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Transmission dynamic modelling of the impact of human papillomavirus vaccination in the United Kingdom

Yoon Hong Choi[a,b,*], Mark Jit[a,e], Nigel Gay[a], Andrew Cox[a], Geoff P. Garnett[c], William John Edmunds[a,d]

[a] Modelling and Economics Unit, HPA Centre for Infections, 61 Colindale Avenue, Colindale, London, United Kingdom
[b] Immunisation Department, HPA Centre for Infections, 61 Colindale Avenue, London, United Kingdom
[c] Division of Epidemiology, Public Health and Primary Care, Imperial College London, United Kingdom
[d] Infectious Disease Epidemiology Unit, London School of Hygiene and Tropical Medicine, London, United Kingdom
[e] Health Economics Unit, University of Birmingham, Birmingham, United Kingdom

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ABSTRACT

Many countries are considering vaccination against human papillomavirus (HPV). However, the long-term impact of vaccination is difficult to predict due to uncertainty about the prevalence of HPV infection, pattern of sexual partnerships, progression of cervical neoplasias, accuracy of screening as well as the duration of infectiousness and immunity. Dynamic models of human papillomavirus (HPV) transmission were developed to describe the infection spread and development of cervical neoplasia, cervical cancer (squamous cell and adenocarcinoma) and anogenital warts. Using different combinations of assumptions, 9900 scenarios were created. Each scenario was then fitted to epidemiological data and the best-fitting scenarios used to predict the impact of vaccination. Results suggest that vaccinating 12-year-old girls at 80% coverage will result in a 38–82% reduction in cervical cancer incidence and 44–100% reduction in anogenital warts incidence after 60 years of an ongoing vaccination programme if vaccine protection lasts 20 years on average. The marginal benefit of vaccinating boys depends on the degree of protection achieved by vaccinating girls.

1. Introduction

Human papillomavirus (HPV) infection is necessary for the development of cervical cancer in women as well as anogenital warts in both men and women. Most diagnosed cervical cancers are squamous cell carcinomas; however, the incidence of adenocarcinomas has been increasing rapidly [1] and now accounts for up to 20% of all cancer diagnoses in the United Kingdom (UK). Two HPV types (16 and 18) are responsible for about 70% of squamous cell carcinomas [2] and 85% of adenocarcinomas [3], while another two types (6 and 11) cause over 90% of cases of anogenital warts [4].

Two prophylactic vaccines against HPV have been developed: a bivalent vaccine (Cervarix™) against types 16 and 18, and a quadrivalent vaccine (Gardasil™) that also includes types 6 and 11. In clinical trials, use of either vaccine in HPV-naive females resulted in at least 90% reduction in persistent infection and associated disease during 30 months of follow-up [5,6]. The quadrivalent vaccine has also been shown to be highly effective at preventing anogenital warts [7].

The vaccines have the potential to reduce the substantial burden of HPV-related disease. However, they are likely to be priced at levels significantly higher than other vaccines in national vaccination schedules, so their epidemiological and economic impact needs to be carefully considered. Because of the complexity of HPV infection and pathogenesis, as well as the long delays between infection and the most serious disease endpoints (cervical cancer), mathematical models are required to estimate the impact of vaccination.

The majority of existing studies (reviewed in Ref. [8]) use static models, which explore the natural history of HPV infection on an individual level, but underestimate the population-wide impact of vaccination. Studies using dynamical models are rarer because of their greater demands in terms of both model complexity and data requirements in order to represent sexual contact patterns. However, they are required to take into account herd immunity and hence estimate the wider impact of vaccination. To date, one theoretical HPV transmission model has been published [9], and transmission models have been applied to assess HPV vaccination in the United States [10], Finland [11,12], Brazil [13] and the UK [14]. Most of these models assume a fixed structure to represent HPV transmission and progression between stages of disease. However, there are still significant gaps in our knowledge of

* Corresponding author at: Immunisation Department, Centre for Infections, Health Protection Agency, 61 Colindale Avenue, Colindale, London NW9 5EQ, United Kingdom. Tel.: +44 020 83277454; fax: +44 020 82007868.
E-mail address: yoon.choi@hpa.org.uk (Y.H. Choi).

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HPV epidemiology and natural history that make it problematic to assume a single structure for a model of HPV disease and vaccination. In order to capture this uncertainty, we develop here a series of transmission models that represent different possibilities about sexual behaviour, natural immunity, vaccine characteristics, disease progression and screening accuracy. These models are then fitted to available data and used to project the impact of vaccination, providing robust estimates of the possible impact of alternative immunisation programmes. The use of the outcomes of the models to parameterise a cost effectiveness model of HPV vaccination has been described elsewhere [15].

2. Methods

2.1. Model structure

We developed a set of compartmental Markov models to represent acquisition and heterosexual transmission of infection, with an imbedded progression model to represent the subsequent development of HPV-related disease (different stages of pre-cancerous cervical neoplasias, squamous cell carcinomas, adenocarcinomas and anogenital warts). The models are stratified by HPV type, age, sex and sexual activity-based risk group. The model time step was 1 month [16].

HPV types in the model are divided into five groups: type 16, type 18 and other oncogenic high-risk types for cervical cancers, plus type 6 and type 11 for anogenital warts. When fitting to data, women were assumed to have the most oncogenic HPV type present: type 16 in preference to type 18, and both in preference to other HPV types (that is, if data showed someone to be positive to both HPV 16 and 18, that person was classified as HPV 16). For simplicity, we did not model interactions between HPV types, such as synergistic or antagonistic progression of lesions and cross-protection in natural immunity. Such interactions are difficult to model partly because their existence and nature are still being debated [17–19]. Double counting of disease outcomes is avoided by attributing cancer-related outcomes to the most oncogenic HPV type present (HPV 16, or HPV 18 if HPV 16 is not present).

For oncogenic HPV types in females, there are type-specific model compartments for being susceptible to HPV infection, infected with HPV, immune to HPV infection, having cervical intraepithelial neoplasias (CINs) of different grades (CIN1, CIN2 or CIN3), having CIN3 carcinoma in situ (CIS) or undiagnosed squamous cell carcinoma, having diagnosed invasive squamous cell carcinoma and having had a hysterectomy (see Fig. 1). Adenocarcinomas were modelled separately. The same model structure was adopted, except that states for CIN1, CIN2 and CIN3 were replaced with states for cervical glandular intraepithelial neoplasia grades I, II and III respectively (CGIN1, CGIN2 and CGIN3). Males can only occupy the susceptible, HPV infected and immune states. Females move through the various HPV disease states (HPV infected, CIN1, CIN2, CIN3, CIS or cancer) at rates independent of their age and of the time already spent in the state. They may regress to less severe disease states or to the immune state, either as a result of natural regression (at rates independent of age) or of age-dependent cervical screening rates followed by treatment. They are also subject to an age-dependent background hysterectomy rate. The data sources used to fit the rates of natural progression and regression of lesions are described in Section 2.6 below. Rates were assumed to be age independent as we were able to fully explain findings from epidemiological studies without recourse to age-dependent rates (details in Ref. [16]).

The dynamics of infection by HPV 6 and 11 are modelled using three compartments in both females and males, representing being susceptible to infection, being infected and being immune to infection. A proportion of susceptibles who become newly infected were assumed to acquire symptomatic warts and present for treatment, thereby contributing towards anogenital warts incidence. Complete model equations are specified in Appendix I (see supplementary material).

