Clinical impact and cost-effectiveness of primary human papilloma virus testing

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Executive Summary

A stochastic, individual-based model of human papillomavirus (HPV) infection and natural history leading to cervical cancer was used to evaluate the cost-effectiveness of primary HPV testing in the currently unvaccinated adult female population. The model was used to compare lifetime clinical and economic outcomes for screening cohorts following three protocols:

1. primary cytological screening followed by HPV testing of women with borderline or mild cytology results ("primary cytology protocol") with a recall interval for screen negatives for women of 3 years for women aged 25 to 50 years, and 5 years for women over 50 years;
2. primary testing for high-risk HPV followed by cytology of HR HPV positives ("primary HPV protocol") with the same recall interval as above;
3. primary testing for high-risk HPV followed by cytology of HR HPV positives ("5 year primary HPV protocol") with a 5 year recall interval for screen negatives women of all ages.

Compared to the primary cytology protocol, the standard recall primary HPV protocol, as modelled in this report, is expected to:

a. lead to a 4% increase in primary screens; an 18% increase in number of colposcopies; and a 29% increase in detection of cervical intraepithelial lesions of grade 2 or worse.
b. lead to a median decrease in cervical cancer incidence of 310 cases per year, and reduction in cancer-related deaths of 73 per year.
c. lead to a saving of 0.0026 discounted life years per women. The impact on quality adjusted life years (QALYs) is not well determined and is shown to be highly sensitive to the choice of screening-derived QALY detriments.
d. reduce net health-related costs by £15.8 million per year (due to the decrease in cytological testing, which is more expensive than HPV testing; in addition to a saving on cancer treatments).

Compared to the primary cytology protocol, the 5 year recall primary HPV protocol, as modelled in this report, is expected to:

a. lead to a 17% decrease in primary screens; while providing a 14% increase in detection of cervical intraepithelial lesions of grade 2 or worse.
b. lead to a median decrease in cervical cancer incidence of 159 cases per year, and reduction in cancer-related deaths of 54 per year.
c. lead to a saving of 0.0008 discounted life years per women. As above, the absolute impact on QALYs is not well determined, but the trade-off between screening- and cancer- related QALY losses means that a switch to a 5 year primary HPV protocol is more favourable in terms of net quality-adjusted life years than a switch to standard primary HPV testing.
d. reduce net health-related costs by £35 million per year

Introduction

Since the introduction of the National Health Service Cervical Screening Programme (NHSCSP) in England, in 1988, the primary assessment has been based on cytology testing to identify cervical abnormalities. Currently, testing for high risk human papillomavirus (HR-HPV) is used to determine management of women with borderline or low-grade abnormalities, and as a test-of-cure for recently treated women. In 2013, a pilot study of implementing screening in which the primary assessment is a test for HR-HPV was initiated at several sites across England.

The clinical evidence suggests that HPV testing has higher sensitivity for high-grade lesion detection[1,2], and provides stronger negative predictive power than cytology [3,4]. The costs associated with HR-HPV testing are also favourable compared to cytology testing. The purpose of this study is to evaluate the potential impact and cost-effectiveness of national implementation of HPV testing across the NHSCSP. To do this, we use a stochastic, individual-based simulation model that we have developed to characterise HPV infection and the natural history leading to cervical cancer. The framework builds on existing compartmental markov-models used to appraise UK vaccine policy [5] and screening practice [6]. This work is part of a longer-term project that will integrate this model with our existing transmission dynamic model of HPV vaccination in order to have a single model that can investigate the overall impact of combined vaccination and screening strategies.

Methods

Model

A stochastic, individual-based simulation model is used to evaluate primary HPV testing and the current primary cytology protocol. The key model components are: (a) acquisition of HPV infection; (b) natural progression of HPV infection, cervical intraepithelial neoplasia (CIN) and cervical cancer; and (c) detection and treatment of women with cervical abnormalities through cervical screening. Women are categorised according to HPV infection status, as illustrated in Figure 1. The model simulates a large population of women with individual histories. Women can acquire multiple, possibly simultaneous, HPV infections, and each infection follows its own timeline to clearance or emergence of a pre-invasive cancer lesion, adenocarcinoma or squamous cell carcinoma. Women undergo screening and the life history is changed according to any treatment undertaken (screening algorithms illustrated in Figures 2-3).

The risk of **HPV acquisition** is determined by a number of behavioural factors: (i) age of sexual debut; (ii) acquisition of new partners; (iii) duration of partnerships; (iv) frequency of sex acts; and (v) age of new partners. In the model, these behavioural components are parameterised using data collected by the National Survey of Sexual Attitudes and Lifestyles 2010 (NATSAL-3)[7]. We generated a model of sexual behaviour that captures decrease in sexual activity with age, as well as heterogeneity among individuals of a given age (described in more detail in the appendix A1).

A static model of **transmission** was applied in which male prevalence was assumed to be constant throughout the duration of model simulation; i.e. the introduction of primary HPV testing in cervical screening is assumed to have no effect on the prevalence of HPV in males. The probability of transmission of HPV is described as a function of (i) HPV prevalence among male partners according to

age; and (ii) the probability of transmission per contact with an infected individual (described in more detail in the appendix A2). The rate of HPV **clearance** is modelled by a decreasing function of time post-infection using a weibull distribution. The prevalence of HR-HPV among the female English population has been well characterised[8]. The model was calibrated using pre-vaccination surveillance data collected by PHE that measures type-specific prevalence of HPV in women[9,10] and HPV sero-prevalence measured in males[11] (described in more detail in the appendix A2). A MCMC algorithm was implemented in R to simultaneously identify the posterior distribution for the probability of transmission, clearance and male sero-conversion for each model HPV strain. As a validation of the parameterisation process, we compare the HPV positivity expected by the model under a primary HPV testing protocol, and the HPV positivity observed between May 2013 and August 2014 in the primary HPV pilot study (Figure 4). The model is parameterised completely independently of the primary pilot dataset, however, we are satisfied that the observations lie within the 95% prediction interval.

Disease progression and regression are modelled as continuous processes; the probability of a given cytological abnormality is determined as a function of time since infection. We use a nested conditional probability structure to generate a model in which the probability of a normal outcome decreases, while the probability of a severe outcome increase with time since infection (described in more detail in the appendix A3). The model was calibrated using observed cytological outcome and HPV typing data measured as a function of age in residual samples collected by the NHSCSP[10]. Incidence of invasive squamous cell carcinoma and adenocarcinoma of the cervix was characterised by the increasing risk of disease progression as a function of time following high-risk HPV infection, using a gamma distribution to model the wait time to a squamous cell carcinoma or adenocarcinoma. Cancer incidence was calibrated using cancer registrations in England reported by ONS and evidence from the NHSCP audit of cervical cancers[12]. A MCMC algorithm was implemented in R to simultaneously identify the parameters defining the natural progression of cytological abnormalities to cervical cancer for each model HPV strain, in a population that is undergoing screening according to the current national algorithm. The parameterisation is described in full in appendix A3.

The **screening behaviour** of women is characterised using age-dependent attendance as reported by the cervical screening programme and lifetime behavioural screening patterns derived from data collected by the cervical cancer audit team (personal communication with Alex Castanon & Peter Sasieni). The age at first screen is well characterised by a 'delayed' lognormal distribution. The waiting time to subsequent screens, under a standard recall, is modelled as a function of previous 'punctuality' (described in detail in appendix A4). This framework captures the behaviour of women who regularly attend screening appointments within a small window of their recall date; women who consistently demonstrate poor adherence to the recommended screening appointments; and women who begin with a poor adherence record but then switch to regular screening adherence behaviour.

Screening

Two alternative strategies were considered: (i) primary cytological screening with HPV testing to determine further management of cytology abnormals ("primary cytology protocol"), which is current screening practise, and (ii) primary HPV testing ("primary HPV protocol"), with cytology testing to determine further management of HR HPV positives.

Under the primary cytology protocol, a negative test leads to recall in 3 years (or 5 years for women over 50 years old); a high grade cytological outcome leads directly to a colposcopy referral; and identification of a borderline or mild cytological abnormality is followed by HPV triage where a negative HPV outcome leads to a standard recall, while a positive result leads to an immediate colposcopy referral (Figure 2). Under the primary HPV protocol, a negative HR HPV test leads to recall to screening in 3 years (or 5 years for women over 50 years old), while a positive HR HPV test results lead to cytological assessment of the same sample; all non-negative cytological results (including borderline) are referred to colposcopy; a negative cytology leads to a 12-month follow up. In the follow up arm, 3 successive positive HR HPV results lead to referral for colposcopy (Figure 3).

