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UK National Screening Committee

Modelling studies addressing HPV screening

Draft Report v 1.1

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Contents

Section 1: Introduction

1.1 BACKGROUND

Worldwide, cervical cancer is thought to be responsible for around 275,000 deaths per year which ranks it as the second most common cause of cancer deaths in women after breast cancer. Screening for pre-invasive changes in cervical epithelium, by means of cervical cytology, has resulted in a major fall in both incidence and deaths in the developed world. As a result of screening, cervical cancer now ranks 15th in female cancer deaths in the UK and mortality has fallen from 6.4 per 100,000 population in 1988 to 2.2 per 100,000 population in 2012.

Current policy recommendation

The UK NSC recently recommended that the National Cervical Screening Programme (NCSP) should change from a cytology strategy. The currently recommended strategy is based on detection of human papilloma virus (HPV) as the primary screening test followed by triage using liquid cytology in those with positive HPV tests. Women aged 25 – 64 are eligible for HPV based screening.

This primary change to the programme was based on trial evidence of clinical effectiveness, cost effectiveness evaluation and piloting in the UK.

The NCSP is now preparing to implement the new programme and policy recommendations are required on a number of key questions. These are identified below. While evidence is emerging on these questions direct evidence is very limited or non-existent. In countries which have adopted HPV based screening, policy development has therefore centred on outputs from modelling exercises.

Previous modelling of HPV in the UK

A UK model was developed by Bains in 2015. This unpublished study used disease transmission modelling to compare three strategies:

- Primary cytology followed by HPV triage (non-genotyped) of women with borderline/mild cytology results. Three-year and five year recall for negative women aged 25-50 and 50 years respectively.
- Primary high-risk (HR) HPV testing with cytology triage for HR HPV positive women with recall as above
- Primary HR HPV testing with cytology triage for HR HPV positive women with five year recall for negative women of all ages

Findings from the Bain's model suggested that compared to primary cytology with non-genotyped triage, either primary HR HPV testing strategy would be cost and life year saving. Five year recall for HR HPV would have the greatest saving (£35 million per year (£38 per woman) compared to £15.8 million (£14 per woman) with age dependent recall) but five year recall would generate a lower life year gain (0.0008 discounted life years compared to 0.0026 with age dependent recall).

Whilst the total saving per year is large, it is driven primarily by a lower cost of HR HPV testing compared to cytology. The discounted life year saved per woman with either HR HPV strategy were very small, at 0.3 days for five year intervals and 0.9 days with age

dependent intervals compared to primary cytology. Further, the impact on QALYs is not clear and was shown to be sensitive to how utility decrements were chosen and applied for screening and the results of screening. Whilst the Bain's model therefore seems robust in terms of HR HPV being cost and life year saving to the NHS in England compared to cytology with non-genotyped HPV triage, the modelling is unclear as to whether

- HR HPV is actually cost-effective in terms of the cost per QALY gained over a primary cytology strategy
- HR HPV is cheaper but less effective in terms of QALYs generated than a primary cytology strategy
- Fixed repeat screening intervals for all HR HPV negative women are cost effective compared to variable intervals by age

1.2 OBJECTIVE

Whilst the Bain's model provided information that could help guide the UK NSC on an appropriate screening strategy in the UK, the UK NSC wished to put the findings of the model in the context of other models published in the UK and internationally. In this regard the UK NSC wanted to explore three key areas:

i) Screening intervals for HPV negative women

The NCSP would like to recommend that primary HPV cervical screening should be offered:

- five yearly following a negative HR-HPV test for women aged 25-49
- ten yearly following a negative HR-HPV test for women aged 50-64 (or at 64 if aged 55-60 at the previous screening test).

As such, this study should identify what published models have reported on the clinical, cost and resource implications of these screening intervals in HPV negative women. The primary question is therefore:

- have five year screening intervals for HPV negative women been found cost effective in published models?

With the following sub questions:

- have published studies explored screening intervals by age group and if so what have they found?
- What is the duration of protection from cervical abnormalities in women over the age of 64 (or how was this been incorporated into models)?

ii) Surveillance recall intervals in HPV positive / cytology negative women

Diverging strategies have been proposed by the English and Scottish Screening Programmes for managing women in this group.

Both strategies would aim to recall women who screened HPV positive and cytology negative for HPV surveillance testing at 12 months.

- those who are HPV negative would return to screening at 5 yearly intervals
- those who are HPV positive and cytology positive would be referred to colposcopy

The strategies diverge on the use of HPV genotyping to inform the onward management of women with persistent HPV positive and cytology negative results:

- in Scotland, the proposal is that all women in this group would be recalled for repeat HPV testing in a further 12 months.
- in England, the proposal is that women with HPV 16 or 18 results would be referred for colposcopy. Women with all 'other type' HPV results would be recalled for repeat testing in a further 12 months.

An analysis of models addressing the clinical, cost and resource implications of these surveillance strategies is required to inform a UK NSC recommendation on this issue to answer the following questions:

- Have modelled estimates of surveillance recall strategies for women testing HPV + / cytology – identified an optimum approach?
- Have models compared approaches taking genotype (e.g. HPV 16 and 18) into account with those which do not?

iii) Options for women with HPV positive and cytology negative at the 'programme exit' test

The NCSP would also like to recommend that women who are HR-HPV positive at their final screening test should be recalled at 12 months and, if still HPV positive, be referred for colposcopy. If colposcopy is:

- decisively negative this would prompt discharge from the programme
- decisively positive this would prompt the offer of loop excision
- indecisive this would prompt the offer of loop excision or recall a further 12 months later.

An analysis of models addressing the clinical outcomes from this or other programme exit strategies is required to inform a UK NSC recommendation on this issue by answering the following questions:

- Have models explored programme exit strategies for women with positive HR-HPV results at the final screening test?
- What is the risk of cervical abnormalities developing in women who are HPV + / colposcopy-?
- should women who are HPV + / colposcopy indecisive be offered a choice of loop excision or further annual surveillance?
- how many rounds of annual surveillance should be offered to women who are HPV + / colposcopy indecisive?

Section 2: Methodology

A Rapid Evidence Assessment was undertaken to identify models published since 2005 that provided evidence against the key research questions.

2.1 PICOS

The PICOS for the evidence assessments for the three issues are provide in tables 2.1 to 2.3. In all cases studies were limited to full papers in peer reviewed journals (abstracts or posters were excluded), those in economically developed countries with a publication date of 2005 or later and to English language studies only. Only studies considering a screening age starting at 25 or older were included.

Table 2.1: Issue 1 (Screening intervals for HPV negative women) PICOS

Question	Have modelled estimates found five-year routine screening intervals for HPV negative women to be effective?
Sub-questions	Has interval variation by age group been modelled? What is the duration of protection against cervical abnormalities in women older than 64 years?
Population	Women screened for cervical cancer
Intervention	HPV based screening 5-year screening intervals
Comparator	Cytology based screening HPV based screening with different interval duration
Outcomes	Modelled outcomes including the following where reported: <u>Clinical measures</u> Cumulative incidence of CIN2+, CIN3+ and cancer Mortality Treatment of precancerous lesions / cancer prevented <u>Service resource use, expected number of:</u> Cytology tests HPV tests Colposcopies Histology evaluations Treatment for precancerous lesions Treatment of cancer <u>Lifetime / individual expected number of:</u> Screening / follow up episodes Colposcopies <u>Cost effectiveness, cost comparisons between strategies</u>
Study types	Economic evaluations with modelling

Table 2.2: Issue 2 (Surveillance recall intervals in HPV positive / cytology negative women) PICOS

Question	Have modelled estimates of surveillance recall strategies for women testing HPV + / cytology – identified an optimum approach?
Sub-questions	Have models compared approaches taking genotype (e.g. HPV 16 and 18) into account with those which do not?
Population	Women with HPV + / cytology – screening test results
Intervention	HPV based screening 'untyped'
Comparator	Cytology based screening HPV based screening using different strategies e.g. genotyping
Outcomes	Modelled outcomes including the following where reported: <u>Clinical measures</u> Cumulative incidence of CIN2+, CIN3+ and cancer Mortality Treatment of precancerous lesions / cancer prevented <u>Service resource use, expected number of:</u> Cytology tests HPV tests Colposcopies Histology evaluations Treatment for precancerous lesions Treatment of cancer <u>Lifetime / individual expected number of:</u> Screening / follow up episodes Colposcopies <u>Cost effectiveness, cost comparisons between strategies</u>
Study types	Economic evaluations with modelling

Table 2.3: Issue 3 (Options for women with HPV positive and cytology negative at the 'programme exit' test) PICOS

Question	Have models explored programme exit strategies for women with positive HR-HPV results at the final screening test?
Sub-questions	i) what is the risk of cervical abnormalities developing in women who are HPV + / colposcopy –? ii) should women who are HPV + / colposcopy indecisive be offered a choice of loop excision or further annual surveillance? iii) how many rounds of annual surveillance should be offered to women who are HPV + / colposcopy indecisive?
Population	Women 64 years of age with HPV infection in post screening surveillance rounds.
Intervention	i) discharge from routine HPV based screening in women who are HPV + / colposcopy – ii) loop excision or annual surveillance in women who are HPV + / colposcopy indecisive iii) multiple rounds of annual surveillance of women who are HPV + / colposcopy indecisive
Comparator	Any other strategy for women aged 64 years of age HPV+ in post screening surveillance rounds
Outcomes	Incidence of abnormalities requiring management in the above groups. Abnormalities are: • CIN2+ • CIN3+ • Invasive cervical cancer
Study types	Economic evaluations with modelling

2.2 LITERATURE SEARCH

2.2.1 Search Strategy

A search strategy was developed in conjunction with PHE to identify suitable studies (Appendix A). The search was conducted in Medline, Embase and the Cochrane Library on 20 November 2017.

2.3 STUDY SELECTION

As a REA study selection was undertaken by one reviewer.

