Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Health technology assessment of human papillomavirus testing as the primary screening method for prevention of cervical cancer

24 May 2017

Safer Better Care

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The Health Information and Quality Authority (HIQA) is an independent authority established to drive high quality and safe care for people using our health and social care services in Ireland. HIQA's role is to develop standards, inspect and review health and social care services and support informed decisions on how services are delivered.

HIQA aims to safeguard people and improve the safety and quality of health and social care services across its full range of functions.

HIQA's mandate to date extends across a specified range of public, private and voluntary sector services. Reporting to the Minister for Health and engaging with the Minister for Children and Youth Affairs, HIQA has statutory responsibility for:

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- **Regulation** – Registering and inspecting designated centres.
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Foreword

Cervical cancer is the eighth most commonly diagnosed cancer (excluding non-melanoma skin cancer) in women in Ireland. There are, on average, 88 deaths from cervical cancer each year. Data from the National Cancer Registry Ireland (NCRI) from 2012 to 2014 indicate that, on average, 2,873 women were diagnosed with cervical carcinoma *in situ* and 277 women were diagnosed with invasive cervical cancer. NCRI data from this period indicate that 1 in 13 women will be diagnosed with pre-invasive cervical cancer (cervical carcinoma *in situ*) in their lifetime (up to age 74), 1 in 112 will be diagnosed with invasive cervical cancer and 1 in 333 will die from cervical cancer.

Cervical cancer is associated with persistent infection with human papillomavirus (HPV). Therefore, there are two complementary approaches to preventing cervical cancer: primary prevention through vaccination to prevention HPV infection, and secondary prevention through screening to detect and treat precancerous abnormalities and early stage invasive cervical cancer. Over the last 10 years, increasing evidence has become available that, when used as a primary screening test, HPV testing can improve the accuracy of cervical screening compared with cytology-based testing for the prevention of cervical cancer.

CervicalCheck– Ireland's National Cervical Screening Programme, which forms part of the Health and Wellbeing Division of the Health Service Executive requested that the Health Information and Quality Authority (HIQA) undertake a health technology assessment (HTA) of human papillomavirus testing as the primary screening method for prevention of cervical cancer. Noting the potential of the HTA to impact on a population of over one million women, CervicalCheck highlighted emerging evidence of an opportunity to increase the clinical effectiveness and cost-effectiveness of its organised screening programme. This HTA will provide the evidence to inform decisions about potential changes to CervicalCheck

Work on the assessment was undertaken by an Evaluation Team from the HTA Directorate in HIQA. A multidisciplinary Expert Advisory Group was convened to advise HIQA during the course of the assessment. HIQA would like to thank its Evaluation Team, the members of the Expert Advisory Group and all who contributed to the preparation of this report.

Dr Máirín Ryan

Deputy Chief Executive and Director of Health Technology Assessment

Advice to the Minister for Health and the National Screening Service

The Health Information and Quality Authority (HIQA) carried out a health technology assessment (HTA) of human papillomavirus (HPV) testing as the primary screening method for prevention of cervical cancer in Ireland, following a request from CervicalCheck - Ireland's National Cervical Screening Programme, which forms part of the Health and Wellbeing Division of the Health Service Executive (HSE).

As economic models incorporate a number of assumptions and depend on the quality of data available, the results are subject to a degree of uncertainty. Given the conservative estimates and assumptions that were used in this analysis and arising from the findings described below, HIQA's advice to the National Screening Service, the Health Service Executive (HSE) and the Minister for Health is as follows:

- A change to primary HPV screening followed by liquid-based cytology (LBC) triage at five-yearly intervals for all eligible women aged 25 to 60 years would improve the efficiency of the CervicalCheck programme (that is, women would require fewer lifetime screens to achieve similar benefits). This strategy provides comparable effectiveness to the current screening programme, and would lead to a net cost saving of up to €35 million over the first eight years of its implementation (2018 to 2025). For women who have not been vaccinated against HPV, this strategy is cost-effective at a willingness-to-pay threshold of €20,000 to €45,000 per QALY.
- For women who have only had access to organised screening from age 50, consideration should be given to extending screening to age 65 years. While not cost-effective, this would lead to improved clinical outcomes for this group. If implemented, it would need to be combined with a targeted campaign to increase the uptake of screening in those aged over 60 years.
- Consideration should also be given to providing three-yearly primary HPV screening to women aged under 30 years who have not been vaccinated against HPV. While not cost-effective, this would lead to improved clinical outcomes for this group. Ongoing evaluation will be required to inform the future screening and surveillance of these women.
- Given their lower risk of developing cervical cancer, screening women vaccinated against HPV at five-yearly intervals may not be cost-effective. However, given the uncertainty about this cohort, screening at five-yearly intervals should continue

while giving consideration to increasing the screening interval as evidence emerges to support the long-term effectiveness of screening women vaccinated against HPV.

This HTA assessed the impact of changing from the current policy of primary liquid-based cytology (LBC) screening to a policy of using HPV testing as the primary screening method. Strategies for triage were assessed along with alternative screening intervals and age bands.

All strategies were assessed in a cohort of women vaccinated against HPV 16 and HPV 18 and in an unvaccinated cohort. The HTA examined the clinical effectiveness, safety and cost-effectiveness of different screening strategies, as well as the organisational, societal and ethical implications of any changes to the screening programme.

The key findings of this HTA, which informed and preceded HIQA's advice, were:

- Cervical cancer is the eighth most commonly diagnosed cancer (excluding non-melanoma skin cancer) in women in Ireland. On average, 2,873 cases of cervical carcinoma *in situ* and 277 cases of invasive cervical cancer are diagnosed each year. There are on average 88 deaths from cervical cancer each year - the median age of death is 56 years. The incidence of cervical cancer in Ireland is increasing and, based on demography alone, is predicted to increase by 18% by 2040. The cumulative lifetime risk (to age 74) of a diagnosis of cervical carcinoma *in situ* is 1 in 13, and 1 in 112 for a diagnosis of invasive cervical cancer. The cumulative lifetime risk of death due to cervical cancer is 1 in 333.

- A cervical screening programme aims to reduce the incidence of, and the morbidity and mortality from cervical cancer through detection and treatment of precancerous abnormalities and early stage invasive cervical cancer.

- CervicalCheck – Ireland's National Cervical Screening Programme began in September 2008. Women between the ages of 25 and 44 years are offered screening at three-yearly intervals. Women between the ages of 45 and 60 years are offered screening at five-yearly intervals. Liquid-based cytology (LBC) to detect cellular (cytological) abnormalities is used as the primary screening test. HPV triage of low-grade cytological abnormalities was introduced in May 2015. Five-year coverage to the end of December 2016 was 79.6%.

- CervicalCheck currently processes approximately 280,000 smear tests each year. Between September 2008 and August 2015, it reported 1,082 biopsy-confirmed

invasive cervical cancers, 41,417 high-grade abnormalities (CIN 2 and CIN 3) and 29,505 low-grade abnormalities (CIN 1).

- Certain oncogenic strains of HPV (denoted high-risk HPV or hrHPV) are associated with an increased risk of developing precancerous abnormalities and invasive cervical cancer. Preliminary Irish data indicate a crude hrHPV prevalence of 14.6%. Prevalence of HPV is highest in women under 30 years of age and decreases with advancing age. The data indicate that 32% of women who test positive for HPV are positive for HPV 16 and 18, the particular genotypes of HPV that are associated with 70% of cervical cancers.

- Since September 2010, Ireland has had a nationally funded, school-based, girls-only HPV vaccination programme. The first cohort of vaccinated girls will be eligible for CervicalCheck screening in 2018-2019.

- No cervical screening programme can prevent all cervical cancer cases. Harms related to taking the screening test sample itself are minimal and short term. Cervical screening tests are not 100% accurate. Most adverse effects of a cervical screening programme relate to false negative test results, false positive test results and overdiagnosis. False negative test results lead to potentially missed or delayed opportunities to intervene in women with treatable precancerous abnormalities or early invasive cervical cancer. False positive test results lead to unnecessary colposcopic examination. Overdiagnosis refers to identification of precancerous abnormalities that would not otherwise become clinically significant and may lead to increased surveillance, potentially increasing stress and anxiety, and or unnecessary treatment. Cervical cancer may develop in the time between a negative screening test and a woman's next screening (interval cancer). This is another potential harm of any cervical screening programme.

- Primary HPV screening may result in worry and anxiety for some women. Potential issues relate to the fear of testing positive for HPV because of the possible implications for their health, their relationships and the inability to treat HPV infection. The informed consent process would have to be carefully managed to ensure that women are given sufficient information about the new testing process and its potential risks and benefits in a way they could understand. Women who test positive for HPV should be reassured about the meaning of HPV infection and their concerns about transmission allayed as far as possible.

- The diagnostic accuracy of primary HPV and cytology (LBC and conventional cytology) screening for the prevention of cervical cancer was evaluated. Meta-

analysis of 23 studies undertaken in industrialised countries using the Hybrid Capture 2 (HC2) HPV assay indicates that the pooled sensitivity of HC2 in detecting CIN 2+ and CIN 3+ was 95.2% (CI 92.5-97.1%) and 98.2% (CI 96.7%-99.1%), respectively. These were significantly higher than the diagnostic accuracy of cytology, where the pooled sensitivity was 75.0% (CI 64.1%-83.3%) for CIN 2+ and 78.0% (CI 63.5%-88.4%) for CIN 3+. This means that compared with primary cytology-based screening, primary HPV screening would result in fewer women receiving a false negative result compared with primary cytology-based screening.

- However, when compared with primary cytology-based screening, primary HPV screening would result in more women receiving a false positive result. The pooled specificity of HC2 was significantly lower in detecting CIN 2+ and CIN 3+ at 88.2% (CI 82.9%-92.0) and 87.5% (CI 78.7%-93.2%), respectively compared with cytology with a pooled specificity of 95.0% (CI 92.2%-96.8%) for CIN 2+ and 95.1% (CI 91.6%-97.3%) for CIN 3+.

- The diagnostic accuracy of triage strategies following primary HPV screening was evaluated based on the synthesis of evidence from 15 studies across eight randomised controlled trials (RCTs). The RCTs were typically large-scale trials conducted within population-based cervical screening programmes; seven of the eight RCTs were conducted in Europe. Five triage strategies were considered: 1) cytology; 2) partial genotyping for HPV 16 and HPV 18; 3) co-testing with cytology and partial genotyping for HPV 16 and HPV 18; 4) partial genotyping for HPV 16 and HPV 18 followed by cytology as a second triage test; and 5) testing for the $p16^{INK4a}$ protein alone or in combination with Ki-67 protein (which have been identified as surrogate markers of transforming infections). Some of these strategies appear to be advantageous and long term outcomes on the development of interval cancers suggest they can be safely used within screening intervals, typically used in Ireland.

- For a cohort of women not vaccinated against HPV 16 and HPV 18, primary HPV screening followed by liquid-based cytology (LBC) triage (that is LBC testing if the HPV test is positive) at five-yearly intervals from age 25 to 60 is cost-effective with an incremental cost-effectiveness ratio (ICER) of €29,788 per quality-adjusted life year (QALY). This strategy has similar clinical effectiveness and is cost saving relative to current practice. While a number of other strategies are more effective, their incremental gain in effectiveness would not be considered cost-effective for the additional increase in cost.

- For a cohort vaccinated against HPV 16 and HPV 18, none of the strategies modelled in this HTA (which considered a maximum screening interval of five years) are considered cost-effective when compared with no screening at a willingness-to pay threshold of €45,000 per QALY. Of those considered, the strategy with the lowest ICER (€58,745 per QALY) is primary HPV screening followed by an LBC triage test at five-yearly intervals from age 25 to 60.

- With a maximum screening interval of five years, none of the strategies modelled in the HPV-vaccinated cohort are cost-effective. However, it must be noted that there is uncertainty around how vaccinated women will progress through the precancerous states from HPV infection to cervical cancer. The risk of developing cervical cancer is assumed to be 70% lower in women vaccinated against HPV 16 and 18. This estimate is very influential on the predicted cases of cervical cancer within the model and thus whether the modelled strategies are cost-effective. A policy of continued screening at five-yearly intervals may be reasonable until further long-term data emerge on the development of cervical cancer in these women.

- As more effective HPV vaccines become available, the risk of cervical cancer may reduce even further. Given their lower risk of developing cervical cancer, less intensive screening strategies, which have not been modelled in this evaluation (which simulated screening intervals up to a maximum of five years), may be more appropriate for HPV-vaccinated women.

- The budget impact analysis shows that when compared with the current cervical screening programme, changing to primary HPV screening followed by LBC triage testing at five-yearly intervals from age 25 to 60 would result in a net saving of €3 million for the cohort of women vaccinated against HPV 16 and 18, up to €32 million for the unvaccinated cohort, and up to €35 million for the whole CervicalCheck population over an eight-year period from 2018 to 2025.

- Two subgroup analyses were conducted at the request of the Expert Advisory Group. The first considers extending access to screening from age 60 to 65 years for women who did not have access to organised cervical screening from the age of 25 years, but who were first offered screening from age 50 (that is, women who were 50 years of age when CervicalCheck began in 2008). While extending the screening age is more effective, it is not cost-effective at a willingness-to-pay threshold of €20,000 to €45,000 per QALY. Given their historic underscreening, it may be considered appropriate to extend screening to age 65 years for these women for ethical reasons. However, to ensure the benefits of this additional screening round are maximised, a targeted campaign to encourage uptake in

those over 60 would be necessary given the lower uptake of screening in older women.

- The second subgroup analysis considered alternative screening strategies in unvaccinated women under the age of 30 years in the context of primary HPV screening and LBC triage at five-yearly intervals being provided from age 30. Women under 30 years have a high prevalence of both HPV infection and cervical abnormalities, and there is concern that five-yearly screening could lead to an increase in interval cancers within this subgroup. While more effective, none of the strategies that considered an additional screening round (that is, screening at three-year intervals in women aged less than 30 years) were found to be cost-effective. If three-yearly screening is provided on clinical grounds, ongoing evaluation and monitoring of its effectiveness will be required, taking into consideration the proportion of the population vaccinated against HPV and the prevalence of HPV infection. Furthermore, both the optimal screening interval and the surveillance pathways for women who screen HPV-positive, but on triage have no identified cytological abnormalities (LBC-negative) is unclear and will require ongoing evaluation.

- Adopting primary HPV screening and extending screening to five-yearly intervals for all eligible women would lead to women having fewer lifetime screens to achieve similar benefits. Compared with current practice, it is estimated this strategy will lead to an overall net reduction of 15% in the total number of cervical screening tests and 16% in colposcopy referrals between 2018 and 2025. Due to phased implementation, no reduction in routine screening activity would occur until at least year four. Screening activity would increase in the initial years due to the surveillance of women identified as HPV-positive, but LBC-negative.

- A recommendation to switch from primary cytology screening to primary HPV screening is in keeping with developments in other high-income countries. Australia, Italy, Netherlands, New Zealand, Sweden and the UK have all recommended the implementation of primary HPV screening. Extending the screening interval to five-yearly is also consistent with recent recommendations in Australia and New Zealand.

- The impact of extending the screening interval from three to five years on programme coverage is not known. Ongoing audit of coverage and tracking of non-responders will allow changes in adherence to be identified in a timely fashion. Switching to primary HPV screening could allow for self-sampling, and may provide an opportunity to improve screening coverage through an initial engagement with women who have never attended CervicalCheck or who are

underscreened because they do not attend at the recommended screening intervals.

- Adoption of primary HPV screening would represent an incremental change with minimal disruption for CervicalCheck, as the programme is relatively new and has already implemented many of the necessary requirements for primary HPV screening. There would be no change to the way the cervical screening sample is collected. Test processing has already been centralised in a small number of sites by CervicalCheck which will allow for efficiency gains in high throughput HPV testing platforms while maintaining sufficient cytology throughput to maintain staff expertise and for quality assurance purposes.

- CervicalCheck uses a comprehensive linked screening registry and a call-recall based invitation system. It is linked to the national HPV vaccination programme, with access to the HPV vaccination records of the women eligible for CervicalCheck. These mechanisms would allow CervicalCheck to develop a formal, ongoing evaluation process of HPV risk-based screening and would allow future screening to be tailored to the individual's risk and screening history, thereby providing a mechanism to evaluate the effectiveness of the national HPV vaccination programme.

- The proposed changes to the cervical screening programme outlined above, that is adoption of primary HPV screening followed by LBC triage at five-yearly intervals for all eligible women aged 25 to 60 years, will increase efficiency (that is achieve comparable benefits with fewer screenings in a woman's lifetime) and lower costs compared with the current cervical screening programme. This would free resources for use elsewhere in the healthcare system, allowing for further increases in overall population benefits.

- Cervical screening programmes will need to continue to evolve. Increased protection through a nonavalent HPV vaccine (that protects against five additional strains of HPV) will further reduce the risk of cervical cancer in the population. Increasing evidence on the long-term benefits of HPV vaccination will potentially allow for longer intervals between screening rounds. Ongoing advances in HPV testing techniques including in the range of biomarkers that discriminate between transient acute infection and transforming infection, may also lead to further refinement in triage strategies.

Executive Summary HPV HTA

Background and terms of reference

The Health Information and Quality Authority (HIQA) agreed to undertake a health technology assessment (HTA) in relation to proposed changes to the national cervical screening programme. The formal request for a HTA was made by CervicalCheck - Ireland's National Cervical Screening Programme, which forms part of the Health and Wellbeing Division of the Health Service Executive (HSE). Noting the potential of the HTA to impact on a population of over one million women, CervicalCheck highlighted emerging evidence of an opportunity to increase the clinical- and cost-effectiveness of its organised screening programme. Irish data from 2012 to 2014 indicate that the cumulative lifetime risk of a diagnosis (up to age 74) of pre-invasive cervical cancer (cervical carcinoma *in situ*) was 1 in 13 and 1 in 112 for a diagnosis of invasive cervical cancer. The cumulative lifetime risk of death due to cervical cancer was 1 in 333.

Knowledge of the natural history of cervical cancer has increased since the role of 'oncogenic types' (so called high-risk human papillomavirus [HPV] or hrHPV genotypes) as a causative factor in the development of cervical cancer was confirmed in the 1990s. Cervical cancer is associated with persistent infection with HPV. There are two complementary approaches for the prevention of cervical cancer:

1. primary prevention through vaccination to prevent HPV infection,
2. and secondary prevention through screening to detect and treat precancerous abnormalities.

Since it was established in 2008, CervicalCheck has used primary liquid-based cytology screening for the detection of precancerous cervical abnormalities and early stage cervical cancer. Over the last 10 years, evidence has emerged that using HPV testing as the primary screening method has a higher sensitivity (that is more people with the disease will have a positive test result) for the detection of precancerous abnormalities and early stage invasive cervical cancer than liquid-based cytology. Evidence has also emerged of the potential to increase the screening interval with a HPV-based testing programme. Technological advances in the methods of detecting HPV now provide additional information regarding the clinical relevance of a HPV infection.

A final consideration is the issue of HPV vaccination which reduces the risk of cervical cancer and decreases the efficiency of cytology as a screening tool in a HPV-

vaccinated cohort. The first cohort of schoolgirls vaccinated against HPV 16 and HPV 18 in Ireland through the national vaccination programme will be eligible for CervicalCheck in 2018-2019. As the number of women vaccinated against HPV 16 and HPV 18 increases, vaccinated women will represent a growing proportion of those eligible for screening through CervicalCheck.

The Terms of Reference agreed between HIQA and CervicalCheck - Ireland's National Cervical Screening Programme for this HTA were to:

- describe the epidemiology of cervical cancer and HPV in Ireland
- examine the current evidence of efficacy and safety for HPV testing as a primary screening test for the prevention of cervical cancer
- review the international cost-effectiveness literature of HPV testing as a primary screening test for the prevention of cervical cancer
- estimate the clinical implications and cost-effectiveness of HPV testing as a primary screening test for the prevention of cervical cancer, including potential changes to the sequence of testing, the screening interval and the exit age compared with the current programme of primary screening with liquid-based cytology (LBC)
- estimate the resource implications and budget impact of HPV testing as a primary screening test for the prevention of cervical cancer
- consider any wider ethical or societal implications that HPV testing as a primary screening test for the prevention of cervical cancer may have for women, the general public or the healthcare system
- advise on the optimal screening strategy for the prevention of cervical cancer, based on this assessment.

Methodology

This research was carried out in accordance with HIQA's guidelines for the conduct of health technology assessments. In summary, the following took place:

- The Terms of Reference of the HTA were agreed between HIQA and the National Screening Service.
- An Expert Advisory Group was convened, with representation from health policy decision-makers, clinicians, patient representation, professional bodies and national and international experts in cervical screening, health services research and economic evaluation. An Evaluation Team was appointed comprising HIQA staff. Professor Deirdre Madden, Faculty of Law, University College Cork provided the ethical commentary.