The actions following colposcopy are the same in both protocols. A negative outcome at colposcopy is assumed to lead to discharge to standard recall; CIN1 is untreated but leads to a 12 month follow up; while identification of precancerous lesions of grade CIN2 or worse leads to treatment followed by 'Test of Cure' triage at 6 months.

The sensitivity of cytological testing is explicitly built into the model; cytology outcome is defined probabilistically and varies as a function of time since infection (in detail in appendix A3). The sensitivity of the HPV test was assumed to lie between 90-95% for high risk HPV.

Attendance and outcome at colposcopy under a primary cytology protocol are constrained according to cytology result at referral, as reported by the cervical screening programme 2012-2013 (Table 1). The probability of attending colposcopy, and the likely outcomes, are assumed to be identical for women referred following low-grade cytology followed by HPV positivity under a primary cytology protocol, as for women referred for a positive HPV test followed by low-grade cytology result under a primary HPV protocol[13]. Colposcopy outcomes for women referred following a positive HPV test and high-grade cytology, under primary HPV protocol, are not significantly different from those reported following a high grade referral under the current primary cytology protocol. This has been evidenced in preliminary data from the pilot primary HPV programme (Table 1).

We assumed that of all cases of CIN2 or worse that should all be recommended for treatment, 83.1% return for treatment and 66.0% attend follow up appointments (source: cervical screening programme 2012-2013). The split between diagnostic biopsy and excision for those women that undergo treatment was assumed to be 63.2:2.6 in those originally referred due to low grade abnormalities, and 37.6:49.1 in those attending colposcopy following a high grade referral (source: cervical screening programme 2012-2013). In the absence of recent data to inform this model parameter, the type of procedure recommended is assumed to be unchanged in the context of the HPV primary screening, however, this decision may be sensitive to knowledge that an individual is HR-HPV positive. In accord with previous cost-effectiveness studies of screening in England, the success rate of treatment is assumed to be 95% for clearance of lesions, however, 16% of treated women are assumed to remain HPV positive[14].

Economic Assumptions

A cost-effectiveness analysis was conducted by comparing the incremental costs and outcomes over the lifetime of cohorts beginning screening in 2014 under the primary cytology and primary HPV protocols. Guidelines for the reference case of the National Institute for Health and Care Excellence (NICE) were followed. Costs were estimated from the perspective of the health care provider. Outcomes were

measured in terms of number of additional health care costs, cancers prevented, life years saved and quality-adjusted life years (QALYs) saved. A discount rate of 3.5% was used throughout. Costs were inflated to 2013/14 using the Hospital and Community Health prices index. Probabilistic sensitivity analysis was conducted incorporating uncertainty in both epidemiological and economic parameters.

Screening costs were obtained from previous economic analyses in which original data was collected at cervical screening sites in England[15–19]. Costs were inflated to 2013/2014 values using the hospital and community health index. Current cytology costs were also obtained for a sample laboratory taking part in the primary HPV pilot study. Costs were broken down according to initial sample collection; equipment and consumables; sample preparation and reading time; and other laboratory overhead costs. Historical economic were used to calculate an expected value for each cytology cost. In studies where overheads and other laboratory administrative costs were not reported, missing values were replaced with an average from studies in which costs were available. Given the improved economies in HPV testing technology over time and the change in costs that accompanies a switch to the primary HPV protocol, compared to HPV in triage, we do not inflate costs from all historical studies. Instead, we incorporate costs from recent studies from 2010 onwards[14,16,19], recommended costs of HPV tests according to the NHS supply chain in 2014 and costs reported by a site taking part in the primary HPV testing pilot. Where overheads and staff costs are missing for HPV testing, we augment costs using additional costs reported by the primary pilot site. A breakdown of all screening costs and sources can be found in Table 2 (described in detail Appendix A5).

The cost of cancer treatment was derived using the observed treatment preferences as a function of cervical cancer stage at diagnosis, as reported in the cervical cancer audit[20]:cone biopsy or loop excision, trachelectomy, hysterectomy alone, radiotherapy (with or without hysterectomy); chemotherapy (with or without hysterectomy); chemo-radiotherapy (with or without hysterectomy) (Table 2; described in detail in Appendix A5).

QALY weights for screening outcomes were based on previous values used in England[19,21–23], and more recent studies exploring QALY loss relating specifically to HPV primary screening in the Netherlands[24] and Australia[25]. We calculated a score for each combination of screening outcomes; the mean value is taken to be the mean score generated using utility scores from multiple sources. The 95% confidence intervals reflect the extreme utility scores generated in previous studies (Table 3). We implemented a quality of life detriment for 18 months following treatment for cervical cancer using the same approach as above and values taken from the literature[5,22,24,26–28]. Cancer mortality rates were calculated using the 1 and 5 years survival rates published by ONS; the data were used to parameterise an age-dependent mortality hazard function following diagnosis of cancer (described in appendix A3). In the model, women who survive beyond five years were assumed to avoid cervical cancer-related mortality, but incur a lifelong post cancer treatment quality of life detriment.

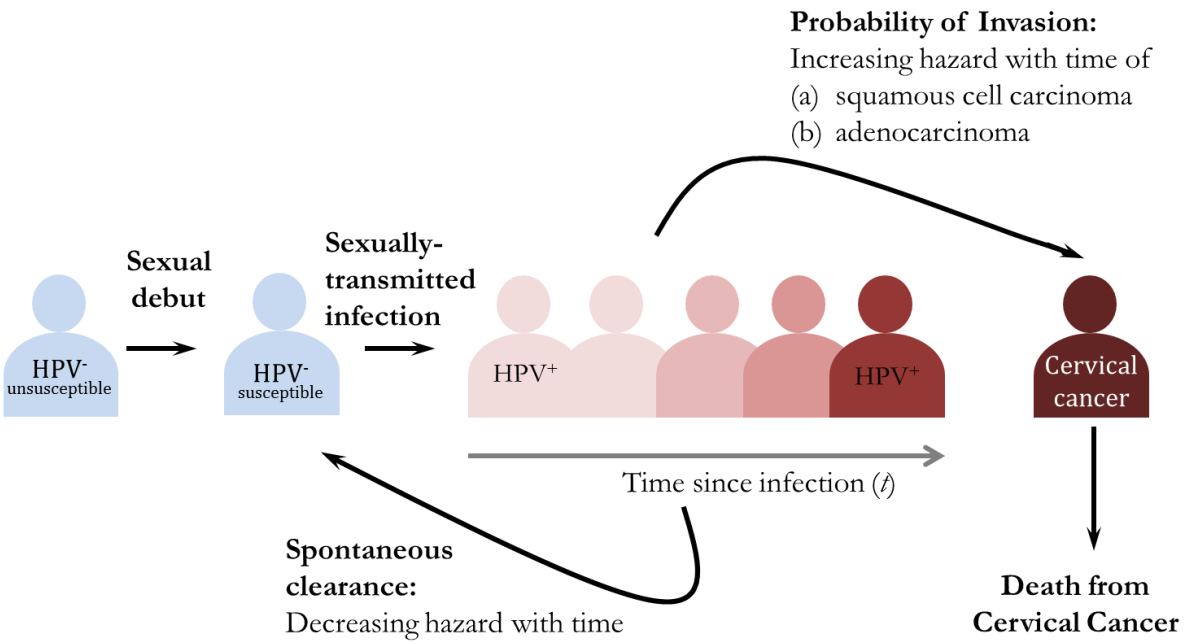


Figure 1: Model outline of HPV transmission and progression to cancer. The model simultaneously considers transmission of HPV-16, 18, 31, 33, 45, 51, 52 and 58.