2.4 DATA EXTRACTION

The following items were extracted from each study:

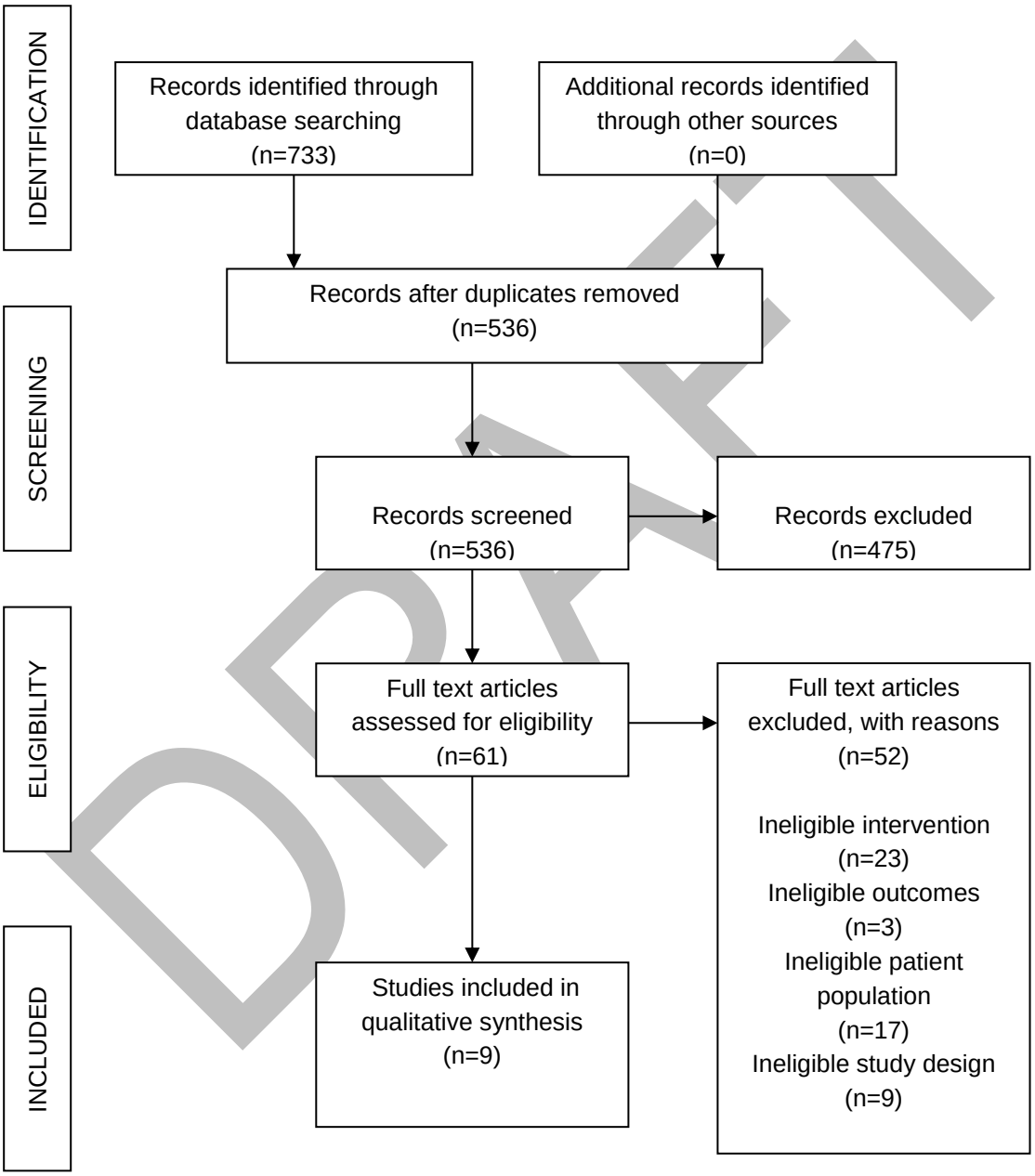
- Population in which the modelling took place;
- Country and setting;
- Detailed description of screening strategies compared (including frequencies);
- Description of modelling approach

    - Time horizon
    - Type of model
- Study results (including outcomes as set out in tables 2.1 to 2.3

3.1 STUDIES IDENTIFIED AND SELECTED

In total 733 potential records were identified across the three databases with 536 unique records. The record selection process is shown in Figure 3.1.

Figure 3.1: Study selection process



Section 4: Results

4.1 SUMMARY OF IDENTIFIED STUDIES

Nine studies were identified that met the inclusion criteria for the three issues to be addressed by the REA. Of these studies, one was in England[5], two in the Netherlands[2,4] and one each in Australia[8], Canada[6], Germany[9], Italy[1], New Zealand[7] and Norway[3].

All published studies essentially used the same broad modelling structure with some form of microsimulation of disease transmission coupled with markov processes of disease progression and decision analytical process for the outcomes from screening with calibration of model findings to published national epidemiological data. All studies had to use assumptions on compliance with screening for HPV acknowledging that this is unknown and may vary by the risk of HPV infection.

All but one study[9] were lifetime models with two studies[3,5] explicitly pointing out that findings from HPV screening studies from one country would not be generalizable to another due to differences between countries in the natural history of HPV infections (including age related incidence and transmission rates) and screening adherence. If this is the case the one study of an English population[5], provides results with the most relevance to the research issues.

A summary extraction table with key methods and findings is presented in Table 4.1 with full extraction tables in Appendix B.

4.2 ISSUE 1: SCREENING INTERVALS FOR HPV NEGATIVE WOMEN

All nine studies provided evidence for Issue 1, with the cost effectiveness of 5-year HPV screening compared to cytology assessed in all studies and the cost effectiveness of different intervals of HPV screening assessed in eight studies[1-6,8,9].

All studies – including the one English study - concluded that five-year HPV screening was an efficient strategy compared to cytology screening, with HPV screening costing less and in most scenarios considered having better outcomes than cytology. There was some evidence that in some scenarios outcomes were not always better with HPV screening with QALY losses in three models[5,7,8] . These scenarios were where a significant utility decrement for abnormal readings was applied. Whilst five-year HPV screening was considered to be efficient in all studies, two[1,6] studies looking at three-year intervals suggested that three-year screening was the optimal strategy. The difference in lifetime QALYs in all studies (when reported) between different screening intervals was around 0.005 per woman

In unvaccinated women, the English study[5] suggests that, depending on the follow up strategy for HR HPV positive women, five and six-year HR HPV (any oncogenic infection) screening strategies would result in a reduction in lifetime costs compared to cytology of £13-£16 and £24-£27 respectively. The model suggest QALY gains of 0.0003 to 0.0008 with five-year screening and 0.0007 to 0.0013 with six-year screening. The cost differential and QALY gains with five-year screening reported are therefore broadly in line with those from the Bain's model.

Six-year screening to age 49 followed by ten-year screening to age 64 would be £4 less costly than six-year screening for all ages with a QALY gain of 0.0004. This suggests that six-year screening to 49 followed by ten-year screening to age 64 is likely to be cost and QALY saving compared to six-year screening although the QALY differentials are very small between strategies. It is noted that a six-year HR HPV screening strategy may result in a small life year loss for six year followed by ten-year screening at age 49 both resulting in slight losses in life years (0.0004 to 0.0005 LY) compared to cytology screening.

For HR HPV screening using partial 16/18 genotyping in unvaccinated women, the English study provided evidence that five and six-year screening intervals would result in a reduction in lifetime costs compared to cytology of £3 and £15 per women respectively. HR HPV screening with partial genotyping would result in a QALY gains of 0.0009 with five-year screening and 0.0020 with six-year screening depending on the follow up strategy for HR HPV positive women. For six-year HR HPV screening in unvaccinated women to age 49 followed by ten-year screening to age 64 estimated that such screening intervals would be £4 less costly than six-year screening for all ages with a QALY gains of 0.0022. Six-year screening to age 49 followed by ten-year screening to age 64 would seem to be cost effective compared to six-year screening for all ages. Again, however, it is noted that the QALY gains are very small and could result in a very small loss in life years (0.0001) for a HR HPV with partial genotyping screening strategy compared to cytology.

In summary, the English study results would seem to provide evidence that for unvaccinated women HR HPV screening every six years until age 49 with ten-year screening to age 64 would be the most cost-effective strategy, but the result is somewhat ambiguous due to the very small QALY differences between all strategies and the loss in life years with this strategy (albeit again small) compared to cytology screening.

For vaccinated women, the English study reported almost identical results regardless of whether HPV non-genotyping or HR HPV testing was undertaken. Six-year screening would result in a QALY gain of 0.0021 to 0.0022 QALYs compared to cytology screening with a cost saving per woman of £28 to £29. Five-year screening would have a lower QALY gain of between 0.0001 and 0.0002 QALYs with a lower cost saving per woman of £15 to £16. Six-year screening (HPV non-genotyping or HR HPV testing) to age 49 followed by ten-year screening to age 64 would result in a QALY gain compared to six-year screening (HPV non-genotyping or HR HPV testing) of all ages of 0.0004 and a cost saving of £4 to £5.

As was the case for unvaccinated women, six-year HPV screening strategy to age 49 followed by ten-year HPV screening to age 64 was the most cost effective strategy for

vaccinated women although the use of HPV genotyping or not is essentially immaterial to the cost effectiveness results. However, it is noted again that the results are driven by very small differences in QALYs between strategies and that such an age dependent strategy always resulted in a slight loss in life years of 0.0003 per woman compared to cytology screening despite generating the highest QALY gain.

4.3 ISSUE 2: SURVEILLANCE RECALL INTERVALS IN HPV POSITIVE / CYTOLOGY NEGATIVE WOMEN

Four studies[3,6,8,5] assessed the cost effectiveness of different strategies for women who are HPV+/cyt-.

Three of these studies[5,7,8] assessed genotyping and the two which were outside the UK[7,8] concluded that management of HPV+ women using genotyping was the most cost effective approach.

The English study[5] assessed 12 month recall for HPV+/cyt- women against 24 month recall with differing strategies for HPV+ women by genotype.

For unvaccinated women, the shorter recall period was found to cost in the region of an additional £15 to £17 over a woman's lifetime compared to the longer recall with a QALY loss of between 0.0012 and 0.0016 with a 12 month as opposed to 24-month recall interval. However, the shorter recall did result in a life year gain of between 0.007 and 0.0011 depending on the genotyping strategy.

For vaccinated women, the results were essentially identical for unvaccinated women with shorter recall intervals incurring additional costs of £11 regardless of genotyping strategy with QALY losses of between 0.0013 and 0.0014 but life year gains of 0.0003 to 0.0004 compared to the longer recall intervals.

The evidence on 12-month recall compared to 24 month recall for HPV+/cyt- women from the English study would suggest that the shorter interval is likely to be costlier than the longer interval, but in terms of effectiveness the evidence is somewhat contradictory with a loss in QALYs but a gain in life years with 12 compared to 24-month recall. These results are independent of whether and how HPV genotyping is used in the overall screening strategy.

The findings in England on shorter recall periods are supported by the findings from a Norwegian study[3] that reported that a 6, 12 or 18-month recall period for HPV+ women make quite significant differences to cancers prevented and treated although minimal difference to the lifetime cervical cancer rate. The study did not report the discounted costs of different strategies and so did not report on the relative cost effectiveness of different recall intervals.

4.4 ISSUE 3: OPTIONS FOR WOMEN WITH HPV POSITIVE AND CYTOLOGY NEGATIVE AT THE 'PROGRAMME EXIT' TEST

No studies were identified that provided evidence for differential strategies for women on exit.