2.2. Vaccination

Clinical trials for both the quadrivalent and bivalent HPV vaccine indicate close to 100% vaccine efficacy against clinical endpoints (vaccine-type CIN) in HPV naïve females, with slightly lower efficacy reported against persistent vaccine-type HPV infection [20]. The model simplifies these results by assuming that vaccine-protected individuals have 100% protection against any vaccine-type HPV infection. However, vaccine-induced protection can wane at a constant rate, moving vaccinated individuals to the susceptible compartment. There is evidence for immunological and clinical efficacy of vaccination in individuals who are non-naïve to HPV, but who are HPV DNA negative at the time of vaccination (and hence have cleared their HPV infection) [5,21]. Hence we have assumed that the vaccine is fully effective in this group. The vaccine is assumed to have no effect on the rate of HPV clearance in infected individuals. However, non-naïve vaccinated individuals who subsequently clear their infection are protected from re-infection – there is some evidence for this from clinical trials, although full details will only become clearer in future years [5]. Vaccinated individuals who are infected at the time of vaccination remain infectious until they clear their infection. In the baseline scenario, it was assumed that vaccination does not protect against non-vaccine types. However, one of the scenarios considered was based on an assumption that vaccination provided cross-protection with efficacy of 27% against oncogenic non-vaccine HPV types. This is based on around 27% efficacy reported against non-vaccine HPV types (accounting for about 98% of cases of cervical cancer worldwide [2]) noted in trials of both vaccines ([22] and Brown D, poster presented at the 47th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) 2007, Chicago, USA).

2.3. Population

The model population consists of 49 million people at equilibrium, divided into 780 monthly birth cohorts between 10 and 74 years old, equally split between males and females. At the end of each month, surviving individuals become 1 month older (i.e. monthly age group i becomes age group $i+1$ after accounting for age- and gender-specific natural mortality) and a fixed number of susceptibles enter the first cohort. No migration either in or out of the population is assumed. Age- and gender-specific mortality rates were obtained from the Office for National Statistics [23].

2.4. Sexual behaviour

Sexual transmission was modelled using a structure similar to that previously developed for HIV [24]. Briefly, the model population is further stratified into three sexual behaviour groups (low risk, moderate risk and high risk). The low-risk group represents people in the lowest 80th percentile in terms of the number of new sexual partners they acquire per year; the next 15th percentile is classified as moderate risk, and the highest 5th percentile as high risk. A sex-dependent partner change rate (average number of new partners per year) was defined for each of ten age groups (12–13, 14–15, 16–19, 20–24, 25–29, 30–34, 35–44, 45–54, 55–64 and 65–74 years). The number of sexual partners in each risk and age group was determined by a sexual mixing matrix that was constructed so as to balance partnerships between sex, age and risk groups. The parameters of the matrix were governed by two param-

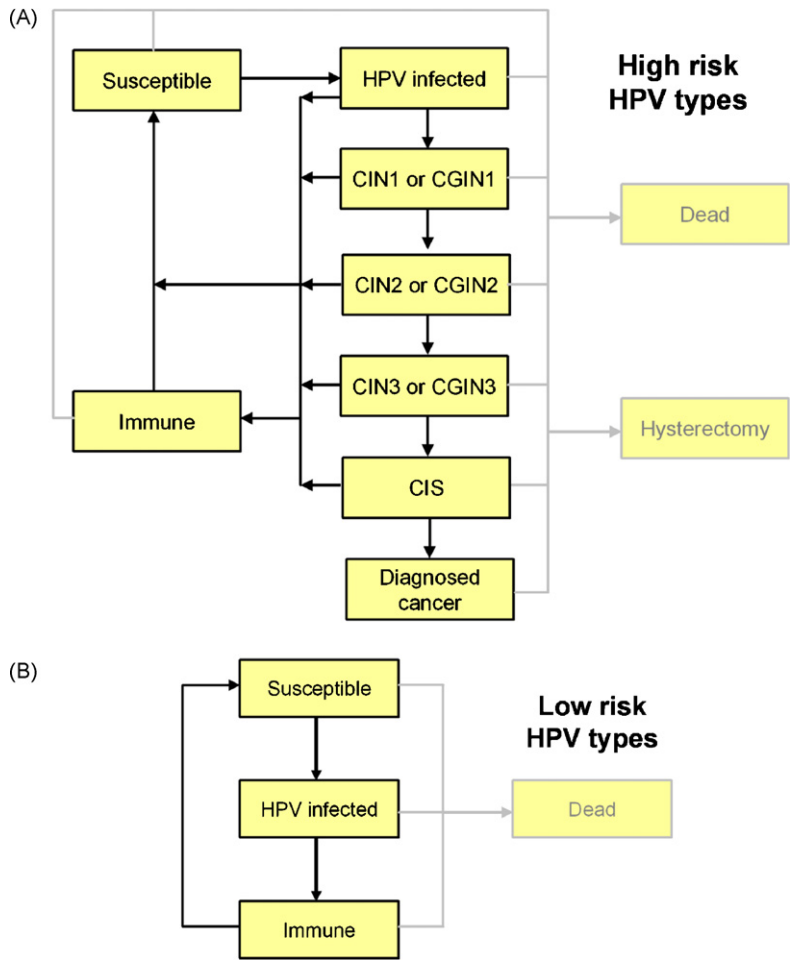

Fig. 1. Flow diagram for models of (A) high-risk (oncogenic) HPV infection and disease in females, and (B) low-risk (warts-related) HPV infection in females or any HPV infection in males.

eters representing the assortativeness of mixing by age and by risk group, allowing mixing to vary between being completely proportionate (an individual is equally likely to choose any available individual as a partner) and completely assortative (an individual only chooses partners from the same age or risk group). The force of infection for each age and risk group was determined by the distribution of sexual partners for that age and risk group together with the number of HPV infected individuals of the opposite sex in those groups.

Age and risk group-dependent partner change rates were estimated from the mean number of new partners in the last year reported by respondents to the National Survey of Sexual Attitudes and Lifestyles II (NATSAL II) [25]. Partner change rates were highest between 16 and 29 years of age, peaking slightly earlier in females than males. As is frequently observed in such studies males reported higher rates than females. We followed a previously described procedure [24] to balance partnerships between the two groups (Appendix I (see supplementary material) for details).

People below 16 or above 45 years old were not sampled in the survey. The sexual partner change rate for people below 16 years old was determined by multiplying the rate in the 16–19 age group by the relative proportion of people in younger age groups who had reached sexual debut (based on their responses to a question about the age at which they started heterosexual activity). Children below 12 years old were assumed to have no sexual partners. The partner change rate in each age group above 45 years was assumed to be 50% of the rate in the previous age group. Modifying this assumption to a decline of 30% or 70% of the rate in the previous age group had a very small effect on the outcomes predicted by the model, with the reduction in diagnosed cervical cancer cases due to vaccination changing by less than 10% (data not shown). The assortativeness of mixing across age groups was estimated using the difference between age of respondent and age of most recent sexual partner reported in NATSAL II. Considerable assortativeness was observed with a mean age difference of 3 years.