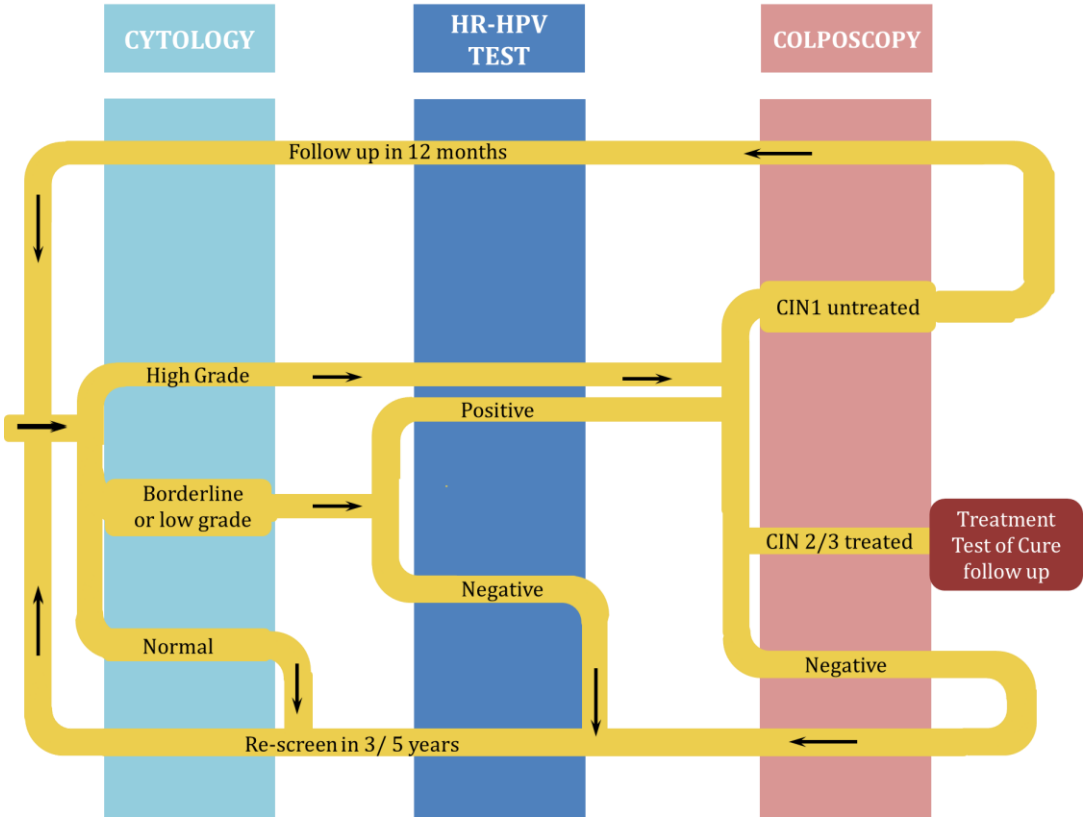


Figure 2: Primary cytology protocol – current screening practise.

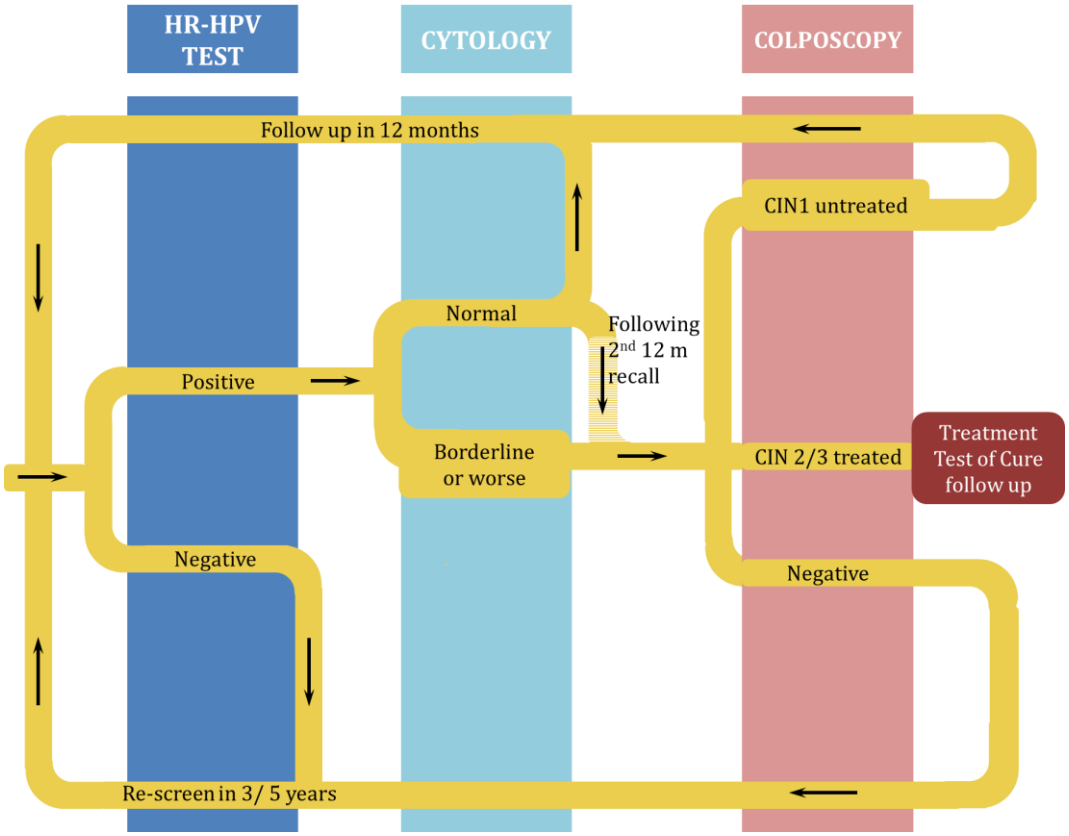


Figure 3: Primary HPV protocol

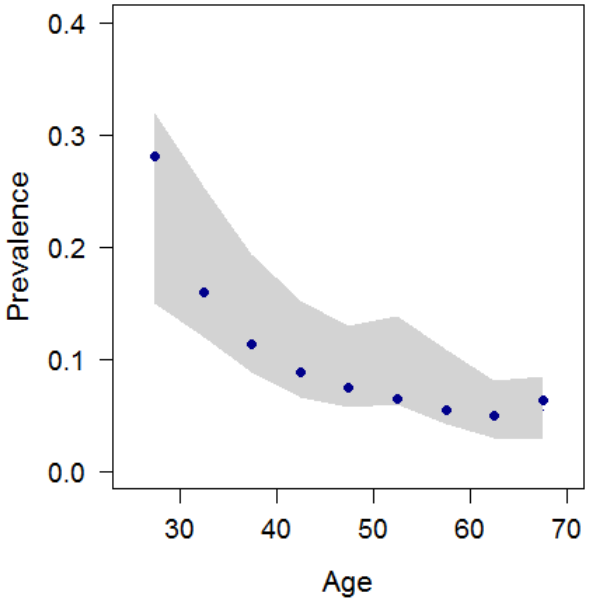


Figure 4: **Validation of model parameterisation**. HPV positivity projected by the model for women aged 25-70 undergoing primary HPV testing (grey shaded area = 95% interval) is parameterised using surveillance data collected by PHE that measures type-specific prevalence of HPV in women[9,10]. HPV positivity observed in the preliminary data from the primary HPV testing pilot sites (October 2014).

	Percentage attendance	Probability of normal outcome	Probability CIN1 detected	Probability CIN2 or worse detected
Current screening practise				
Borderline or Mild referral (n=21,977)	75.2%	55.4%	26.9%	17.7%
Moderate or worse referral (n=38,570)	78.0%	7.4%	8.1%	84.5%
Preliminary Primary HPV pilot outcomes				
Borderline or Mild referral (n=1473)	79.6%	66.1%	17.6%	16.4%
Moderate or worse referral (n=853)	88.0%	10.9%	6.1%	83.0%

Table1: Colposcopy outcomes under primary cytology algorithm (annual screening report 2012-2013), and preliminary outcomes form primary HPV pilot sites (October 2014).