Table 4.1 Summary data extraction table

Paper	Country	Model structure	Screening strategies considered	Screening schedules (years)	Summary of cost effectiveness results	Study recommendation
Accetta 2010[1]	Italy	Markov with nine health states and death: Healthy, HPV infection (lrHPV, hr HPV 16/18, hrHPV non-16/18) pre-cancer lesions (low and high severity) and cancer (local, regional, distant). Women progress through model one at a time with annual cycles with state dependent probabilities	No screening, Cytology, primary HPV, Cytology followed by HPV triage, HPV followed by cytology triage	3 and 5	Current strategy of primary cytology every three years is dominated by primary HPV with cytology triage every three years. Five-year screening would be less expensive but with slightly worse outcomes.	Three-year screening with HPV with cytology triage
Berkhof 2010[2]	Netherlands	Markov with six monthly cycles. Health states not well described but can be inferred to include HPV free and HPV states with HPV low risk and high-risk states. Patients can develop CIN2+ only if in the HPV high risk state but can develop CIN1 in all HPV states. Progression to CIN3 was age dependent. Patients can progress from CIN states to cancer or back to a well state.	Cytology, HPV with cytology triage, Combination cytology and HPV, Cytology with HPV triage.	5, 6, 7.5 and 10	Strategies with a screening interval over 7.5 years were not cost effective with a willingness to pay threshold of €20,000/QALY. The optimal strategy was five-year screening with HPV followed by cytology triage	Five-year screening with HPV with cytology triage
Burger 2017[3]	Norway	Model starting at age 8 where girls/women have a probability over time of type-specific HPV incidence and clearance. This can progress to lesions and cancer which are a function of age, lesion and duration of infection. The model is stratified by HPV genotype, CIN grades and cancer stage.	**1. HPV followed by cytology triage** HPV+Cyt- women are re-tested after 12 months. HPV+ women at this point have colposcopy. HPV- women return to previous screening period. Wait time between re-testing between 6 and 18 months was explored as was 1,2 or 3 HPV+cyt- results required before referral for	3, 4, 5, 6, 8 and 10	Lengthening the time between screenings did have impact on the cancer incidence rate with more frequent screening reducing the cancer rate. However, the most important factor was starting screening at age 25. Different intervals between re-testing of HPV+/cyt- women or altering the point at which	HPV-based screening among unvaccinated women should start at age 25 with an appropriate use of cytology triage to control colposcopy referrals. No recommendation was made on the frequency of testing

Paper	Country	Model structure	Screening strategies considered	Screening schedules (years)	Summary of cost effectiveness results	Study recommendation
			colposcopy. **2. Cytology with HPV triage (current strategy)** **Cyt+(minor lesions) and** HPV+ (for high risk HPV) women are re-tested with cytology and HPV test after 6-12 months. High grade lesions on cytology are referred for immediate colposcopy.		colposcopy occurs for these women made little impact on the cancer incidence rate	
de Kok 2012[4]	Netherlands	Patient simulation model where women have a probability over time of type-specific HPV incidence and clearance. This can progress to lesions (which can clear) and cancer which are a function of age, lesion and duration of infection. The model is stratified by high risk HPV (but not specific genotype), CIN grades and cancer stage.	Nine strategies were considered with 171 policy combinations of start age and screening frequency. The only strategies considered with results reported were cytology, HPV with cytology triage followed by a second cytology triage at 6 months for HPV+/cyt- women with HPV sensitivity of 90% and 95%	3 to 10. Only results for 5 years presented	The cost effectiveness results of strategies were not presented. The summary of the results states in most scenarios primary HPV screening is the preferred scenario in women over 30	Where screening is well controlled, European countries should switch from cytology to HPV screening
Kulasingham 2009[6]	Canada	Poorly described but a cohort model with yearly cycles where women can move from healthy to precancer, cancer and death. Women can move from diseased back to healthy states	Eight strategies considered for a start age of 25 (a further 19 strategies for people under 25). HPV testing only, cotesting, cytology with HPV triage, HPV with cytology triage.	1, 2, 3 and 5	HPV testing every three years followed by cytology triage may be more effective and less costly than cytology screening alone	HPV with cytology triage from age 25 with three-year screening
Petry 2017[9]	Germany	Model is not described beyond being a cohort model with a decision tree component. No detail of health states was provided.	Multiple HPV strategies considered in terms of type of HPV test and cytology and also cotesting. Only results for cytology (annual) and HPV with cytology triage (3 and 5 years) are extracted	1 (cytology), 3 and 5 (HPV with cytology triage)	Screening strategies for HPV results in fewer cancers at a lower cost than cytology alone. Screening of HPV at intervals less than five years does result in more	No recommendation for a specific HPV screening strategy

Paper	Country	Model structure	Screening strategies considered	Screening schedules (years)	Summary of cost effectiveness results	Study recommendation
					cancers detected but at a higher cost than five-year screening	
Lew 2017[8]	Australia	Women cycle through following states: susceptible, HPV infected (and genotype), CIN1-3 and cancer (6 stages). Women can also be vaccinated or become immune. At each screening point the screening and treatment model is applied with a probability of screening attendance. Modules within the screening and treatment model include a colposcopy, biopsy and treatment modules and post treatment natural history module. Model outcomes were calibrated to observed data on cancer, cancer death rates and histology and abnormality rates	Seven strategies considered. Only extracted were cytology (with 5 years screening), HPV with cytology triage or HPV genotyping. All HPV+ women at discharge from screening are offered colposcopy. Current cytology practice is 3 years cytology screening (5 years at 45) Various other elements of screening strategies were considered including: different options for HPV+/low grade cytology (direct colposcopy or reflex HPV); whether women are invited to attend a first screening or not; different levels of compliance with call and recall programmes	2 (cytology), 5 and 6 (HPV)	The authors conclude that HPV testing every five years with partial genotyping or cotesting with cytology were the most effective. Sending those with HPV16/18 for colposcopy and other genotypes for reflex cytology was described as "one of the most cost-effective" strategies. Whilst the analysis is unambiguous that all strategies will result in lower cost and HPV strategies are likely to dominate non-HPV strategies (at least if only life years and not QALYs are considered) there is no full incremental analysis of strategies, QALY gains are small across strategies and may be negative for some HPV strategies and a wide range of different scenarios were undertaken making it difficult to isolate the actual effect of different aspects of strategies.	HPV testing every five years with partial genotyping and direct colposcopy if 16/18
Kitchener 2014[5]	England	Same model as Lew 2017	HPV with cytology triage and cytology alone are two main strategies. Within the HPV triage there are sub strategies	5 and 6 years and 6 years 25-49 followed by 10 years 50-64	HPV testing is a cost-effective strategy compared to cytology. Whilst most of the	The most feasible and cost-effective strategy in terms of delivery could involve a single policy

Paper	Country	Model structure	Screening strategies considered	Screening schedules (years)	Summary of cost effectiveness results	Study recommendation
			depending on the treatment pathway should a woman screen as HPV+/cyt negative. **Strategy 1**: HPV+/cyt- women are recalled for HPV with cytology triage in 24 months. HPV+/cyt- women are again recalled at 24 months **Strategy 2**: Initial screen is for HPV genotype. HR HPV+/cyt- women are recalled for HPV genotype with cytology triage in 24 months. 16/18 positive women are referred to colposcopy. Other HR+ (OHR) are referred for cytology with cyt- women again recalled at 24 months. **Strategy 3**: Initial screen is for HPV genotype. 16/18 positive women are referred to colposcopy. HPV+/cyt- women are recalled for HPV genotype with cytology triage in 24 months. Other HR (OHR)+ are referred for cytology with cyt- women again recalled at 24 months and move onto a 24-month retest cycle whilst they remain OHR+/cyt-. 16/18 positive women at retest are referred to colposcopy In all strategies, recall at 12 rather than 24 months was considered.		strategies considered were cost and QALY saving, they all resulted in greater numbers of colposcopies and biopsies in unvaccinated women. The QALY gains per woman were small with any strategy although primary HPV genotype testing only appears to be an efficient strategy in vaccinated women.	across the screening age range with 5- or 6-yearly screening intervals and 12-month recall for HPV positive women with negative cytology.

Paper	Country	Model structure	Screening strategies considered	Screening schedules (years)	Summary of cost effectiveness results	Study recommendation
Lew 2016[7]	New Zealand	Same model as Lew 2017	"Cytology, HPV with cytology triage, HPV with genotyping. Within the HPV triage there are sub strategies depending on the treatment pathway should a woman screen as HPV+/cyt negative. Strategies for HPV+ women are as follows **HPV with cytology triage**: HPV+/cyt- women are recalled for HPV and cytology cotest in 12 months. HPV+ or cyt+ women are sent for colposcopy. HPV-/cyt- back onto normal screening cycle **HPV with genotyping**: HPV16/18 sent for colposcopy. OHR+ are referred for cytology with cyt- women recalled at 12 months. HPV+ women at recall are referred to colposcopy and HPV- women back onto normal screening cycle	3 (cytology), 5 (HPV)	At a WTP threshold of $50,000/LY, in both unvaccinated and vaccinated women HPV genotyping was the most cost-effective strategy. When QALYs were considered (although detailed findings not presented in body of report) findings are reported to vary widely. If disutility for screening and/or a minor disutility for abnormal findings are considered, then HPV genotyping remains the cost-effective choice. If there is no disutility from screening itself but a major disutility from abnormal findings then all HPV strategies are less effective than cytology screening	Primary HPV with genotyping

Section 5: Discussion

This rapid evidence assessment identified nine studies that provided evidence against two of the three key issues it was designed to address. Evidence is available on the cost-effectiveness of five-year HPV screening and on differential approaches to strategies for HPV+/cyt- women but no studies reported differential cost effectiveness results for different strategies for women on exit from screening.

Whilst not a key research question, where it has been looked at by published studies HPV vaccination does not seem to significantly influence the relative cost-effectiveness of HPV versus cytology screening (i.e. if HPV was found to be efficient with a strategy of no vaccination it was also found to be efficient if vaccination was being undertaken).

Two key findings or conclusions can be drawn in relation to the original research questions.

Key finding one: Five-year HPV screening is reported as being an efficient strategy compared to cytology screening but the true cost-effectiveness of this (and the optimal screening period) is uncertain

All published models have reported that HPV screening is likely to be an efficient strategy compared to cytology screening. This is in line with the previous unpublished UK model.