There is no direct information about the probability of HPV transmission per partnership. Each risk group was assumed to have an associated per partnership transmission probability; for the medium and high-risk groups the probabilities were assumed to be a multiple of the transmission probability for the low-risk group. Both this constant factor and the transmission probability for the low-risk group were estimated by fitting the models to data. The transmission probability distributions for HPV 16 are shown in Appendix I (see supplementary material); characteristics of the distributions for each HPV type are shown in Table A5 of Appendix II (see supplementary material). Two assumptions were explored: the first in which the transmission probability of a particular partnership depends on the risk group of the partner with the higher risk group, and the second in which it depends on the risk group of the partner with the lower risk group.

2.5. Screening and treatment

Women were assumed to be screened at rates consistent with guidelines set by the National Cervical Screening Programme, i.e. once every 3 years for women aged 25–49 year and once every 5

years for older women aged 50–64 years. Coverage data from the Cervical Screening Programme for England in 2005–2006 [26] were used to estimate the age-specific proportion of women called for screening who actually attend. The denominator (all women called for screening) excluded women who never attended screening in their lifetime, but included women who had their recall ceased, and women with no cytology records or no adequate smears. The success rate of screening at detecting women with different grades of cervical neoplasias was estimated using median values from a meta-analysis of the sensitivity of Pap testing [27], which were similar to values from a more recent meta-analysis [28]. The probability that women with positive smears were referred for colposcopy was estimated based on a retrospective study (91% for CIN1, 86% for CIN2 and 100% for CIN3) [29]. The sensitivity of colposcopy in detecting a lesion was assumed to be 82% [30], while the probability of treatment following a positive colposcopic results was assumed to be 30% for CIN1 [31], and 90% for more serious lesions [32]. Treatment was assumed to be successful and to move women with different stages of pre-cancer to an HPV-free state. However, a recent Swedish study showed that women treated for CIN3 have more than twice the risk of subsequently developing invasive cancer compared to the general population [33]. Hence for the case of carcinoma in situ, we assumed that treatment was only successful 50% of the time. The figure of 50% was chosen because it allowed natural history of progression to cancer to fit well with overall data on pre-cancerous neoplasias and cancer incidence (discussed in Ref. [16]). Age-specific background hysterectomy rates were estimated from the literature [34]. The monthly rates of hysterectomy, mortality, screening and successful treatment by age are provided in Table A2 of Appendix II (see supplementary material).

2.6. Scenarios

In order to estimate the rates at which females infected with oncogenic HPV types move between different disease states, a Markov progression model with the same step size (1 month) was constructed [16]. The model was fitted to data from a trial of HPV DNA testing in women with known cytological status [35], as well as the cytological status of women undergoing cervical screening collected by the national cervical screening programme [26]. A range of scenarios were fitted to the data, covering different combinations of assumptions about the age-dependent prevalence of HPV infection (HPV acquisition starting at age 12, HPV acquisition starting at age 14 and HPV acquisition following the same pattern as anogenital warts diagnoses), the accuracy of cervical screening (low, medium or high), the way lesions regress (stepwise or immediately back to HPV-free) and the way HPV DNA testing should be interpreted (clinically 100% specific, clinically 99.75% specific and clinically 99.5% specific). The specificity of HPV DNA testing was varied to represent possible cross-reactivity in the HPV DNA test to types not being tested for, and hence possibly not clinically relevant.

Certain combinations of assumptions about HPV prevalence and the interpretation of HPV DNA testing fitted epidemiological data particularly badly. Only the assumptions (and corresponding parameter sets) that fitted data well were used in the dynamic transmission modelling described here. The scenarios that were used were those corresponding to high or medium screening accuracy, and (a) HPV acquisition starting at age 12 and HPV DNA test specificity of 99.75%, (b) HPV acquisition starting at age 14 and HPV DNA test specificity of 99.75% and (c) HPV acquisition based on anogenital warts reports and HPV DNA test specificity of 99.5%. Together with the two possibilities for lesion regression, the combinations of good fitting natural history assumptions produced 12 scenarios per HPV type for squamous cell carcinomas and 6 per type for adenocarcinomas (since there are no assumptions about screening for adenocarcinomas), which were combined with additional assumptions about sexual transmission, natural immunity and vaccine-induced protection.

For HPV 6 and 11, the key parameters governing model predictions about annual anogenital warts diagnoses are the proportion of warts diagnoses linked to HPV 6 infection and the proportion of HPV 6 and 11 infections that lead to clinically diagnosed symptoms. In terms of causal HPV types, in the same way as for oncogenic HPV types, we have assumed a hierarchy of warts-causing HPV types, where a wart lesion is associated with HPV 6 (the most prevalent type in warts lesions) if HPV 6 is present, otherwise it is associated with HPV 11. Using this assumption, the prevalence of HPV 11 in warts lesions varies between 10% [36] and 25% [37], so we have used the two values (10%, 25%) as possible assumptions. Other HPV types have also been found in condyloma acuminata lesions but these are almost always accompanied by type 6 or 11 [36,37], so we have assumed the remainder of lesions are caused by type 6. The proportion of infections causing clinical symptoms was determined by matching the age-dependent pattern of annual anogenital warts cases to the seroprevalence of HPV 6 and 11 in a recent UK convenience sample [38], assuming a seroconversion rate of 60–80% [39,40]. Values for this parameter that lay between 10% and 30% matched data well, so three such values were considered (10%, 20% and 30%).

For each of the 18 oncogenic HPV (12 squamous and 6 adenocarcinoma) and 6 low-risk HPV scenarios, a total of 150 combinations of assumptions governing the transmission of HPV infection, natural immunity and vaccine-induced protection were considered. These comprised of five possibilities for the duration of natural immunity (0 months i.e. no natural immunity, 3 years, 10 years, 20 years, and lifelong), five possibilities for the duration of infection (6 months, 9 months, 12 months, 15 months and 18 months), three possibilities for the assortativeness parameter governing mixing between risk groups (0, 0.5. 0.9) and two possibilities about the probability of HPV transmission per partnership (based on high-risk group values, based on low-risk group values). Thus, 2700 combinations of assumptions were investigated for each oncogenic type (16, 18 and other oncogenic types), and 900 parameter combinations were investigated for each warts type. Hence in total, 9900 scenarios were fitted. Table A4 of Appendix II (see supplementary material) lists the parameter values that are used in each scenario.

2.7. Scenario fitting

For each of the 9900 combination of assumptions the equilibrium prevalence of the dynamical model was fitted to a data-derived HPV prevalence curve associated with that scenario, by altering the two parameters governing HPV transmission: the probability of transmission per sexual partnership for the low-risk group, and the coefficient by which this probability is multiplied to get the corresponding probability for the medium and high-risk groups. These parameters were estimated by minimising the sum of squared residuals weighted by the variance of the HPV prevalence curve over all age groups. Numerical fitting was conducted using the Brent method [41]. Total numbers of clinical outcomes for each set of assumptions were obtained by summing up type-specific outcomes over HPV and histological types. A complete list of fixed parameters used in the model is given in Tables A1–A3 of Appendix II (see supplementary material).