Parameter	Costs	95 % range	Source
Screening			
Sample collection	15.31	(12.5, 18.63)	Karnon (2003), Moss (04), Kitchner (2011), LeGood (2012); Kitchner (2014)
HPV test per sample (includes consumables, equip,ment, staff time & other overheads)	9.75	(7.23, 13.03)	LeGood (2012); Kitchner (2014); NHS supplier chain (2014); Primary HPV pilot site (2014)
Cytology test per slide (includes consumables, equip,ment, staff time, other overheads)	18.15	(14.95, 22.02)	Karnon (2003), Moss (2004), Kitchner (2011), LeGood (2012); Kitchner (2014)
Treatment of pre cancer and cancers			
Colposcopy	151.18	(124.18, 184.08)	Martin-hirsch (2007)
Biopsy	79.84	(65.35, 97.71)	Sherlaw-Johnson (2004)
Excision	382.6	(313.89, 468.41)	Martin-hirsch (2007)
Hysterectomy	2583.5	(2222.28, 3039.77)	Martin-hirsch (2007)
Chemotherapy	5089	(4203.03, 6188.00)	Salter (2014)
Trachalectomy	5485.67	(4500.32, 6646.50)	Salter (2014)
Radiography	19078	(15709.73, 23126.39)	Salter(2014)
Stage 1	4,619		Salter (14); Cervical Cancer Audit (10)
Stage2	20,704	(17927.10, 23509.72)	Salter (14); Cervical Cancer Audit (10)
Stage 3	20,387	(17638.43, 23509.18)	Salter (14); Cervical Cancer Audit (10)
Stage 4	17,320	(14953.77, 20008.25)	Salter (14); Cervical Cancer Audit (10)

Table 2: Model inputs: economic parameters and sources.

	Utility loss per episode	95 % range	Sources
Screening outcomes			Simonella (2014);
Routine screen			Gold (1998) as used by Mandelblatt (2002) and de Kok (2014);
Negative cytology; Negative HPV	0.0001	(0.00002, 0.00023)	Myers (2007) as used in Elbasha (2007) and Kitchner (2014);
Abnormal result with routine recall			Insigna (2007);
Low grade cytology & negative HPV;	0.0011	(0.00023, 0.002)	TOMBOLA (2007)
Abnormal result with 12 month follow up			
Positive HPV & normal cytology	0.0040	(0.00023, 0.0089)	
Normal outcome at colposcopy			
Low grade cytology, positive HPV & normal colposcopy;			
High grade cytology & normal colp;			
Positive HPV, abnormal cytology & normal colposcopy	0.0147	(0.0015, 0.04)	
CIN1 outcome at colposcopy			
Low grade cytology, positive HPV & CIN1;			
High grade cytology & CIN1;			
Positive HPV, abnormal cytology & CIN1	0.0618	(0.005, 0.11)	
CIN2 outcome at colposcopy			
Low grade cytology, positive HPV & CIN2 or worse;			
High grade cytology & CIN2 or worse;			
Positive HPV, abnormal cytology & CIN2 or worse	0.0783	(0.003, 0.13)	
Cancer			Gold (1998), Stratton(2000) and Wolfson(1996)
stage 1	0.295	(0.19, 0.51)	as used in Goldie (2004), Kahn(2008),
stage 2	0.385	(0.33, 0.58)	deKok (2014) and Kitchner (14);
stage 3	0.440	(0.44, 0.58)	Myers (2004) as used by Elbasha (2007) and Jit (2011);
stage 4	0.520	(0.4, 0.64)	Klee (2000) and Korfage (2009)
post treatment			
stage 1	0.030	(0.01, 0.27)	
stage 2	0.065	(0.02, 0.32)	
stage 3	0.065	(0.02, 0.32)	
stage 4	0.205	(0.031, 0.53)	

Table 3: Model inputs: utility loss due to screening

Results

Clinical outcomes

A summary of clinical outcomes under the primary HPV and cytology protocols is shown in Table 4. The annual number of primary screening tests carried out is expected to increase by 4% under the standard primary HPV protocol from 3.03 million to 3.16 million per annum (Table 4); the largest increase is expected in women aged 25 to 35 and represents additional follow up testing for women found to be hpv positive but cytology negative (Figure 5).

Inevitably, the primary HPV protocol resulted in a large reduction in the absolute number of women undergoing cytological testing, from 2.999 to 0.305 million tests annually. One knock-on effect of this was that the proportion of women with non-negative cytology outcomes, among those undergoing cytology, increased from 10% under primary cytology protocol to 47% under primary HPV protocol (Figure 6). A more detailed breakdown of number of tests and outcomes is shown for each screening strategy in Tables 5 and 6.

The model predicted an 18% increase in the number of women attending colposcopy. There was a ~29% increase in the number of cases of CIN 2 or worse identified annually; reflecting ~18,000 additional cases detected per year through the screening programme (Tables 6 and 7; Figure 7). Over half of these additional incidences of CIN 2 or worse were identified in women under the age of 35 years. The model predicts an increase in the 'efficiency of screening' as measured by number of women screened to identify a single case of CIN2 or worse; 50 women need to be screened using the primary cytology protocol, compared to 40 under the primary HPV protocol, to identify a single case if CIN2 or worse.

The rare nature of cervical cancer means that the best fitting model simulations cover a wide range of scenarios for cancer incidence when we combine cases of squamous cell carcinoma and adenocarcinoma for HPV types 16,18, 31, 33, 51, 52 and 58 (Figure 8), however, the model predicts a median decrease in the incidence of cervical cancer of 310 cases per year (IQR(-647, 1379)) (Table 5). Despite the noisy model projections for both scenarios, we see a consistent decrease in cancer incidence within each 5 year age-band for women of screening age; with the largest benefits expected in women from aged 30 years onwards (Figure 8). In terms of the 'efficiency of primary screening', we find that primary HPV protocol requires an additional 397 primary screens per cancer case avoided. This reduction in cancer incidence leads to a median the saving of 73 lives per year (IQR(-168, 348)).

Economic outcomes

The primary HPV protocol is expected to have lower net costs compared to the primary cytology protocol (Table 5); the benefit of avoiding cytological screens, which are more expensive than HPV tests, outweigh the cost of increased primary screens, colposcopies and treatments. The annual screening costs are predicted to be £134 million under a primary cytology strategy and £120 million under a primary HPV strategy. In terms of total health-related costs, including the cost of cancer treatment, this increases to £153 million under primary cytology, and £136 million under primary HPV; resulting in a median saving of £15.8 million (IQR=(2.7m, 27m)). The median discounted cost savings over the lifetime is forecast to be £14 per woman.

The primary HPV is expected to be life-saving, the median saving of 73 lives; with cervical cancer resulting in 520 and 461 deaths per year under primary cytology and primary HPV, respectively. This life saving translates into a median discounted per-woman life year saving of 0.0018 (-0.0043, 0.0082).

The model predicts that a switch to primary HPV protocol would lead to a median increase in the discounted number of quality adjusted life years (QALYs) lost, per women, of 0.0026 (interquartile range= (-0.0013, 0.0064). The gain in life years and reduction in cancers is counteracted by the countered by a larger increase in the utility cost of increased primary testing, colposcopies and women being treated for CIN2 or worse under primary HPV testing. The large confidence intervals predominantly reflect the variation associated with screening-related QALY detriments, in addition to the model uncertainty surrounding the projected number of cancers. In our primary analysis, we use QALY weights that are an average of those reported in the literature and assume a normal distribution to cover all reported values, however, this potentially unfairly skews the qalys towards higher values. We find that some older studies[22,23] report a qaly detriment associated with colposcopy that is of the order of 16-37 fold higher than that of more recent studies[24,25]. To explore the sensitivity of our results to screening-related QALY detriments, we repeat the analysis using QALY values from the study reporting the strongest ("Insigna Basis"[23]) and weakest ("Simonella Basis" [25]) screening-related detriments. Using the Simonella QALY basis, we find a small median gain in discounted per-woman lifetime QALYs of 0.0005 associated with a move from the primary cytology to primary HPV protocol, while, using the Insinga study, gives a median loss of 0.0033.

Extended screening interval

Evidence for the stronger negative predictive power of HPV over cytology and the concern regarding the over-testing in young women, in whom there is a high prevalence of HPV infection, have led to a discussion in the health care community regarding the extension of the standard screening recall interval associated with primary HPV testing. We consider the impact of increasing the recall interval, following a negative primary HPV screen, to 5 years for all women regardless of age (5 year primary HPV protocol). This fixed interval compares to current practise whereby women under 50 years are recalled at 3 year intervals, and women over 50 are recalled at 5 year intervals.

As we might expect, the model predicts a 17% decrease in the number of primary tests carried out when the recall interval is extended from 3 to 5 years for women under 50 (from 3.034 to 2.514 million tests per year). The number of colposcopies is predicted to remain unchanged with a move from primary cytology to primary HPV with 5 year recall; however, the model predicts an increase in the number of CIN2 or worse cases detected from 61,504 to 70,400 per year. The increased 'rate' of detection per colposcopy under a 5 year protocol arises from the increased proportion of women attending colposcopy following a moderate or severe cytological referral. Overall, the increased detection and subsequent treatment of precancerous lesions results in a drop in cancer incidence of 159 cases per year under the 5 year primary HPV protocol, saves 54 lives per year, and leads to a discounted per-woman lifeyear saving of 0.0008.