- Approaches to the prevention of cervical cancer were identified and described.
- The burden of precancerous cervical abnormalities and cervical cancer in Ireland was assessed along with the burden of HPV infection.
- A systematic review and meta-analysis was carried out to summarise the available evidence on the efficacy of using primary HPV screening as an alternative to cytology screening for prevention of cervical cancer. A second systematic review summarised the available evidence on the efficacy of alternative triage test strategies for women with a positive HPV screening test.
- A systematic review was undertaken to summarise the available cost-effectiveness evidence for primary HPV screening for cervical cancer.
- An original economic evaluation was performed to estimate the cost-effectiveness and budget impact of 32 different screening strategies compared with current practice.
- A budget impact analysis reporting the incremental costs associated with changes to the cervical screening programme over an eight-year time horizon was performed from the perspective of the public health system.
- An analysis of the organisational, social and ethical implications that changing to primary HPV screening for the prevention of cervical cancer may have was undertaken with a view to identifying broader considerations that may influence decision-making.
- Draft versions of the report were reviewed and commented on by the Expert Advisory Group (which met on four occasions), before a final draft was submitted to the Board of HIQA for approval.
- The completed assessment was submitted to the National Screening Service, the HSE and the Minister for Health as advice and published on the HIQA website.

Technology description

Human papillomavirus (HPV) is a double-stranded DNA virus that infects the skin and mucous membranes of the upper respiratory tract and the anogenital tract. There are more than 100 known types of HPV, approximately 40 of which can infect the genital tract. HPV infection is a sexually transmitted infection. It is extremely common in young women and men in their first decade of sexual activity, however approximately 90% of HPV infections resolve spontaneously.

Cervical cancer is associated with persistent infection with 'oncogenic types', so called high-risk HPV (16, 18, 31, 33, 39, 45, 51, 52, 56, 58 and 59). Benign cellular

changes may occur after an acute HPV infection, the majority of which regress without any treatment. However, persistent HPV infection may lead to changes in cervical cells which result in the development of moderate or severe precancerous abnormalities of the cervix. A proportion of these abnormalities will progress, if not treated, to cervical cancer over a period of 10 to 20 years.

HPV vaccination

As noted, there are two complementary approaches to the prevention of cervical cancer: primary prevention through vaccination to prevent infection with HPV, and secondary prevention through cervical screening to detect and treat precancerous abnormalities and early stage cervical cancer. In 2010, quadrivalent vaccination against HPV 6, 11, 16 and 18 was introduced to the Irish national immunisation schedule for all girls in the first year of second level school or age equivalent. A catch-up programme targeting girls in sixth year or age equivalent was run from 2011 until 2014. HPV 6 and HPV 11 are associated with approximately 90% of anogenital wart cases. HPV 16 and HPV 18 are associated with approximately 70% of squamous cell carcinomas (the most common histological type of cervical cancer globally and in Ireland). Cervical screening of women who have been vaccinated against HPV is recommended because the current quadrivalent vaccine does not protect against cervical cancers caused by other high-risk HPV types. The first cohort of young women vaccinated against HPV is due to enter the CervicalCheck programme in 2018-2019.

Cervical screening

Cervical screening is a form of secondary prevention that aims to identify those at increased risk of developing cervical cancer. Precancerous abnormalities do not produce symptoms, but can be detected by screening. In contrast, most women with cervical cancer present with symptoms. The aim of a cervical screening programme is to reduce the incidence of and morbidity and mortality from cervical cancer through detection and treatment of precancerous abnormalities and early stage cervical cancer.

Internationally, organised cervical screening programmes have reduced cervical cancer incidence and mortality. The reduction in mortality has been shown to be up to 80% at population level. However, no cervical screening programme can prevent all cervical cancers and a balance needs to be struck between effectiveness and efficiency. Cervical screening tests are not 100% accurate and cervical cancer may develop in the time interval between a negative screening test and the next scheduled screening. Therefore, cervical screening programmes require regular defined screening intervals.

A balance needs to be struck between screening too frequently (over-screening) and screening too infrequently (under-screening). Over-screening results in both short-term and long-term effects associated with the cervical screening test, unnecessary referral to colposcopy, overdiagnosis and unnecessary treatment. Under-screening results in higher numbers of interval cervical cancer cases and cervical cancer deaths.

Screening technologies

Cervical screening tests may be broadly classified into those designed to detect cytological (cellular) abnormalities and those designed to detect HPV infection. Cervical screening tests may be performed as:

(a) a primary screen,

(b) a primary screen followed by one triage test

(c) or a primary screen followed by multiple triage tests carried out and acted upon either sequentially or together (co-testing).

The International Agency for Research on Cancer defines triage as 'the detection of cases of cervical cancer or of its precursor lesions among women who were initially found to have an abnormal screening test that requires further evaluation'.

A variety of tests have been used in primary screening and in triage. These can be broadly divided into three categories: cytology, HPV testing (which includes partial genotyping for HPV 16 and HPV 18) and molecular biomarkers. Cytology, through the observation of abnormal cells in a cervical screening test, can identify precancerous cytological abnormalities or cervical cancer. Conventional cytology, also known as a Pap test or Pap smear, was developed in the 1920s to identify invasive cervical cancer. Liquid-based cytology (LBC) was introduced in the mid-1990s as an improvement on conventional cytology. The presence or absence of high-risk HPV (hrHPV) in a cervical screening sample can be determined by HPV testing. While HPV testing can be used to identify HPV infection, it does not provide information on which hrHPV types are present. The use of partial genotyping for HPV 16 and HPV 18 potentially provides additional risk stratification for women who have a positive HPV test, as these genotypes are associated with a higher risk of developing precancerous abnormalities and cervical cancer compared with other hrHPV genotypes.

As women who are vaccinated against HPV types 16 and 18 will form an increasing proportion of the population to be screened over time, the usefulness of partial genotyping for HPV 16 and 18 will decline as the prevalence of these genotypes decreases. A disadvantage of HPV testing is that it cannot discriminate between

acute transient HPV infection and transforming HPV infection (when production of oncoproteins responsible for abnormal cellular changes begins). New molecular biomarkers, such as $p16^{INK4a}$ protein and Ki-67 protein, have been proposed to inform triage of women who are positive for HPV. Their detection may improve the identification of women with transforming HPV infection who are at increased risk of developing cervical cancer.

Primary screening and triage tests do not provide a diagnosis. Abnormal screening or triage tests require further assessment in the form of a diagnostic test using colposcopy, which allows microscopic assessment of the cervix. The 'gold standard' for the diagnosis of precancerous abnormalities, pre-invasive cervical cancer or invasive cervical cancer is the histological examination of biopsies obtained at colposcopy.

Current screening practice

Since September 2008, CervicalCheck has been available to women aged 25 to 60 years who live in Ireland. Women aged 25 to 44 years are offered screening at three-yearly intervals and women aged 45 to 60 years are offered screening at five-yearly intervals. There is considerable variation in cervical screening programmes between countries. CervicalCheck currently uses primary liquid-based cytology screening. CervicalCheck introduced HPV testing following treatment in colposcopy in 2012 and since 2015 has used triage with HPV testing when low-grade cytological abnormalities are detected on primary liquid-based cytology screening. Women with low-grade cytological abnormalities who are negative for HPV are at a very low risk of developing severe precancerous abnormalities within the next five years and may be returned to routine cervical screening. In contrast, women with high-grade cytological abnormalities are at higher risk of developing severe precancerous abnormalities and need to be referred to colposcopy.

Burden of disease

Cervical cancer (invasive cervical cancer or invasive cervical carcinoma) is usually preceded by precancerous abnormalities and pre-invasive cervical cancer (carcinoma *in situ*). Between 2012 and 2014, cervical cancer was the eighth most commonly diagnosed cancer (excluding non-melanoma skin cancer) in women in Ireland. On average, there were 88 deaths from cervical cancer per year. The median age at death was 56 years. There has been an overall increasing trend in incidence of cervical cancer in Ireland with further increases predicted based on changes in sexual behaviour and demography.

Between 2012 and 2014, there were on average 2,873 cases of cervical carcinoma *in situ* diagnosed per year. The most common age at diagnosis was 25 to 29 years.

The age-standardised incidence of cervical carcinoma *in situ* increased from 48.9 per 100,000 population at risk in 1994 to 107.7 per 100,000 population at risk in 2014. There were on average, 277 cases of invasive cervical cancer diagnosed per year. The most common age at diagnosis was 40 to 44 years. In 2012, the estimated incidence of cervical cancer in Ireland was 15.1 per 100,000 (European age-standardised rate [EASR]) compared with an incidence of 11.3 per 100,000 in the European Union 27 (EU-27) member states.

In 2012, the estimated mortality from invasive cervical cancer in Ireland was 4.3 per 100,000 (EASR) compared with the EU-27 mortality of 3.7 per 100,000. The prognosis for invasive cervical cancer is linked with the stage at diagnosis. The net five-year age-standardised survival probability was 63.6% for those diagnosed at stage II disease compared with 21.6% for those diagnosed at stage IV disease. Five-year survival probability (not age-standardised) for those diagnosed at stage I disease was 93.9%.

Coverage is a measure of the proportion of the target population screened within a period and indicates the effectiveness of a screening programme in reaching the target population. CervicalCheck's objective is to achieve coverage of 80% or more over a five-year period. The five-year coverage to 31 December 2016 was 79.6% with coverage improving over time. Participation was higher in younger than older women.

On average, in 2015 and 2016, CervicalCheck processed approximately 281,000 smear tests per annum, declining from a peak of almost 367,000 tests in 2013. On average, between 2012 and 2015, 7.7% of smear tests showed low-grade cytological abnormalities and 1.6% showed high-grade cytological abnormalities.

When an abnormality is suspected at colposcopy, a diagnostic punch biopsy is usually performed to confirm the diagnosis histologically. CervicalCheck classifies histological abnormalities according to cervical intraepithelial neoplasia (CIN) terminology. In the seven years since CervicalCheck commenced in 2008 (to August 2015), it has detected 1,082 invasive cervical cancer cases, 41,417 high-grade histological abnormalities (CIN 2 and CIN 3) and 29,505 low-grade histological abnormalities (CIN 1).

Surgical treatments for CIN 2 and CIN 3 include large loop excision of the transformation zone (LLETZ), ablation (cold coagulation) and cone biopsy. Between 2014 and 2015, CervicalCheck treated 5,269 women with LLETZ, 1,224 women with ablation (cold coagulation) and 16 women with cone biopsy. Short-term side effects following treatment include pain, bleeding and vaginal discharge. Treatment dependent long-term side effects relate to the impact of treatment on the outcomes

of future pregnancies and include an increased risk of preterm premature rupture of membranes, preterm birth, low birthweight, stillbirth and neonatal death.

Treatment for invasive cervical cancer is stage dependent. While early stage disease (stage IA1) may be managed conservatively, treatment options for more advanced disease include surgery, radiotherapy and or the combination of chemotherapy and radiotherapy (chemoradiotherapy). Women who present with metastatic (FIGO stage IVB) or recurrent disease, are usually symptomatic. They are generally offered palliative chemotherapy with or without immunotherapy and or individualised radiotherapy to relieve symptoms and to improve their quality of life.

As noted earlier, certain hrHPV types are associated with an increased risk of developing precancerous abnormalities and cervical cancer. Preliminary data from CERVIVA in collaboration with CervicalCheck, indicate a crude hrHPV prevalence rate of 14.6% in women attending for routine screening. Prevalence is highest (20.4%) in women under the age of 30 years, and it decreases with advancing age. Of those testing positive for HPV, the data indicate that 32% are positive for HPV genotypes 16 and 18, the particular genotypes of HPV associated with 70% of cervical cancers.

Clinical effectiveness and safety

Diagnostic test accuracy indicates the performance characteristics of a screening test and describes how well the test discriminates between those who do, and do not have the disease. Sensitivity is the ability of a screening test to accurately identify those who have the disease, that is, the proportion of people with the disease who have a positive test result. A more sensitive test will result in fewer women receiving a false negative result. The specificity of a screening test is its ability to correctly identify those who do not have the disease, that is, the proportion of people without the disease who have a negative test result. A test with a high specificity will result in fewer women receiving a false positive result. While it is obviously desirable to have a test that is both highly sensitive and highly specific, usually this is not possible, and there is a trade-off to be made between sensitivity and specificity.

No cervical screening programme can prevent all cervical cancer cases. Cervical screening tests are not 100% accurate. False negative and false positive test results are potential harms of any screening programme. CervicalCheck may fail to diagnose women with precancerous abnormalities and cervical cancer as a consequence of false negative results, leading to potentially missed or delayed opportunities to intervene in those with treatable precancerous abnormalities or early stage cervical cancer. These negative screening tests may also provide false reassurance to the woman. False positive test results lead to unnecessary referral to colposcopy, overdiagnosis, unnecessary treatment and their associated short-term and long-term

side-effects. Overdiagnosis refers to the identification of precancerous abnormalities that would not otherwise have become clinically significant. Overdiagnosis may lead to increased surveillance, potentially increasing a woman's stress and anxiety, and or unnecessary treatment. Cervical cancer may develop in the time interval between a negative screening test and the next scheduled screening, which is another potential harm of any cervical screening programme.

As mentioned previously, there are three grades of CIN: CIN 1, CIN 2 and CIN 3. If left untreated, CIN can develop into cervical cancer, however it can also regress. It is not possible to determine which CIN will regress or progress, so currently all CIN 2+ (grade 2 or higher) are treated. As such, CIN 2+ is the clinically relevant point in the development of cervical cancer that a screening test needs to be able to accurately detect.

A systematic review was conducted to identify relevant studies about the diagnostic accuracy of:

- primary HPV screening
- primary cytology (conventional cytology and liquid-based cytology) screening
- triage strategies following primary HPV screening

in the prevention of cervical cancer.

The diagnostic accuracy of primary HPV and cytology (LBC and conventional cytology) screening for the prevention of cervical cancer were evaluated. Meta-analysis of 23 studies undertaken in industrialised countries using the Hybrid Capture 2 (HC2) HPV assay indicate that the pooled sensitivity of primary HPV screening in the detection of CIN 2+ and CIN 3+ was 95.2% (95% CI: 92.5% to 97.1%) and 98.2% (95% CI: 96.7% to 99.1%), respectively. This was significantly higher than the pooled sensitivity of primary cytology screening which was 75.0% (95% CI: 64.1% to 83.3%) and 78.0% (95% CI: 63.5% to 88.4%), respectively. Thus, primary HPV screening using HC2 would result in fewer women receiving a false negative result, compared with primary cytology screening.

Based on meta-analysis, the pooled specificity of primary HPV screening in the detection of CIN 2+ and CIN 3+ was 88.2% (95% CI: 82.9% to 92.0%) and 87.5% (95% CI: 78.7% to 93.2%), respectively. This was lower than the pooled specificity of primary cytology screening which was 95.0% (95% CI: 92.2% to 96.8%) and 95.1% (95% CI: 91.6% to 97.3%), respectively. Thus, primary HPV screening using HC2 would result in more women receiving a false positive result, compared with primary cytology screening. Evidence from long-term follow-up of women who have undergone primary cytology screening or primary HPV screening has shown that

over a six-year interval, women with negative primary HPV screening at baseline are less likely to develop severe precancerous abnormalities than women with negative primary cytology screening at baseline.

The diagnostic accuracy of triage strategies following primary HPV screening was evaluated based on the synthesis of evidence from 15 studies across eight randomised controlled trials (RCTs). The RCTs were typically large-scale trials conducted within population screening programmes, with seven of the eight RCTs conducted in Europe. Five triage strategies of interest were considered:

1) cytology;
2) partial genotyping (HPV 16/18);
3) co-testing with partial genotyping (HPV 16/18) and cytology;
4) partial genotyping (HPV 16/18) followed by cytology as a second triage test; and
5) testing for the $p16^{INK4a}$ protein alone or in combination with Ki-67 protein (which have been identified as surrogate markers of transforming infections).

All of the considered strategies were carried out on a single cervical screening test. For all strategies, few comparable trials were available. Some of these strategies appear to be advantageous and long term data on the development of interval cancers would suggest they can be safely used within screening intervals typically used in Ireland.

Economic evaluation

A systematic review was carried out to assess the available evidence on cost-effectiveness for primary HPV screening as part of an organised screening programme for the prevention of cervical cancer. Consistent evidence was found that cervical screening programmes using primary HPV screening are cost-effective and potentially cost saving when compared with programmes using primary cytology screening. The studies identified were not considered applicable to CervicalCheck and or the Irish healthcare system because of differences in the cervical screening programmes and healthcare delivery costs. Therefore, an economic model specific to the Irish setting was required due to the lack of applicable published cost-effectiveness evidence from another setting.

A decision analysis model was built to compare the total net costs and benefits associated with different HPV-based screening strategies for the prevention of cervical cancer compared with the current CervicalCheck strategy of primary liquid-based cytology (LBC) screening followed by triage with HPV. A Markov model structure based on the natural history of cervical cancer was developed. Model parameters were derived from CervicalCheck, Irish datasets, peer-reviewed literature

and expert opinion. Costs and benefits were assessed from the perspective of the publicly-funded health and social care system. Effectiveness was measured as quality-adjusted life years (QALYs) gained for each of the potential screening strategies. The difference in QALY gains is the most valid way to compare the overall effectiveness of the alternative strategies rather than the relative number of cancer cases and cancer deaths. QALYs take into account differences in the quantity and quality of life and, and so capture, for example, differences in the stage at which a cancer is diagnosed. Both quantity and quality of life may differ substantially for those diagnosed with earlier stage disease (stage 1 disease confined to the cervix) versus advanced disease that has spread to other parts of the body (stage IV).

QALYs also take into account any difference in the duration of survival of those who die from cervical cancer. QALYs also account for harms due to screening, including overdiagnosis. Overdiagnosis may lead to a loss of quality of life due to increased surveillance of CIN 1 (potentially increasing stress and anxiety) and unnecessary treatment of CIN 2 and CIN 3 lesions. QALY estimates are discounted to reflect society's preference for benefits to be realised sooner and undesirable effects to be realised further into the future.

This HTA considered 32 different screening strategies, including different primary screening tests (HPV or LBC), triage tests, screening intervals, and screening exit ages. Triage consisted of a single test, sequential testing or co-testing. Triage tests consisted of liquid-based cytology (LBC); partial genotyping for HPV 16 and 18; and dual staining for $p16^{INK4a}$/Ki-67. The prevalence of HPV infection is higher in women under the age of 30 years than it is in women aged 30 years and older. This may reduce the clinical effectiveness of primary HPV screening in this age group. Therefore, one alternative age-based strategy was considered: primary liquid-based cytology (LBC) screening with HPV triage in women under the age of 30 years with primary HPV screening with liquid-based cytology triage in women aged 30 years and over. Finally, given recommendations from the International Agency for Research on Cancer that cervical screening should be considered for all women aged 25 to 65 years when resources permit, all of the proposed strategies also considered extending the upper age limit from 60 to 65 years. All strategies were considered for both unvaccinated and vaccinated cohorts of women. Conventional cytology was not considered because CervicalCheck has used liquid-based cytology (LBC) since its establishment in 2008.

The model was used to predict the financial cost, number of lifetime screens, referrals to colposcopy, cervical cancer cases, cervical cancer deaths, QALYs and life-years gained (LYG) for each of the 32 proposed strategies in unvaccinated and vaccinated cohorts. Incremental cost effectiveness ratios (ICERs) were calculated for each strategy. The total net costs and benefits associated with each of these

screening strategies were determined by modelling one year's cohort from age 25 years to end of life.

For the cohort of women who have not been vaccinated against HPV 16 and 18 (the unvaccinated cohort), CervicalCheck's current strategy was more costly and either less or equally effective, when compared with all other options (apart from extending the current strategy to age 65 and primary HPV screening followed by triage comprising co-testing with partial genotyping and p16INK4a/Ki-67 with screening extended to age 65). Similarly, for the cohort of women who have been vaccinated against HPV 16 and 18, CervicalCheck's current strategy was less effective and more costly compared with all other strategies (apart from extending the current strategy to age 65 years).

For the unvaccinated cohort, given willingness-to-pay thresholds in the range of €20,000 to €45,000 per QALY, primary HPV screening with liquid-based cytology triage at five-yearly intervals from age 25 to 60 years was found to be cost-effective with an ICER of €29,788 per QALY gained. While this strategy provides comparable clinical effectiveness to current screening practice, a number of other strategies were found to be more effective, and would also lead to a reduction in costs compared with current practice.