The finding that HPV screening is efficient compared to cytology screening is driven by the higher sensitivity/specificity of HPV compared to cytology and the lower number of screenings that are required with HPV screening. This, in turn, is the main driver towards the conclusion that HPV screening will be cost saving. However, the impact on outcomes is more ambiguous than may be suggested by the economic models both published and unpublished for the following reasons:

- Life year gains were small in all studies as were the absolute number of cancers reduced as a percentage of the total population screened. For example, one study, found that more frequent cytology screenings may reduce mortality compared to less frequent HPV screening. Similarly, depending on utility values chosen for the results of an abnormal screening, some studies found that HPV screening could result in a reduction in QALYs compared to cytology screening.

  As stated explicitly by the one study from England[5] findings from studies of HPV screening strategies in one country are unlikely to be transferable to another given the differences between countries in HPV prevalence, the natural history of HPV in populations based upon lifestyle choices and the adherence by women to screening intervals. This means that in studies other than the English study, it is likely that the costs and outcomes reported for different strategies have limited generalisability to the UK context.

- Costs and benefits of HPV screening are driven by assumptions that have to be made on the compliance rates for screening intervals for what is essentially an STD. One Dutch study[4] found that for HPV screening to be cost-effective HPV screening had to be 'well controlled'. How this will differ for all women and for those who see themselves as low and high risk is currently unknown.

- The numbers of colposcopies could go up or down with HPV screening depending on the exact nature of the screening strategy and model assumptions employed. The exact direction (an increase or decrease in colposcopies) was uncertain with the unpublished UK model predicting a rise in colposcopies with HPV screening with 3 year intervals compared to three year cytology but no change in the number with 5 year HPV screening. The published English study predicted a fall in the number of colposcopies with a six-year HPV screening strategy but an increase with six year screening with primary partial HPV genotyping.

- The loss of utility from attending screening, having abnormal results or having a colposcopy is not well understood which generates uncertainty in overall findings for HPV compared to cytology screening strategies. This was acknowledged as a key weakness in the report describing the unpublished UK model.

Given the uncertainties inherent in modelling HPV testing to cytology based screening, there are even greater uncertainties around recommendations from studies on HPV screening intervals. Putting aside concerns about the potential limited generalisability of findings from other countries, the published studies suggest that increasing the HPV screening intervals reduces the costs of screening but reduces the potential benefits. The one English study[5] also reported this to be the case but only looked at 5 year, 6-year and 6 year followed by 10 year intervals at age 49. This study essentially found the same as the unpublished model – that shorter screening intervals had higher costs but lower gains in life expectancy. However, the differences per woman in both cost and especially QALYs and life years were very small in both the published English study and in the unpublished model with the difference in QALYs across all strategies never more than one quality adjusted life *day* over a lifetime. In addition, depending on the strategy there are differences in, for example, colposcopy rates or CIN2 detection that may be taken into account by decision makers.

It is very difficult to say with certainty which strategies are the most cost effective with such small incremental differences even without the significant uncertainties in the model results already identified. The authors of the English study for example concluded that a five or six year strategy "could be" the most cost effective strategy, although it is not clear how they reached this conclusion it appears to be based upon essentially a cost-consequences analysis based upon potential differences in, for example, colposcopy rates. If the evidence from the model supported "five or six" year screening it also supported six year screening to age 49 followed by ten year screening to age 64 depending on the weight put on QALYs over life years and other outcomes. It also supported HPV partial genotyping as the primary screening method.

Consideration of screening intervals will depend on the relative weight placed on the burden of screening, the likelihood of attendance of all women or women in different risk groups, the potential reduction in cancers and deaths and the change in the number of abnormal readings or colposcopies.

In summary, if the assumptions that have been made on HPV screening compliance in published studies represents reality, it is likely that five-year HPV screening with its longer intervals and better test parameters compared to cytology is likely to be cost saving compared to cytology screening. The Bain's model is therefore consistent with other published findings. If the disutility is not too great for abnormal screening results then it is likely that HPV screening also generates more QALYs than cytology screening. Once a decision on HPV modelling has been reached, the incremental costs and benefits of different screening intervals per woman are very small and the choice of HPV screening interval will depend on how decision makers wish to interpret model results (especially the weight they put on different utility sets and/or on non-QALY outcomes) and the assumptions they most believe on future HPV screening compliance.

Key finding two: Evidence on management of women who are HPV+/cyt- is unclear and limited by the modelling approaches chosen

Whilst four studies had made recommendations on the use of HPV genotyping and or/recall intervals in terms of the management of women who were HPV+/cyt-, the recommendations were all different. The one English study made a strong recommendation on 12 month rather than 24 month recall intervals for HPV+/cyt- women with no mention of genotyping as part of the strategy whilst studies from New Zealand and Australia – using essentially the same model – recommended some form of HPV genotype testing strategy. As stated, it was not clear in the English study how a conclusion of 12 month intervals was reached given 24 month intervals appeared to potentially be more cost effective.

Examination of the four studies revealed that, as was the case for differing primary HPV screening intervals, the results were very sensitive to the utility values chosen with the difference in QALYs regardless of the utility value set chosen in the region of quality adjusted life *hours* over a woman's lifetime. With differences that are so marginal coupled with the inherent uncertainty around compliance with HPV screening again decision makers could interpret model outputs to justify almost any strategy.

Recommendations for future modelling

It is our opinion that outside of modelling different lengths of screening, the modelling approaches that have been undertaken in the identified studies are perhaps inappropriate to answer questions about different strategies for women who test HPV+/cyt-, exit strategies for women at age 64 (or indeed any age) who are HPV+ at last screening or indeed any strategy for HPV+ women. By attempting to model both screening over a lifetime and strategies for the small percentage of women who have abnormal results the potential differential cost effectiveness of strategies for abnormal results has the potential to be drowned out by the noise and assumptions from the overall model. The reasons for this are twofold:

- Any potential cost and outcome (including QALY) differences with different strategies for dealing with abnormal results will be averaged out across all women. As the vast majority of women never have an abnormal result this heavily dilutes the cost and outcome differences between strategies for the average woman.
- The small absolute differences for the average woman from different strategies will be reduced even further by discounting. With a lifetime horizon and five year screening cycles, abnormal screenings that occur in anything other than the first screen will be discounted. With a 3.5%pa discount rate any costs and benefits of different strategies will reduce by 16% at the second screen, 30% at the third screen and 41% by the fourth screen.

To assess the cost effectiveness of different strategies for abnormal readings the correct approach – in our opinion - is to model a cohort that has an abnormal reading *only* with the model starting *at the time of the abnormal reading.* This is equally true for strategies for HPV+/cyt- at any point in the screening timeline or for women who are HPV+ at any point including the last screening.

For all future models of cervical cancer screening, utility values for colposcopy, false negatives, abnormal screenings and screening itself should be identified and collected if necessary. Close monitoring of the five year HPV screening strategy should also continue so screening compliance rates can be monitored with the model adapted with real world data rather than assumption when it becomes available.

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Appendix A Search strategy

Literature search for HPV modelling studies – November 2017

All literature searches carried out on 20th November 2017

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

1. Papillomavirus Infections/ (22984)
2. (human adj (papilloma virus or papillomavirus)).tw. (35425)
3. HPV.tw. (36968)
4. 1 or 2 or 3 (48399)
5. ((primary or first or initial or main) adj (screen$3 or test or tests or testing or detect$3 or assessment)).tw. (35835)
6. 4 and 5 (593)
7. ((primary HPV or human papillomavirus) adj2 (screen$ or test or tests or testing)).tw. (1709)
8. HPV-DNA test$3.tw. (1136)
9. 6 or 7 or 8 (2922)
10. Uterine Cervical Neoplasms/ (73355)
11. cervical cancer.tw. (40563)
12. (cervical intraepithelial neoplasia or CIN).tw. (12533)
13. cancer of the cervix.tw. (3398)
14. 10 or 11 or 12 or 13 (90217)
15. Models, Theoretical/ (145978)
16. Models, Economic/ (9253)
17. Logistic models/ (129507)
18. Computer Simulation/ (183239)
19. Cost-Benefit Analysis/ (77128)
20. Markov Chains/ (13461)
21. Health Care Costs/ (36712)
22. Technology Assessment, Biomedical/ (9769)
23. ((Markov or mathematical or theoretical or microsimulation or simulation or economic or cost$ or clinical or benefit or effective$ or decision) adj (model$ or analy$ or evaluation$ or assessment$ or comparison$)).tw. (235286)
24. (model adj (analy$ or simulation or input$)).tw. (12555)
25. decision analy$ model$.tw. (2908)
26. 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 (747071)
27. 9 and 14 and 26 (215)
28. limit 27 to yr="2005 -Current" (173)

Embase 1996 to 2017 Week 47

1. papillomavirus infection/ (10584)
2. (human adj (papilloma virus or papillomavirus)).tw. (34937)
3. HPV.tw. (41450)
4. 1 or 2 or 3 (50794)
5. ((primary or first or initial or main) adj (screen$3 or test or tests or testing or detect$3 or assessment)).tw. (37905)
6. 4 and 5 (847)
7. ((primary HPV or human papillomavirus) adj2 (screen$ or test or tests or testing)).tw. (1931)
8. HPV-DNA test$3.tw. (1477)
9. 6 or 7 or 8 (3613)
10. uterine cervix cancer/ (47257)
11. cervical cancer.tw. (44676)
12. (cervical intraepithelial neoplasia or CIN).tw. (13701)
13. cancer of the cervix.tw. (1652)
14. 10 or 11 or 12 or 13 (71484)
15. theoretical model/ (65783)
16. economic model/ (683)
17. statistical model/ (142222)
18. computer simulation/ (97496)
19. "health care cost"/ (151225)

20. biomedical technology assessment/ (10234)
21. "cost effectiveness analysis"/ (122121)
22. ((Markov or mathematical or theoretical or microsimulation or simulation or economic or cost$ or clinical or benefit or effective$ or decision) adj (model$ or analy$ or evaluation$ or assessment$ or comparison$)).tw. (233245)
23. (model adj (analy$ or simulation or input$)).tw. (14229)
24. decision analy$ model$.tw. (3914)
25. 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 (721982)
26. 9 and 14 and 25 (348)
27. limit 26 to yr="2005 -Current" (287)