2.8. Scenario selection

The approach that we have taken has been to present the uncertainty in the results, and not impose any prior beliefs about model assumptions within the plausible range of structures described in the model. However, some combinations of assumptions fit

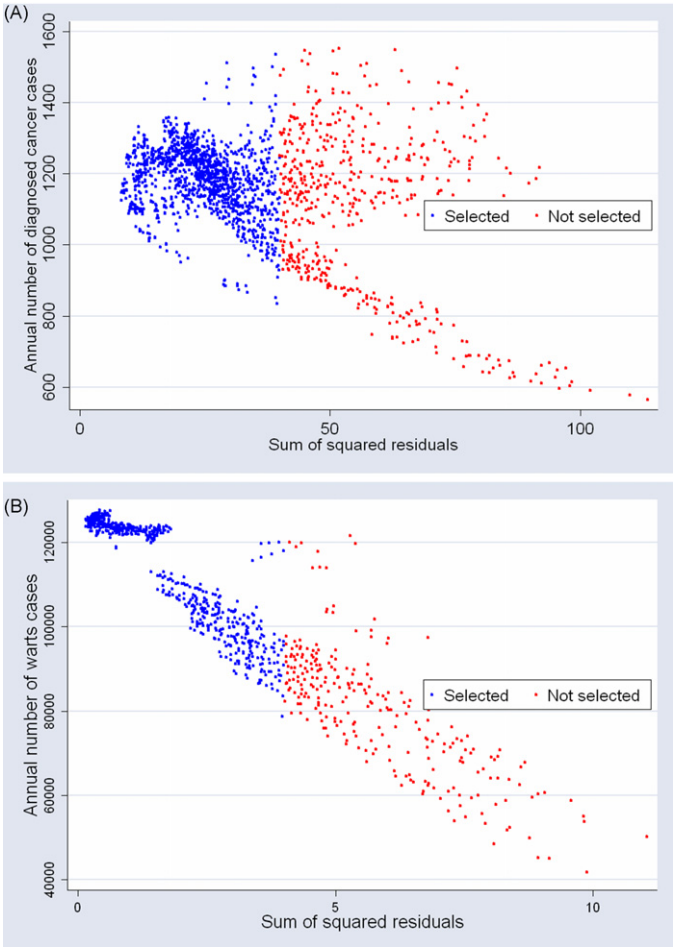

Fig. 2. Relationship between (A) estimated annual cancer incidence and sum of squared residuals for each scenario of oncogenic HPV types, (B) estimated annual warts incidence and sum of squared residuals for each scenario of non-oncogenic HPV types.

HPV prevalence data better than others. For oncogenic HPV types, almost all the poorly fitting scenarios fell into two categories (i) scenarios with very short duration of infection and very long duration of natural immunity (which underestimated HPV prevalence in all age groups) and (ii) scenarios with long duration of infection and short duration of natural immunity (which overestimated HPV prevalence in older age groups, and hence in the best fits underestimated HPV prevalence in younger age groups to compensate). These poor fitting scenarios correspond to model assumptions that are probably unrealistic in their representation of HPV biology and epidemiology. Both categories of poorly fitting scenarios tended to underestimate cancer incidence. Additionally, there is a fairly strong association between goodness of fit to age-dependent HPV prevalence and to age-dependent cancer incidence. In particular, the poorly fitting scenarios to HPV prevalence also fit cancer incidence poorly (Appendix IV (see supplementary material)).

In order to eliminate these unrepresentative scenarios, only cancer scenarios with sum of squared residuals lying below a goodness of fit cut-off of 40 were used for subsequent analysis, representing 72% of all squamous cell carcinoma scenarios. This cut-off was chosen so that the remaining scenarios would match known data about cervical cancer cases. Fig. 2 shows the number of cervical cancers a year indicated by models with different values of the sum of squared residuals.

About 1200 squamous cell carcinomas and 300 adenocarcinomas are reported to cancer registries every year, after adjusting for cohort effects in older women by assuming a linearly decreasing trend in cervical cancer incidence after it peaks around age 35 [42]. In terms of model outputs, the median number of squamous cell carcinoma cases occurring a year before vaccination predicted by all scenarios was 1185 (range 566–1552), while the median for adenocarcinomas was 448 (range 196–602). After eliminating scenarios above the goodness of fit threshold, the median number of cancers predicted to occur a year becomes 1193 (range 834–1534) for squamous cell carcinomas, 456 (range 202–552) for adenocarcinomas and 1645 (range 1122–1990) in total. Also, 25% of the dropped scenarios had both long duration of immunity (lifelong or 20 years) and short duration of infection (6 or 9 months), while a further 38% had both the short duration of immunity (3 years or no natural immunity) and long duration of infection (15 or 18 months).

For warts, a goodness of fit threshold of 4 for the sum of squared residuals was adopted, based on reports of new and recurrent cases of anogenital warts (KC60 codes C11A and C11B). In 2005, there were about 120,000 such reports in males and females [43]. Eliminating the 28% of scenarios falling above the goodness of fit threshold shifts the median number of warts cases annually from 105,000 (range 42,000–128,000) to 122,000 (range 79,000–128,000). There is a strong association between goodness of fit and duration of natural immunity. None of the scenarios with duration of natural immunity 3 years or fewer were eliminated; conversely, 72% of scenarios with lifelong natural immunity were eliminated.

Fig. 3 shows the age-dependent prevalence of HPV infection for the types modelled predicted by each scenario before and after elimination of poorly fitting scenarios. Adopting different cut-off values for retained models makes very little difference to the mean and median number of squamous cell carcinomas and warts cases predicted by the model (Appendix II (see supplementary material)). The primary effect of retaining all of the scenarios would be to extend the uncertainty in the results (widen the error bars).

2.9. Vaccination strategies

HPV infection was assumed to have attained steady state (endemic equilibrium) prior to the introduction of vaccination. In the base-case scenario, routine quadrivalent vaccination was delivered to 12-year-old girls with no catch-up campaign. Coverage of 80% for the full three doses was assumed, based on reported three-dose coverage from the trial of a school-based hepatitis B vaccination programme [44].

The duration of vaccine-induced protection is uncertain, although in clinical trials protection remains high for at least 3 years [7] and antibody levels remain high for at least 3 years [45]. Hence the epidemiological effects of vaccines with three possible mean durations of protection (10 years, 20 years and lifetime) were modelled. Vaccinated individuals are assumed to lose protection at a constant rate, since no data are available on the distribution of vaccine-induced immunity. This results in an exponential decline in the proportion protected with time since vaccination.

Alternative vaccination scenarios were considered: (i) vaccinating girls at the age of 13 or 14 years instead of 12 years, (ii) vaccinating boys at age 12 years in addition to girls at age 12 years, assuming the vaccine fully protects boys against infection by all four vaccine types, (iii) vaccinating girls with three-dose coverage of 70% or 90% instead of 80%, (iv) catch-up campaigns for girls up to age 14, 16, 18, 20 or 25 years old, and (v) vaccinating 12-year-old girls with a vaccine that provides cross-protection against oncogenic non-vaccine types with efficacy of 27% as suggested by clinical trials ([22] and Brown D, poster presented at the 47th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) 2007, Chicago, USA).