For all strategies, extending the screening age to 65 years decreases both the number of cervical cancer cases and cervical cancer deaths. However, as these benefits occur far into the future, the effect of discounting means that the number of QALYS gained is small. Although more effective, the incremental benefit of extending the screening age is small relative to their incremental cost. As such, this would not be considered cost-effective when compared with primary HPV screening with liquid-based cytology triage at five-yearly intervals from age 25 to 60 years. Using the willingness-to–pay threshold based on QALYs allows for comparison to be made across the entire health service and identifies when interventions can be considered good value for money. Applying the willingness-to-pay threshold to guide the choice regarding the optimal strategy ensures that where the health gains are small, relative to the increase in costs, this is highlighted and consideration can be given to redistributing resources to elsewhere within the health system to maximise the benefit for the entire population.

Two subgroup analyses were conducted at the request of the Expert Advisory Group. The first considered extending the screening exit age from 60 to 65 years in a cohort who have not had the benefit of lifetime access to CervicalCheck from the age of 25 years (that is, for women who were 50 years old when CervicalCheck commenced in 2008). This analysis confirmed that extending the upper screening age limit from age 60 to age 65 years provides a clinical benefit, but is not cost-effective under

willingness-to-pay thresholds in the range of €20,000 to €45,000 per QALY, irrespective of when access to organised screening starts (25 or 50 years). Given their historic underscreening, it may be considered appropriate to extend screening to age 65 years for these women for ethical reasons. However, to ensure the benefits of this additional screening round are maximised, a targeted campaign to encourage uptake in those over 60 years of age would be necessary given the lower uptake rate of screening in older women.

The second subgroup analysis considered how best to screen women under the age of 30 years not vaccinated for HPV 16 and 18, in the context of primary HPV screening followed by liquid-based cytology triage at five-yearly intervals being adopted from age 30 years. These women have a high prevalence of both HPV infection and cervical abnormalities, and five-yearly screening may lead to an increased risk of interval cancers within this subgroup. However, infection is also more likely to clear spontaneously within this age group, and in the absence of persistent infection, cytological abnormalities will typically regress.

The optimal screening strategy for this subgroup of unvaccinated women under the age of 30 years was found to be primary HPV screening followed by liquid-based cytology triage at five-yearly intervals from age 25 to age 60 years. Providing three-yearly screening for those aged under 30 (that is, adding one more screening round) increases the effectiveness of this strategy, but also increases its cost. With an ICER of €48,501 per QALY, this would not be considered cost-effective under willingness-to-pay thresholds in the range of €20,000 to €45,000 per QALY. If three-yearly screening to age 30 is adopted for clinical reasons, ongoing evaluation and monitoring of its effectiveness will be required, taking into consideration the proportion of the population vaccinated against HPV and the prevalence of HPV infection.

Furthermore questions still remain as to the optimal surveillance for unvaccinated women aged less than 30 years who screen positive for HPV, but negative on liquid-based cytology triage. Two alternative referral pathways were considered in this subgroup analysis. In the first, women who were HPV positive at 12 months were referred directly to colposcopy and in the second, women were only referred to colposcopy if they tested positive on partial genotyping test for HPV 16 or HPV 18 at 12 months. Both referral pathways lead to similar clinical outcomes and costs. The requirement for a positive partial genotyping test would reduce the number of colposcopy referrals in this age group, but lead to repeated annual screening and thus potentially high levels of anxiety for some women. The efficacy of screening in this cohort will therefore require ongoing evaluation.

For the cohort of women who have been vaccinated against HPV 16 and 18, none of the modelled strategies were considered cost-effective when compared with no screening at a willingness-to-pay threshold of €45,000 per QALY. The strategy with the lowest ICER of €58,745 per QALY was primary HPV screening with liquid-based cytology triage at five-yearly intervals from age 25 to 60 years. Given that CervicalCheck was only established in 2008 and is thus relatively new, extending beyond five-yearly screening was considered to be unacceptable at this point, so longer screening intervals were not included in the model. There is uncertainty about how women who have been vaccinated against HPV 16 and 18 will progress through the precancerous states from infection with HPV to invasive cervical cancer. It was assumed that when compared with unvaccinated women, the risk of developing cervical cancer is 70% lower in women who have been vaccinated against HPV 16 and 18. This was very influential on the number of cervical cancer cases predicted by the model and whether or not the modelled strategies were cost-effective. While screening strategies with longer intervals than those modelled may be more appropriate for women who have been vaccinated against HPV 16 and 18, a policy of continued screening at five-yearly intervals may be reasonable until further long-term data emerge on the development of cervical cancer in these women.

The budget impact analysis was conducted from the perspective of the publicly-funded health and social care system. The budget impact analysis, over an eight-year period from 2018 to 2025, of switching from the current strategy to primary HPV screening with liquid-based cytology triage at five-yearly intervals from 25 to 60 years estimated a net saving of up to €3 million for the CervicalCheck population who have been vaccinated against HPV 16 and 18, €32 million for the CervicalCheck population who have not been vaccinated against HPV 16 and 18 and up to €35 million for the entire CervicalCheck population.

Organisational and social implications

A change to the sequence of screening tests and the screening interval used by CervicalCheck would have implications for women, CervicalCheck, healthcare professionals, administrative staff, laboratory services and colposcopy services. However, because CervicalCheck was only established in 2008 and was based on best international practice at the time, it has an advantage over many other national cervical screening programmes in that it has fewer legacy issues, minimising the disruption of the proposed changes.

A change to primary HPV screening would not impact the way the cervical screening sample is collected. Test processing has already been centralised in a small number of sites by CervicalCheck. Centralised processing provides efficiency gains, allowing a high throughput in the HPV testing platforms while also ensuring that there were still

be sufficient cytology throughput to maintain staff expertise for quality assurance purposes. Changes in laboratory practices and workloads would need to be negotiated as part of routine tendering process and should not otherwise have organisational implications for CervicalCheck.

When combined with liquid-based cytology triage, primary HPV screening would identify a new cohort for surveillance as those woman who are HPV positive, but cytology negative, are at increased risk of developing high-grade histological abnormalities and invasive cervical cancer (CIN 2+). The economic model assumed that these women would be recalled for surveillance after one year and at that point a repeat positive HPV test would warrant referral to colposcopy. A switch to primary HPV screening would have resource implications, including adaptation of literature and training resources for healthcare professionals and women in relation to the implications of positive and negative tests. There would also be an increase in the time taken to explain primary HPV screening to women, to allow informed consent.

Based on current screening uptake rates, adopting primary HPV screening and extending the screening interval to five-yearly screening for all women is estimated to result in approximately two fewer lifetime screens (from 8.0 to 5.9) per woman on average. This would lead to a reduction in CervicalCheck screening activity and colposcopy referrals and increase the efficiency of the programme (that is women will require fewer lifetime screens to achieve similar benefits). Due to phased implementation, no reduction in screening activity would occur until at least year four, with screening activity in fact estimated to increase in the initial years due to the surveillance of women identified as HPV positive, but cytology negative. The budget impact analysis estimated a net reduction of 15% in the total number of screening tests and a 16% reduction in colposcopy referrals over the eight-year period between 2018 and 2025. Reduction in screening activity and colposcopy referrals is predicted for both the cohort of women who have been vaccinated against HPV 16 and 18 and the unvaccinated cohort, with the reduction being greater in the latter.

The current waiting time targets for colposcopy appointments are two weeks for an urgent referral, four weeks for high-grade cytological abnormalities and eight weeks for low-grade cytological abnormalities. As of June 2016, all colposcopy services contracted by CervicalCheck met these targets with any excess capacity being used to support symptomatic services. Despite a predicted increase in colposcopy referrals in the first three years after implementing primary HPV screening, the availability of this additional capacity would allow CervicalCheck to continue to meet its waiting time targets. However, the long-term decrease in numbers of colposcopy referrals would have funding implications for colposcopy clinics and would potentially free additional capacity for the management of women attending through symptomatic

services. An implementation plan will be required for this transitional phase to avoid excessively large fluctuations in workload due to a change in the screening interval.

It has been speculated that an increase in the screening interval from three to five years in women between the ages of 25 and 44 years may lead to either reductions or improvements in the adherence to cervical screening, but there are no published data available to support this. CervicalCheck provides a quality-assured screening programme with a comprehensive call-recall based invitation system: women are sent invitations and reminders for screening visits and there is a facility to track non-responders. As with any cervical screening programme, the success of CervicalCheck relies in part on maximising coverage rates. Monitoring of coverage and reporting against established targets (the current five-year coverage target is a minimum of 80%) will continue to represent an important performance indicator and will allow any change in adherence to be detected in a timely fashion should it occur. Primary HPV screening could be suitable for self-sampling (that is, where the woman takes the sample herself) and may provide an opportunity to improve coverage through an initial engagement with eligible women who have never attended CervicalCheck or who are underscreened because they do not attend at the recommended screening intervals.

Ethical considerations

Primary HPV screening may result in worry and anxiety for some women. To be able to provide informed consent, women will need to be given sufficient information about the new process and its potential risks and benefits in a way they can understand. There is no treatment for HPV infection which is a potential cause of distress and anxiety for women. There will be a need to reduce the anxiety and uncertainty that women may experience as a result of a positive primary HPV screening test.

The poor specificity (high rate of false positives) of primary HPV screening in the detection of precancerous abnormalities is a cause for concern. This poor specificity is due in part to the high rate of HPV infection, particularly in women under the age of 30 years. Using primary HPV screening alone would result in the unnecessary referral of women to colposcopy services, causing unnecessary anxiety to women and placing additional demands on colposcopy services. Therefore, the proposed screening strategy includes the subsequent triage of women with a positive primary HPV screening test. In order to alleviate anxiety and to minimise the harms of screening, women must be fully informed of the implications of false positive test results, including potential side-effects of colposcopic examination and or treatment and the implications of false negative test results which may lead to failure to detect all cases of cervical cancer.

The relative risk of cervical cancer rises with increasing population density, level of unemployment and lower educational attainment. There is ongoing concern about the inequitable burden of cervical cancer among women in lower socio-economic groups. These women may also be less likely to present for vaccination against HPV 16 and HPV 18 and or attend cervical screening than women in higher socio-economic groups. A change to primary HPV screening will not change the screening process from the woman's perspective, therefore it is anticipated that the existing social inequities will neither increase nor decrease.

The proposed changes to the screening programme will increase efficiency, meaning women would require fewer screenings to achieve similar benefits. Changing to primary HPV testing would also lead to lower costs compared with the current screening programme. This would free resources for use elsewhere in the healthcare system, allowing for further increases in overall population benefits.

In considering the time interval to be used in the new screening programme, any potential for an increased rate of undetected cervical cancer must be considered as well as the importance in maintaining public confidence in CervicalCheck. Other issues to be taken into account in the decision-making process include safety, public tolerance and acceptability of change, and the best use of public resources in population health measures.

Discussion

An optimal cervical screening programme detects and treats as many women with precancerous abnormalities and early stage invasive disease as possible. However, no cervical screening programme can prevent all cervical cancers and a balance needs to be struck between effectiveness and efficiency.

Based on a systematic review of the literature, good-quality evidence was found to support the effectiveness of primary HPV screening. However, insufficient data were found to determine the optimal screening programme, particularly in light of a HPV vaccination programme that will lead to a reduction in the prevalence of HPV 16 and HPV 18 and the background risk of disease. Evidence from the cost-effectiveness model supports that a change to primary HPV screening with liquid-based cytology (LBC) triage at five-yearly intervals for all women aged 25 to 60 years will lead to improvements in the efficiency of CervicalCheck.

International context

The finding that primary HPV screening is cost-effective and cost-saving when compared with primary cytology screening is consistent with the published

economic literature. A recommendation to switch from primary cytology screening to primary HPV screening is in keeping with developments in other high-income countries. Australia, Italy, Netherlands, New Zealand, Sweden and the UK have all recommended the implementation of primary HPV screening.

In January 2017, the Netherlands was the first country with an organised cervical screening programme to fully transition from primary cytology screening to primary HPV screening at five-yearly intervals for women aged 30 to 60 years. The screening interval is extended to 10-yearly for HPV-negative women aged at least 40 years. Australia plans to transition to five-yearly primary HPV screening for women between the ages of 25 and 69 years from December 2017. New Zealand plans to transition to this strategy in 2018.

In proposing changes to the cervical screening programme, it is important to also examine the broader context in relation to the history of screening and level of engagement with primary prevention through HPV vaccination. In contrast to Ireland where CervicalCheck only began in 2008, there is a long history of organised cervical screening in the Netherlands, the UK, Australia and New Zealand where national programmes were established in the 1980s and early 1990s. By comparison CervicalCheck is a relatively new national cervical screening programme, and potentially a culture of screening is not as well embedded in the population. However, the coverage rate for CervicalCheck for the five years to 31 December 2016 is 79.6%. This compares well with coverage rates achieved elsewhere including Australia (82.7% for the period between 2010 and 2014) and the Netherlands (64% up to 2011 to 2102). In England reductions in the mortality from invasive cervical cancer of up to 70% have been observed as a result of a national cervical screening programme. In time, a similar reduction is expected in Ireland.

Differences remain in the entrance and exit ages to national cervical screening programmes in high-income countries. In adopting primary HPV screening, Australia and New Zealand will raise the age at which screening starts to 25 years (from 18 and 20 years, respectively). This is consistent with International Agency for Research on Cancer recommendations and current practice in Ireland. The Netherlands offers screening from the age of 30. The screening exit age also differs: it is 69 years in both Australia and New Zealand while in Ireland and the Netherlands the exit age is 60 years.

HPV vaccination, as a primary prevention for cervical cancer, substantially reduces the risk of cervical cancer for the individual, and depending on sufficient uptake to achieve herd immunity, vaccination provides a protective effect at a population level. Differences in national HPV vaccination policies and uptake rates could influence the

risk of cervical cancer at a population level. Historic HPV vaccination uptake rates in Ireland compare favourably with those seen elsewhere. Reported HPV vaccination rates range from 60% in New Zealand to 85.1% in the UK. The Irish HPV vaccination uptake rate was 86.9% in the year 2014 to 2015, but dropped to 72.3% in the year 2015 to 2016. There are reports of a further decline in uptake in 2016 to 2017 due to concerns about vaccine safety following high-profile negative publicity. Whether uptake will drop further, stabilise at a lower rate, or return to the previous high uptake rate is unknown.

While international practice in terms of cervical cancer prevention varies, due to ongoing high uptake of an effective HPV vaccine that will lead to a reduced disease prevalence, and good evidence to support primary HPV screening as a more effective screening test, many organised programmes are moving to less intensive screening based on primary HPV testing.

Future research and developments

Evidence continues to develop on the role of HPV infection and the potential benefits of HPV vaccination and different cervical screening strategies in the prevention of morbidity and mortality from cervical cancer.

There is evidence that following a negative primary HPV screening test, the screening interval can be safely extended to six years. Further evidence has emerged from a national screening programme that it is safe to extend the screening intervals up to 10 years in women aged at least 40 years who are HPV negative. Given that CervicalCheck was only established in Ireland in 2008, extending the screening interval beyond five years was not considered appropriate at this time. However, a potential extension of the screening interval should be considered in the future when a five-yearly screening interval has been successfully embedded and more evidence becomes available to support an extension to the screening interval. Irrespective of the strategy adopted, close monitoring of the number of interval cancers will continue to be required.

There is currently limited evidence about the performance of cytology or HPV testing in women who have been vaccinated against HPV 16 and HPV 18 and as such have a substantially reduced risk of cervical cancer. Evaluation of these data as they become available will help to inform cervical screening programmes regarding the optimal strategy for vaccinated women. This economic evaluation assumed use of the bivalent or quadrivalent HPV vaccine, that is, a 70% reduction in the risk of cervical cancer associated with vaccination against HPV 16 and HPV 18. Future adoption of the nonavalent HPV vaccine (which protects against five additional

strains of HPV) will further lower the risk of cervical cancer in vaccinated women and will require re-evaluation of the potential benefits and harms of cervical screening.

It is noted that the quantity of data available for the various triage strategies was less than that available for primary HPV screening, with few comparable trials. While a number of the strategies appear to be advantageous with long term data to support that they may be safely used within screening intervals typically used in Ireland, data from ongoing trials will help to further inform the choice of triage test.

Triage strategies have been implemented in national cervical screening programmes in an attempt to identify women's individual risk of developing cervical cancer. This risk-based approach to cervical screening could improve efficiency, but it also increases complexity making it more challenging to maintain a high-quality screening programme. CervicalCheck already has a comprehensive linked screening registry and a call-recall based invitation system in place; both of which are prerequisites for a risk-based approach to screening. It also has an established link to the national HPV vaccination programme. This system will allow CervicalCheck to develop an ongoing evaluation process for HPV risk-based screening, to validate the applicability of the international data in the Irish setting and the long-term safety of HPV-based strategies. Linking with the national HPV vaccination programme will also provide an opportunity to evaluate the effectiveness of the vaccination programme. The first cohort of schoolgirls vaccinated against HPV 16 and HPV 18 through this programme will be eligible for CervicalCheck in 2018-2019.

The success of a cervical screening programme depends in part on maximising participation in screening. In countries with long-established cervical screening programmes, it is noted that the majority of cervical cancers occur in women who do not participate in regular screening. Thus switching to primary HPV screening is not expected to lead to a substantial reduction in cervical cancer rates, unless participation in screening can be improved. There are limited data regarding screening participation of women who have been vaccinated against HPV 16 and HPV 18. These data provide conflicting evidence that attendance is higher and lower than for unvaccinated women. Moreover, it is not known how extending the interval between screenings will impact CervicalCheck's coverage, with speculation that five-year coverage could either improve or decrease. Ongoing monitoring of CervicalCheck's coverage and also the number of interval cervical cancers observed with a HPV-based screening programme will therefore be necessary.

Conclusions

Health technology assessment (HTA) supports evidence-based decision-making in relation to making best use of resources in healthcare services. Measured investment

and disinvestment decisions are essential to ensure that overall population health gain is maximised, particularly given constrained healthcare budgets and increasing demands for services provided.

Bearing in mind the estimates and assumptions that were used in this HTA, the following conclusions may be drawn.

Evidence from a systematic review of randomised controlled trials carried out as part of this HTA suggests that primary HPV screening is significantly more sensitive than primary cytology screening, that is, it will result in fewer women receiving a false negative result compared with cytology-based screening. However, it would also result in more women receiving a false positive result, therefore the triage of women who test positive for HPV is important to identify those women at higher risk of precancerous abnormalities and early stage invasive cervical cancer.

An economic evaluation was undertaken in order to determine the cost-effectiveness and budget impact of changing to primary HPV screening in Ireland. Options for triage were also assessed along with alternative screening intervals and age bands. All options were assessed both in a cohort of women vaccinated against HPV 16 and HPV 18 and in an unvaccinated cohort.

Taking into account the assumptions used in the economic model and the uncertainty of the parameter values, changing to a strategy of primary HPV screening followed by liquid-based cytology triage at five-yearly intervals for all eligible women aged 25 to 60 years would improve the efficiency of the CervicalCheck programme (that is, women would require fewer lifetime screens to achieve similar benefits). This strategy provides comparable efficacy to the current screening programme, and would lead to a net cost saving of up to €35 million over the first eight years of its implementation (2018 to 2025). For women who have not been vaccinated against HPV, this strategy is cost-effective at a willingness-to-pay threshold of €20,000 to €45,000 per QALY.

For women not vaccinated against HPV a change to primary HPV screening followed by liquid-based cytology (LBC) triage at five-yearly intervals for all eligible women aged 25 to 60 years would be cost-effective at a willingness-to-pay threshold of €20,000 to €45,000 per QALY.

For women who have only had access to organised screening from age 50, consideration should be given to extending screening to age 65 years. While not cost-effective, this would lead to improved clinical outcomes for this group. If implemented, it would need to be combined with a targeted campaign to increase the uptake of screening in those aged over 60 years.

Consideration should also be given to providing three-yearly primary HPV screening to women aged under 30 years who have not been vaccinated against HPV. While not cost-effective, this would lead to improved clinical outcomes for this group. Ongoing evaluation will be required to inform the future screening and surveillance of these women.

Given their lower risk of developing cervical cancer, screening women vaccinated against HPV at five-yearly intervals may not be cost-effective. However, given the uncertainty about this cohort, screening at five-yearly intervals should continue while giving consideration to increasing the screening interval as evidence emerges to support the long-term effectiveness of screening women vaccinated against HPV.

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Health Protection Surveillance Centre
National Cancer Registry Ireland
National Immunisation Office, Health Service Executive (HSE)
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The ethical analysis was written by Prof Deirdre Madden, Faculty of Law, University College Cork.

Conflicts of Interest

None reported.