Cochrane Library

#1 MeSH descriptor: [Papillomavirus Infections] this term only (755)
#2 ("human papilloma virus" or "human papillomavirus"):ti,ab,kw (1439)
#3 HPV:ti,ab,kw (1519)
#4 #1 or #2 or #3 (1948)
#5 ((primary or first or initial or main) and (screen* or test* or detect* or assessment)):ti,ab,kw (149875)
#6 #4 and #5 (464)
#7 (("primary HPV" or "human papillomavirus" or "human papilloma virus") and (screen* or test*)):ti,ab,kw (711)
#8 ("HPV-DNA test*" or "HPV DNA test*"):ti,ab,kw (94)
#9 #6 or #7 or #8 (896)
#10 MeSH descriptor: [Uterine Cervical Neoplasms] this term only (2028)
#11 "cervical cancer":ti,ab,kw (1907)
#12 ("cervical intraepithelial neoplasia" or CIN):ti,ab,kw (1259)
#13 "cancer of the cervix":ti,ab,kw (46)
#14 #10 or #11 or #12 or #13 (3598)
#15 MeSH descriptor: [Models, Theoretical] this term only (983)
#16 MeSH descriptor: [Models, Economic] this term only (1565)
#17 MeSH descriptor: [Logistic Models] this term only (4920)
#18 MeSH descriptor: [Computer Simulation] this term only (1846)
#19 MeSH descriptor: [Cost-Benefit Analysis] this term only (18506)
#20 MeSH descriptor: [Markov Chains] this term only (2177)
#21 MeSH descriptor: [Health Care Costs] this term only (4693)
#22 MeSH descriptor: [Technology Assessment, Biomedical] this term only (632)
#23 ((Markov or mathematical or theoretical or microsimulation or simulation or economic or cost* or clinical or benefit or effective* or decision) and (model* or analy* or evaluation* or assessment* or comparison*)):ti,ab,kw (413383)
#24 (model and (analy* or simulation or input*)):ti,ab,kw (39283)
#25 "decision analy* model*":ti,ab,kw (340)
#26 #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 (423980)
#27 #9 and #14 and #26 Publication Year from 2005 to 2017 (273)

Search results	
Medline	173
Embase	287
Cochrane Library	273

Total	**733**

Appendix B Full data extraction tables

Paper	Country	Objective	Time Horizon	Discount rate	Model type	Model structure
Accetta 2010	Italy	To assess the cost effectiveness of HPV screening in Italy	Lifetime	3% (costs and QALYs)	Markov model with micro simulation	Markov with nine health states and death: Healthy, HPV infection (lrHPV, hr HPV 16/18, hrHPV non-16/18) pre cancer lesions (low and high severity) and cancer (local, regional, distant). Women progress though model one at a time with annual cycles with state dependent probabilities
Berkhof 2010	Netherlands	To assess the cost effectiveness of HPV screening strategies in the Netherlands	To age 100	1.5% for QALYs and 4.0% for costs.	Markov model with micro simulation	Markov with six monthly cycles. Health states not well described but can be inferred to include HPV free and HPV states with HPV low risk and high risk states. Patients can develop CIN2+ only if in the HPV high risk state but can develop CIN1 in all HPV states. Progression to CIN3 was age dependent. Patients can progress from CIN states to cancer or back to a well state.
Burger 2017	Norway	To assess the resource use (notably colposcopy) and outcomes of different HPV testing algorithms (notably the time from switching from cytology to primary HPV screening)	Lifetime	NR	Microsimulation model	Model starting at age 8 where girls/women have a probability over time of type-specific HPV incidence and clearance. This can progress to lesions and cancer which are a function of age, lesion and duration of infection. The model is stratified by HPV genotype, CIN grades and cancer stage.
de Kok 2012	Netherlands	To assess whether and it what form HPV testing is preferable to cytology in the Netherlands, including the frequency of tests	Lifetime	3% (costs and QALYs)	Microsimulation model (MISCAN)	Patient simulation model where women have a probability over time of type-specific HPV incidence and clearance. This can progress to lesions (which can clear) and cancer which are a function of age, lesion and duration of infection. The model is stratified by high risk HPV (but not specific genotype), CIN grades and cancer stage.
Kulasingham 2009	Canada	To determine the cost-effectiveness of HPV testing in three Canadian provinces	Lifetime	3% (costs and QALYs)	Markov model	Poorly described but a cohort model with yearly cycles where women can move from healthy to precancer, cancer and death. Women can move from diseased back to healthy states
Petry 2017	Germany	To evaluate the cost effectiveness of HPV screening scenarios compared to cytology	10 years (5 year screening) 6 years (3 year screening)	3% (costs only - QALYs not included in analysis)	Markov model	Model is not described beyond being a cohort model with a decision tree component. No detail of health states was provided.
Lew 2017	Australia	To evaluate different screening options - including HPV with partial genotyping - in an Australian context	Lifetime	5% (costs and benefits)	Dynamic model of HPV transmission and vaccination with Markov model for natural history of CIN and cancer	Women cycle through following states: susceptible, HPV infected (and genotype), CIN1-3 and cancer (6 stages). Women can also be vaccinated or become immune. At each screening point the screening and

Paper	Country	Objective	Time Horizon	Discount rate	Model type	Model structure
					survival coupled with a deterministic screening and treatment model	treatment model is applied with a probability of screening attendance. Modules within the screening and treatment model include a colposcopy, biopsy and treatment modules and post treatment natural history module. Model outcomes were calibrated to observed data on cancer, cancer death rates and histology and abnormality rates
Kitchener 2014	England	To determine the cost effectiveness of HPV screening compared to cytology in England	Lifetime	3.5% (Costs and QALYs)	Same model as Lew 2017	Same model as Lew 2017
Lew 2016	New Zealand	To determine the cost effectiveness of HPV screening compared to cytology in New Zealand	Lifetime	3.5% (Costs and QALYs)	Same model as Lew 2017	Same model as Lew 2017

Paper	Screening strategies considered	Screening schedules (years)	Screening start age	Screening end age
Accetta 2010	No screening, Cytology, primary HPV, Cytology followed by HPV triage, HPV followed by cytology triage	3 and 5	25	65
Berkhof 2010	Cytology, HPV with cytology triage, Combination cytology and HPV, Cytology with HPV triage.	5, 6, 7.5 and 10	30	65
Burger 2017	**1. HPV followed by cytology triage** HPV+Cyt- women are screened after 12 months. HPV+ women at this point have colposcopy. HPV- women return to previous screening period. Wait time between rescreening between 6 and 18 months was explored as was 1,2 or 3 HPV+cyt- results required before referral for colposcopy. **2. Cytology with HPV triage (current strategy)** **Cyt+(minor lesions) and** HPV+ (for high risk HPV) women are screened with cytology and HPV test after 6-12 months. High grade lesions on cytology are referred for immediate colposcopy.	3, 4, 5, 6, 8 and 10	25 (28, 31 and 34 in study but these ages are a combination of initial cytology followed by HPV)	69
de Kok 2012	Nine strategies were considered with 171 policy combinations of start age and screening frequency. The only strategies considered with results reported were cytology, HPV with cytology triage followed by a second cytology triage at 6 months for HPV+/cyt- women with HPV sensitivity of 90% and 95%	3 to 10. Only results for 5 years presented	25, 27, 30 and 32	Maximum of 70
Kulasingham 2009	Eight strategies considered for a start age of 25 (a further 19 strategies for people under 25).HPV testing only, cotesting, cytology with HPV triage, HPV with cytology triage.	1, 2, 3 and 5	25	Not clear but appears to be 70
Petry 2017	Multiple HPV strategies considered in terms of type of HPV test and cytology and also cotesting. Only results for cytology (annual) and HPV with cytology triage (3 and 5 years) are extracted	1 (cytology), 3 and 5 (HPV with cytology triage)	30	65
Lew 2017	Seven strategies considered. Only extracted were cytology (with 5 years screening), HPV with cytology triage or HPV genotyping. All HPV+ women at discharge from screening are offered colposcopy. Current cytology practice is 3 years cytology screening (5 years at 45) Various other elements of screening strategies were considered including: different options for HPV+/low grade cytology (direct colposcopy or reflex HPV); whether women are invited to attend a first screening or not; different levels of compliance with call and recall programmes	2 (cytology), 5 and 6 (HPV)	25	64-74
Kitchener 2014	HPV with cytology triage and cytology alone are two main strategies. Within the HPV triage there are sub strategies depending on the treatment pathway should a woman screen as HPV+/cyt negative. **Strategy 1**: HPV+/cyt- women are recalled for HPV with cytology triage in 24 months. HPV+/cyt- women are again recalled at 24 months	5 and 6 years and 6 years 25-49 followed by 10 years 50-64	25	64

Paper	Screening strategies considered	Screening schedules (years)	Screening start age	Screening end age
	Strategy 2: HPV+/cyt- women are recalled for HPV genotype with cytology triage in 24 months. OHR+ are referred for cytology with cyt- women again recalled at 24 months. 16/18 positive women are referred to colposcopy **Strategy 3**: Initial screen is for HPV genotype. 16/18 positive women are referred to colposcopy. HPV+/cyt- women are recalled for HPV genotype with cytology triage in 24 months. OHR+ are referred for cytology with cyt- women again recalled at 24 months and move onto a 24 month retest cycle whilst they remain OHR+/cyt-. 16/18 positive women at retest are referred to colposcopy In all strategies, recall at 12 rather than 24 months was considered.			
Lew 2016	"Cytology, HPV with cytology triage, HPV with genotyping. Within the HPV triage there are sub strategies depending on the treatment pathway should a woman screen as HPV+/cyt negative. Strategies for HPV+ women are as follows **HPV with cytology triage**: HPV+/cyt- women are recalled for HPV and cytology cotest in 12 months. HPV+ or cyt+ women are sent for colposcopy. HPV-/cyt- back onto normal screening cycle **HPV with genotyping**: HPV16/18 sent for colposcopy. OHR+ are referred for cytology with cyt- women recalled at 12 months. HPV+ women at recall are referred to colposcopy and HPV- women back onto normal screening cycle	3 (cytology), 5 (HPV)	20 (cytology), 25 (HPV)	84

Paper	Source of natural history data	Source of screening effectiveness data	Source of costs	Currency and cost year	Cost of cytology and HPV tests in model	Utilities used and source
Accetta 2010	Previous models and published literature. Model was calibrated against published literature	Published studies (HPV Ranco 2008), Cytology (Goldhaber Fiebert 2008 and Kim 2007)	Activity based costing undertaken by the authors	Euro 2006	NR	Age related utilities and cancer related quality of life from Goldhaber-Fiebert. No disutility for screening or abnormal tests
Berkhof 2010	Published literature , notably the POBASCAM study against which the model results were calibrated	Published studies (unclear which studies actually drove test sensitivity/specificity parameters)	Published studies	Euro 2007	€30.87 (HPV test). €27.51 (cytology)	Utilities in model for positive screening, CIN treatment and cancer from Mandelblatt 2002, Goldie 2004 and Maissi 2004. Positive screening utility is 0.97 which seems high and the source (Madellatt) from which this value is taken comes from a paper by Gold (1998) which is a study of utilities for a range of health conditions - none of which relate to cervical cancer or positive test results and the value chosen (0.97) which is used in the Berkhof model is not present.
Burger 2017	Published data with calibration against epidemiological data from Norway	Published literature (Ronco 2014, Arbyn 2008, Nanda (2000)	No costs reported	NR	NR	NR
de Kok 2012	Not well described. MISCAN model appears to be populated with real data on the Dutch population. Model considers other hypothetical populations with different risks of cancer, HPV and whether previous	Assumption and previously published model (Berkhof 2005)	Published Dutch cost studies	Euro 2008	€21-€33 (HPV). €26-€52 (cytology)	NR