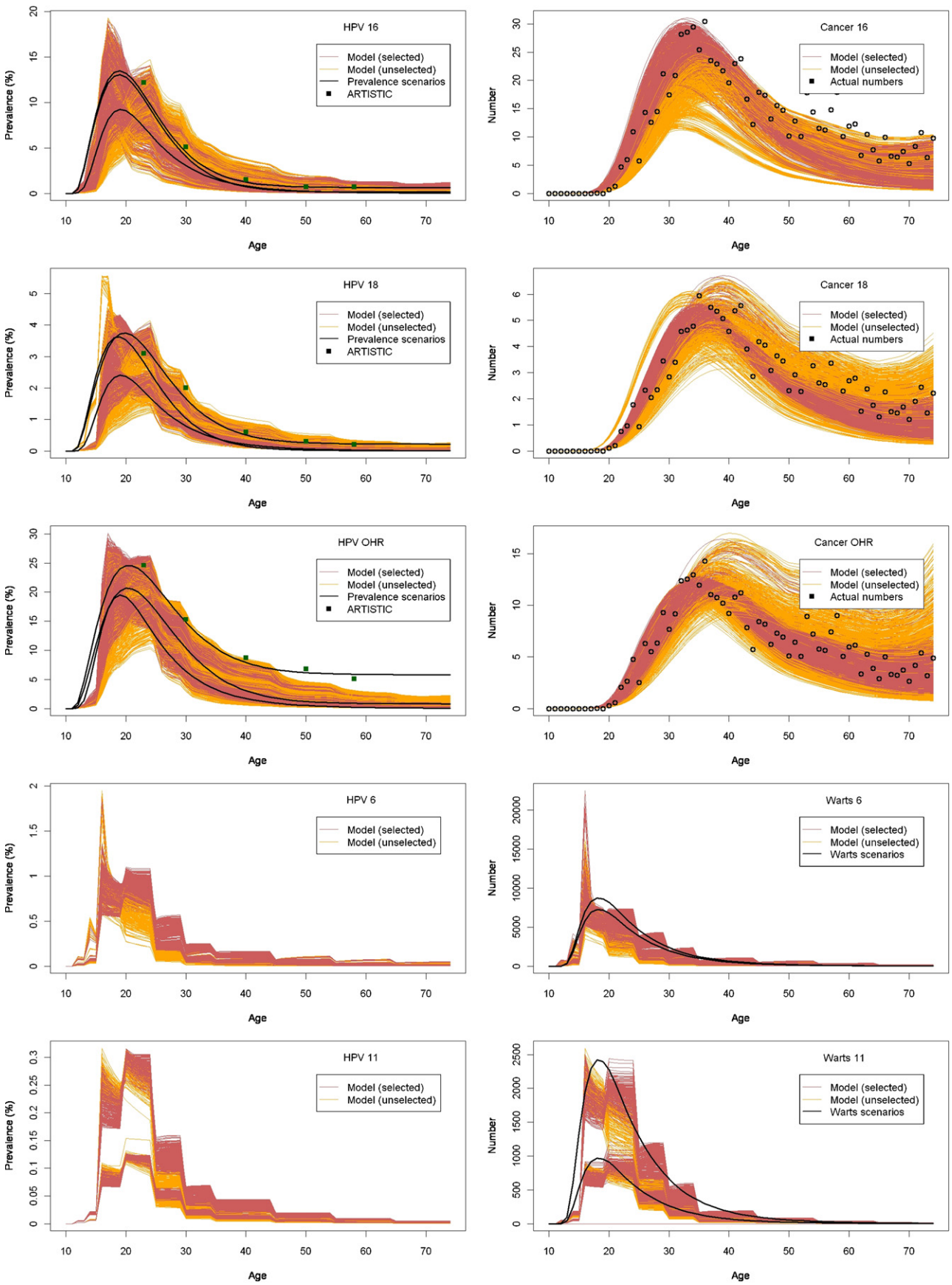

Fig. 3. Comparison of model results with prevalence curves for high-risk and low-risk HPV types. The left-hand panels show the HPV prevalence curve for each scenario, and the right-hand panels are corresponding outcomes (cancer or warts incidence). Selected scenarios are in red, and discarded scenarios are in orange (see text for details on scenario selection).

The combined effect of vaccination on cervical cancer incidence was calculated by summing results for HPV 16, HPV 18 and other high-risk HPV scenarios with the same assumptions. Similarly, the combined effect on anogenital warts was calculated by summing results for HPV 6 and HPV 11 scenarios with identical assumptions.

3. Results

3.1. Base-case vaccination programme

Fig. 4 shows the estimated impact of vaccinating 12-year-old girls at 80% coverage on diagnosed HPV 6/11/16/18-related disease for different assumptions about the duration of vaccine protection. Large reductions in incidence of cervical dysplasia, cervical cancer and anogenital warts cases are expected, provided vaccine-induced immunity lasts for 10 years or more, although the reduction in cervical cancer takes much longer to become apparent (note the change of scale).

One of the key biological uncertainties is the length of naturally acquired immunity to HPV. Fig. 5 shows that the expected post-vaccination incidence of cervical cancer is influenced by assumptions on the duration of natural immunity. The equivalent graph for anogenital warts is not shown as few scenarios associated with a short duration of natural immunity remain after eliminating poor fitting scenarios. If immunity is very short (approximate SIS structure), then the long-term reduction in the incidence of disease would be expected to be greater than if natural immunity is long-lived. This is to be expected, and has been noted previously [8,46]. Infections that do not generate any immunity (SIS) are generally easier to control (they have lower basic reproduction numbers) than infections that result in long-lasting immunity. For instance, a vaccine giving lifelong protection against HPV 16 and 18 eliminates vaccine-type HPV in 94% of the SIS scenarios, 81% of scenarios with duration of immunity of 3 years, but only 4% of scenarios with a duration of immunity of 10 years or greater.

3.2. Vaccine coverage

Increasing vaccine coverage reduces the post-vaccination incidence of disease (Fig. 6). However, even at 70% coverage in girls it