List of abbreviations used in this report

AGUS	atypical glandular cells of undetermined significance
AIS	adenocarcinoma in situ
ASCUS	atypical squamous cells, undetermined significance
BIA	budget impact analysis
CC	conventional cytology
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CGIN	cervical glandular intraepithelial neoplasia
CIN	cervical intraepithelial neoplasia
DNA	deoxyribonucleic acid
EAG	expert advisory group
EVPI	expected value of perfect information
FDA	Food and Drug Administration
FIGO	(Féderation Internationale de Gynecologie et d'Obstetrique (International Federation of Obstetrics and Gynaecology)
HC2	Hybrid Capture 2
HIQA	Health Information and Quality Authority
HPRA	Health Products Regulatory Authority
HPSC	Health Protection Surveillance Centre
HPV	human papillomavirus
hrHPV	high-risk human papillomavirus
HSE	Health Service Executive
HSIL	high-grade squamous intraepithelial lesion
HTA	health technology assessment

IARC	International Agency for Research on Cancer
ICER	incremental cost-effectiveness ratio
ITT	intention-to-treat
LBC	liquid-based cytology
LEEP	loop electrosurgical excision procedure
LLETZ	large loop excision of the transformation zone
LSIL	low-grade squamous intraepithelial lesion
LYG	life years gained
NCPE	National Centre for Pharmacoeconomics
NPV	negative predictive value
NIAC	National Immunisation Advisory Committee
OR	odds ratio
PCR	polymerase chain reaction
PPV	positive predictive value
QALY	quality-adjusted life year
RCT	randomised controlled trial
RNA	ribonucleic acid
RR	relative risk
SCC	squamous cell carcinoma
SIL	squamous intraepithelial lesion
TN	true negative
TP	true positive
WTE	whole time equivalent

1 Introduction

1.1 Background to the request

In March 2015 the Health Information and Quality Authority (HIQA) agreed to undertake a health technology assessment (HTA) in relation to proposed changes to CervicalCheck – Ireland's National Cervical Screening Programme. The formal request for a HTA was made by CervicalCheck, which forms part of the Health and Wellbeing Division of the Health Service Executive (HSE).

Noting the potential of the HTA to impact on a population of over one million women, CervicalCheck highlighted emerging evidence of an opportunity to increase the clinical effectiveness and cost-effectiveness of its organised screening programme. Irish data from 2012 to 2014 indicate that the cumulative lifetime risk (up to age 74) of a diagnosis of pre-invasive cervical cancer (cervical carcinoma *in situ*) was over 1 in 13 and 1 in 112 for a diagnosis of invasive cervical cancer. The cumulative lifetime risk of death due to cervical cancer was 1 in 333.[(1)]

There are two complementary approaches for the prevention of cervical cancer:

1. primary prevention through vaccination to prevent HPV (human papillomavirus) infection,

2. secondary prevention through screening to detect and treat precancerous abnormalities.

Persistent infection with HPV is a well-established cause of cervical cancer. Currently, 12 types of HPV are considered by the International Agency for Research on Cancer (IARC) to be associated with a higher risk of cancer. Of these, HPV types 16 and 18 are responsible for approximately 70% of invasive cervical cancer cases worldwide, and when combined with five additional oncogenic (cancer causing) types, account for approximately 90% of invasive cervical cancer cases. A HPV vaccination programme for girls targeting HPV 16 and HPV 18, as well as two non-carcinogenic types (HPV 6 and 11), commenced in Ireland in September 2010.

Organised cervical screening programmes have reduced cervical cancer incidence and mortality.[(2)] Internationally, at population level, up to an 80% reduction in mortality associated with cervical cancer has been achieved with organised screening. The level of reduction is related to the coverage of the cervical screening programme.[(3)] Organised screening programmes have been widely implemented in

high-income countries. However, they vary considerably in their target ages, types of screening test used, screening intervals and protocols.[3]

CervicalCheck, Ireland's National Cervical Screening Programme, commenced in September 2008 and is aimed at women aged 25 to 60 years. The programme uses liquid-based cytology as the primary screening test. Eligible women aged 25 to 44 years are offered screening at three-year intervals and women aged 45 to 60 years are offered screening at five-year intervals.

Over the last decade, evidence has emerged that using human papillomavirus (HPV) testing as the primary screening method has a higher sensitivity for the detection of precancerous abnormalities and early stage invasive cervical cancer than liquid-based cytology. Evidence has also emerged of the potential to increase the screening interval with a HPV-based testing programme. Technological advances in the methods of detecting HPV now provide additional information regarding the clinical relevance of an HPV infection. Another consideration is the issue of HPV vaccination which reduces the risk of cervical cancer and decreases the efficiency of cytology as a screening tool in a HPV-vaccinated cohort. The first cohort of schoolgirls vaccinated against HPV through the national vaccination programme will be eligible for CervicalCheck in 2018-2019. As the number of vaccinated women increases, they will represent a growing proportion of those eligible for screening through CervicalCheck.

In consideration of all of the above factors, other high-income countries such as Australia, Italy, the Netherlands, New Zealand, Sweden and the UK, which have had organised cervical screening in place for over 20 years, have recommended changes to their screening programmes.[4] All have recommended implementing HPV testing as the primary screening method. In January 2017, the Netherlands became the first country with an organised cervical screening programme to fully transition from primary screening with cytology to HPV testing.[5] Australia plans to transition in December 2017[6] and New Zealand in 2018.[7] With the transition to HPV-based testing, both countries will extend their current screening intervals from screening every two and three years, respectively to screening every five years.

1.2 Terms of reference

This HTA was carried out to assess the impact of changing from a policy of using liquid-based cytology (LBC) as the primary screening test (hereafter referred to as primary LBC screening) to a policy of using HPV testing as a primary screening test (hereafter referred to as primary HPV screening). The sequence of screening tests including options for triage were assessed along with alternative screening intervals and age bands, including both for HPV-vaccinated and unvaccinated cohorts.

Based on the available evidence in this HTA, a decision will be made if there should be a change in policy from using liquid-based cytology to using HPV testing as the primary screening method for the prevention of cervical cancer. In consultation with the National Screening Service, the Evaluation Team developed questions in relation to the critical information required to inform such a decision. The evidence in this HTA will inform the decision of the National Screening Service, the Health Service Executive (HSE) and the Department of Health.

The Terms of Reference were to:

- describe the epidemiology of cervical cancer and HPV in Ireland
- examine the current evidence of efficacy and safety for HPV testing as a primary screening method for the prevention of cervical cancer
- review the international literature on cost-effectiveness of HPV testing as a primary screening method for the prevention of cervical cancer
- estimate the clinical implications and cost-effectiveness of HPV testing as a primary screening test for the prevention of cervical cancer, including potential changes to the screening interval, age ranges and test sequencing compared with the current programme of liquid-based cytology screening
- estimate the resource implications and budget impact of HPV testing as a primary screening test for the prevention of cervical cancer
- consider any wider ethical or societal implications that HPV testing as a primary screening test for the prevention of cervical cancer may have for patients, the general public or the healthcare system
- based on this assessment to advise on the optimal screening strategy for the prevention of cervical cancer.

1.3 Overall approach

Following an initial scoping of the technology, the Terms of Reference of this assessment were agreed between HIQA and CervicalCheck - Ireland's National Cervical Screening Programme.

HIQA convened an Expert Advisory Group comprising representation from relevant stakeholders including the Department of Health, the National Cancer Control Programme, National Cancer Registry, the National Screening Service, clinicians and nurses with specialist expertise, a representative of a patient organisation and international experts. The role of the Expert Advisory Group was to inform and guide the process, provide expert advice and information, and to provide access to data

where appropriate. A full list of the membership of the Expert Advisory Group is available in the acknowledgements section of this report.

The Terms of Reference of the Expert Advisory Group were to:

- contribute to the provision of high-quality and considered advice by HIQA to the Minister for Health
- contribute fully to the work, debate and decision-making processes of the group by providing expert guidance, as appropriate
- be prepared to provide expert advice on relevant issues outside of group meetings, as requested
- provide advice to HIQA regarding the scope of the analysis
- support the Evaluation Team led by HIQA during the assessment process by providing access to pertinent data, as appropriate
- review the project plan outline and advise on priorities, as required
- review the draft report from the Evaluation Team and recommend amendments, as appropriate
- contribute to HIQA's development of its approach to HTA by participating in an evaluation of the process on the conclusion of the assessment.

HIQA appointed an Evaluation Team comprising staff from the Health Technology Assessment Directorate to carry out the assessment. Professor Deirdre Madden, Faculty of Law, University College Cork provided the ethical analysis.

The Terms of Reference of the HTA were reviewed by the Expert Advisory Group at the initial meeting of the group. Draft findings regarding the clinical and cost-effectiveness of HPV testing as a primary screening method for the prevention of cervical cancer were discussed at subsequent meetings of the Expert Advisory Group along with considerations regarding the organisational, social and ethical implications of a change to the cervical screening policy. Draft versions of the report were circulated on several occasions to the Expert Advisory Group with amendments made, as appropriate. This final draft was submitted to the Board of HIQA for approval. The completed assessment was submitted to the National Screening Service, the HSE and the Minister for Health as advice and published on HIQA's website.

2 Description of the technology

Cervical cancer is associated with persistent infection with oncogenic types of human papillomavirus (HPV). The natural history of cervical cancer in immunocompetent women is one of a very slow progression from infection to pre-cancer to invasive cancer. The long period of time between pre-cancer and cancer (10 to 20 years) offers opportunities to screen, detect and treat precancerous abnormalities thereby avoiding progression to invasive cancer.

Given the aetiology and natural history of cervical cancer, there are two complementary approaches for its prevention:

1. primary prevention through vaccination to prevent HPV infection
2. secondary prevention through screening to detect and treat precancerous abnormalities and early stage invasive cervical cancer.

Tests used in cervical screening include those designed to identify precancerous abnormalities and early stage invasive cervical cancer, and those intended to detect the presence of HPV infection. This chapter will provide an overview of the principles of screening and a brief description of the screening technologies used for the prevention of cervical cancer. HPV vaccination is discussed in terms of its relevance to the prevention of cervical cancer. An overview of current Irish and international policies for the prevention of cervical cancer is also provided.

2.1 Screening

Screening is a form of secondary prevention. Its aim is to reduce the impact of a disease or injury that has already occurred. A cervical screening programme aims to reduce the incidence, morbidity and mortality from cervical cancer through early detection and treatment of precancerous abnormalities and early stage invasive cervical cancer. Vaccination, and its relevance as a primary preventive measure for cervical cancer, is discussed in Section 2.2.

Screening is typically applied to a large, apparently healthy population at risk for a given disease. Population-based cancer screening programmes allow systematic testing of a defined population, who have no symptoms of the disease and who may feel otherwise healthy for precancerous abnormalities and cancer. In contrast to opportunistic testing, organised screening programmes can achieve greater equity in screening access and are a more efficient use of healthcare resources by ensuring that all individuals at risk are targeted within the most appropriate timeframe.[2] The European Code Against Cancer advocates participation in organised screening

programmes for bowel, breast and cervical cancer. They highlight that in addition to improving equity of access and efficient use of healthcare resources, organised screening programmes provide better conditions for ensuring that quality assurance guidelines for screening are followed in order to achieve the greatest benefit with the least harm.[8] In 2004, the International Agency for Research on Cancer (IARC) estimated that well-organised cervical screening programmes incorporating cytology-based screening at three-to-five year intervals for women aged 35 to 64 years would reduce the incidence of cervical cancer by at least 80% among those screened.[9]

Screening tests are not 100% accurate. Coupled with the fact that the disease could develop at any time, this means that screening programmes require regular defined screening intervals. Screening intervals are based on a balance of over- and under-screening to minimise any associated risks or harms. Although screening can reduce the risk of developing or dying from a disease, it does not guarantee that the disease will not occur or, that if it occurs, it can be cured.[10]

Interval cancers are those that develop in the interval between routine screenings for that cancer. In the context of cervical screening, a woman is considered to have an interval cancer if a primary cervical cancer is diagnosed within three and a half years of her last negative screening test when on three-yearly screening interval, or within five and a half years if on a five-yearly screening interval.[11] Screening may result in overtreatment, that is, where precancerous abnormalities are identified and treated when, in the absence of treatment, they would never have developed into invasive cancer.

There is also a risk that screening will identify abnormalities which do not require treatment but which warrant surveillance, potentially contributing to stress and anxiety. Furthermore, there is a risk of both false negative and false positive test results with any screening programme. False negative test results may cause women and clinicians to be falsely reassured that no precancerous changes exist. False positive test results can lead to unnecessary referral and possible overtreatment. Ethical considerations in relation to screening are discussed in detail in Chapter 7.

The key features of any screening programme are that:

- it identifies individuals at sufficiently high risk of disease for whom further investigation or direct therapy is warranted. Typically, a positive screening test is a precursor to a confirmatory diagnostic test
- it is systematically offered to a target population who are asymptomatic and have not sought medical attention for the disease of interest
- the benefits outweigh the harms.[9]

The extent to which harms outweigh benefits is subject to a variety of factors including the characteristics of the screening test, the prevalence of disease in the screened population, and the risk of disease progression if untreated. The effectiveness of a cervical screening programme to reduce the incidence and mortality of cervical cancer depends then on a range of factors including the:

- participation rate
- sensitivity of the screening test
- compliance with follow up
- sensitivity of triage and diagnostic work-up
- natural history of the disease (rate of onset of precancerous abnormalities, progression and regression rate of precancerous abnormalities, distribution of sojourn times)
- screening policy (target age group, screening interval, clinical thresholds for follow up and treatment)
- efficacy of treatment of screen-detected abnormalities.[12]

For many diseases, factors such as test accuracy, prevalence and disease progression may vary with age. Important considerations in the design of any screening programme therefore include:

- the age at which screening should start (sufficient prevalence of the condition to justify screening)
- the age at which screening should stop (insufficient prevalence, low risk of disease progression, or limited benefit due to life expectancy)
- which test or tests to use in screening (diagnostic test accuracy)
- the interval between screening rounds (risk of disease progression, diagnostic test accuracy).

Diagnostic test accuracy reflects the performance characteristics of a screening test and describes how well the test discriminates between those who do, and do not have the disease. To determine the accuracy of a new test, its performance must be compared with that of a 'gold standard' diagnostic test, which in the case of cervical cancer is by histological[‡] confirmation of one or more diagnostic punch biopsies obtained during colposcopy. As illustrated in Table 2.1, individuals are classified according to whether the screening test is positive or negative, and whether the 'gold standard' is positive (disease present) or negative (disease absent).

[‡] Histology is the study of the microscopic structure of tissues.

Table 2.1 Relationship between a screening test result and the occurrence of disease

		True disease status*	
		Disease present	Disease absent
Test result	Positive	True positive (group a)	False positive (group b)
	Negative	False negative (group c)	True negative (group d)

* As determined by the 'gold standard' diagnostic test

Sensitivity is the ability of a screening test to accurately identify those who have the disease, that is, the proportion of the people with the disease who have a positive test result. As per Table 2.1, sensitivity is calculated as a/(a+c). The specificity of a screening test is its ability to correctly identify those who do not have the disease, that is, the proportion of the people without the disease who have a negative test result. As per Table 2.1, specificity is calculated as d/(b+d). While it is desirable to have a test that is both highly sensitive and highly specific, this is not usually possible and there is a trade-off between sensitivity and specificity. Changing the cut-off point between a positive and negative screening test result changes its sensitivity and specificity.

2.1.1 Screening technologies

A range of tests have been used in cervical screening programmes. Traditional screening tests are designed to identify precancerous abnormalities and invasive cervical cancer. Newer screening tests are designed to detect the presence of certain subtypes of the HPV virus which are necessary for the development of most cervical cancers. The various screening tests are described in this chapter, while their clinical performance (sensitivity and specificity) is assessed in detail in Chapter 4. The epidemiology of cervical cancer is discussed in detail in Chapter 3, however it is important to note that not all histological subtypes of cervical cancer can be prevented by screening.

Cytology screening is most effective against squamous cell carcinoma of the cervix and is less protective against precursors of adenocarcinoma, which are difficult to detect as well as difficult to treat.[13] Squamous cell carcinoma of the cervix is the most common histological type of invasive cervical cancer; accounting for over 76% of invasive cervical cancers diagnosed in Ireland between 1994 and 2012. Adenocarcinoma accounted for just over 15% of cases. Currently, screening does not protect against rarer types of invasive cervical cancer such as neuroendocrine cervical cancers.

2.1.1.1 Conventional cytology

Conventional cytology for the identification of invasive cervical cancer was developed in the 1920s by Papanicolaou and Babes.[9] The test was subsequently refined for use in identifying high-grade precancerous abnormalities. Cytology aims to identify the presence of a cervical abnormality through the observation of abnormal cervical cells in the test sample. Further diagnostic tests are required to confirm if the abnormality is a precancerous or cancerous one.

The test, also known as a Pap test or Pap smear, is carried out by scraping the cervix with a spatula to collect a cell sample. The area on the cervix which represents the site where most cervical cancers and abnormalities are detected is called the transformation zone and it is important that cells from this area are sampled. The exfoliated cells are smeared onto a glass slide and fixed using alcohol or a specially formulated fixative spray to prevent air drying which obscures cellular detail and hinders interpretation. The slide is then sent to a pathology laboratory for staining and microscopic assessment. The smear test is regarded as a safe procedure. Adverse events are limited, with some women experiencing discomfort or minor bleeding that resolves spontaneously.

In the laboratory, the pathologist classifies the result based on the appearance of the cells, in particular the nuclei. The terminology has changed over the years with the description of these abnormal cells as dyskaryosis, dysplasia or squamous intraepithelial lesions. A number of cytological classification systems have been developed over the last 60 years, including; the Papanicolaou system (1954), World Health Organization terminology (1973), the British Society for Clinical Cytology (BSCC) classification (1986) and the Bethesda System (1988).[9] These classification systems have been modified in line with increasing understanding of the relationship between precancerous abnormalities and invasive cervical cancer. The current classification systems partially map onto each other (Table 2.2). The Bethesda system is used in most countries, apart from the UK which uses the BSCC classification. CervicalCheck – Ireland's National Cervical Screening Programme currently uses the Bethesda system to classify cytological findings and cervical intraepithelial neoplasia (CIN) terminology to classify histological findings.

As noted, the epidemiology of cervical cancer is discussed in detail in Chapter 3. However, to provide context for how the results of the diagnostic tests are reported, a brief summary of the pathological changes are also included here to aid clarity.

Squamous cell abnormalities occur in the ectocervix, the vaginal section of the cervix, which is covered by squamous epithelium. Glandular abnormalities occur in the endocervical canal which is lined by columnar or glandular epithelium. Most

cervical cancers develop from abnormal epithelial changes which arise in an area of the cervix called the transformation zone. Where these abnormal changes arise in squamous epithelium, they are reported as cervical intraepithelial neoplasia (CIN). The degree of CIN is determined by the location within the epithelium of these abnormal cells. CIN 3 refers to abnormal cells present throughout the full thickness of the epithelium; CIN 2 if the abnormal cells are present in two thirds of the epithelium; and CIN 1 if they are present in the lower one third only. Less frequently, the abnormalities arise in glandular epithelium. These cases are reported as cervical glandular intraepithelial neoplasia (CGIN) or Adenocarcinoma in Situ (AIS). Findings from the histological examination of biopsy specimens obtained in colposcopy are reported in terms of the degree of CIN in the tissue.

The diagnostic test accuracy of conventional cytology has been evaluated in a number of studies and summarised by the IARC.[9] The reported sensitivity in the detection of CIN 1+ ranged from 40% to 86%, and the reported specificity ranged from 62% to 98%. A high specificity indicates a good ability to accurately exclude those that do not have disease (that is, few false positives); however, the moderate sensitivity reported indicates a lower ability to accurately detect abnormalities, and a higher likelihood of false negatives. Screening using conventional cytology therefore involves rescreening at regular intervals to increase the likelihood of detecting precancerous abnormalities during the long pre-invasive stage of squamous cell carcinoma on the cervix.

