshold for a QALY, modal parameters from posterior used, and a £10 administration charge per dose. Mean values are shown as vertical lines. Top plots assume 3.5% discount rates applied, bottom plots assume 1.5% discount rates applied. Left plot: comparing girls-only vaccination to halted vaccination. Right plot: comparing gender-neutral vaccination to continuing girls-only vaccination. When comparing a strategy to girls-only vaccination the same vaccine is used for correct comparison.

Additional file 11 — Table S7

The mean prevalence of different HPV strains (as a percentage) in different ages and genders, after 50 years of simulating a range of vaccination strategies.

Group	Halted vac.	Girls, bi.	Girls, quad.	Girls, nona.	G&B, bi.	G&B, quad.	G&B, nona.
M, 16-25, 16/18	10.735	1.036	1.022	0.999	0.123	0.116	0.113
M, 16-25, 6/11	8.868	8.854	0.676	0.689	8.900	0.091	0.087
M, 16-25, 31/33/45/52/58	15.132	8.858	11.949	1.046	7.037	9.323	0.156
M, 26-35, 16/18	5.866	1.200	1.223	1.187	0.436	0.417	0.423
M, 26-35, 6/11	5.148	5.234	0.984	0.955	5.272	0.366	0.341
M, 26-35, 31/33/45/52/58	10.183	6.575	8.588	2.046	5.222	7.214	0.658
M, 36-50, 16/18	3.102	1.275	1.269	1.251	1.066	1.010	1.050
M, 36-50, 6/11	3.038	3.078	1.371	1.354	3.108	1.256	1.214
M, 36-50, 31/33/45/52/58	5.988	4.621	5.456	2.667	4.153	5.041	2.202
F, 16-25, 16/18	7.992	0.328	0.317	0.303	0.113	0.111	0.115
F, 16-25, 6/11	6.678	6.665	0.160	0.162	6.738	0.091	0.088
F, 16-25, 31/33/45/52/58	11.651	6.299	8.694	0.313	5.470	7.287	0.160
F, 26-35, 16/18	3.907	0.356	0.366	0.336	0.150	0.142	0.143
F, 26-35, 6/11	3.368	3.372	0.239	0.222	3.399	0.144	0.134
F, 26-35, 31/33/45/52/58	6.407	3.721	5.160	0.535	3.243	4.490	0.342
F, 36-50, 16/18	1.780	0.693	0.693	0.681	0.536	0.544	0.543
F, 36-50, 6/11	1.868	1.854	0.849	0.854	1.871	0.811	0.808
F, 36-50, 31/33/45/52/58	3.411	2.682	3.129	1.556	2.493	2.891	1.479

Table S7: The average prevalence of HPV (as a percentage of the population), by gender (M/F), age (16-25, 26-35 and 36-50) and strain (16/18, 6/11 and 31/33/45/52/58), over 200 simulations. For each simulation numbers are taken 50 years after the vaccination strategy has been in place. The strategies considered are: halted vaccination, and for vaccinating either girls or girls and boys together, using one of the three vaccines (bi. = bivalent, quad. = quadrivalent, nona. = nonavalent).

Additional file 12 — Table S8

Cases of disease for different vaccination strategies.

Health effect	Halted vac.	Girls, bi.	Girls, quad.	Girls, nona.	G&B, bi.	G&B, quad.	G&B, nona.
Cervical cancer	8.259	1.627	1.801	0.767	1.310	1.460	0.495
Anal cancer	3.354	1.200	1.196	1.025	1.124	1.011	0.838
Vulvar cancer	3.291	2.459	2.291	2.143	2.304	2.346	2.249
Vaginal cancer	0.641	0.489	0.491	0.409	0.462	0.466	0.434
Penile cancer	1.946	1.416	1.393	1.319	1.405	1.167	1.315
Oropharyngeal cancer	24.264	19.214	18.877	18.698	18.524	18.441	17.857
CIN (grades 2/3)	80.720	35.356	36.450	30.588	34.307	34.965	29.893
Genital warts	243.837	244.175	64.457	64.271	243.268	53.931	53.110
RRP	0.091	0.089	0.023	0.017	0.060	0.030	0.019

Table S8: The average number of cases of different health effects per 100,000 individuals, over 500 simulations. For each simulation annual numbers are averaged over 51 and 70 years after the vaccination strategy has been in place. The strategies considered are: halted vaccination, and for vaccinating either girls or girls and boys together, using one of the three vaccines (bi. = bivalent, quad. = quadrivalent, nona. = nonavalent).

Additional file 13 — Tables S9 and S10, and Figure S5

Incremental cost-effectiveness ratios.