Moving from primary cytology to primary HPV testing, in combination with a regular 5 year screening interval, would lead to a substantial total health-care cost saving of £35 million (22.4m, 47.2m). The

annual screening costs are expected to be £97.7 million. The discounted lifetime cost saving per women is estimated to be £38 (25,49).

In line with the observations for standard primary HPV protocol, when we use our mixed QALY weighting basis, the gain in life years associated with a switch to a 5 year primary HPV protocol are dominated by the QALY detriment resulting from increased detection and treatment of CIN2 cases; the modelling predicts a median discounted per-woman lifetime QALY loss of 0.001 (-0.0047, 0.0028). As before, we show that the resulting QALY outcome is highly sensitive to the screening-associated QALY weights used. The Simonella basis for screening-related QALYs leads to a median gain in discounted per-woman lifetime QALYs of 0.0052, while the Insinga basis leads to a median loss in discounted per-woman lifetime QALYs of 0.0009.

Summary

The modelling work presented here predicts that a move from the current primary cytology to a primary HPV screening protocol will be both life-saving and cost-saving. However, the benefits as measured by quality adjusted life years are more difficult to determine due to the uncertainty associated with screening associated quality of life detriments. We find that a switch to primary HPV screening can be shown to result in: (i) QALY gains when using screening-associated quality of life detriments measured in a recent study looking explicitly at primary HPV testing by Simonella and colleagues[25]; but also (ii) QALY losses when using more severe quality of life detriments screening-associated as reported by Insinga and colleagues[23],where life year gains are obscured by QALY detriments resulting from significant increases in colposcopy referrals and identification and treatment of precancerous lesions.

In terms of clinical outcomes, moving from the current cervical screening protocol to one employing primary HPV testing is expected to: (i) increase the number of primary screening tests carried out; (ii) increase the number of women referred to colposcopy; and (iii) increase the number of lesions of grade 2 or worse identified and treated through colposcopy. The model projects a positive impact on cervical cancer incidence and cancer-related mortality.

The impact of increasing the standard recall interval, following a negative primary HPV screen, to 5 years for all women, regardless of age, is also considered within the primary HPV protocol. The switch from a primary cytology to 5 year primary HPV protocol is expected to: (i) reduce cancer incidence; (ii) reduce cancer-related deaths; and (iii) reduce costs. As above, the predicted change in QALYs is a mixed bag; the optimistic Simonella basis predicts a QALY gain, while the more severe Insinga basis predicts a QALY loss.

The model predicts a sizable total health-care cost saving of £35 million (22.4m, 47.2m) with a switch from the current practise primary cytology protocol to the 5 year primary HPV protocol, compared to a saving of £15.8 million (2.7m, 27m) associated with a switch to the standard primary HPV protocol. The median reduction in cervical-cancer related deaths is predicted to be 54 and 73, respectively, following a switch to the 5 year- and standard-, primary HPV protocols. Despite the smaller life-years saving, the trade-off between screening- and cancer- related QALY losses means that a switch to a 5 year primary HPV protocol is more favourable in terms of net quality-adjusted life years than a switch to standard primary HPV testing. The median QALY loss predicted, using an averaged QALY weighting basis, for a switch from current practise to a 5 year recall primary HPV protocol is 0.0010, compared to a QALY loss of 0.0026 associated with a switch from current practise to the standard HPV protocol.

Model Limitations

The model explicitly considers HPV strains 16, 18, 31, 33, 45, 51, 52 and 58, representing the most prevalent strains that are associated with cervical cancer in England. However, commercially available test, such as the commonly used HC2 assay, will also detect cases of hpv-35, 39, 56, 59 and 68. There are also reports that HPV testing may react to non HR-HPV test, however, the validation of model outcomes against preliminary data from the HPV primary pilot give us confidence that we do not underestimate HR-HPV positivity.

Model projections give a large uncertainty range around cancer incidence. This uncertainty is in part explained by the additive uncertainty arising from combining 16 distinct cancer-causing processes– eight hpv strains leading to either squamous cell carcinoma or adenocarcinomas. The rare nature of non hpv 16/18-related cancers means that the underlying parameters can be difficult to constrain for hpv strains other than 16 and 18. Conservatively, the model simulations cover a broad range of scenarios for each HPV type.

In this work, we use the economic costs taken from historical economic analyses of screening in England, and inflate to 2014 values. The limitations of inflating historical costs are that we don't necessarily capture the reduction in technology costs over time. Economies of scale also suggest that a switch to primary screening is likely to result in a reduction in the per sample cost of a hpv test. Overall, this is expected to lead to a further cost saving associated with a switch to primary HPV testing. A more detailed study of work flow and costs in the context of primary HPV testing is planned by the primary HPV pilot screening committee that will provide further insight into the expected changes.

The utility detriment associated with cervical screening is not well defined, reflected in the diverse estimates for QALY loss weights reported in the literature. This is particularly true for primary HPV related screening. In this work, we use a sensitivity approach that captures the extreme values reported in the literature to show that the choice of published screening-associated QALY loss values can determine whether an intervention is beneficial or detrimental. The work highlights a need for further study of QALY loss associated with screening, in order to appropriately judge the increase in colposcopy and treatment of precancerous CIN2 lesions we are willing to accept in order to reduce the incidence and death related to cervical cancer.

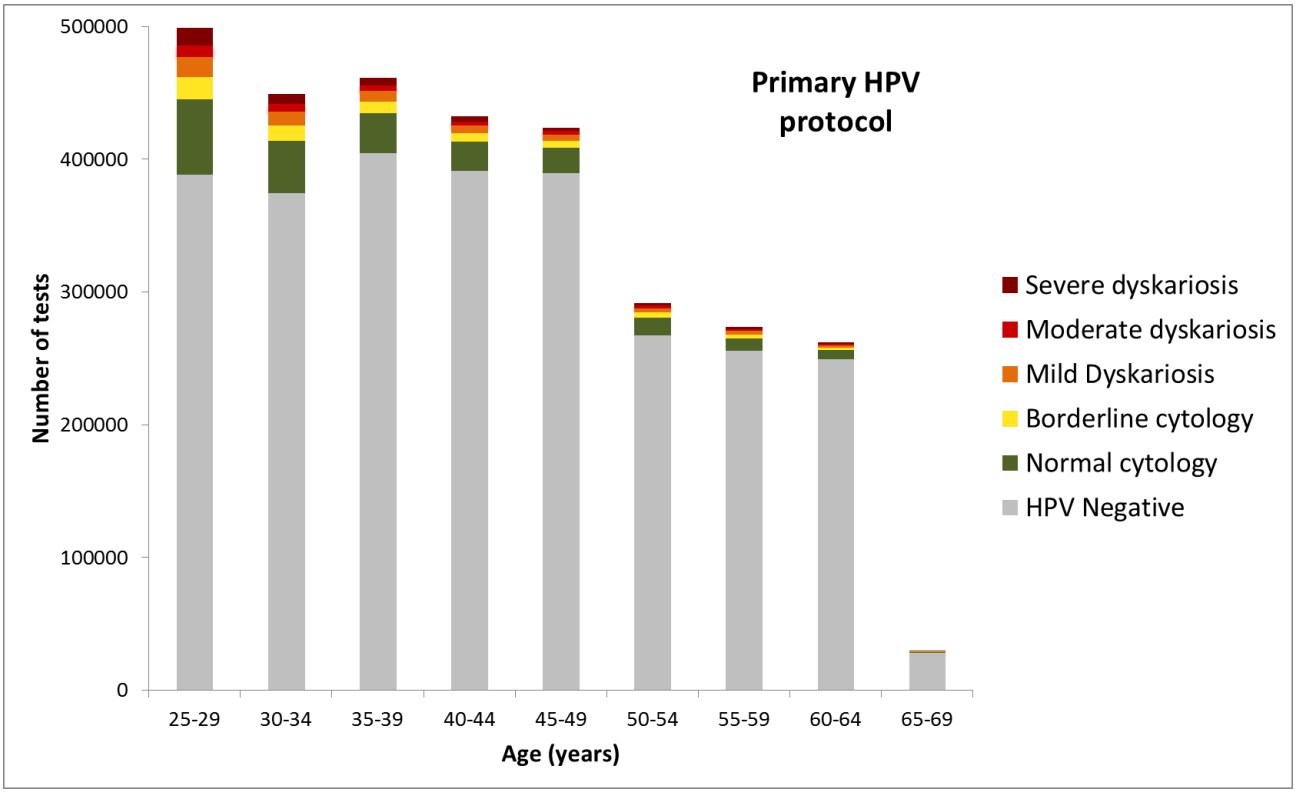
The current analysis is based on a static model of infection, this means that we are unable to incorporate changes in male prevalence that might arise following vaccination due to herd immunity; and limits the projections that we can make about the suitability of HPV testing to an unvaccinated female population. The introduction of a national HPV vaccination programme, in 2008, means that it is relevant to consider the implications of vaccination on HPV prevalence and disease incidence as vaccinated cohorts approach screening age. The model is currently being developed to include a dynamic disease transmission element that will allow further work to consider the optimal screening protocol for vaccinated women. It is possible that alternative scenarios, in which the screening interval is further extended or HPV 16/ 18 genotyping is included, might prove more cost-effective than primary HPV testing alone.