Table 2.2 Conversion table for different cytological classification systems[9, 11]

Cytology classification systems		
WHO terminology	**BSCC classification**	**Bethesda system**
	Negative	Negative for intraepithelial lesion or malignancy
	Inadequate	Unsatisfactory for evaluation
Benign cellular changes	Borderline nuclear abnormalities (includes koilocytosis)	Atypical squamous cells of undetermined significance (ASC-US) Atypical glandular cells (AGC) (specify endocervical, endometrial or not otherwise specified) Atypical squamous cells, cannot exclude HSIL (ASC-H)
Mild dysplasia	Mild dyskaryosis	Low-grade squamous intraepithelial lesion (LSIL)
Moderate dysplasia	Moderate dyskaryosis	High-grade squamous intraepithelial lesion (HSIL)
Severe dysplasia	Severe dyskaryosis	HSIL
Carcinoma in situ	Severe dyskaryosis/query squamous cell carcinoma	Query squamous cell carcinoma
Endocervical dysplasia	Borderline nuclear abnormalities (glandular)	Atypical glandular cells (AGC)/ Atypical glandular cells favouring neoplastic process (AGH)
Adenocarcinoma in situ	Query glandular neoplasia/adenocarcinoma in situ (AIS)	Query glandular neoplasia/adenocarcinoma in situ (AIS)

WHO: World Health Organization

2.1.1.2 Liquid-based cytology

Liquid-based cytology (LBC) was introduced in the mid-1990s as a means to improve cytology test performance. The sample is collected in a similar manner to that for conventional cytology but using a brush instead of a spatula. LBC eliminates the need for bedside preparation of the cytological specimen. Instead, the head of the brush containing the cells is broken or rinsed into a vial containing liquid preservative solution. The sample is then sent to a specially equipped laboratory for processing, using one of the commercially available LBC systems. Two of the most widely used and best-characterised systems are ThinPrep® and SurePath™. These use different technical methods for processing the cells before they are placed on a slide. ThinPrep® uses a cell filtration system to eliminate contaminating cells, whereas SurePath™ uses density gradient centrifugation; in each case the separated epithelial cells are ultimately transferred to a glass microscopic slide for review by a cytologist.[9, 10, 14]

Suggested benefits of LBC over conventional cytology include

- a more representative transfer of cells from the collection device to the glass slide,
- uniform spread of epithelial cells in a thin layer facilitating microscopic interpretation,
- fewer unsatisfactory cytology specimens, availability of residual cellular material for making additional glass slides or subsequent molecular testing (for example HPV testing),
- and potential for automation including the use of automated image analysis.

Automated image analysis allows the cytologist to be directed to the area on the slide that is most likely to contain abnormal cells, reducing both the time to read a slide and, potentially, detection error.[9, 14] While there is evidence of fewer unsatisfactory samples and a 30% reduction in the average duration of microscopic interpretation, a 2008 systematic review by Arbyn et al. concluded that LBC is neither more sensitive nor more specific than conventional cytology.[14]

The use of LBC in lieu of conventional cytology has been assessed in a number of economic analyses with cost-effectiveness dependent on the inadequacy rates for conventional cytology and the relative cost of LBC technology. LBC systems typically require proprietary sampling tools, fixatives, and preparation devices which increase the unit cost of tests compared with that of conventional cytology. In a systematic review of the economic literature, Mendes et al. reported that LBC was recommended in 18 of 27 economic analyses, eight recommended conventional cytology, and findings from one study was equivocal.[15] The comparative

effectiveness of cytology and HPV testing as a primary screening tool is assessed in Chapter 4.

2.1.1.3 HPV testing

There are over 100 different types of HPV, about 40 of which are found to infect the genital tract. Some of these, collectively referred to as the 'oncogenic types', have been linked to the development of precancerous abnormalities and invasive cervical cancer. Infection with HPV is necessary, but not sufficient for the development of invasive cervical cancer. Benign cellular changes (see Table 2.2.) and mild low-grade cytological abnormalities may occur after an acute HPV infection, but approximately 90% will regress without any treatment.[16] However, persistent HPV infection may lead to high-grade cytological abnormalities, a proportion of which will progress, if not treated, to invasive cervical cancer over a period of 10 to 20 years.

Twelve HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59) are considered by the International Agency for Research on Cancer (IARC) to be carcinogenic (class I) and associated with a higher risk of progression to malignancy; these are often referred to by the acronym, 'hrHPV'.[17] HPV 16 and HPV 18 are associated with approximately 70% of squamous cell carcinomas.[18] When combined with HPV 45, they are associated with approximately 85% of adenocarcinoma cases.[19] HPV 16, HPV 18 and HPV 45 combined with four additional oncogenic types (31, 33, 52, 58) account for approximately 90% of all invasive cervical cancer cases.[20] HPV 66 is classified as probably carcinogenic (Group 2A) by the IARC, while 12 other types are considered possibly carcinogenic (Group 2B).[17] The association between HPV infection and invasive cervical cancer is discussed in more detail in Section 3.6 of Chapter 3.

The HPV genome can be accessed from exfoliated cells. This allows HPV testing to be performed on cells from a cervical sample collected using a specific swab or on the residual cells of a LBC sample.[21] A conical brush is used to collect a sample of cells from the outer opening of the cervix at the transformation zone, similar to the practice with LBC. Once a sample has been retrieved, the specimen is transferred to a collection tube and then transported to a laboratory where it can be stored for a number of months. The ThinPrep® LBC test currently used by CervicalCheck is suitable for residual testing for HPV. HPV testing is suitable for self-sampling, which can be useful in resource-constrained settings to improve uptake in populations with low uptake or that are otherwise hard-to-reach.[9]

There are a number of different methods available for HPV testing. The two most common are nucleic acid amplification techniques (NATs) and signal amplification. In the case of the latter, RNA probes are used to hybridise the viral deoxyribonucleic

acid (DNA). The HPV RNA/DNA hybrids are then identified by a secondary capture system which ultimately yields a light signal (recorded in relative light units [RLUs]), the intensity of which relates to the viral load. The standard cut-off used is one RLU. Nucleic acid amplification techniques are heterogeneous in respect of the amplification chemistry, the particular HPV gene targeted, the molecule amplified (DNA or RNA) and the detection range (HPV type-specific or broad spectrum).[21]

The Hybrid Capture 2 (HC2) HPV DNA assay (Qiagen), which uses signal amplification, was the first to become commercially available.[22] It identifies 13 HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68). The GP5+/6+ PCR-enzyme immunoassay (EIA) is a nucleic acid amplification assay that identifies 14 HPV types (the same types targeted by HC2, plus HPV 66). These and other first-generation HPV assays detect HPV in aggregate (pooled positive or negative finding) and do not specify the particular genotype or genotypes detected.

The HPV E6, E7 mRNA assay is an in vitro diagnostic test to detect precancerous changes in cervical cells. Following HPV infection, overexpression of the E6, E7 viral oncogenes which produce the oncoproteins responsible for the abnormal cellular changes are a key feature of neoplastic progression. The test is conducted using residual cellular material collected during LBC screening. The test provides both a quantitative measure of the expression of the E6 and E7 oncogenes, and the proportion of cells exhibiting neoplastic change. Genetic information is transferred by messenger RNA (mRNA) to the cellular sites of protein synthesis.[23] The presence of mRNA transcripts of the E6 and E7 oncoproteins can be detected by reverse-transcriptase PCR or nucleic acid sequence–based amplification, with higher mRNA expression being associated with increasing disease severity.[24]

There is evidence that tests to identify HPV mRNA have a similar sensitivity and may have a higher specificity than HPV DNA tests.[25] The APTIMA HPV assay targeting E6/E7 mRNA of HPV has been fully validated and, once longitudinal data are available, can be considered as acceptable for primary screening.[26]

In 2009, an international expert committee proposed criteria for the validation of HPV assays in the context of primary screening for cervical cancer. It required that new tests should be highly reproducible and at least as accurate as the HC2 or GP5+/6+ PCR-EIA assay (defined as a relative sensitivity and specificity of ≥0.90 and ≥0.98, respectively to detect CIN 2+in a screening cohort aged 30 or older).[27] A 2015 review identified at least 193 commercial HPV tests, representing a more than 50%growth in number compared with 2012. Despite the exponential growth rate, only 35% of the tests were identified as having performance evaluations published in peer-reviewed literature.[25] Only a limited number of these tests are considered clinically validated for use.[17]

HPV testing is indicated for primary cervical screening in selected age groups, in triage of women with borderline or low-grade cytological abnormalities, and as follow up to the treatment of high-grade histological abnormalities (so called 'test of cure').[28] CervicalCheck introduced HPV testing post treatment at colposcopy in 2012 and has used HPV testing in the triage of low-grade cytological abnormalities since May 2015. In both these scenarios, HPV testing differentiates between those that do, and do not have HPV. Women who are HPV negative following assessment in colposcopy are at very low risk of developing invasive cervical cancer during the next three years and can be returned to routine screening in three years (see Appendix 1).

In primary screening, there is strong evidence that compared with cytology, HPV testing is associated with a higher sensitivity for CIN 2+ and CIN 3+ and that the cumulative incidence of CIN 3+ in the second round of screening is significantly lower in HPV-negative compared with cytology-negative women.[28] Other reported advantages for HPV testing compared with cytology include higher reproducibility, and ability to be easily automated and centralised, which facilitates laboratory specimen throughput and quality assurance.[29] The efficacy and safety of HPV testing both as a primary screening test is reviewed in detail in Chapter 4.

2.1.1.4 HPV partial genotyping

While HPV DNA tests can be used to identify HPV infection, they do not provide information on which HPV types are present. The use of genotype-specific information for HPV potentially provides additional risk stratification in HPV-positive women due to the marked difference in risk of precancerous abnormalities and invasive cervical cancer with the various HPV types. This is of particular relevance in the detection of HPV types 16 and 18, as prognostic studies have shown that they are associated with a higher risk of developing high-grade histological abnormalities than other oncogenic HPV types.[30-32]

Novel HPV tests, with the capacity for concurrent or reflex partial genotyping, have been developed that detect the main HPV genotypes and distinguish those such as HPV 16 and HPV 18 which are associated with highest oncogenic potential. As with the HPV screening tests described in Section 2.1.1.3 above, only a limited number of the available tests are considered clinically validated for use.[17] For example, the Roche Cobas 4800 HPV test is a quantitative test that specifically identifies HPV 16 and HPV 18, while concurrently detecting the presence or absence of 12 additional HPV genotypes (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68).

Use of partial genotyping is indicated in the triage of women who are HPV-positive and cytology-negative. Positivity for either HPV 16 or HPV 18 may warrant an earlier

referral to colposcopy because of the higher risk associated with these genotypes. As women who are vaccinated against HPV types 16 and 18 will form an increasing proportion of the screened population over time, the utility of HPV 16 and HPV 18 genotyping will decline as the prevalence of these genotypes decreases.

Full genotyping HPV DNA tests are also commercially available, which allow all of the hr-HPV genotypes to be distinguished in a single test.[25] These are not currently used in screening applications, and may be more suitable for use in vaccine development and epidemiological studies.

2.1.1.5 Molecular biomarkers

As noted in Section 2.1.1.5, HPV testing is indicated for triage of low-grade cytological abnormalities. However, while the tests can indicate the presence of HPV and potentially the specific HPV genotype, they cannot distinguish between transient acute infection of minor clinical relevance and transforming infection. When used as a triage tool for women with low-grade cytological abnormalities, a substantial proportion of women are still referred unnecessarily to colposcopy. New molecular biomarkers have therefore been proposed for the management of HPV-positive women.

Following HPV infection, overexpression of the E6and E7 viral oncogenes which produce the oncoproteins responsible for the abnormal cellular changes are a key feature of neoplastic progression. The activation of E6 and E7 can be detected indirectly by identifying the accumulation of the $p16^{INK4a}$ protein in the cell. This $p16^{INK4a}$ protein has been identified as a surrogate marker of transforming infection. In normal cells it is expressed at a very low level and is almost undetectable by immunochemistry; in dysplastic cells (see Table 2.2), it is strongly overexpressed with upregulation of the protein reported to be significantly correlated with the increasing severity of the abnormalities. Use of $p16^{INK4a}$ protein may help improve selection of women positive for HPV who are at higher risk of progression to invasive cervical cancer. $P16^{INK4a}$ has been reported to be a sensitive and specific biomarker of high-grade squamous cell and glandular cell abnormalities (AGH and AIS).[33] The Ki-67 protein has also been identified as a proliferation marker. Combined $p16^{INK4a}$/Ki-67 cytology can increase the specificity of diagnosis of high-grade squamous cell and glandular cell abnormalities compared with HPV tests alone.[33] For women with low-grade cytological abnormalities, $p16^{INK4a}$ immunocytochemistry has been found to have improved accuracy (similar sensitivity, higher specificity) in the triage of ASCUS and in the detection of high-grade histological abnormalities (such as CIN 2+) compared with HPV testing, and to be more specific, but less sensitive in triage of low-grade cytological abnormalities (such as LSIL]).[34]

Although not used in cervical screening programmes at present, $p16^{INK4a}$/Ki-67 staining may be adopted in the future. These tests may be used as a primary screening test, in combination with, or as a replacement for other triage tests (for example, HPV testing or repeat cytology) to guide colposcopy or biopsy referral in women who have had a positive or equivocal primary screening test. Of note, however, combined use of $p16^{INK4a}$ and the Ki-67 counterstain may result in differences in the sensitivity and specificity to that reported for $p16^{INK4a}$ in isolation, and in the absence of validation studies should not be considered interchangeable. The CINtec $p16^{INK4a}$ cytology test, upon which evidence of $p16^{INK4a}$ as a triage test following primary HPV screening is based, has been replaced by the CINtecPLUS test kit which allows for dual staining for the proliferation marker, Ki-67.[35]

2.1.1.6 Colposcopy

Colposcopy is a procedure to examine an illuminated, magnified view of the cervix and the tissues of the vagina and vulva for evidence of abnormalities. Solutions such as normal saline, dilute acetic acid and Lugol's iodine are applied in sequence to the cervical epithelium. Abnormalities are graded according to acetowhiteness, margins, blood vessels, and iodine uptake. The assessment relies on pattern recognition to differentiate between normal and abnormal tissue, as well as between grades of abnormality. It facilitates the collection of colposcopically directed biopsies to confirm the presence or absence of a precancerous abnormalities or invasive cervical cancer, as well as colposcopically directed treatment.[9] When an abnormality is suspected at colposcopy, a diagnostic punch biopsy is recommended to confirm the diagnosis histologically.

The use of colposcopy in primary screening has typically been as a tool to guide collection of cytology specimens. Constraints to its use as a primary screening tool include the absence of evidence that it contributes to improved cervical screening test quality (when used in conjunction with cytology), high cost relative to cytology obtained through conventional smear taking, resource constraints in terms of the availability and accessibility of adequately trained colposcopists, and low specificity due a lower ability of colposcopy to detect glandular abnormalities.[9] Studies evaluating the diagnostic test accuracy of colposcopy are subject to substantial bias, as the 'gold standard' test is an examination of histology. As the histological samples are collected during colposcopy, it is not possible to get a fully independent assessment.

Indications for colposcopy include: a positive screening test result; a suspicion regarding the appearance of the cervix on clinical examination; the presence of clinically apparent leukoplakia; and an increased risk of invasive cervical cancer.[9] Risks associated with colposcopy include psychological distress, which is typically short term,

and physical effects including pain, bleeding and vaginal discharge which may be associated with ablation or excisional treatment performed during colposcopy.[9]

Quality assurance of colposcopy services is essential to ensure optimal management of women with detected smear test abnormalities and to assure accurate diagnosis and effective treatment. CervicalCheck - Ireland's National Cervical Screening Programme publishes an annual report which confirms their adherence to stated organisational and clinical quality assurance standards that are compliant with internationally agreed best practice (www.CervicalCheck.ie).[11]

2.1.2 Sequence of tests

A primary screening test is not designed to provide a diagnosis, but rather to identify potential cases which require further testing. Cytology is used to identify cellular abnormalities. The presence or absence of precancerous abnormalities or invasive cervical cancer is generally confirmed through histology review of biopsies taken during colposcopy. HPV testing, on the other hand detects the presence of HPV infection. The presence of HPV infection is distinct from the identification of precancerous abnormalities or invasive cervical cancer. Hence, further testing is required to determine if infection with HPV has led to the development of cytological abnormalities and, if so, to determine if they are precancerous abnormalities or invasive cervical cancer.

Screening may be based on a single or multiple tests. In most cervical screening programmes, a single primary test is used followed by a triage test. For example, the primary test may be cytology which can be followed by repeat cytology, HPV testing, or both for those with low-grade cytological abnormalities. Those with high-grade cytological abnormalities are referred immediately to colposcopy. For the triage group, a second positive test would indicate the need for referral to colposcopy. Repeat cytology requires the woman to make a second visit and may result in substantial loss to follow-up, whereas HPV testing as a triage test can be carried out on residual cell matter from the original LBC sample.[36] As noted in Section 2.1.1.3, women with low-grade cytological abnormalities who are HPV negative are at very low risk of developing CIN 3 within the next three years and may be returned to routine screening. Similarly, concerns about overdiagnosis with primary HPV testing (due to its lower cross-sectional specificity for high-grade abnormalities compared with cytology) can be managed through triage of HPV-positive women with cytology, partial genotyping or potentially use of a molecular biomarker such as $p16^{INK4a}$/Ki-67. Both the primary and triage test can be undertaken using the same sample, so only one visit is required by the woman.

Women who are referred to colposcopy either enter surveillance for a period or return to routine screening, depending on the clinical findings and the results of HPV testing and histopathology. For example, surveillance is indicated for women identified as having CIN 1 at colposcopy. These women are offered combined cytology and HPV testing at 12 months (in the colposcopy clinic). If hrHPV is detected or the cytology indicates high-grade abnormalities, these women will have repeat colposcopy and treatment, if required.[37]

2.2 Vaccination

HPV infection is commonly found in the anogenital tract of men and women with and without clinical abnormalities. The aetiological role of HPV infection among women with invasive cervical cancer is well established, as HPV infection is thought to cause the vast majority of cervical cancer cases. Persistent HPV cervical infection results in cervical morphological changes ranging from normal findings to various stages of precancerous abnormalities to invasive cervical cancer.[9]

HPV vaccines that prevent against certain high-risk strains of HPV are now available and have the potential to reduce the incidence of cervical and other HPV-related cancers. Worldwide, HPV 16 and 18 contribute to 70% of squamous cell carcinoma cases[18] with HPV 31, 33, 35, 45, 52 and 58 accounting for an additional 20% of all cases of squamous cell carcinoma. HPV 16, HPV 18 and HPV 45 are associated with approximately 85% of adenocarcinoma cases.[19] The burden of HPV infection in Ireland is discussed in Chapter 3.

2.2.1 Vaccines

As of February 2016, two vaccines are licensed and marketed for use in Ireland to prevent HPV infections: a bivalent vaccine Cervarix®, produced by GlaxoSmithKline (licensed in September 2007) which contains HPV 16 and 18 antigens;[38] and a quadrivalent Gardasil®, produced by Sanofi Pasteur MSD (licensed in September 2006) which contains HPV 6, 11, 16 and 18 antigens.[39] A summary of the key characteristics of these vaccines including the indications for which they are currently licensed is included in Table 2.3.

In June 2015, the European Medicines Agency approved a nonavalent vaccine produced by Sanofi Pasteur MSD, Gardasil 9® that is directed against nine HPV types (6, 11, 16, 18, 31, 33, 45, 52 and 58). It is indicated for prevention of the following conditions associated with the nine HPV sub-types: cervical, vulval and vaginal cancers and precancerous abnormalities in girls, and prevention of anal cancers and anogenital warts in both girls and boys.[40] These nine HPV types are associated with almost 90% of precancerous abnormalities and invasive cervical cancers.