Paper	Source of natural history data	Source of screening effectiveness data	Source of costs	Currency and cost year	Cost of cytology and HPV tests in model	Utilities used and source
	screening had occurred. The Dutch population was considered low risk					
Kulasingham 2009	Epidemiological studies in Canada	Published literature (Mayrand 2007, Mayrand 2006)	Fee schedules and published literature	CAN$ 2006		NR
Petry 2017	Published literature	ATHENA trial	Clinicians and published literature	Euro 2016	NR	NR
Lew 2017	Published literature	Published studies (unclear which studies actually drove test sensitivity/specificity parameters)	Medicare Benefits Schedule, National Hospital Cost Data Collection, Pharmaceutical Benefits Schedule	AUD 2013	Actual cost of HPV test not reported. Cost of cytology $19	Two utility sets are used to derive QALYs but neither are defined in paper or Appendix. Cross referencing of other studies (Kitchener) suggests that one set of weights (Set A) included disutilities from screening, triage, testing and management whilst the other (Set B) did not have a disutility associated with screening.
Kitchener 2014	Published literature updated with the ARTISTIC trial data	Meta-analysis (Cuxick 2006) and ARTISTIC trial results	Manufacturers of HPV tests, MAVARIC study for cytology, published studies on cancer management (Martin-Hirsch 2007 and Sherlaw-Johnson 2004)	UK£ 2010	£9.38 (HPV). £5.45 (-ve), £15.40 (Low grade), £15.56 (High grade)	Two utility sets are used to derive QALYs 1. Disutility for screening, even if negative (Simonella 2014 based on SG of 43 women from general population). 2. No disutility for screening but high disutility if abnormal screening (Insinga 2007 based on TTO with 150 women from general population) .
Lew 2016	As in Lew 2017 but calibrated to Australian/UK HPV rates and NZ age specific rates	Meta-analysis for both cytology (Arbyn 2008) and HPV (Arbyn 2012). NZ registry data was	National Cervical Screening Programme	NZD 2017/18 (published in 2016?)	$35 for HPV test. $31.10 for cytology.	Broadly as Lew 2017 but with three scenarios. 1. Disutility for screening, even if negative

Paper	Source of natural history data	Source of screening effectiveness data	Source of costs	Currency and cost year	Cost of cytology and HPV tests in model	Utilities used and source
	of lesions, cancer and cancer mortality	used for screening attendance rates				(Simonella 2014 based on SG of 43 women from general population). 2. No disutility for screening but high disutility if abnormal screening (Insinga 2007 based on TTO with 150 women from general population) . 3. As 2 but with small disutility if abnormal screening (Drolet EQ5D of 490 women with abnormal screen and 460 women with normal screen).

Paper	Incidence of CIN2+	Incidence of CIN3+	Lifetime cervical cancer risk	Mortality	Treatment of lesions prevented	Cancer prevented
Accetta 2010	NR	NR	**Five year screen** Cytology: 0.77% HPV test only: 0.64% Cytology followed by HPV triage: 0.79% HPV followed by cytology triage: 0.62% **Three year screen** Cytology: 0.65% HPV test only: 0.61% Cytology followed by HPV triage: 0.70% HPV followed by cytology triage: 0.61%	NR	NR	NR
Berkhof 2010	**Reduction compared to 5 year cytology** HPV with cytology triage: 31% Combination: 34% Cytology with HPV triage: 1% Once the screening interval reached 10 years, cancer cases with HPV with cytology triage exceeded those with 5 year cytology	NR	**Reduction compared to 5 year cytology** HPV with cytology triage: 23% Combination: 26% Cytology with HPV triage: 3% Once the screening interval reached 10 years, cancer cases with HPV with cytology triage exceeded those with 5 year cytology	NR	NR	NR
Burger 2017	NR	NR	**Reduction with HPV with cytology triage (5 year cytology with HPV triage 88.7%)** Three year screen (wait time for rescreen of HPV+cyt- women all based on 2 recalls before colposcopy. Difference with 1 or 3 recalls changed values 0.1%) 6 month: 96.8%	NR	NR	**Cancers prevented per 1,000 women with HPV with cytology triage (Cancer incidence with 5 year cytology with HPV triage 3.75)** Three year screen 6 month: 2.55 12 month: 2.68 18 month: 2.59 Five year screen

Paper	Incidence of CIN2+	Incidence of CIN3+	Lifetime cervical cancer risk	Mortality	Treatment of lesions prevented	Cancer prevented
			12 month: 96.6% 18 month: 96.4% Five year screen 6 month: 96.6% 12 month: 96.3% 18 month: 96.1% Ten year screen 6 month: 95.5% 12 month: 95.1% 18 month: 94.7%			6 month: 2.69 12 month: 2.58 18 month: 2.49 Ten year screen 6 month: 2.14 12 month: 2.02 18 month: 1.88
de Kok 2012	All results 5 year screening starting age 30 and ending age 60 and % of first primary smears with CIN2+ lesions Cytology: 0.3% HPV 90% sensitivity and two times cytology triage: 0.3% HPV 95% sensitivity and two times cytology triage: 0.3%	NR	All results 5 year screening starting age 30 and ending age 60 and cancer cases per 100,000 life years Cytology: 5.7 HPV 90% sensitivity and two times cytology triage: 5.3 HPV 95% sensitivity and two times cytology triage: 5.2	All results 5 year screening starting age 30 and ending age 60 and deaths from cervical cancer per 100,000 life years Cytology: 2.6 HPV 90% sensitivity and two times cytology triage: 2.5 HPV 95% sensitivity and two times cytology triage: 2.4	NR	NR
Kulasingham 2009	NR	NR	NR	NR	NR	All compared to no intervention and per 100,000 women HPV with cytology triage (5 years screening): 1,409 HPV with cytology triage (3 years screening): 1,978 HPV only (5 years screening): 1,559 HPV only (3 years screening): 1,784 Cytology with HPV triage (1 year screening): 1,781

Paper	Incidence of CIN2+	Incidence of CIN3+	Lifetime cervical cancer risk	Mortality	Treatment of lesions prevented	Cancer prevented
						Cotesting (5 years screening): 1,697 Cotesting (3 years screening): 1,810 Cotesting (2 years screening): 1,916
Petry 2017	**Five year screening (10 years)** Cytology alone: 0.74% HPV with cytology triage (5 year): 0.37% **Three year screening (six years)** Cytology alone: 0.51% HPV with cytology triage: 0.33%	**Five year screening (10 years)** Cytology alone: 1.41% HPV with cytology triage (5 year): 0.76% **Three year screening (six years)** Cytology alone: 1.12% HPV with cytology triage: 0.74%	NR	NR	NR	**Five year screening** HPV with cytology triage: 17,413 over ten years in population of 16 million 30-65 women compared to cytology. Reduction of 50.0% compared to cytology **Three year screening** HPV with cytology triage: 9,584 over ten years in population of 16 million 30-65 women compared to cytology. Reduction of 38.3%
Lew 2017	Change in overall cases compared to current cytology screening practice provided as range within all testing scenarios considered. Based upon total population of Australian women in 2015 **Unvaccinated** Cytology: (-2,851, -1,632) HPV with cytology triage: (-2,908, -862) HPV with partial genotyping: (-2,332, -	Change in overall cases compared to current cytology screening practice provided as range within all testing scenarios considered. Based upon total population of Australian women in 2015 **Unvaccinated** Cytology: (-677, -279) HPV with cytology triage: (492, 997) HPV with partial genotyping: (606, 935)	Range in % change in ASR for cancer compared to current cytology screening programme across all screening methodologies) Unvaccinated Cytology: (4%, 19%) HPV with cytology triage: (-20%,-5%) HPV with partial genotyping: (-21%, -12%) Vaccinated	Range in % change in ASR for cancer mortality compared to current cytology screening programme across all screening methodologies) Unvaccinated Cytology: (4%, 19%) HPV with cytology triage: (-20%,-5%) HPV with partial genotyping: (-21%, -12%) Vaccinated	NR	NR

Paper	Incidence of CIN2+	Incidence of CIN3+	Lifetime cervical cancer risk	Mortality	Treatment of lesions prevented	Cancer prevented
	564) **Vaccinated** Cytology: (-1,833, -1,049) HPV with cytology triage: (-1,941, -603) HPV with partial genotyping: (-1,892, -597)	**Vaccinated** Cytology: (-513, -251) HPV with cytology triage: (173, 532) HPV with partial genotyping: (175, 508)	Cytology: (4%, 17%) HPV with cytology triage: (-18%, -4%) HPV with partial genotyping: (-16%, -8%)	Cytology: (5%, 23%) HPV with cytology triage: (-19%, -5%) HPV with partial genotyping: (-19%, -11%)		
Kitchener 2014	All CIN2/3 for all women in England. Note only provided for 6 year screening strategy **No vaccination** Current practice: 41,309 Strategy 1: 39,464 Strategy 2: 39,850 Strategy 3: 40,585 **Vaccination** Current practice: 24,365 Strategy 1: 22,909 Strategy 2: 22,951 Strategy 3: 23,036	NR	For all women in England. Note only provided for 6 year screening strategy **No vaccination** Current practice: 0.74% Strategy 1: 0.76% Strategy 2: 0.73% Strategy 3: 0.69% **Vaccination** Current practice: 0.32% Strategy 1: 0.33% Strategy 2: 0.33% Strategy 3: 0.32%	Cervical cancer deaths per annum in England. Note only provided for 6 year screening strategy **No vaccination** Current practice: 761 Strategy 1: 741 Strategy 2: 706 Strategy 3: 663 **Vaccination** Current practice: 338 Strategy 1: 333 Strategy 2: 330 Strategy 3: 326	NR	Cervical cancer cases per annum in England. Note only provided for 6 year screening strategy **No vaccination** Current practice: 2,521 Strategy 1: 2,590 Strategy 2: 2,495 Strategy 3: 2,366 **Vaccination** Current practice: 1,064 Strategy 1: 1,104 Strategy 2: 1,096 Strategy 3: 1,083
Lew 2016	All CIN2/3 for 2.3m women in NZ. **No vaccination** Cytology: 4,308 HPV with cytology triage: 3,704 HPV genotyping: 3,995 **Vaccination**	NR	Age standardised rate (per 100,000 women) **No vaccination** Cytology: 9.1 HPV with cytology triage: 9.1 HPV genotyping: 7.7 **Vaccination**	Age standardised rate (per 100,000 women) of cervical cancer death **No vaccination** Cytology: 1.5 HPV with cytology triage: 1.5 HPV genotyping: 1.3 **Vaccination**	NR	Absolute number of cervical cancer cases per 100,000 women **No vaccination** Cytology: 160 HPV with cytology triage: 161 HPV genotyping: 140 **Vaccination**