	Primary cytology protocol	**Primary HPV protocol** with 3 year recall for women under 50, and 5 year recall otherwise
Number of cytology tests	**3,034,422**	**372,980**
	(2958719, 3138301)	(276902, 547579)
Normal cytology	**2,713,165**	**196,037**
	(2615090, 2786752)	(118158, 324281)
Borderline changes	**136,302**	**57,997**
	(99507, 176631)	(39417, 92495)
Mild dyskariosis	**94,194**	**52,260**
	(60763, 134127)	(27734, 88093)
Moderate dyskariosis	**40,029**	**28,673**
	(11360, 92688)	(6126, 80683)
Severe dyskariosis	**50,657**	**37,938**
	(16230, 112887)	(11304, 89923)
Number of HPV tests	**282,571**	**3,157,452**
	(203349, 391713)	(3079357, 3273993)
HPV negative	**180,767**	**2,748,233**
	(128577, 255488)	(2641853, 2818555)
HPV positive	**101,785**	**409,200**
	(56110, 176393)	(298156, 605681)
Number of colposcopies	**147,925**	**174,996**
	(68894, 317668)	(106505, 301443)
Normal	**61,665**	**63,398**
	(36021, 101136)	(42764, 100978)
CIN 1	**25,169**	**32,686**
	(12373, 50388)	(21843, 51877)
CIN 2 or worse	**61,054**	**78,875**
	(18710, 166379)	(34027, 167638)

Table 4: Summary of clinical outcomes and resource usage (mean and 95%CI). Number of tests calculated assuming an age distribution as observed by ONS in 2013.

	Primary cytology protocol	**Primary HPV protocol** with 3 year recall for women under 50, and 5 year recall otherwise	**Saving under primary HPV**	**Primary HPV protocol** with 5 year recall for all women	**Saving under primary HPV with 5 year recall**
Annual screening-associated costs (£000)	**134,173** (122855, 145382)	**120,479** (112413, 130635)	**13,078** (2924, 22814)	**97,726** (91366, 106906)	**33,958** (23749, 44166)
Annual total health costs (£000) (including cost of cervical cancers)	**153,391** (139306, 164510)	**136,707** (126156, 147393)	**15,756** (2716, 27990)	**114,196** (104471, 126831)	**35,711** (22381, 47182)
Discounted lifetime cost per women (£) (including cost of cervical cancers)	**160** (146, 172)	**145** (134, 157)	**14** (-1, 27)	**121** (108, 131)	**38** (25, 49)
Annual incidence of cervical cancer	**2123** (1208, 3290)	**1828** (1016, 2738)	**310** (-647, 1379)	**1999** (1152, 3022)	**159** (-820, 1070)
Deaths related to cervical cancer (/year)	**520** (290, 812)	**461** (235, 700)	**73** (-168, 348)	**475** (276, 732)	**54** (-192, 272)
Discounted life years lost to cervical cancer per women	**0.0157** (0.0092, 0.0239)	**0.0146** (0.0079, 0.0212)	**0.0018** (-0.0043, 0.0082)	**0.0153** (0.0085, 0.0224)	**0.0008** (-0.0063, 0.0076)
Discounted quality-adjusted life years lost due to cancer and screening	**0.0136** (0.0105, 0.0165)	**0.0160** (0.0128, 0.0198)	**-0.0026** (-0.0064, 0.0013)	**0.0144** (0.0113, 0.0179)	**-0.0010** (-0.0047, 0.0028)
Discounted quality-adjusted life years lost due to cancer and screening, using Simonella basis for screening-related QALY detriment	**0.0060** (0.0037, 0.0080)	**0.0055** (0.0033, 0.0073)	**0.0005** (-0.0013, 0.0026)	**0.0052** (0.0032, 0.0076)	**0.0004** (-0.0018, 0.0025)
Discounted quality-adjusted life years lost due to cancer and screening, using Insigna basis for screening-related QALY detriment	**0.0195** (0.0151, 0.0225)	**0.0225** (0.0184, 0.0262)	**-0.0033** (-0.0004, 0.0064)	**0.0199** (0.0.0162, 0.0237)	**-0.0009** (-0.0040, 0.0020)

Table 5: Summary of costs and health outcomes (mean and IQR).



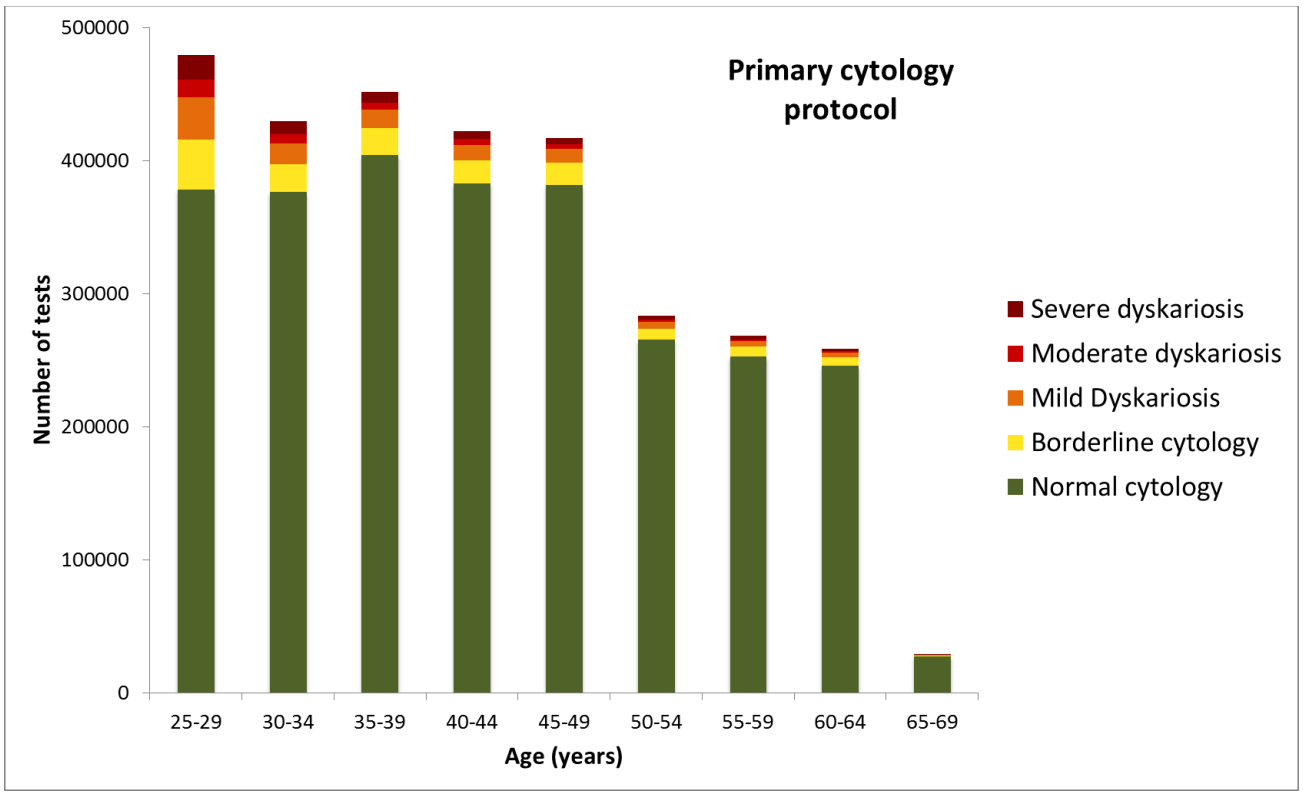


Figure 5: Number of women tested and predicted outcome under primary HPV protocol and primary cytology protocol, assuming age distribution in England as in 2013.