Table 2.3 Summary of key characteristics of the licensed HPV vaccines available in Ireland, Cervarix® and Gardasil®

Characteristic	Cervarix®	Gardasil®
Manufacturer	GlaxoSmithKline	Sanofi Pasteur MSD
Antigens	Bivalent vaccine HPV types 16, 18	Quadrivalent vaccine HPV types 6,11,16,18
Population	Girls and boys ≥9 years	Girls and boys ≥9 years
Therapeutic Indications		
Prevention of the following conditions causally related to certain oncogenic HPV types	Premalignant anogenital (cervical, vulval, vaginal and anal) lesions Cervical cancer Anal cancer	Premalignant anogenital (cervical, vulval, vaginal and anal) lesions Cervical cancer Anal cancer
		Prevention of anogenital warts (condyloma acuminata) causally related to specific HPV types

¥Reference: Summary of Product Characteristics – www.medicines.ie accessed 01/09/2016[38, 39]
http://www.hse.ie/eng/health/immunisation/hcpinfo/guidelines/chapter10.pdf[41]

2.2.2 Efficacy and safety

A high concentration of antibodies to the bivalent and quadrivalent vaccines up to 10 years post-vaccination and a strong anamnestic response post booster with the quadrivalent vaccine indicate that antibodies to HPV vaccines are likely to persist for decades.[42, 43] Evidence of a sustained reduction in the prevalence of HPV 16 and 18 has been reported in population-level studies of partly vaccinated cohorts.[44-46] A 2015 systematic review by Drolet et al. found that in countries with female vaccination coverage of at least 50%, the prevalence of HPV 16 and 18 infections decreased by 68% (RR 0.32, 95% CI: 0.19 to 0.52) among girls aged 13 to 19 years between the pre- and post-vaccination periods.[44] Scottish population-level data have demonstrated a decline in the prevalence of HPV genotypes 16 and 18 in both vaccinated and unvaccinated women in women aged 20 to 21 years.[45] Evidence of cross-protection against other HPV virus genotypes has also been found with significant reductions recorded in HPV genotypes 31, 33 and 45.[44, 45]

The efficacy of HPV vaccination in protecting against cervical abnormalities has been demonstrated. Compared with non-vaccinated women, a Danish study showed that those vaccinated had statistically significant reductions in risk of up to 60% for atypical squamous cells of undetermined significance (ASCUS) or worse, and up to an 80% reduction in risk of high-grade histological abnormalities.[47] Similarly a Belgian study found that compared with non-vaccinated women, vaccination was associated with significant protection versus the HPV types included in the vaccines, as well as cytological and histological precancerous abnormalities associated with HPV 16 and HPV 18. Vaccine efficacy is noted to decline with increasing age. This may be explained by an increasing likelihood of pre-vaccination exposure to HPV.[48]

There is also evidence that vaccination has a protective effect against cervical abnormalities and anogenital warts at a population level.[47] Scottish population-level data demonstrate a reduction in diagnoses of CIN 1 (RR 0.71, 95% CI: 0.58 to 0.87), CIN 2 (RR 0.5, 95% CI: 0.4 to 0.643) and CIN 3 (RR 0.45, 95% CI: 0.35 to 0.58) in both vaccinated and unvaccinated women aged 20 to 21 years associated with high uptake of the HPV vaccine during a catch-up campaign.[49] Similarly, the impact of a population-wide girls-only quadrivalent vaccination programme has been demonstrated in Australia, where a national vaccination programme began in 2007 for girls aged 12 to 13 years (with catch-up provided to age 26 until December 2009). By 2011, a 93% reduction in anogenital wart diagnoses (in women up to 21 years of age)[50] and a 38% reduction in the incidence of high-grade histological abnormalities (in girls less than 18 years of age) were observed.[51] The 82% reduction in anogenital wart diagnoses observed in heterosexual men was attributed to herd immunity.[50] Evidence of protection against anogenital warts through herd immunity has also been observed in other population studies with female vaccination rates of at least 50%.[44]

Data on the safety profile of the quadrivalent vaccine (Gardasil) have been reviewed by the World Health Organization (WHO) Global Advisory Committee for Vaccine Safety (GACVS) and by the European Centre for Disease and Control (ECDC) who have concluded that it is generally safe and well tolerated.[52, 53] In common with most vaccines, the most frequent reported side effects are mild, temporary reactions including local redness and or swelling at the point of injection, headache, nausea and fever. No deaths have been attributed to the vaccine, and while serious incidents have been reported occurring weeks and months after vaccination, no causal relationship has been established.

The European Medicines Agency (EMA) reviewed the possibility of a link between HPV vaccines (Cervarix®, Gardasil/Silgard® and Gardasil 9®) and two rare conditions; complex regional pain syndrome (CRPS) and postural orthostatic

tachycardia syndrome (POTS). Symptoms of CRPS and POTS may overlap with other conditions, making diagnosis difficult in both the general population and vaccinated individuals. The EMA review highlighted that both are rare conditions that also occur in non-vaccinated individuals: available estimates suggest that in the general population around 150 girls and young women per million aged 10 to 19 years may develop CRPS each year, and at least 150 girls and young women per million may develop POTS each year. The review highlighted that they had 'found no evidence that the overall rates of these syndromes in vaccinated girls were different from expected rates in these age groups, even taking into account possible underreporting'. On the basis of this review, the EMA concluded in January 2016, that the evidence does not support a causal link between the vaccines and development of CRPS or POTS.[54]

2.2.3 Relevance to screening

Vaccination is a primary preventive approach whereby it is intended to prevent HPV infection from occurring in the first place. Given the link between HPV infection and cervical cancer, women who have been vaccinated have a substantially reduced risk of developing HPV infection and, consequently, of developing cervical cancer. However, screening will remain necessary even for vaccinated women, as the current vaccine does not cover all virus types that can lead to cervical cancer and may not be effective in those exposed to HPV prior to vaccination.

As discussed in Section 2.1, a key principle of any screening programme is that the benefits outweigh the harms. The ratio of benefits to harms are impacted by the prevalence of disease, as a reduced prevalence implies that fewer women will benefit from screening which lowers the benefit to risk ratio. A screening programme tailored to an unvaccinated cohort may not be optimal for a vaccinated cohort. A variety of factors need to be considered, such as the efficacy of vaccination, duration of effect, and the uptake rate. Ongoing high uptake of an effective vaccine will lead to reduced disease prevalence, suggesting potential for a less intensive screening programme.

2.3 Current practice

Practices in terms of cervical cancer prevention vary across countries and may be a reflection of local conditions regarding disease prevalence, uptake of vaccination and screening, and laboratory infrastructure.

2.3.1 Ireland

At present there are organised national programmes for HPV vaccination and cervical screening in Ireland.

2.3.1.1 Screening

CervicalCheck- Ireland's National Cervical Screening Programme, became available to more than 1.1 million women aged 25 to 60 years living in Ireland on 1 September 2008. It provides a comprehensive call-recall based cervical screening programme to an eligible population of 1.2 million women.[55] The programme comprises primary screening, HPV triage, colposcopy, and treatment and follow up of precancerous abnormalities. Those diagnosed with invasive cervical cancer are referred for treatment within the symptomatic services.

Access to CervicalCheck is provided through primary care and secondary care (public gynaecology, sexually-transmitted infection [STI] and genitourinary medicine [GUM] services). A smear taker must be a medical doctor or a registered general nurse and adhere to CervicalCheck quality assurance standards. The majority (98.7% in 2015)[55] of smear tests are undertaken in primary care, with 93.6% of these provided though GP practices.[56]

Smear Test (liquid-based cytology)

Liquid-based cytology (LBC), based on the ThinPrep® cell filtration system, is currently used as the primary screening test by CervicalCheck. The smear test is collected as described in Section 2.1.1.2, and sent to a specially equipped laboratory for processing. The collection medium is retained for residual testing (reflex HPV testing of low-grade cytological abnormalities), where necessary. Current screening intervals are as follows:

- aged 25 to 44 years – three-year screening interval
- aged 45 to 60 years – five-year screening interval.

Two smear test results with routine screening recommendations are required before moving to a five-yearly screening interval or completing screening. Annual screening from the age of 20 years is offered to women with an increased risk of cancer because they are either HIV-positive, are receiving regular dialysis, or have had an organ transplant and require immunosuppressant medications. Women aged greater than 60 years who have never had a smear test can also avail of CervicalCheck. Women aged 65 years or older entering CervicalCheck require a single normal smear test to complete screening.

A sample pathway which outlines what happens when no abnormalities, low-grade cytological abnormalities and high-grade cytological abnormalities are detected is included in Figure 2.1. Complete details of the CervicalCheck screening process chart are included in Appendix 1.

HPV triage (reflex HPV testing)

In May 2015, CervicalCheck commenced HPV testing in the triage of women with persistent low-grade cytological abnormalities (ASCUS and LSIL).[57] As noted, the collection material from the original smear test is retained for residual testing, so triage testing can proceed without the woman being recalled for an additional smear. The test result indicates the presence or absence of HPV, with no differential diagnosis provided. Women with low-grade cytological abnormalities who are HPV-positive are referred for colposcopy. Women with low-grade cytological abnormalities who are HPV-negative are returned to routine screening. Triage of low-grade cytological abnormalities with HPV testing allows for expedited referral to colposcopy of women who may require treatment. It also reduces the requirement for repeat smear tests in women who are HPV-negative because these women can be reassured that the low-grade cytological abnormalities detected in the smear test are not considered clinically significant.

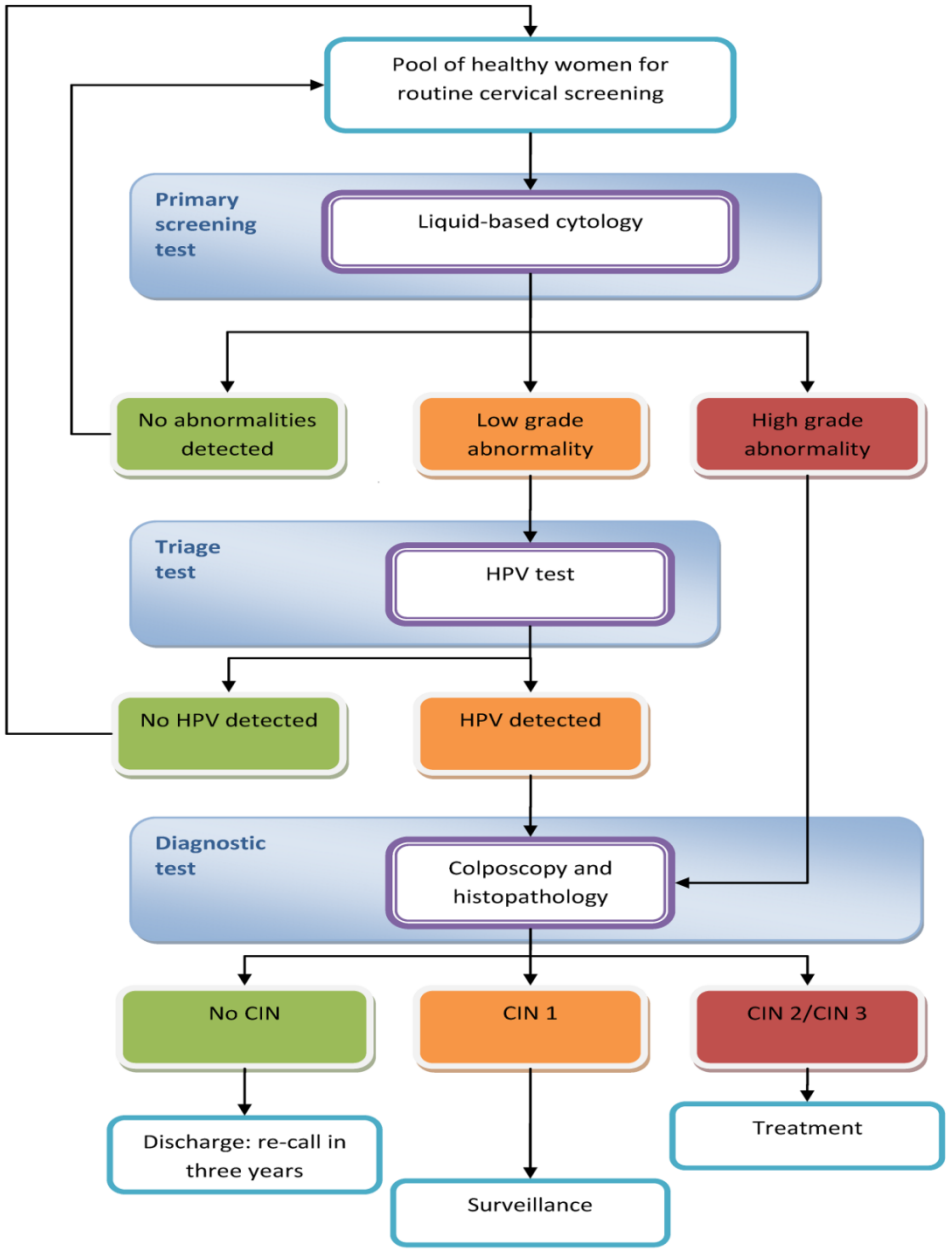
HPV testing in colposcopy

Combined LBC and HPV testing has been provided following treatment (so called 'test of cure') in CervicalCheck colposcopy clinics since 2012.[37] The Hybrid Capture 2 (HC2), Qiagen Inc. was used initially.[55] Since May 2015, the Aptima HPV assay [Hologic] and the cobas® HPV test [Roche Molecular Diagnostics] are used for all HPV testing.[57]

Combined LBC and HPV testing is offered six months after treatment for CIN 2+. Repeat colposcopy is recommended for women with LSIL or a high-grade cytological abnormality on LBC or a positive HPV test. Women with normal (negative) cytology or ASCUS and a negative HPV test are discharged from colposcopy with a recommendation for a repeat smear test in 12 months' time. At this time, women with normal cytology, ASCUS or LSIL and a negative HPV test are discharged from colposcopy and returned to routine screening. All other test results require re-referral to colposcopy.

The addition of HPV testing to LBC has also informed the management of women with persistent low-grade cytological abnormalities who historically were managed with six-monthly LBC and, or colposcopy. Women with CIN 1 who do not require treatment are offered LBC and HPV testing in colposcopy in 12 months' time. At this time, women with high-grade cytological abnormalities on LBC or a positive HPV test are referred for repeat colposcopy. In contrast, women with normal (negative) cytology, ASCUS or LSIL and a negative HPV test are discharged from colposcopy and returned to routine screening. This contrasts with pre-HPV triage policies which necessitated annual surveillance smear tests for up to 10 years.

Figure 2.1 Sample pathway which details what happens when no abnormalities, low-grade cytological abnormalities and high-grade cytological abnormalities are detected



Key: CIN – cervical intraepithelial neoplasia; HPV – human papillomavirus; LBC – liquid-based cytology.
Notes: HPV test is an adjunct to LBC when low-grade cytological abnormalities are detected (ASCUS or LSIL). Surveillance implies repeat cytology at 12 months.

2.3.1.2 Vaccination

Ireland has a nationally funded, school-based, girls-only HPV vaccination programme. This programme commenced in 2010 with a three-dose schedule of the quadrivalent vaccine (Gardasil®) for girls in first and second year of second level schools and age-equivalent girls attending special schools or who were home

schooled. A catch-up programme targeting girls in sixth year in second level schools and for age-equivalent girls (date of birth 1 September 1993 to 31 August 1994) attending special schools, home schooled, Youthreach, and community training centres was provided from September 2011 and repeated for girls in sixth year in 2012 and 2013. Since September 2014, the programme has targeted girls in first year only.[58]

The current Irish national immunisation guidelines recommend a two-dose schedule for those aged nine to less than 15 years and three doses for those aged 15 years and older.[59] Uptake of the vaccine has been consistently high in Ireland with an 86.9% uptake for the two-dose schedule reported among girls in the first year of second level school (typically 12 to 13 years old) in the 2014 to 2015 academic year. There was some evidence of regional variation in uptake (77.4% to 90.8%) among the HSE's nine community healthcare organizations (CHOs), with eight achieving the target of at least 80% uptake. Uptake ranged from 75.1% to 96.9% in HSE Local Health Offices; with 30 of 32 local health offices reaching the target of at least 80% uptake.[60]

Final uptake figures for the 2015-2016 HPV vaccination programme are not yet available. However, preliminary figures indicate a significant decline in uptake with approximately 5,000 fewer girls receiving the vaccine (equating to an approximate 70% uptake) compared with 2014-2015. This decline is attributed to concerns about HPV vaccine safety following high-profile negative publicity. As noted in Section 2.2.2, the possibility of a link between HPV vaccines and two rare conditions complex regional pain syndrome (CRPS) and postural orthostatic tachycardia syndrome (POTS) was reviewed by the European Medicines Agency (EMA). The review process which ran from 13 July 2015 to 12 January 2016 concluded that a causal link with HPV vaccination has not been established.[54] A related decline in HPV vaccination rates due to local safety concerns was documented in a number of other countries including Denmark where rates declined from 81% (3-dose schedule),[61] to 24%.[62] However, high vaccination rates have been maintained elsewhere including Northern Ireland. The annual HPV vaccine coverage for 12 to 13 year olds in Northern Ireland (based on a two-dose schedule) by June 2015 was 86.8%.[63]

Due to differences in the recommended HPV schedule and differences in the delivery of the two-dose schedule, vaccination uptake rates from other countries are not directly comparable. Nonetheless, vaccination uptake rates in the UK have been broadly comparable to those achieved in Ireland, with uptake rates of greater than 80% consistently achieved.[60] Countries that have a school-based HPV vaccination programme have reported higher vaccine uptake rates.[64]

As noted, Ireland's current vaccination programme is based on the quadrivalent vaccine that protects against HPV 16 and HPV 18, thereby only protecting against approximately 70% of cervical cancer cases. Screening for cervical cancer is therefore still recommended for vaccinated cohorts. The first cohort of vaccinated girls (that is, those vaccinated as part of the catch-up programme in 2011) will be eligible for CervicalCheck in 2018-2019.

2.3.2 International practice

International practice in cervical screening and HPV vaccination varies considerably. As approaches to cervical cancer prevention are affected by disease prevalence, this overview focuses on countries with similar disease prevalence and health systems to Ireland as they represent suitable comparisons.

2.3.2.1 Screening

The International Agency for Research on Cancer (IARC) and the 2008 European guidelines for quality assurance in cervical screening recommend that screening programmes should be organised and population-based with a defined target population and screening interval. This should include organised quality assurance at all levels and organised monitoring and evaluation of programme effectiveness over time.[9, 65] The National Health Service (NHS) Cervical Screening Programme in England was established in 1988. This long-established cervical screening programme has led to a reduction in cervical cancer mortality rates. In 2015, it was estimated that screening prevents 70% of all cervical cancer deaths in England.[66] It was estimated that this would increase to 83% if all eligible women attended screening regularly. Between 1989 and 2009-2010, the incidence rate of cervical cancer in England decreased by over a third (from 15.0 to 9.8 per 100,000 female population).[67]

A survey of the quality assurance and organisation of cervical screening programmes in Europe published in 2015 indicated that organised screening was available in 20 of the 29 countries that provided data with screening in the remaining countries limited to opportunistic screening. The recommended screening interval ranged from one year (Austria, Czech Republic, Germany) to five years (Estonia, Finland, Netherlands and Romania). While the target screening age ranged from 17 years (Lichtenstein) to 70 years (Latvia). In seven countries, the screening interval is age or test-dependent. Differences in age range and screening intervals translate to a large difference in the total number of screening tests a woman will receive in her lifetime. Primary screening was predominantly via cytology (conventional cytology: 9; LBC: 7; combination of both: 5), although a number of countries had started to implement primary HPV screening.

With the exception of seven countries that reported not using any HPV testing, the majority reported using HPV testing as triage for cytological abnormalities and, or following treatment for CIN 2+ (so-called 'test of cure'). While quality assurance programmes for screening are implemented in the majority of countries, there is variation in how quality-assurance, monitoring and evaluation are undertaken.[2] A brief sample of historical and current cervical cancer incidence rates, mortality rates and how cervical screening is implemented in European countries is provided in Table 2.4 below.

There is a long history of national cervical screening programmes in countries such as the Netherlands, the UK, Australia and New Zealand. Organised screening commenced in the 1980s in the Netherlands, 1988 in England, 1990 in New Zealand and 1991 in Australia. In contrast, CervicalCheck which commenced in Ireland in 2008 is a relatively new national screening programme. The proportion of women in the target population actually screened within the recommended interval (that is, its coverage) is the main determinant of the success of the programme. The most recent (to 31 December 2016) CervicalCheck five-year coverage compares well with that observed elsewhere (79.6% versus 82.7% in Australia (2010-2014) and 64% in the Netherlands).[68-70] As evident in Table 2.4, incidence of and mortality from cervical cancer have declined in European countries due to long-established screening programmes, and rates are lower than those currently seen in Ireland. Similar trends have been seen elsewhere. 2012 GLOBOCAN data indicate age-standardised incidence and mortality rates of 5.5 and 1.6 per 100,000 population, respectively in combined Australia and New Zealand figures, compared with 13.6 and 3.3 per 100,000 in Ireland.[71]

In response to the introduction of HPV vaccination and publication of high-quality evidence that HPV-based screening provides improved protection against invasive cervical cancer, several countries are transitioning to primary HPV screening. In January 2017, the Netherlands became the first country with an organised cervical screening programme to fully transition from primary cytology screening to primary HPV screening. Australia and New Zealand have recommended the implementation of primary HPV screening, and intend to transition in December 2017[6] and in 2018[7], respectively. Both countries also intend to extend their current screening intervals from two (Australia) and three years (New Zealand) to five years.

It is anticipated that cervical screening programmes will continue to evolve given ongoing advances in HPV testing techniques, including in the range of biomarkers that discriminate between transient acute infection and transforming infection. Further evidence of long-term population-level benefits of HPV vaccination and the

duration of protection afforded by a negative primary HPV screening test are likely to lead to ongoing refinements in cervical screening programmes.

2.3.2.2 Vaccination

In 2006, Austria issued recommendations for a national HPV vaccination programme of girls.[72] It was the first European country to do so, but the programme was not publicly funded until 2014. A survey of the quality and organisation of HPV vaccination programmes in 34 European Union and European Free Trade Agreement countries was conducted between May 2012 and March 2014.[73] Sixteen of the 27 countries that responded had organised programmes, while the remaining countries reported opportunistic vaccination only. Eleven of the organised programmes were school-based. The target age for organised programmes was 10 to 14 years. Nine countries provided a time-limited catch-up vaccination programme to vaccinate older girls who may have still benefited from vaccination.[73] Details of the HPV vaccination programme in a small sample of European countries are provided in Table 2.4.