Paper	Incidence of CIN2+	Incidence of CIN3+	Lifetime cervical cancer risk	Mortality	Treatment of lesions prevented	Cancer prevented
	Cytology: 2,645 HPV with cytology triage: 2,401 HPV genotyping: 2,527		Cytology: 5.2 HPV with cytology triage: 5.2 HPV genotyping: 4.6	Cytology: 0.8 HPV with cytology triage: 0.9 HPV genotyping: 0.7		Cytology: 92 HPV with cytology triage: 93 HPV genotyping: 83

Paper	Cytology tests	HPV tests	Colposcopies	Lifetime number of screens	Histology evaluations	Treatment for lesions	Treatment of cancer
Accetta 2010	NR	NR	NR	NR	NR	NR	NR
Berkhof 2010	NR	NR	NR	NR	NR	NR	NR
Burger 2017	NR	NR	Number of colposcopy referrals with HPV with cytology triage per 1,000 women (567 with 5 year cytology with HPV triage) all based on 2 recalls before colposcopy. Difference with 1 or 3 recalls changed values within +-500 Three year screen (wait time for rescreen of HPV+cyt- women) 6 month: 2,047 12 month: 1,547 18 month: 1,263 Five year screen 6 month: 1,662 12 month: 1,286 18 month: 1,067 Ten year screen 6 month: 1,205 12 month: 961 18 month: 814	Number of tests with HPV with cytology triage per 1,000 women (17,958 with 5 year cytology with HPV triage) Three year screen (wait time for rescreen of HPV+cyt- women all based on 2 recalls before colposcopy. Difference with 1 or 3 recalls changed values within +-1,000) 6 month: 27,258 12 month: 24,274 18 month: 22,545 Five year screen 6 month: 19,422 12 month: 17,195 18 month: 15,900 Ten year screen 6 month: 12,264 12 month: 10,878 18 month: 10,041	NR	NR	**Number of precancer treatments HPV with cytology triage per 1,000 women (197 with 5 year cytology with HPV triage)** Three year screen (wait time for rescreen of HPV+cyt- women) 6 month: 405 12 month: 352 18 month: 320 Five year screen 6 month: 361 12 month: 320 18 month: 293 Ten year screen 6 month: 293 12 month: 266 18 month: 246
de Kok 2012	NR	NR	NR	All results 5 year screening starting age 30 and ending age 60 and mean	All results 5 year screening starting age 30 and ending age 60 and % of primary	NR	NR

Paper	Cytology tests	HPV tests	Colposcopies	Lifetime number of screens	Histology evaluations	Treatment for lesions	Treatment of cancer
				number of primary screens per woman Cytology: 2.13 HPV 90% sensitivity and two times cytology triage: 2.13 HPV 95% sensitivity and two times cytology triage: 2.13	screens ending in cytology Cytology: 3.3% HPV 90% sensitivity and two times cytology triage: 4.8% HPV 95% sensitivity and two times cytology triage: 5.1%		
Kulasingham 2009	NR	NR	NR	NR	NR	NR	NR
Petry 2017	NR	NR	NR	NR	NR	NR	NR
Lew 2017	"Range in % change in annual tests compared to current cytology screening programme across all screening methodologies. (Current practice has 2.4 million tests as context) Unvaccinated Cytology: (-41%, -23%) HPV with cytology triage: (-85%,-82%) HPV with partial genotyping: (-87%, -85%) Vaccinated Cytology: (-42%, -24%) HPV with cytology triage: (-88%, -86%) HPV with partial genotyping: (-91%, -	Range in % change in annual tests compared to current cytology screening programme across all screening methodologies. (Current practice has 54,700 (unvaccinated), 31,100 (vaccinated) as context) Unvaccinated Cytology: (-21%, 81%) HPV with cytology triage: (2,061%,2,250%) HPV with partial genotyping: (2,066%, 2,255%) Vaccinated Cytology: (-24%, 149%) HPV with cytology triage: (3,591%, 3,916%) HPV with partial genotyping: (3,583%, 3,909%)	Range in % change in annual colposcopies compared to current cytology screening programme across all screening methodologies. (Current practice has 81,300 (unvaccinated), 57,900 (vaccinated) as context) Unvaccinated Cytology: (-22%, -12%) HPV with cytology triage: (-7%,20%) HPV with partial genotyping: (12%, 37%) Vaccinated Cytology: (-23%, -13%) HPV with cytology triage: (-16%, 13%) HPV with partial genotyping: (-16%, 13%)	Range in average lifetime screens compared to current cytology screening programme across all screening methodologies. (Current practice 15 as context) Unvaccinated Cytology: (9, 11) HPV with cytology triage: (7, 8) HPV with partial genotyping: (7, 8) Vaccinated Cytology: (9, 11) HPV with cytology triage: (7, 8) HPV with partial genotyping: (7, 8)	Range in % change in annual histology evaluation compared to current cytology screening programme across all screening methodologies. (Current practice has 40,000 (unvaccinated), 28,200 (vaccinated) as context) Unvaccinated Cytology: (-22%, -12%) HPV with cytology triage: (-4%,28%) HPV with partial genotyping: (17%, 46%) Vaccinated Cytology: (-23%, -13%) HPV with cytology triage: (-11%, 22%) HPV with partial	Range in % change in annual treatments (presumed of lesions) compared to current cytology screening programme across all screening methodologies. (Current practice has 21,485 (unvaccinated), 13,203 (vaccinated) as context) Unvaccinated Cytology: (-23%, -13%) HPV with cytology triage: (-21%,-9%) HPV with partial genotyping: (-17%, -8%) Vaccinated Cytology: (-26%, -16%) HPV with cytology triage: (-29%, -15%) HPV with partial genotyping: (-29%, -	NR

Paper	Cytology tests	HPV tests	Colposcopies	Lifetime number of screens	Histology evaluations	Treatment for lesions	Treatment of cancer
	89%) "				genotyping: (-11%, 22%)	15%)	
Kitchener 2014	Total tests in England pa. Note only provided for 6 year screening strategy **No vaccination** Current practice: 3,703,772 Strategy 1: 636,790 Strategy 2: 636,161 Strategy 3: 564,796 **Vaccination** Current practice: 3,663,477 Strategy 1: 493,864 Strategy 2: 493,749 Strategy 3: 486,707	Total tests in England pa. Note only provided for 6 year screening strategy **No vaccination** Current practice: 245,330 Strategy 1: 2,255,505 Strategy 2: 2,251,914 Strategy 3: 2,244,887 **Vaccination** Current practice: 210,687 Strategy 1: 2,272,954 Strategy 2: 2,272,615 Strategy 3: 2,271,942	Total colposcopies in England pa. Note only provided for 6 year screening strategy **No vaccination** Current practice: 128,254 Strategy 1: 110,393 Strategy 2: 123,140 Strategy 3: 154,754 **Vaccination** Current practice: 89,848 Strategy 1: 72,943 Strategy 2: 74,112 Strategy 3: 77,048	NR	NR	NR	NR
Lew 2016	NR	NR	NR	NR	NR	NR	NR

Paper	Total discounted cost of strategies	Total QALYs of strategies	ICERs
Accetta 2010	**Five year screen** Cytology: €120 HPV test only: €176 Cytology followed by HPV triage: €113 HPV followed by cytology triage: €136 **Three year screen** Cytology: €160 HPV test only: €228 Cytology followed by HPV triage: €149 HPV followed by cytology triage: €175	**Five year screen** Cytology: 29.42631 HPV test only: 29.42958 Cytology followed by HPV triage: 29.42594 HPV followed by cytology triage: 29.42991 **Three year screen** Cytology: 29.42822 HPV test only: 29.43042 Cytology followed by HPV triage: 29.42803 HPV followed by cytology triage: 29.43048	Not reported in study. Calculated with five year HPV followed by cytology test triage as reference case **Five year screen** Cytology: extendedly dominated HPV test only: dominated Cytology followed by HPV triage: extendedly dominated **Three year screen** Cytology: dominated HPV test only: €180,392 Cytology followed by HPV triage: dominated HPV followed by cytology triage: €68,421
Berkhof 2010	**Total discounted costs per woman compared to five year cytology only (includes screening, diagnoses and treatment and indirect costs)** **Five year screen** HPV followed by cytology triage: €79.7 Cytology followed by HPV triage: €0.1 Combined: €181.9 **Six year screen** HPV followed by cytology triage: €30.0 Cytology followed by HPV triage: -€34.2 Combined: €114.8 **7.5 year screen** HPV followed by cytology triage: -€17.7 Cytology followed by HPV triage: -€66.6 Combined: €53.2	Not reported although figure in study suggests that QALYs increase as screening interval shortens and that combination testing always has higher QALY gain than HPV followed by cytology triage	**ICER compared to five year cytology only (includes screening, diagnoses and treatment and indirect costs)** **Five year screen** HPV followed by cytology triage: €9,305 (most cost effective strategy) Cytology followed by HPV triage: €3,955 Combined: €16,303 **Six year screen** HPV followed by cytology triage: €6,138 Cytology followed by HPV triage: QALY loss (no ICER calculated) Combined: €12,444 **7.5 year screen** HPV followed by cytology triage: €878 Cytology followed by HPV triage: QALY loss (no ICER calculated) Combined: €11,088 **Ten year screen** HPV followed by cytology triage: QALY loss (no ICER calculated) Cytology followed by HPV triage: QALY loss (no ICER

Paper	Total discounted cost of strategies	Total QALYs of strategies	ICERs
	Ten year screen HPV followed by cytology triage: -€61.8 Cytology followed by HPV triage: -€90.6 Combined: -€7.5		calculated) Combined: €22,452
Burger 2017	NR	NR	NR
de Kok 2012	NR	NR	NR
Kulasingham 2009	NR	NR (ICERs are for life years	ICERs not reported for all strategies and only efficiency frontier shown. For the whole of Canada, the ICER (cost/LY) for HPV with cytology triage with 5 year screening was $6,720. For 3 year screening the ICER was $24,257
Petry 2017	**Five year screening** Cytology: €176.9m pa (population of 16m) HPV with cytology triage: €117.0m pa (34% reduction) **Three year screening** Cytology: €205.6m pa (population of 16m) HPV with cytology triage: €203.9m pa (1% reduction)	NR	NR
Lew 2017	Unvaccinated Current practice: $384 per person Cytology: $242-$294 per person HPV with cytology triage: $260-$310 per person HPV with partial genotyping: $274-$323 per person Vaccinated Current practice: $325 per person Cytology: $193-$243 per person HPV with cytology triage: $202-$243 per person HPV with partial genotyping: $207-$248 per person	Both sets included disutilities with having cancer. QALY gains over current practice across strategies are small with Set A (gains in region of 0.005) and for HPV strategies only negative with Set B (losses in region of 0.002).	NR