An alternative to calculating the threshold dose price is to set the vaccine dose price to a fixed value, and then calculate the incremental cost of each additional QALY for a given vaccination strategy (the incremental cost-effectiveness ratio). These are presented for a range of dose prices (covering the list price for the quadrivalent vaccine of £87.50 per dose), using each of the three vaccines, and vaccinating either girls only or girls and boys. The results are shown in Tables S9 and S10, and Fig S5.

Strategy	£0	£20	£40	£60	£80	£100
Girls, bivalent	strategy dominant	strategy dominant	1943	15930	29916	43903
Girls, quadrivalent	strategy dominant	strategy dominant	strategy dominant	1364	8877	16390
Girls, nonavalent	strategy dominant	strategy dominant	strategy dominant	strategy dominant	6655	13668
Girls & boys, bivalent	strategy dominant	109	26499	52890	79280	105671
Girls & boys, quadrivalent	strategy dominant	strategy dominant	7007	21152	35297	49442
Girls & boys, nonavalent	strategy dominant	strategy dominant	4997	18195	31394	44592

Table S9: Incremental cost-effectiveness ratios for alternative vaccination strategies at alternative assumed vaccine dose prices (minus the £10 administration fee assumed in the analysis - hence the first column represents paying the administration fee plus zero for each vaccine dose). Evaluated strategies are relative to halted vaccination. Note that "strategy dominant" means that the vaccination strategy is on average both cheaper and more effective.

Strategy	£0	£20	£40	£60	£80	£100
Girls & boys, bivalent	strategy dominant	204344	439225	674106	908987	1143868
Girls & boys, quadrivalent	strategy dominant	98425	219913	341401	462889	584377
Girls & boys, nonavalent	strategy dominant	91142	203735	316327	428920	541513

Table S10: Incremental cost-effectiveness ratios for alternative vaccination strategies at alternative assumed vaccine dose prices (minus the £10 administration fee assumed in the analysis). Evaluated strategies are relative to vaccinating girls only.

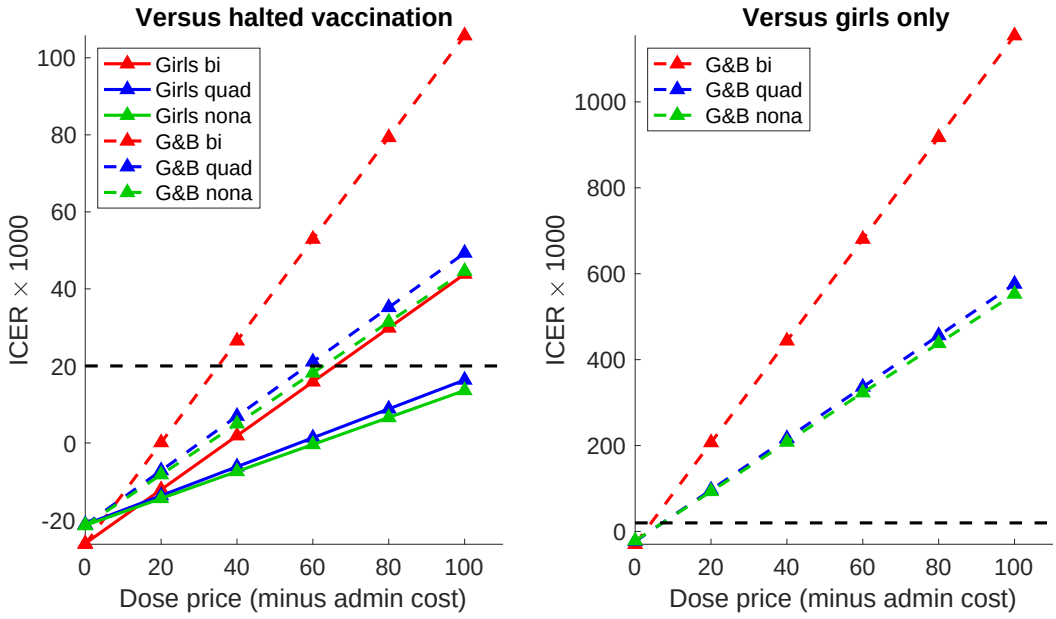

Figure S5: The incremental cost-effectiveness ratios, for all three vaccines, at a range of dose prices. Values for girls-only vaccination are shown by solid lines, gender-neutral by dashed lines. Vaccines are colour coded: red (bivalent), blue (quadrivalent), green (nonavalent). £20,000 threshold shown by horizontal dashed black line. Left plot: compared to halted vaccination. Right plot: compared to girls-only vaccination.