In the UK, a national HPV vaccination programme with the bivalent vaccine commenced for girls aged 12 to 13 years in 2008.[74] The programme switched to using the quadrivalent vaccine in 2012.[75] In England in 2015-2016 the uptake rate of a two dose course was 85.1%.[76] In 2010 the Netherlands commenced a national HPV vaccination programme for girls using a bivalent vaccine.[77] In 2014, the uptake rate of a three dose course was 61%.[77] In 2010, Ireland commenced a national vaccination programme using a quadrivalent vaccine.[78] The uptake rate of a two dose course was 86.9% in 2014-2015,[79] falling to 72.3% in 2015-2016.[80]

The implementation of publicly-funded national school-based programmes of HPV vaccination for girls started in Australia and Canada in 2007.[81] Community-based vaccination for all females up to age 26 years was also provided in Australia until the end of 2009.[82, 83] In 2008, New Zealand implemented a national HPV vaccination programme with the quadrivalent vaccine and offered it to girls and young women up to 20 years of age.[84] In 2014, the uptake rate of a three dose course by the 2001 birth cohort was 60%.[85]

In most European countries, universal HPV vaccination of girls and boys (gender-neutral vaccination) is not currently recommended.[81] Austria was the first European country to recommend a national universal gender-neutral HPV vaccination programme in 2013.[81] A publicly-funded programme was implemented the following year with the HPV vaccine being offered to boys and girls between the ages of nine and 12 years.[86] Since then, policy-makers in Australia, New Zealand, Canada and the US have also recommended universal gender-neutral HPV vaccination. Australia extended the national HPV vaccination programme to include

boys aged 12 to 13 years in 2013[83] with a catch-up programme available for boys aged 14 to 15 years in 2013 and 2014.[82] In 2015, the reported uptake rate of a three dose course was 77.8% in girls and 67.0% in boys.[87] In January 2017, vaccination of girls, boys, young women and young men age nine to 26 years with the nonavalent vaccine was introduced in New Zealand.[84]

The results of cost-effectiveness studies of universal HPV vaccination vary depending on vaccine coverage, vaccine price, time horizon, discount rate and types of HPV-related cancers included in the analysis.[81, 88, 89]

Table 2.4 Summary of the burden of cervical cancer and cervical cancer prevention strategies in a selection of European countries

Country	Disease burden: cervical cancer			Cervical screening programme[2]				HPV vaccination*[73]
	Historical cervical cancer incidence (time interval)/10^5 [2]#	2012 Cervical cancer incidence /10^5 ¥	2012 Estimated mortality/10^5 ¥	Population age range (yrs)	Test type and frequency of testing (yrs)			Recommended age
					CC	LBC	HPV	
Denmark	28.3 (1953–1957)	10.6	1.9	23-65		3 (23-49) 5 (50-65)	Triage, ToC, Pr-Exit	12
France	16.4-18.2 (1975-1977)	6.8	1.9	25-65	3	3	Triage	11-14
Ireland	8.3 (1994–1997)	13.6	3.3	25-60	-	3 (25-44) 5 (45-64)	Triage[90], ToC	12-13
Italy	11.7 (1976–1977)	6.7	1.5	25-64	3	3	Primary Screen (5 yearly), Triage, ToC	11
Netherlands	7.1 (1989–1992)	6.8	1.6	30-60	-	-	Primary Screen (5 yearly)§[5] ToC	13
UK		7.1	1.8	25-64		3 (25-49) 5 (50-64)	Triage, ToC	12-13
England	8.2 (1993–1997)	8.5			-			12-13
Scotland	12.4 (1963–1966)	8.9						12-13
Wales	-	-						12
Northern Ireland	7.9 (1993–1997)	7.6						12-13

Oldest available incidence per 100,000 estimates from IARCs Cancer Incidence in Five Continents
¥Age-standardised rate per 100,000 obtained from GLOBOCAN 2012[71]
* Vaccination introduced as part of an organised programme: Denmark (10/2012); Italy (between 07/2007-11/2008); Netherlands (2009); UK (09/2008). HPV vaccination included in the immunisation schedule in France in 2007, but is not part of an organised vaccination programme.
§ Screening at 10-yearly intervals for women aged ≥40 years following a negative HPV test.
Key: CC – conventional cytology; HPV – human papillomavirus; LBC – liquid-based cytology; PR-Exit – programme exit; ToC – 'test of cure'.[70, 91, 92]

2.4 Discussion

The aim of a cervical screening programme is to reduce the incidence, morbidity and mortality from cervical cancer through early detection and treatment of precancerous abnormalities and early stage invasive cervical cancer. In 2004, the International Agency for Research on Cancer (IARC) estimated that well-organised cervical screening programmes incorporating cytology-based screening at three to five year intervals for women aged 35 to 64 years would reduce the incidence of cervical cancer by at least 80% among those screened. The acknowledged role of persistent infection with HPV in the development, maintenance and progression to cervical cancer, together with technological advances in the methods of detecting HPV, and introduction of a national HPV vaccination programme in 2010 provides a rationale for potential changes to CervicalCheck.

CervicalCheck, which commenced in September 2008, provides a comprehensive, quality-assured cervical screening programme for women aged 25 to 60 years. Consistent with IARC recommendations, screening is at three-yearly intervals for women aged 25 to 44 years and at five-yearly intervals for those aged 45 to 60 years. Current screening comprises primary screening with liquid-based cytology (LBC) and, since May 2015, HPV triage of low-grade cytological abnormalities. Over 98% of screening tests are undertaken in primary care, predominantly through GP practices. Both the primary and triage tests are completed using a single smear test.

Persistent infection with HPV is a necessary, but not sufficient requirement for the development of cervical cancer. As such, the primary prevention of cervical cancer is vaccination against HPV. The current, national vaccination programme is based on a two-dose schedule of the quadrivalent vaccine that protects against HPV 16 and HPV 18. Worldwide, HPV 16 and HPV 18 contribute to 16% to 32% of low-grade abnormalities, 41% to 67% of high-grade abnormalities, and to 70% of squamous cell carcinoma cases.[18] Screening for cervical cancer is therefore still recommended for vaccinated cohorts. However, it is noted that a decline in the prevalence of precancerous abnormalities due to vaccination will lead to a decline in the probability that a woman who tests positive actually has the disease (a decrease in the positive predictive value of LBC).. In Ireland, the first cohort of girls vaccinated against HPV (as part of the catch-up programme in 2011) will be eligible for CervicalCheck in 2018-2019.

Cervical screening programmes in developed countries vary in their recommendations for the age range and frequency of screening. While cytology (conventional cytology or LBC) is currently used as the primary screening test in the majority of the countries, HPV testing is increasingly being adopted as part of

population-based screening programmes. High-income countries such as Australia, Italy, the Netherlands, New Zealand, Sweden and the UK have recommended the implementation of HPV testing as the primary screening method.

HPV testing is indicated for primary cervical screening for selected age groups, in triage of women with low-grade cytological abnormalities, and as follow up to the treatment of high-grade histological abnormalities (so called 'test of cure'). In triage of low-grade cytological abnormalities, HPV testing differentiates between those that do, and do not have HPV, allowing those who are HPV negative and at very low risk of developing cervical cancer for at least five years to return to routine screening.

Developments in the methods of detecting HPV, including developments in HPV genotyping and detection of transforming HPV infections, together with changes in the burden of HPV due to vaccination programmes mean that there is an opportunity to optimise CervicalCheck to ensure its continued success and relevance.

2.5 Key messages

- There are two complementary approaches for the prevention of cervical cancer: primary prevention through vaccination to prevent infection with the human papillomavirus (HPV) and secondary prevention through cervical screening.
- Screening aims to reduce the incidence, morbidity and mortality from cervical cancer through early detection and treatment of precancerous abnormalities and invasive cervical cancer.
- There is well-documented evidence of a reduction in the incidence of and mortality from cervical cancer with long-established cervical screening programmes. For example, the National Health Service (NHS) Cervical Screening Programme in England was established in 1988.The incidence rate of cervical cancer in England decreased by over a third in the 20 years since the establishment of the programme. It is estimated that this screening programme prevents 70% of all cervical cancer deaths.
- Screening tests are not 100% accurate which, coupled with the fact that the disease could develop at any time, means that screening programmes require regular, defined screening intervals. The intervals are based on a balance of over- and under-screening to minimise any associated risks or harms.
- Screening tests may be broadly classified as those designed to identify precancerous abnormalities or invasive cervical cancer (cytology tests) and those designed to detect the presence of the HPV virus, persistent infection with which is a necessary pre-requisite for the development of cervical cancer.
- Screening tests do not provide a diagnosis, but rather identify potential cases which require further testing. Histological review of biopsies obtained via

colposcopy is the 'gold standard' diagnostic test for precancerous abnormalities and invasive cervical cancer.

- On 1 September 2008, CervicalCheck – Ireland's National Cervical Screening Programme became available to more than 1.1 million women aged 25 to 60 years living in Ireland. Women between the ages of 25 and 44 years are offered screening at three-yearly intervals. Women between the ages of 45 and 60 years are offered screening at five-yearly intervals.
- Liquid-based cytology to detect cellular abnormalities is used as the primary screening test by CervicalCheck. Co-testing with HPV post treatment at colposcopy was introduced in 2012. HPV triage of low-grade cytological abnormalities was introduced in May 2015.
- Since September 2010, Ireland has had a nationally funded, school-based, girls-only HPV vaccination programme. The first cohort of vaccinated girls will be eligible for CervicalCheck in 2018-2019.

3 Burden of disease

Cervical cancer, also known as cervical carcinoma, is defined by its location. Cancers of the cervix uteri refer to those situated in the lower constricted part of the uterus or neck which connects the uterus to the vagina.[93] Invasive cervical cancer is usually preceded by precancerous abnormalities and pre-invasive cervical cancer (carcinoma *in situ*). Microscopically, this is characterised by abnormalities which progress from abnormal cervical cells (low-grade or high-grade on cytology or CIN or CGIN on histology) to invasive cervical cancer. When abnormal squamous cells (CIN 3) or abnormal glandular cells (AIS) occupy the full thickness of the epithelium, but they do not extend beyond or invade the basement membrane they are described as *in situ*. Cervical carcinoma *in situ* includes cervical intraepithelial neoplasia 3 (CIN 3) and adenocarcinoma *in situ* (AIS). This chapter describes the burden and epidemiology of cervical carcinoma *in situ* and invasive cervical cancer in Ireland in terms of incidence, mortality and treatment. Infection with 'oncogenic' subtypes 'so called hrHPV' is associated with virtually all cases of cervical cancer. A number of cofactors are also implicated in the progression to cervical cancer. The prevalence of HPV infection and its distribution by cytological finding is discussed in the latter part of the chapter.

3.1 Incidence

In Ireland, cervical cancer was the eighth most commonly diagnosed cancer in women between 2012 and 2014 (excluding non-melanoma skin cancer).[94] Cancer is the second most common cause of death in Ireland. Invasive cervical cancer was the twelfth most common cause of cancer death for women in Ireland between 2011 and 2012.[94]

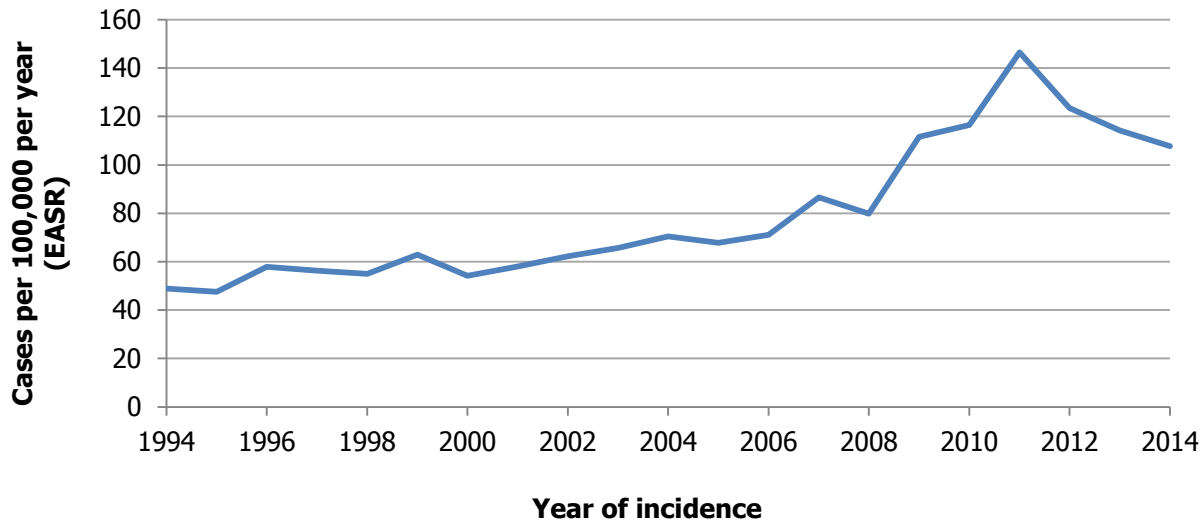
Within a European context, the estimated incidence of cervical cancer varies widely. In 2012, the estimated incidence in Ireland was 15.1 per 100,000 (European age-standardised rate [EASR]), compared with the EU27 incidence of 11.3 per 100,000.[95] Highest rates were recorded in Romania (34.9 per 100,000 EASR), with lowest rates in Switzerland (4.2 per 100,000 EASR), Malta and Finland. Ireland is ranked eighteenth within Europe (40 countries) in terms of cervical cancer incidence.[95]

CervicalCheck, Ireland's National Cervical Screening Programme, commenced in September 2008. Prior to this, the Irish Cervical Screening Programme (ICSP) operated as a pilot programme in Counties Limerick, Clare and North Tipperary from 2000.[96] ICSP Phase One covered nine percent of the eligible population nationally. Opportunistic cytology screening was also common. Nationally, up to 250,000 smear

tests were screened every year, of which 22,000 were carried out as part of the ICSP Phase 1 programme.[97]

Between 1994 and 2014, a total of 38,448 cases of cervical carcinoma *in situ* were diagnosed in Ireland. For the period 2012 to 2014, there were on average of 2,873 cases per year. There was an upward trend in the incidence of cervical carcinoma *in situ* in Ireland with age-standardised rates increasing from 48.9 per 100,000 population at risk in 1994 to 107.7 per 100,000 population at risk in 2014 (Figure 3.1). The average incidence in the last three years of reporting (2012 to 2014) was 115.1 per 100,000 population at risk, corresponding with a cumulative lifetime risk of diagnosis of cervical carcinoma *in situ* (to age 74) of, 1 in 13 women.

Figure 3.1 Age-standardised incidence rates of cervical carcinoma *in situ per 100,000 population at risk by year of diagnosis, Ireland 1994 - 2014**



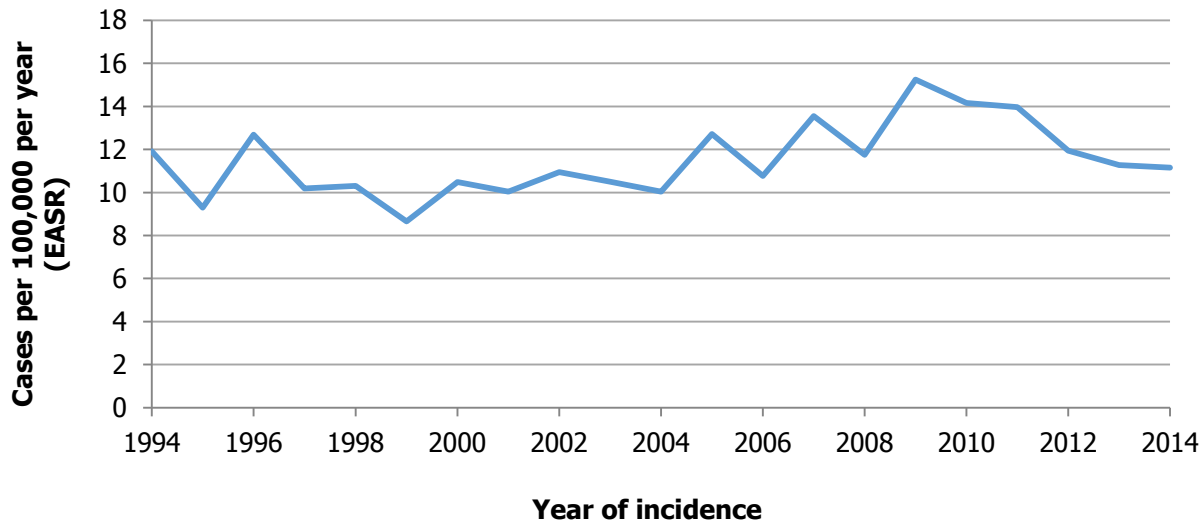
Data: National Cancer Registry Ireland, age–standardised to the European Standard Population (1976)

* Cervical carcinoma *in situ* corresponds with cervical intraepithelial neoplasia III (CIN 3) and adenocarcinoma in situ (AIS)

There was a marked increase in the reported incidence of cervical carcinoma *in situ* after 2008. This coincided with the introduction of CervicalCheck, and the high profile death in 2009 of a celebrity in the UK from invasive cervical cancer, publicity from which led to increased cervical screening uptake, particularly amongst those who were screening-naive.[98] Of note, these figures are based on incidence data for cervical carcinoma *in situ* provided by the National Cancer Registry in Ireland (NCRI). They differ from CervicalCheck treatment data (Section 3.3) as they do not include other conditions treated at colposcopy services such as CIN 2. The changes in method of presentation (for example, symptomatic, screen-detected) are discussed in Section 3.1.4.

Between 1994 and 2014, a total of 4,955 cases of invasive cervical cancer were diagnosed in Ireland. Almost 98% of these were regarded as a first significant tumour. Between 2012 and 2014, there were on average 277 cases diagnosed per annum. The age-adjusted rate of invasive cervical cancer has increased slightly over time. The average incidence in the last three years of reporting (2012 to 2014) was 11.5 per 100,000 population at risk, corresponding with a cumulative lifetime risk of diagnosis (to age 74) of 1 in 112 women. Although there was some year-to-year variation, there was an overall slight increasing trend over time (Figure 3.2). When broken down into thirty-year age bands, this trend was mirrored in the 30 to 59 year old age group. There was less evidence of variation in those aged under 30 and over 60 years, but these age groups accounted for fewer cases.

Figure 3.2 Age-standardised incidence rates of invasive cervical cancer per 100,000 population at risk by year of diagnosis, Ireland 1994 - 2014



* Data: National Cancer Registry Ireland, age–standardised to the European Standard Population (1976)

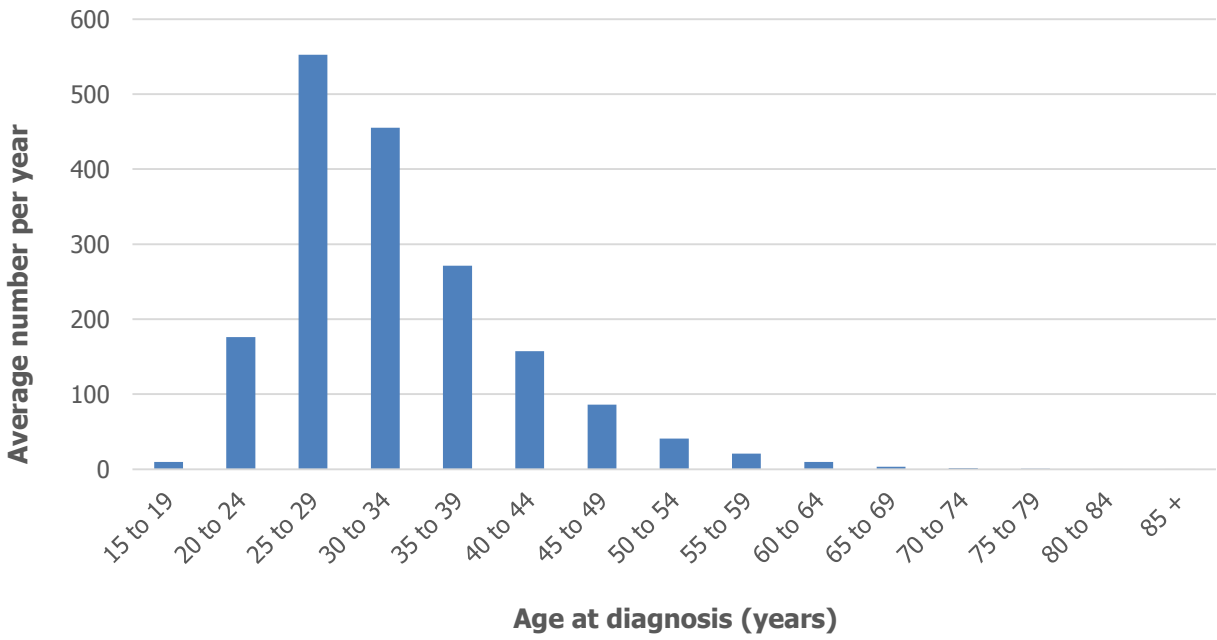
A 2014 cancer projections report, predicted that the numbers of invasive cervical cancers in Ireland would increase by 77 to 88% between 2015 and 2040.[99] Changing sexual behaviour and an increase in the prevalence of HPV were believed to be the most important factors influencing these trends.[99] However, these projections did not take the impact of CervicalCheck and the inclusion of HPV vaccination of schoolgirls in the national immunisation programme into account, and are well above those predicted based on demography alone which estimate an 18% increase in cases of cervical cancer by 2040.[99] A rise in the reported incidence of cancer is expected at the beginning of an organised screening programme due to detection of prevalent cases. The incidence of invasive cervical cancer should

however reduce over time due to the earlier detection and management of precancerous abnormalities and early stage invasive cancer as a result of well organised screening.