Paper	Total discounted cost of strategies	Total QALYs of strategies	ICERs
Kitchener 2014	Total lifetime costs per woman **No vaccination** Current practice: £159 <u>Strategy 1</u> Six year screening (base case): £132 Six year (25-49) & ten year (50+) screening: £128 12 month rather than 24 month recall: £147 Five year screening: £143 <u>Strategy 2</u> Six year screening (base case): £135 Six year (25-49) & ten year (50+) screening: £131 12 month rather than 24 month recall: £152 Five year screening: £146 <u>Strategy 3</u> Six year screening (base case): £144 Six year (25-49) & ten year (50+) screening: £140 12 month rather than 24 month recall: £161 Five year screening: £156 **Vaccination** Current practice: £129 <u>Strategy 1</u> Six year screening (base case): £101 Six year (25-49) & ten year (50+) screening: £97 12 month rather than 24 month	Whilst all strategies generated a QALY gain per woman these changes were only seen in the third decimal place with the difference between the strategy with the lowest QALYs and highest QALYs being 0.0026QALYs (less than 1 quality adjusted life day over a woman's lifetime). These results only apply when utility weightings including a loss for screening were included. With utility weightings with no loss for screening but a significant loss for abnormalities all HPV strategies produced a QALY loss compared to cytology based screening	ICERs not calculated but (with the exception of those listed previous with QALY losses compared to current practice) all strategies and variants were dominant (cost and QALY saving) compared to current practice when a utility decrement for screening was applied.

Paper	Total discounted cost of strategies	Total QALYs of strategies	ICERs
	recall: £112 Five year screening: £112 <u>Strategy 2</u> Six year screening (base case): £102 Six year (25-49) & ten year (50+) screening: £97 12 month rather than 24 month recall: £113 Five year screening: £112 <u>Strategy 3</u> Six year screening (base case): £102 Six year (25-49) & ten year (50+) screening: £98 12 month rather than 24 month recall: £113 Five year screening: £113 Strategy 2: 74,112 Strategy 3: 77,048		
Lew 2016	**No vaccination** Cytology: $31.7m HPV with cytology triage: $28.7m HPV genotyping: $30.4m **Vaccination** Cytology: $25.9m HPV with cytology triage: $22.5m HPV genotyping: $22.7m	In all cases QALY changes were small (less than 0.008). HPV genotyping always had the highest QALY gain for both vaccinated and unvaccinated women if only a small disutility for abnormal screening applied. If utility weights with a high disutility for abnormal screening applied then cytology always produces a QALY gain	In terms of cost/LY saved and cost/QALY HPV genotyping was the most cost effective strategy (saving LY and cost) with HPV testing with cytology triage being less costly but less effective than 3 year cytology screening. Actual ICERs not reported as HPV was either always cost saving compared to cytology

Paper	Summary of cost effectiveness results	Summary of deterministic SA	Summary of PSA	Study recommendation	Limitations
Accetta 2010	Current strategy of primary HPV every three years is dominated by primary HPV with cytology triage every three years. Five year screening would be less expensive but with slightly worse outcomes.	Study explored screening versus vaccination and the sensitivity analysis only explored vaccination efficacy	NR	Three year screening with HPV with cytology triage	Outside of vaccine efficacy, the authors acknowledged the model is based upon Italian costs and more extensive parameter searching may have resulted in different parameter values
Berkhof 2010	Strategies with a screening interval over 7.5 years were not cost effective with a willingness to pay threshold of €20,000/QALY. The optimal strategy was five year screening with HPV followed by cytology triage	The finding that the optimal strategy was five year screening with HPV followed by cytology triage results were insensitive to changes in treatment and test costs, discount rates and HPV test sensitivity and specificity considered by the authors	Not reported but did show results from various calibration settings for CIN2+ detection rates of the model that showed a large variation in the effect of HPV screening on cancer.	Five year screening with HPV with cytology triage	The variation in results based upon calibration settings were stated as a limitation, as was that the model did not account for natural immunity after infection.
Burger 2017	Lengthening the time between screenings did have impact on the cancer incidence rate with more frequent screening reducing the cancer rate. However, the most important factor was starting screening at age 25. Different intervals between rescreening of HPV+/cyt- women or altering the point at which colposcopy occurs for these women made little impact on the cancer incidence rate	Lengthening the time between screenings did have impact on the cancer incidence rate with more frequent screening reducing the cancer rate. However, the most important factor was starting screening at age 25. Different intervals between rescreening of HPV+/cyt- women or altering the point at which colposcopy occurs for these women made little impact on the cancer incidence rate. As such, to minimise the increase in colposcopy that comes with HPV testing more retests for HPV+/cyt- women and/or longer intervals between retests should be considered.	NR	HPV-based screening among unvaccinated women should start at age 25 with an appropriate use of cytology triage to control colposcopy referrals. No recommendation was made on the frequency of testing	No trade off of resource use and benefit was considered. No account of anxiety in longer waiting times between retesting HPV+/cyt- women was taken. The findings on colposcopy were dependent on the initial strategy. HPV genotyping was not considered. There is an absence of data on future screening behaviour and loss to follow up.
de Kok 2012	The cost effectiveness results of strategies were not presented. The summary of the results states in most scenarios primary HPV screening is the preferred	HPV was preferred in all scenarios except if the cost of cytology were low or HPV prevalence was high with a high HPV test cost	NR	Where screening is well controlled, European countries should switch from cytology to HPV screening	Did not consider strategies that varied by age. Personal characteristics were not varied. The model assumed that people who do not go to screening are

Paper	Summary of cost effectiveness results	Summary of deterministic SA	Summary of PSA	Study recommendation	Limitations
	scenario in women over 30				at higher risk and if this is not the case the cost effectiveness results may not hold. No loss of utility from a positive HPV test was considered.
Kulasingham 2009	HPV testing every three years followed by cytology triage may be more effective and less costly than cytology screening alone	Lower discount rates (<2.0%) would favour 5 year screening	PSA takes into account strategies with start age of 18 so difficult to interpret. However, above a WTP threshold of approximately $25,000/LY three year screening would be more likely to be cost effective than five year screening	HPV with cytology triage from age 25 with three year screening	Lack of test performance by age, vaccination was not included
Petry 2017	Screening strategies for HPV results in fewer cancers at a lower cost than cytology alone. Screening of HPV at intervals less than five years does result in more cancers detected but at a higher cost than five year screening	NR	NR	No recommendation for a specific HPV screening strategy	Model does not include costs of treatment outside of initial cancer treatment (e.g. excludes rehabilitation and physio) and does not included costs associated with recurrence. However, this limitation favours cytology and so should not prejudice results. Vaccination was also not included in the model and failure to attend screening was not considered.
Lew 2017	The authors conclude that HPV testing every five years with partial genotyping or cotesting with cytology were the most effective. Sending those with HPV16/18 for colposcopy and other genotypes for reflex cytology was described as "one of the most cost-effective" strategies. Whilst the analysis is unambiguous that all strategies will result in lower cost and HPV strategies are likely to dominate	Range of SA undertaken and scenario analysis undertaken including: Six year HPV screening: Reduces costs for all HPV strategies between 7.5% and 8.5% (unvaccinated) and 9.4% and 10.6% (vaccinated). Increases cancer incidence or cancer mortality by between 3.1% and 4.0% (vaccinated and unvaccinated)	The PSA results suggest that across the HPV strategies considered genotyping and non-genotyping show little difference in costs or benefits with life years gains from the best performing genotype strategy and worse performing non-genotype strategy being different by less than 0.0005LY (equivalent to approximately 4 hours over a lifetime) with a discounted lifetime cost	HPV testing every five years with partial genotyping and direct colposcopy if 16/18	Results are sensitive to screening assumptions such as the return rate. The authors acknowledge there is little clinical evidence on the outcomes with referral straight to colposcopy with HPV 16/18 or reflex cytology.

Paper	Summary of cost effectiveness results	Summary of deterministic SA	Summary of PSA	Study recommendation	Limitations
	non-HPV strategies (at least if only life years and not QALYs are considered) there is no full incremental analysis of strategies, QALY gains are small across strategies and may be negative for some HPV strategies and a wide range of different scenarios were undertaken making it difficult to isolate the actual effect of different aspects of strategies.		difference between the most expensive and least expensive strategies of $50 per person		
Kitchener 2014	HPV testing is a cost effective strategy compared to cytology. Whilst most of the strategies considered were cost and QALY saving, they all resulted in greater numbers of colposcopies and biopsies in unvaccinated women. The QALY gains per woman were small with any strategy although primary HPV genotype testing only appears to be an efficient strategy in vaccinated women.	Results were sensitive to test characteristics of HPV and cytology and level of compliance with 12 or 24 month follow up for those recalled with HPV+/cyt- results	PSA was only conducted around sexual behaviour assumptions. The PSA did not indicate that the assumptions matter to the overall model results	HPV testing every five to six years with no more than 12 months recall for women who are HPV+/cyt-	A number of assumptions had to be made about future population behaviour and future costs of HPV screening for which there is little evidence.
Lew 2016	At a WTP threshold of $50,000/LY, in both unvaccinated and vaccinated women HPV genotyping was the most cost effective strategy. When QALYs were considered (although detailed findings not presented in body of report) findings are reported to vary widely. If disutility for screening and/or a minor disutility for abnormal findings are considered, then HPV genotyping remains the cost	Only undertaken for HPV with genotyping. Total costs were found to be sensitive to the cost of cytology and HPV tests, test characteristics of HPV and aggressiveness of natural history of HPV. Life years were found to be sensitive to the aggressiveness of natural history of HPV and adherence to screening strategy	NR	Primary HPV with genotyping	Parameters related to future screening practice were assumptions, notably the cost of the HPV test with HPV screening not being cost saving if the cost of the HPV test increased from the base case of $35 to $40. It is not commented on in the paper that the current cost of the test is £43 and they have assumed it would be $35 if HPV screening was the strategy adopted. How this assumption is derived is not described.

Paper	Summary of cost effectiveness results	Summary of deterministic SA	Summary of PSA	Study recommendation	Limitations
	effective choice. If there is no disutility from screening itself but a major disutility from abnormal findings then all HPV strategies are less effective than cytology screening				