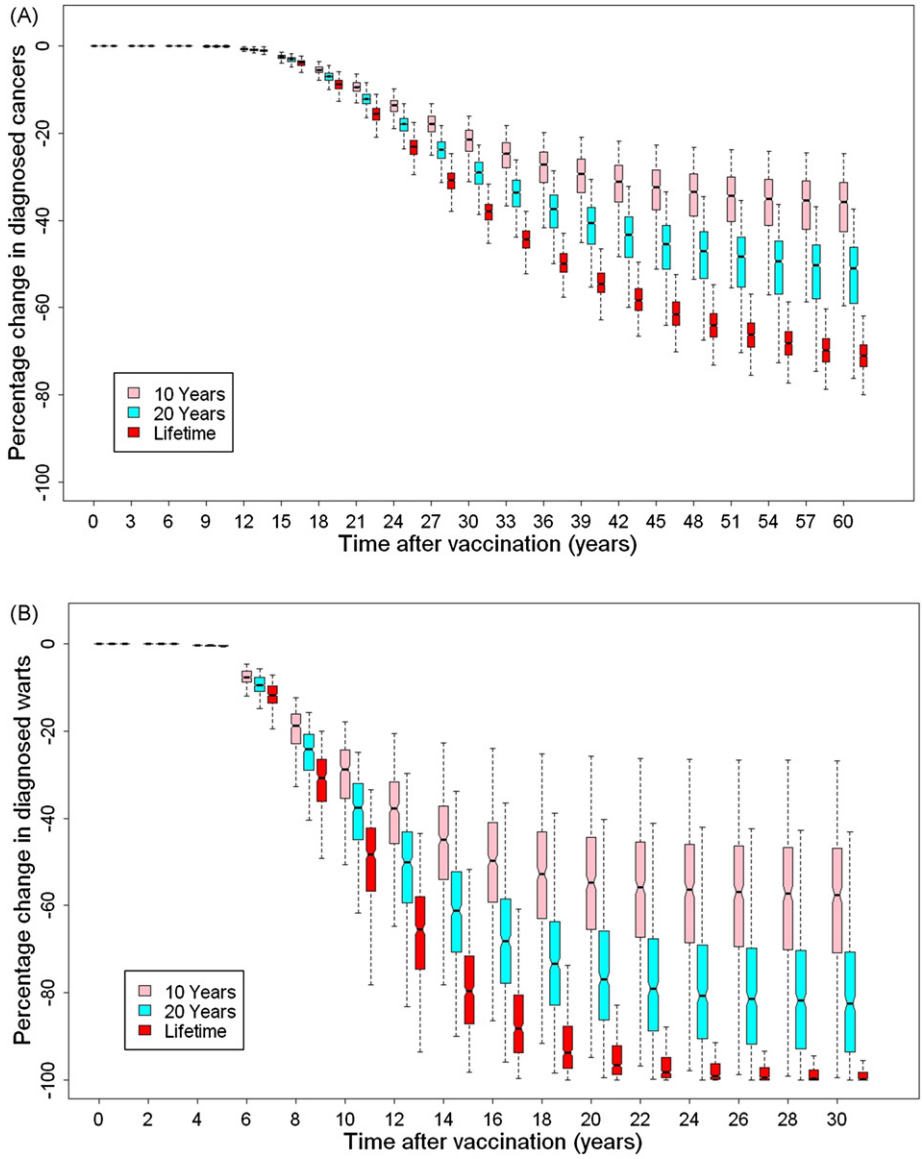

Fig. 4. Percentage change in the estimated annual number of cases of (A) cervical cancers and (B) anogenital warts following vaccination of girls at 12 years of age (base-case programme, 80% coverage). The different coloured boxes represent different average periods of vaccine-induced immunity. The box encompasses 50% of the data, the "whiskers" represent 99% of the data and the notch is the median (50th percentile).

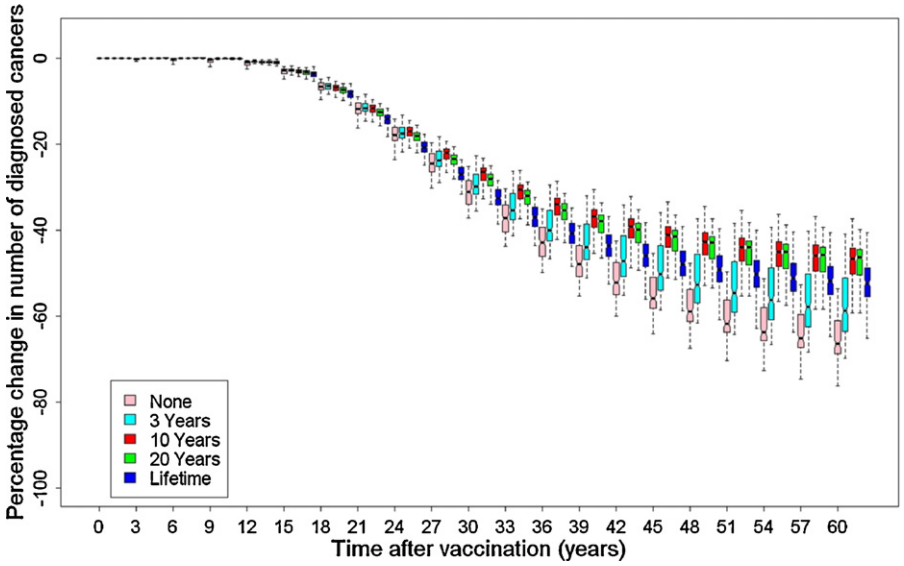

Fig. 5. Percentage change in the annual number of diagnosed cervical cancer cases following vaccination of 12-year-old girls, for different assumptions about the duration of natural immunity. Ten-year vaccine-induced protection is assumed and 80% vaccine coverage is assumed.

is possible to eliminate vaccine-type HPV in some model scenarios when vaccine protection is assumed to be lifelong, particularly those with short duration of natural immunity, because females who are not directly protected from being vaccinated are protected indirectly (by herd immunity).

3.3. Age of vaccination

Offering routine vaccination at a later age speeds the reduction in disease (data not shown), since vaccine is given closer to the age at which HPV is acquired. Since the risk of infection is still very low in 14-year-olds, there is very little increase in infection caused by opening a 2-year window (from 12 to 14 years of age) for infection to occur before vaccination. Furthermore, if vaccine-induced immunity is relatively short-lived (10 years), then offering vaccination later in childhood protects women for more of the highest risk period of HPV acquisition (late teens and early twenties). Thus vaccination at 14 years of age provides slightly improved outcomes compared with 12 years of age if vaccine-induced immunity is not lifelong (Fig. 6). Note, however, that we are assuming that the same level of coverage can be maintained at the later ages, which may not be the case [47].

3.4. Cross-protection against non-vaccine types

Scenarios where vaccination provides cross-protection with 27% efficacy against oncogenic non-vaccine HPV types show on average about 5–10% extra reduction in cancer incidence following vaccination, with a broadly similar pattern across assumptions about duration of vaccine protection (Fig. 6). However, this represents an optimistic scenario which assumes that vaccination provides the same degree of protection against each non-vaccine

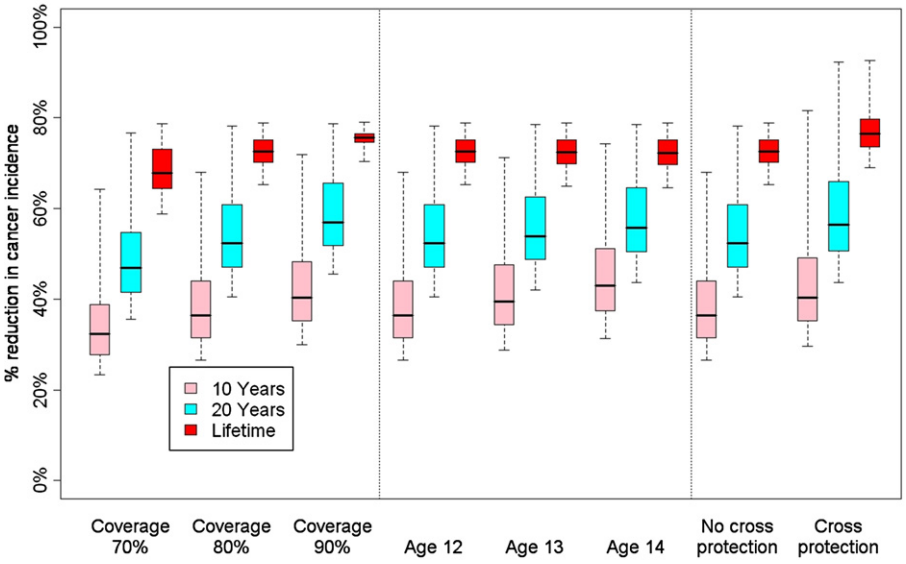

Fig. 6. The effect of vaccine coverage, age of vaccination and existence of cross-protection against non-vaccine HPV types on reduction in annual cervical cancer cases 100 years after vaccination begins. Vaccination of 12-year-old girls is assumed when varying vaccine coverage; 80% vaccine coverage is assumed when varying age of vaccination.