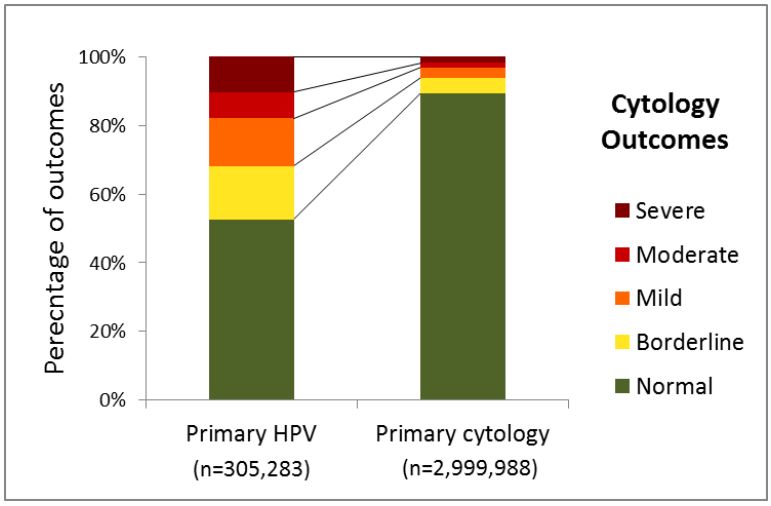


Figure 6: Outcome of cytology tests under primary cytology protocol (left) and primary hpv protocol.

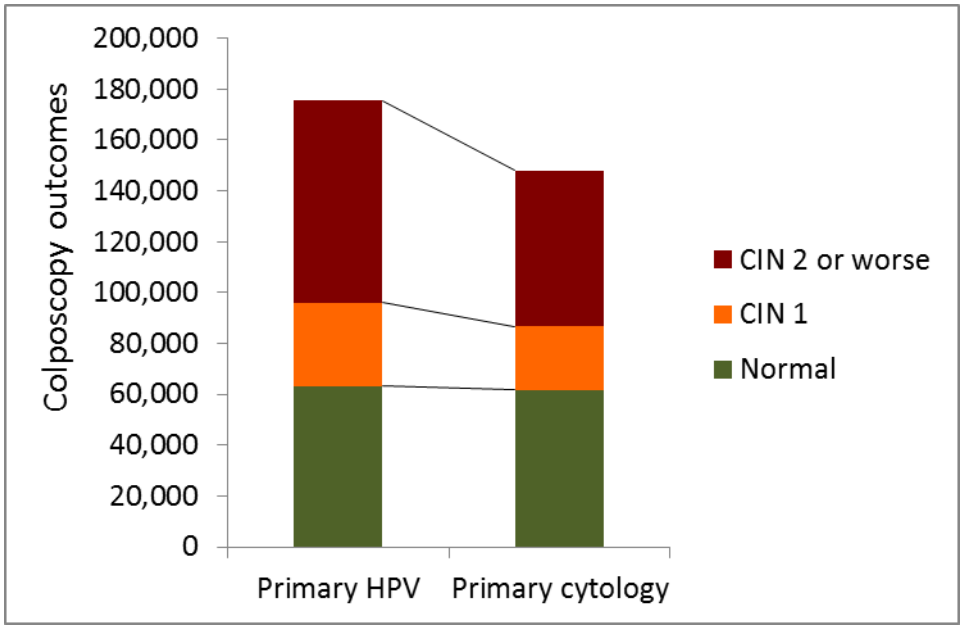


Figure 7: Predicted number and outcome of colposcopy tests undertaken.

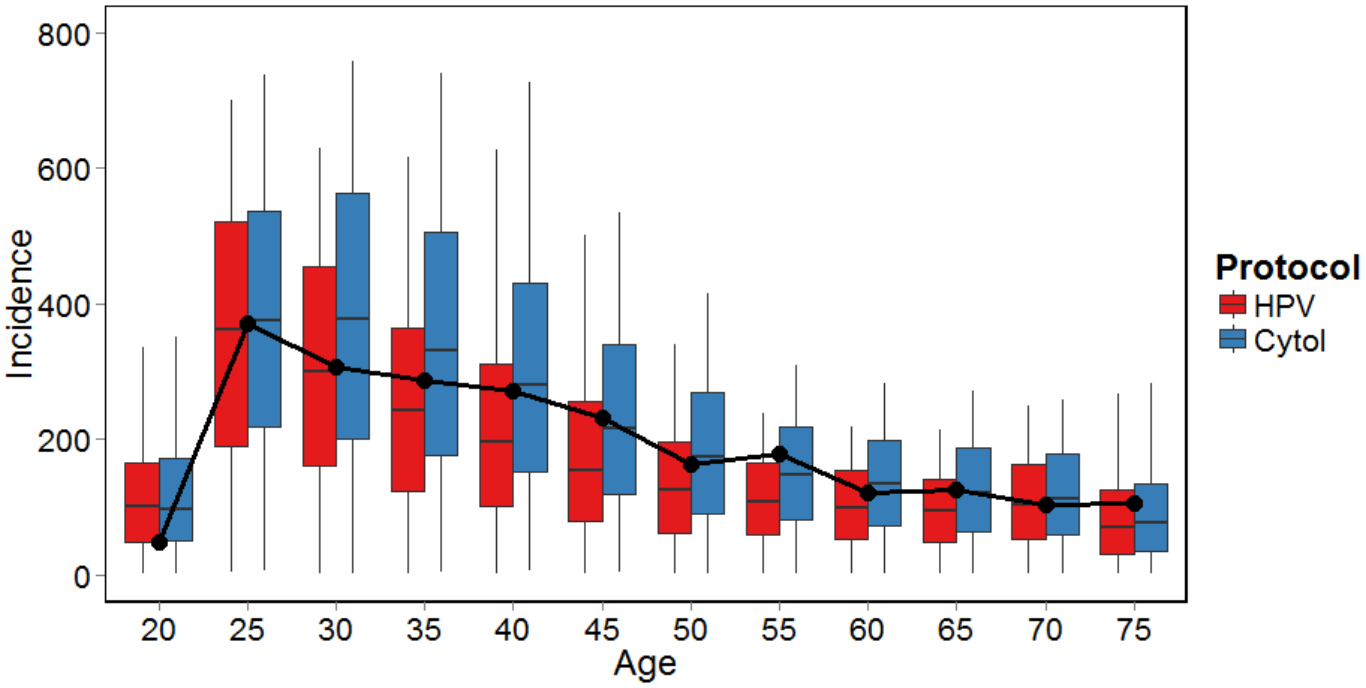


Figure 8: Cervical cancer incidence observed in 2012 (points) compared to model outcomes under primary cytology and primary HPV protocols. Boxes represent the interquartile range range of model predictions for cancer incidence (primary cytology =blue; primary hpv= red).

	Age									
	25 - 29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	**All**
Number of cytology tests	**110,338**	**74,439**	**56,436**	**40,700**	**34,161**	**24,617**	**18,132**	**12,754**	**1,404**	**372,980**
	(81673, 160273)	(55816, 107816)	(42196, 82586)	(30144, 60559)	(25664, 50617)	(18245, 36491)	(13102, 27486)	(9082, 19512)	(980, 2239)	(276902, 547579)
Normal cytology	56,149	38,853	30,049	21,769	18,788	13,401	9,535	6,754	738	196,037
	(34030, 91710)	(23523, 63728)	(18463, 49045)	(13011, 36063)	(11406, 31176)	(7878, 22697)	(5553, 16599)	(3877, 11944)	(418, 1320)	(118158, 324281)
Borderline changes	16,803	11,681	8,904	6,358	5,422	3,928	2,769	1,922	211	57,997
	(11484, 26620)	(7988, 18443)	(6127, 14083)	(4284, 10227)	(3694, 8679)	(2633, 6327)	(1824, 4561)	(1252, 3191)	(131, 364)	(39417, 92495)
Mild dyskariosis	15,371	10,609	7,970	5,733	4,689	3,426	2,519	1,748	193	52,260
	(8315, 25364)	(5605, 17747)	(4224, 13443)	(3074, 9736)	(2412, 8159)	(1760, 5946)	(1316, 4321)	(922, 3039)	(106, 341)	(27734, 88093)
Moderate dyskariosis	8,921	5,734	4,223	3,046	2,426	1,815	1,422	980	106	28,673
	(1923, 24227)	(1233, 16047)	(915, 11935)	(660, 8728)	(505, 6941)	(376, 5372)	(291, 4207)	(199, 2929)	(23, 297)	(6126, 80683)
Severe dyskariosis	13,085	7,552	5,281	3,785	2,826	2,038	1,877	1,341	153	37,938
	(3462, 32565)	(2337, 17191)	(1719, 11989)	(1246, 8603)	(927, 6476)	(630, 4863)	(543, 4605)	(393, 3272)	(47, 359)	(11304, 89923)
Number of HPV tests	504,798	457,864	467,404	436,767	427,406	294,728	275,439	263,416	29,630	3,157,452
	(483460, 535001)	(442663, 481441)	(457877, 482145)	(428105, 450261)	(420751, 437499)	(288540, 304578)	(270302, 282813)	(258880, 269371)	(28778, 30883)	(3079357, 3273993)
HPV negative	388,228	374,410	404,511	391,256	389,692	266,977	255,653	249,489	28,018	2,748,233
	(355827, 409882)	(355911, 386154)	(387233, 415050)	(380439, 398100)	(379801, 395972)	(260879, 271345)	(249820, 259920)	(244415, 253595)	(27527, 28538)	(2641853, 2818555)
HPV positive	116,568	83,452	62,891	45,508	37,712	27,748	19,784	13,925	1,611	409,200
	(85431, 170019)	(61117, 121951)	(46173, 92900)	(32821, 68080)	(27781, 56038)	(20052, 41858)	(14016, 30503)	(9701, 21718)	(1066, 2614)	(298156, 605681)
Number of colposcopies	49,804	36,715	26,967	19,441	15,434	11,690	8,385	5,850	711	174,996
	(27944, 89477)	(23139, 61167)	(17041, 44960)	(12287, 32599)	(9750, 26343)	(7411, 19910)	(5030, 15266)	(3476, 10469)	(427, 1253)	(106505, 301443)
Normal	16,874	13,543	10,067	7,260	5,863	4,483	2,980	2,070	259	63,398
	(11283, 26449)	(9258, 21420)	(6870, 16105)	(4904, 11657)	(4017, 9301)	(2995, 7218)	(1950, 4916)	(1328, 3456)	(158, 456)	(42764, 100978)
CIN 1	8,800	6,959	5,172	3,722	2,998	2,290	1,542	1,069	133	32,686
	(5745, 13918)	(4733, 10899)	(3537, 8125)	(2509, 5962)	(2035, 4772)	(1521, 3665)	(1000, 2531)	(681, 1776)	(80, 229)	(21843, 51877)
CIN 2 or worse	24,126	16,208	11,724	8,454	6,569	4,911	3,858	2,707	319	78,875
	(9264, 53662)	(7279, 33202)	(5378, 24070)	(3899, 17316)	(3006, 13848)	(2288, 10361)	(1627, 8565)	(1137, 5950)	(148, 665)	(34027, 167638)

Table 6: Model-generated number and outcome of HPV, cytology and colposcopy tests, per annum, under a primary HPV protocol; mean (lower & upper bound). Resident female population size and age demographic as observed in England in 2013 (source: ONS).

	Age									
	25 - 29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	**All**
Number of cytology tests	**478,489**	**429,077**	**451,045**	**421,524**	**416,611**	**283,045**	**267,892**	**258,378**	**28,361**	**3,034,422**
	(457843, 507404)	(414645, 450578)	(441944, 463634)	(413615, 432915)	(409993, 424870)	(277068, 290522)	(262543, 274852)	(253334, 264273)	(27734, 29253)	(2958719, 3138301)
Normal cytology	378,522	376,087	403,957	382,686	381,388	265,191	252,657	245,673	27,004	2,713,165
	(348961, 397886)	(360253, 387322)	(388912, 414118)	(372955, 390835)	(371664, 389701)	(259319, 270441)	(246551, 257897)	(240118, 250872)	(26357, 27680)	(2615090, 2786752)
Borderline changes	37,488	21,266	20,361	17,561	16,755	8,409	7,281	6,482	700	136,302
	(29423, 45705)	(15891, 27523)	(14760, 26489)	(12555, 23095)	(11753, 22042)	(5649, 11526)	(4802, 10112)	(4224, 9150)	(450, 989)	(99507, 176631)
Mild dyskariosis	31,609	15,158	13,680	11,312	10,331	4,715	3,879	3,174	336	94,194
	(22313, 41186)	(9520, 22862)	(8697, 19805)	(7227, 16336)	(6412, 14870)	(2637, 7424)	(2121, 6093)	(1665, 5021)	(170, 529)	(60763, 134127)
Moderate dyskariosis	13,549	7,123	5,804	4,491	3,803	2,137	1,718	1,274	132	40,029
	(5406, 28865)	(1604, 17734)	(1442, 13747)	(1081, 10287)	(913, 8238)	(373, 5624)	(306, 4532)	(215, 3315)	(18, 345)	(11360, 92688)
Severe dyskariosis	17,312	9,434	7,234	5,465	4,324	2,584	2,349	1,767	188	50,657
	(5451, 39302)	(2775, 21335)	(2510, 15549)	(1885, 11645)	(1483, 8970)	(819, 5941)	(733, 5647)	(517, 4070)	(57, 428)	(16230, 112887)
Number of HPV tests	**81,403**	**47,987**	**42,580**	**35,145**	**31,764**	**16,646**	**13,985**	**11,800**	**1,261**	**282,571**
	(61055, 107277)	(32981, 71057)	(30713, 59336)	(25687, 48056)	(23420, 42622)	(11112, 24721)	(9539, 20212)	(7999, 16645)	(845, 1788)	(203349, 391713)
HPV negative	52,065	27,352	26,422	23,775	22,306	10,136	9,252	8,527	932	**180,767**
	(40544, 68381)	(18205, 43000)	(18415, 37654)	(16985, 32927)	(16053, 29963)	(6429, 15848)	(5858, 13918)	(5473, 12434)	(614, 1363)	(128577, 255488)
HPV positive	29,336	20,632	16,156	11,368	9,455	6,508	4,730	3,271	329	**101,785**
	(16062, 49235)	(11312, 35428)	(9105, 27481)	(6415, 20079)	(5203, 17175)	(3519, 12094)	(2554, 8515)	(1765, 5768)	(175, 618)	(56110, 176393)
Number of colposcopies	**46,262**	**28,682**	**22,445**	**16,370**	**13,468**	**8,580**	**6,761**	**4,856**	**500**	**147,925**
	(21996, 99207)	(12842, 62011)	(10765, 46499)	(7744, 34843)	(6328, 28615)	(3813, 19260)	(2996, 15302)	(2186, 10796)	(225, 1133)	(68894, 317668)
Normal	20,087	11,195	9,242	6,983	6,051	3,390	2,601	1,917	197	**61,665**
	(12722, 31512)	(6317, 18978)	(5345, 14856)	(3887, 11227)	(3341, 9867)	(1845, 6076)	(1437, 4604)	(1027, 3647)	(100, 369)	(36021, 101136)
CIN 1	7,373	5,104	3,951	2,787	2,285	1,583	1,181	822	83	**25,169**
	(3542, 14711)	(2501, 10169)	(2004, 7586)	(1399, 5536)	(1149, 4736)	(776, 3339)	(577, 2497)	(385, 1633)	(40, 181)	(12373, 50388)
CIN 2 or worse	18,797	12,378	9,248	6,595	5,127	3,603	2,975	2,112	218	**61,054**
	(5279, 52470)	(3784, 33045)	(3031, 23982)	(2167, 17688)	(1708, 14177)	(1148, 10125)	(906, 8415)	(620, 5856)	(65, 620)	(18710, 166379)

Table 7: Model-generated number and outcome of cytology and HPV tests, per annum, under a primary cytology protocol; mean (lower & upper bound). Resident female population size and age demographic as observed in England in 2013 (source: ONS).

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