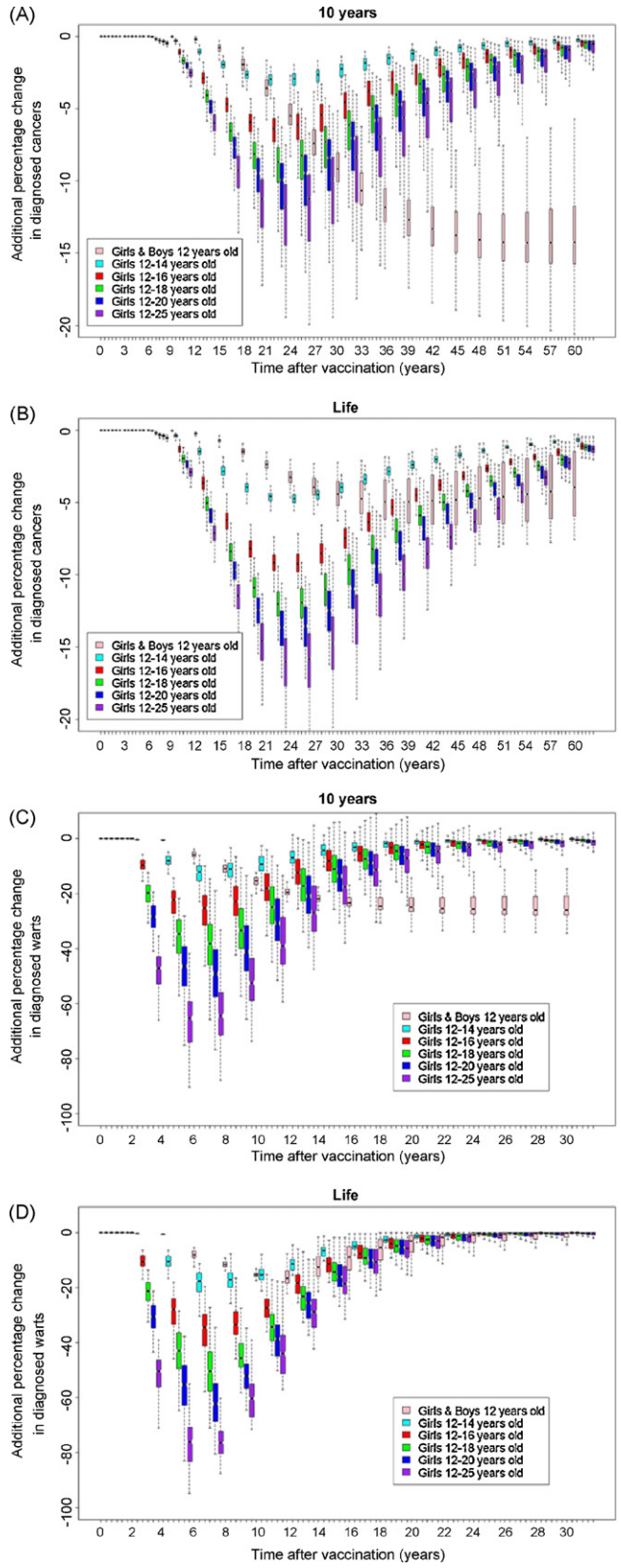

Fig. 7. The estimated impact of extending vaccination to boys or including a catch-up campaign on annual cervical cancer and anogenital warts cases. Three-dose coverage is assumed to be 80%. Graphs show the additional percentage change in number of diagnosed cancer or warts cases prevented compared to the base-case programme of vaccinating 12-year-old girls only. Results are shown for (A) 10 years and (B) lifelong vaccine protection for cancer, as well as (C) 10 years and (D) lifelong vaccine protection for warts.

type. If the vaccine provides better cross-protection against some types than others then this simplification causes the model to overestimate the benefit of herd immunity for non-vaccine HPV types.

3.5. Vaccination of boys in addition to girls

Extending vaccination to boys provides additional benefit in terms of reduction of cervical cancer and anogenital warts compared to vaccinating girls alone (Fig. 7). The effect on anogenital warts cases is slightly greater since males acquire warts but not cervical cancer. However, there is also an indirect effect on cervical cancer incidence since vaccinating boys prevents males from infecting females with oncogenic HPV types. However, the effect on both disease endpoints is small because vaccinating girls alone already reduces HPV prevalence to a very low level, especially if duration of vaccine protection is long. Indeed, vaccinating girls alone at 80% coverage and lifelong protection results in elimination of vaccine types in many of the simulations. The additional benefit of vaccinating boys is more pronounced if the period of vaccine-induced immunity is short or coverage is low (data not shown).

3.6. Catch-up campaigns

Catch-up campaigns usually have a more dramatic short-term effect than extending vaccination to boys on cervical cancer and anogenital warts incidence (Fig. 7). However, the effect of a catch-up campaign is minimal beyond 20 years after the advent of the campaign. There are decreasing marginal returns from extending the catch-up programme to older age groups, particularly if the average duration of vaccine protection is long. In particular, if vaccine protection is lifelong, the reduction in cancer incidence of using a campaign up to the age of 25 years is not greatly different from the more limited campaigns.

4. Discussion

We present here a dynamical model of heterosexual HPV transmission and the development of cervical dysplasia, cervical cancer and anogenital warts in the UK. Model results indicate that vaccinating 12-year-old girls at 80% coverage over 60 years will result in substantial reductions in cervical cancer and anogenital warts incidence. The magnitude of the reduction depends on a number of parameters, particularly the duration of vaccine protection. Catch-up campaigns reduce short-term incidence but have little effect after 30 years. Extending the upper age of catch-up campaigns results in decreasing marginal returns due to an increasing prevalence of pre-existing infection. The marginal benefit of vaccinating boys depends on the degree of protection achieved by vaccinating girls.

A unique feature of our approach is that instead of adopting a single model, we have generated thousands of combinations of assumptions, and then fitted them to prevalence data. The assumptions allow us to capture the effect of uncertain knowledge about both parameters such as the duration of vaccine protection, as well as in biological assumptions governing model structure. Models that fit prevalence data poorly are then discarded as the data do not support their use, but the majority are retained. Each of these retained models is then used to generate predictions about the impact of a range of different vaccination programmes.

Our novel methodology allows a more robust and comprehensive exploration of the uncertainty in model results than many earlier modelling studies of HPV vaccination. Many published transmission models [9–12] are based on a single model structure, with a fixed set of parameters that are determined by a combination of assumption, literature search and calibration in order to obtain

results visually close to epidemiological data. Key uncertainties in HPV modelling such as the duration of both natural and vaccine-induced immunity are often not explored, or only in a univariate fashion (for example [10]). The most similar approach to ours is Kim and co-workers' Brazilian model [13,48], in which thousands of parameter sets were sampled and those that are sufficiently close to prevalence data selected. Indeed, that study highlighted the influence of assumptions such as the degree of natural immunity, although it did not explore other key parameters such as the duration of vaccine protection, and the dynamic model did not include screening details as it only evaluated vaccination strategies and not screening. The results of the dynamic model were used to inform a separate, more detailed, progression model.

This is also the first model to comprehensively capture the effect of HPV vaccination on both cervical cancer and warts. All HPV types in the vaccines (6, 11, 16 and 18) are modelled separately, unlike some previous studies that only looked at a single HPV type in isolation [9,11,12], or grouped some of the vaccine types for the purposes of analysis [10,14]. Also, no previous (static or dynamic) model explicitly models adenocarcinomas, which make up about 20% of the cervical cancers in the UK. We have, however, combined high-risk non-vaccine HPV types into a single group instead of modelling each type separately. This could cause some inaccuracy in estimates of the impact of HPV vaccination on non-vaccine types (if any), since actual vaccine protection against non-vaccine types is not uniformly 27% against every type. Also, we have not modelled penile, vulval, vaginal, anal, head and throat cancers as these are poorly described in the vaccine trials and have less well-known natural history compared to cervical cancers. Models incorporating these cancers may become more important when exploring the effect of targeted HPV vaccination for specific risk groups such as homosexual and bisexual men.

Because our approach is computationally intensive, we have focused on exploring the sources of uncertainty that were felt to have most impact on vaccination outcomes, and for which the most evidence-based ranges of assumptions could be adopted. For example, we assumed that vaccine-mediated protection against HPV-related disease was accomplished by protecting against HPV infection. This excludes the possibility of vaccinated individuals being protected against disease but not against infecting other people. In fact, clinical trials of both vaccines indicate that they may not be totally protective against HPV infection, only against disease [22,49]. However, it is uncertain whether vaccine-protected individuals are able to infect others since infectivity requires not only the presence of viral DNA, but also viral replication, integration of viral DNA into the host chromosome and subsequent shedding of viral particles [50]. We have also assumed that vaccination has no effect on the progression or regression of lesions in vaccines who are already HPV infected. Also, assumptions had to be made about sexual behaviour in age groups for which data were not directly available. For adolescents 16 years old and under, data about the age of sexual debut reported by adults was used to estimate the partner change rate. For individuals over 44 years old, the partner change rate in each age group was assumed to be 50% of the rate in the previous age group. Varying this parameter only had a small effect on the total number of cancers prevented by vaccination each year, so results for other values are not reported.

Another simplification was to model progression and transmission of each HPV type using separate models. This implies that infection and recovery of the different types are independent of each other – that is, that there is no interaction between the types in multiply infected individuals. This assumption was adopted because the evidence of type interaction is contradictory [16,17], and because it reduced the complexity of the model enormously. Another implication of this assumption is that progression of multiply typed lesions is attributed to the most oncogenic (i.e. fastest progressing) HPV type, using a previously described hierarchy of oncogenicity [34]. This may cause some lesions to be misattributed on an individual level, leading to discrepancies in the fitted progression rates. However, in practice it is difficult if not impossible to determine the HPV type (or types) responsible for the progression of a lesion. Furthermore, it was felt that this method would be an improvement over existing methods of simplification used in previous models such as combining HPV types [10], or assuming that only uninfected women can acquire an HPV infection [47]. However, one issue that remains unaddressed is whether the elimination of vaccine types from multiply typed lesions could "unmask" an underlying non-vaccine-type lesion. Such an effect is not captured in our model, or in existing models which mainly ignore non-vaccine types. However, using an individual-based simulation that tracked all HPV infections at the same time we found that such an effect, if it exists, could introduce discrepancies in a model with individually modelled HPV types [51]. Hence investigating the existence of unmasking is an important area for future epidemiological and modelling research.

The model is fitted to data from a screened population, assuming average screening rates. However, there is likely to be significant heterogeneity in screening patterns between women (some women may only be screened sporadically, for instance). It is difficult to capture this heterogeneity using our compartmental model structure, as the number of compartments would need to increase exponentially for each group of women stratified by screening behaviour, and data are not available to fit the model to. Clearly this is an area of work that needs to be developed in the future, particularly if decisions are to be made on the optimal screening programme in the presence of vaccination. The data required to robustly parameterise such a model (likely to be individual-based) and the computational burden that this may pose is not insignificant.

A key parameter in determining the impact of a vaccination programme is the duration of vaccine protection. However, unlike other transmission models [10,12], we found that even a vaccine with an average duration of protection of 10 years can have a significant impact on cervical cancer and anogenital warts. An American model [10] indicated that using such a vaccine would cause a rebound in warts incidence 10–15 years after a vaccination programme started. Our model suggests that such a rebound is highly unlikely to occur in the UK because anogenital warts reports peak before age 20 years during which vaccinees are still protected against infection [43]. A Finnish model [12] indicated that using a vaccine with duration of protection of less than 15 years had no effect on cancer incidence. However, this conclusion relies on HPV clearance rates being age-dependent; in particular, older women are less likely to clear an infection in the model regardless of when they acquired their infection. In fact, recent epidemiological [19] and modelling [16] studies have shown that the observed shift towards persistent infections in older women can be explained by the fact that these infections were acquired less recently and hence are more likely to have progressed to more severe neoplastic states. Thus, the Finnish study [12] may overestimate the impact of declining vaccine-induced immunity.

Our results suggest that vaccination of 12-year-old girls at the levels of coverage likely to be achieved in the UK is expected to have a large impact on the incidence of HPV-related disease, provided vaccine-induced immunity lasts for at least 10 years. If vaccine-induced immunity is not lifelong, then offering vaccine at a slightly older age (13–14 years) is expected to result in somewhat greater reductions in incidence. This is because infection appears to be relatively uncommon in these age groups, and delaying vaccination protects women for longer during their high-risk years (late teens and early twenties). These results are, however, contingent on achieving equally high levels of coverage in older children, which

may be difficult in practice. In addition, model predictions for the under 16s are complicated by a lack of data on sexual partner change rates in this age group. We have attempted to capture some of the epidemiological uncertainty by taking different prevalence scenarios (based on data about HPV seroprevalence and anogenital warts incidence), which differed in the rate of acquisition of markers in teenagers. Nevertheless, predictions of the benefits of vaccinating at different ages should be treated with some caution.

Heterosexual males are protected by vaccination of girls alone. However, vaccinating males as well as females produces additional benefits both for the males themselves (by reducing their risk of warts), and to a lesser extent for females (by reducing the overall HPV prevalence). The direct effect of vaccinating males (on reducing their risk of warts) is particularly true for homosexual men, who are not included in this model and who are likely to benefit less than their heterosexual counterparts from vaccination of girls only. The marginal benefits derived from vaccinating boys depend on the extent to which HPV incidence is reduced by vaccination of girls only. In many scenarios (particularly those that assume short periods of natural immunity) vaccinating girls alone reduces the incidence of vaccine-preventable types to very low levels (elimination might even be achieved at 80% coverage). Under these circumstances vaccination of boys brings few additional benefits (although it does mean that the probability of elimination is greater). However, if the period of immunity is shorter then the additional benefits from vaccinating boys are greater. Clearly, these benefits are larger for prevention of anogenital warts as males benefit directly from vaccination against this disease.

Catch-up campaigns have no effect on long-term incidence. However in the short-term they can bring about a more rapid reduction in disease, particularly for acute diseases (anogenital warts and low-grade neoplasias) associated with HPV infection. As the effects of the campaign wear off it is possible to get a resurgence of disease some time after vaccination (a post-honeymoon epidemic), before the system settles into its new equilibrium state. There are decreasing marginal returns associated with a catch-up programme as the upper age at which vaccination is offered is extended. This is because the probability of remaining susceptible to the vaccine-preventable types falls rapidly after the age of about 15 years. Indeed, the incremental benefits of extending a catch-up programme over the age of compulsory schooling are likely to be more modest than the model predicts, since it assumes that 80% coverage is maintained in the older age groups, which seems unlikely [47].

We have developed and parameterised a family of transmission dynamic models of infection and disease with oncogenic and anogenital warts-associated HPV types. By developing a large number of related models that make differing assumptions about the natural history of HPV infection and disease, we have assessed structural as well as parameter uncertainty and propagated this through our analyses. The results of these analyses provide a robust evidence base for economic analyses of the potential impact of HPV vaccination.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.vaccine.2009.09.125.

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