3.1.1 Age profile

Cervical carcinoma *in situ* and invasive cervical cancer is predominantly a disease of younger women. The average annual number of cases of cervical carcinoma *in situ* by age at diagnosis for the period 1994 to 2013 is shown in Figure 3.3. The most common age at diagnosis was between 25 and 29 years.

Figure 3.3 Average annual number of cases of cervical carcinoma *in situ* * by age at diagnosis, 1994 to 2013

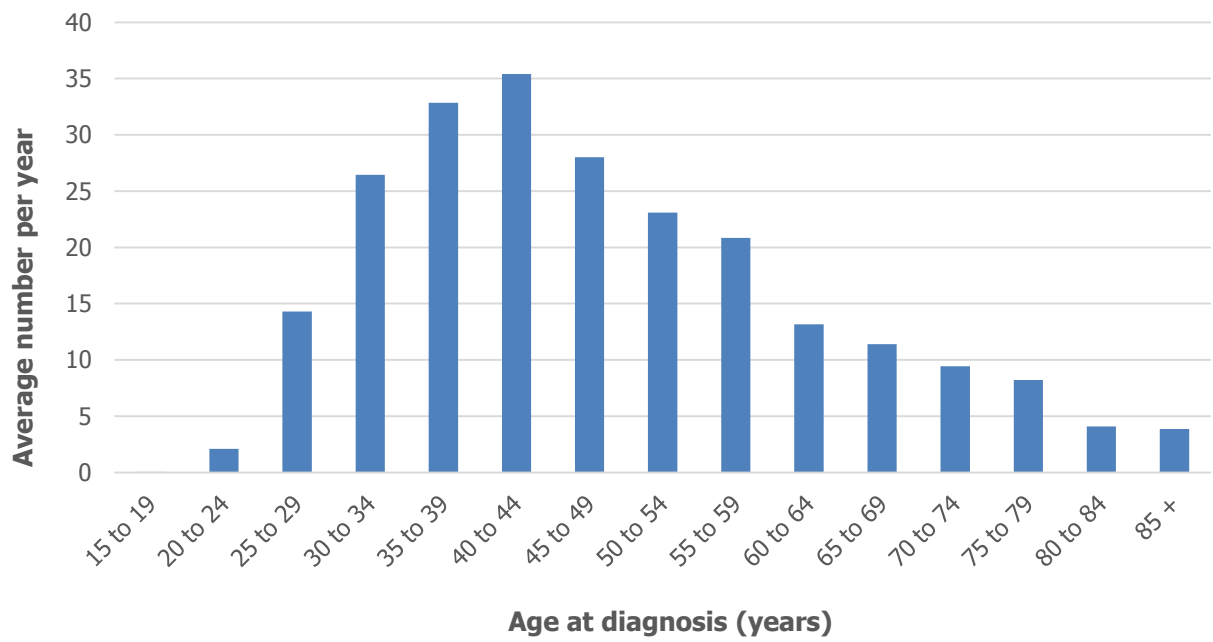


Data courtesy of National Cancer Registry, Ireland

* Cervical carcinoma *in situ* corresponds with cervical intraepithelial neoplasia III (CIN 3) and adenocarcinoma in situ (AIS)

The average annual number of cases of invasive cervical cancer by age at diagnosis for the period 1994 to 2013 is shown in Figure 3.4. The most common age at diagnosis was between 40 and 44 years.

Figure 3.4 Average annual number of cases of invasive cervical cancer by age at diagnosis, 1994 to 2013



Data courtesy of National Cancer Registry, Ireland

3.1.2 Geographic distribution

The relative risk of cervical cancer increases with increasing population density, level of unemployment and lower educational attainment.[7] Areas of highest relative risk of cervical cancer are concentrated around Dublin, along Wexford's east coast and west into the midlands. Lower relative risks have been observed in the south-west of Ireland, Mayo and Donegal.[100] Based on NCRI data from 2008 to 2012, the age-standardised rates of cervical cancer were significantly higher in urban than in rural populations (1.21; 95% CI: 1.09 to 1.35).

Globally there is a marked socio-economic gradient whereby those with lower socio-economic status have a higher incidence of cervical cancer.[101] Information on deprivation index (SAHRU) was available for almost 93% of cervical cancers diagnosed in Ireland between 1994 and 2012. For those for whom the SAHRU deprivation score (based on the 2002 census) was known, 17% had a score of one (least deprived) and 40% a score of five (most deprived).[102] Data from 2008 to 2012 indicate that age-standardised rates increased linearly with increasing levels of deprivation, with rates of cervical cancer noted to be twice as high in the most deprived compared with the least deprived stratum (2.23; 95% CI: 1.88 to 2.64).[103] Urban populations showed stronger evidence of disparities in incidence by level of deprivation.[103]

3.1.2 Anatomical sites and histological types

The cervix or cervix uteri forms the lower third of the uterus, projecting into the upper portion of the vagina. It runs through the endocervical canal which connects the vagina with the uterine cavity. The endocervical canal is lined by columnar or glandular epithelium. The ectocervix, which is the vaginal section of the cervix, is covered by squamous epithelium. The junction where these meet is called the squamocolumnar junction (SCJ).[104] The location of the SCJ is not constant and changes with the changes which occur in the volume of the cervix in response to hormonal stimulation.[11] After menopause it can be found at the endocervical canal following its retreat from the ectocervix. The transformation zone is the area between the original and new SCJ and is the area where the majority of precancerous abnormalities are detected (Figure 3.5).[11]

Figure 3.5 Location of the squamocolumnar junction and the transformation zone

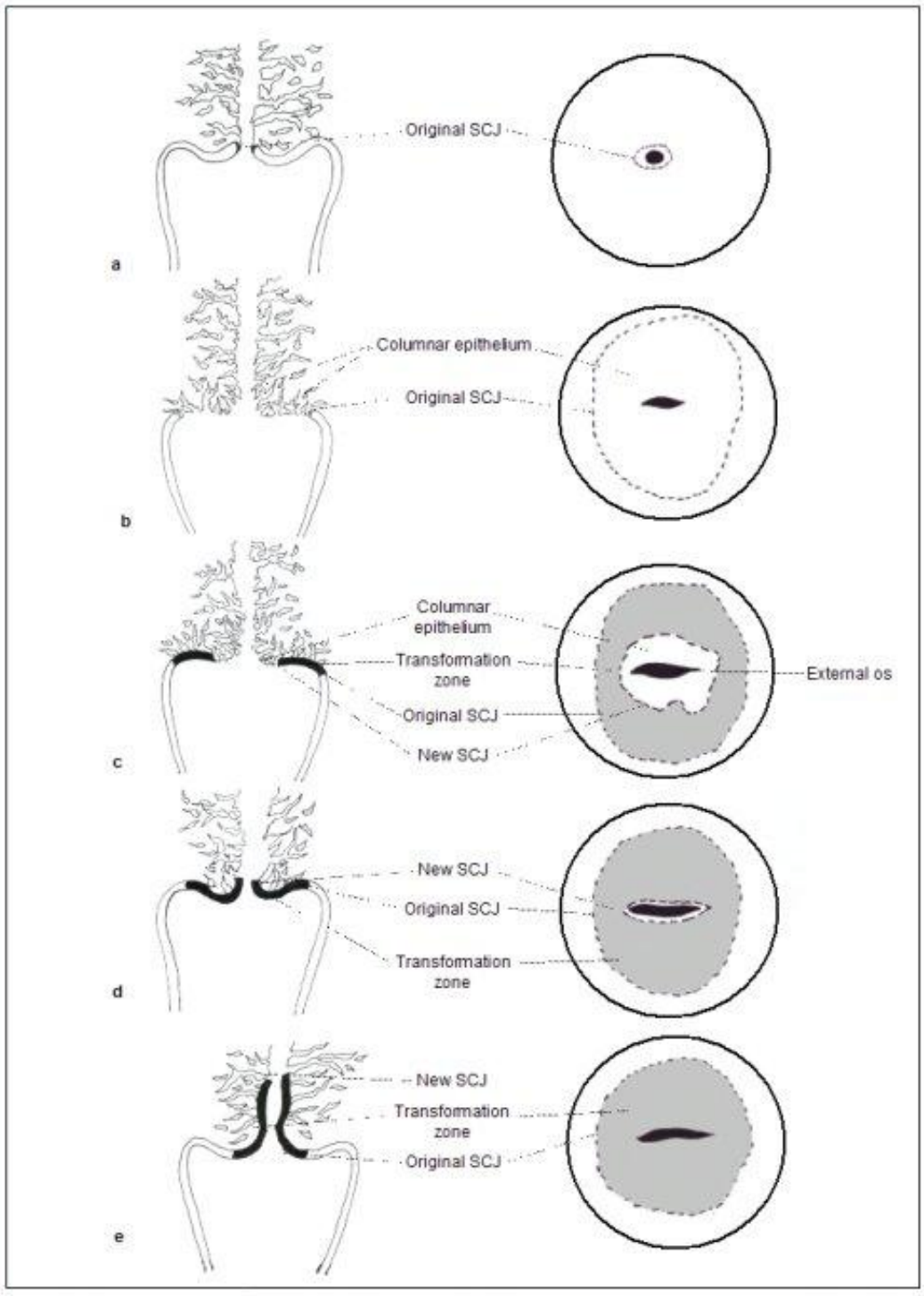


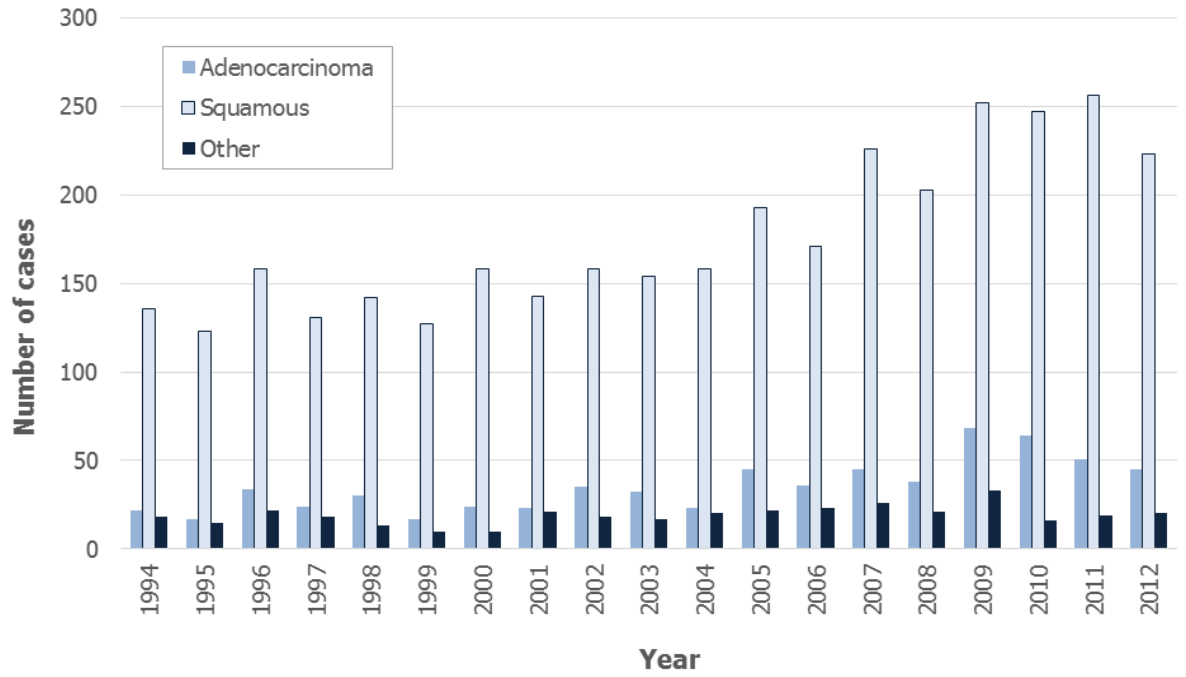
FIGURE 1.7: Location of the squamocolumnar junction (SCJ) and transformation zone; (a) before menarche; (b) after puberty and at early reproductive age; (c) in a woman in her 30s; (d) in a perimenopausal woman; (e) in a postmenopausal woman.

Reproduced with permission from Sellors J.W. and Sankaranarayanan R. Colposcopy and Treatment of Cervical Intraepithelial Neoplasia. A Beginner's manual. Lyon, France, IARC Press, 2003, http://screening.iarc.fr/doc/Colposcopymanual.pdf

Data from the NCRI show that microscopic verification was available for all but one of the 32,993 cases of cervical carcinoma *in situ* diagnosed between 1994 and 2012. Ninety-eight percent of cases were squamous cell in origin with the remainder being adenocarcinoma (1.5%) or unspecified (0.5%).

Data from the NCRI show that microscopic verification was available for more than 98% of the 4,394 cases of invasive cervical cancers diagnosed between 1994 and 2012. Squamous cell carcinoma was the most common histological type followed by adenocarcinoma (see Figure 3.6). Others included sarcomas, basal cell, unspecified or other cancer or carcinomas.

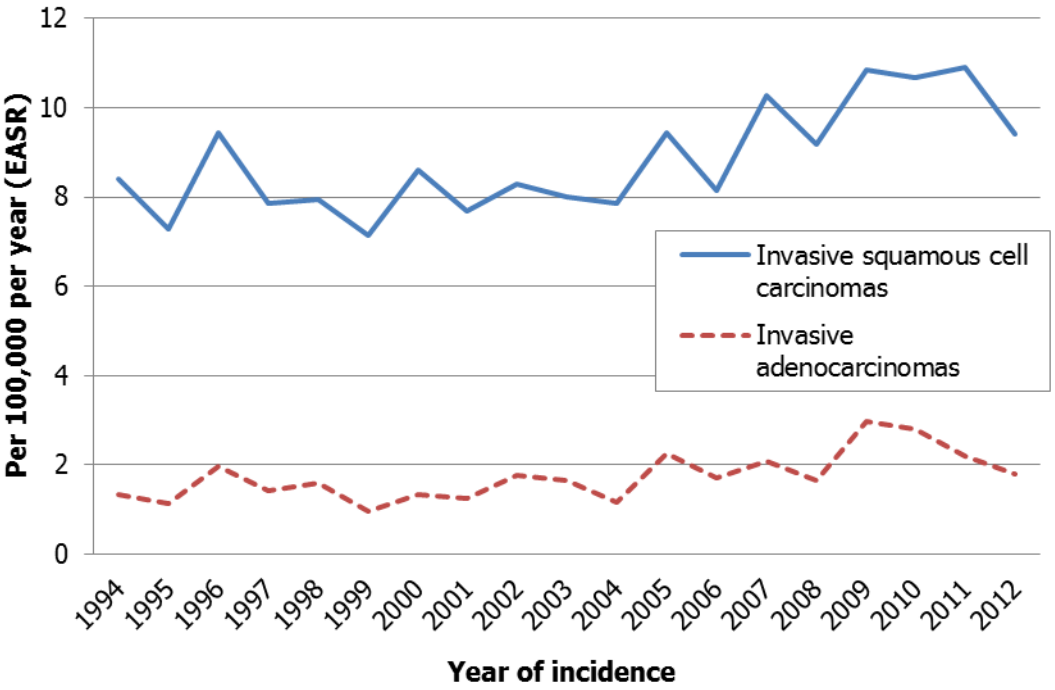
Figure 3.6 Histological types of invasive cervical cancer by year of diagnosis, 1994 to 2012



Data courtesy of National Cancer Registry, Ireland

Rates of invasive squamous cell carcinoma and invasive adenocarcinoma standardised to the European 1976 standard population are shown in Figure 3.7. These mirrored the overall age-standardised rate of invasive cervical cancer in this period. Peaks in the rates are seen in 2009 following the introduction of CervicalCheck in 2008.

Figure 3.7 Incidence of invasive squamous cell carcinoma and invasive adenocarcinoma by year of diagnosis, 1994 to 2012



Histological data courtesy of National Cancer Registry Ireland, age–standardised to the European Standard Population (1976)

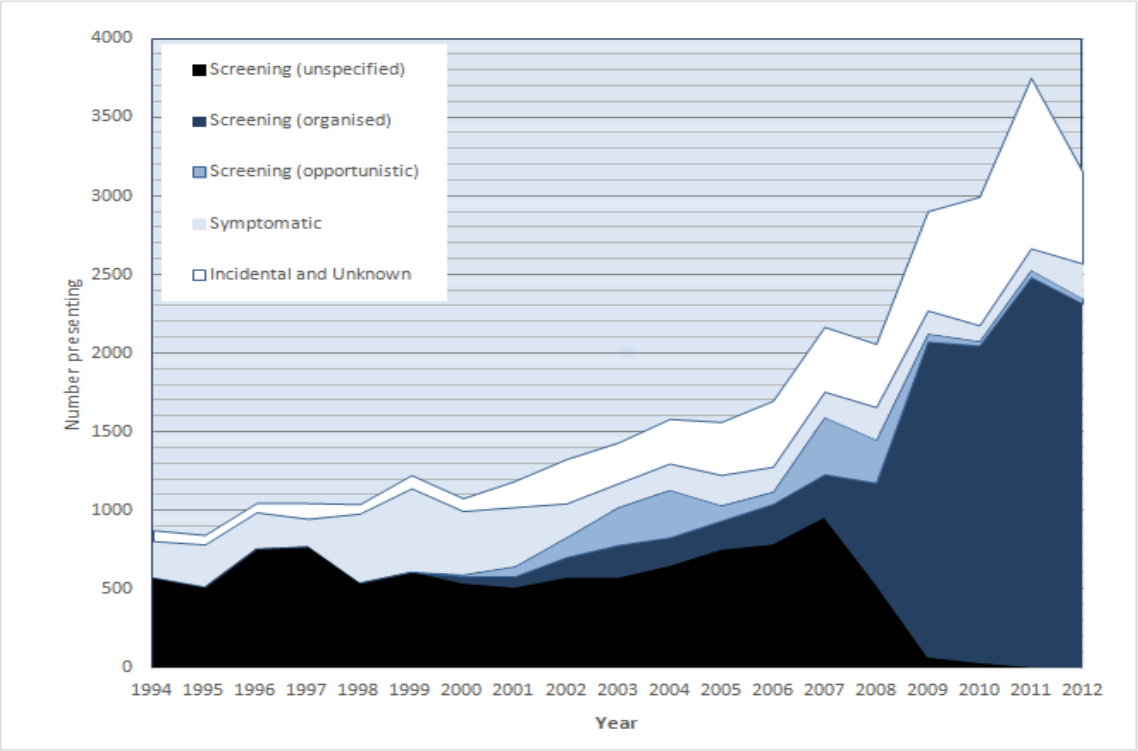
Age-standardised rates of invasive adenocarcinoma have increased throughout Europe, with increases ranging from 0.5% to greater than or equal to 3% per annum.[105] The year-on-year fluctuation in age-standardised rates of invasive cervical cancer in Ireland can be seen in Figure 3.7. Squamous cell carcinomas constitute most cases of invasive cervical cancer where there is poor population coverage with cervical screening.[106, 107] Cervical screening is associated with a reduced risk of both squamous cell carcinoma and adenocarcinoma, but the reduction is significantly greater for squamous cell carcinoma than it is for adenocarcinoma.[107] The relative proportion of adenocarcinoma increases when an organised cervical screening programme is in place because to date organised cervical screening programmes have been better at detecting exocervical than endocervical abnormalities.[106, 107]

3.1.3 Method of presentation

Between 1994 and 2012, NCRI data indicate that 68.4% of the 32,993 cases of cervical carcinoma *in situ* presented through screening, 13.6% presented with symptoms and the method of presentation was unknown in the remainder (Figure 3.8). Symptoms can include abnormal vaginal bleeding (intermenstrual bleeding, post-menopausal bleeding or post-coital bleeding) and vaginal discharge. The

number of cases of cervical carcinoma *in situ* presenting through screening increased in the year following implementation of CervicalCheck in 2008 (Figure 3.8).

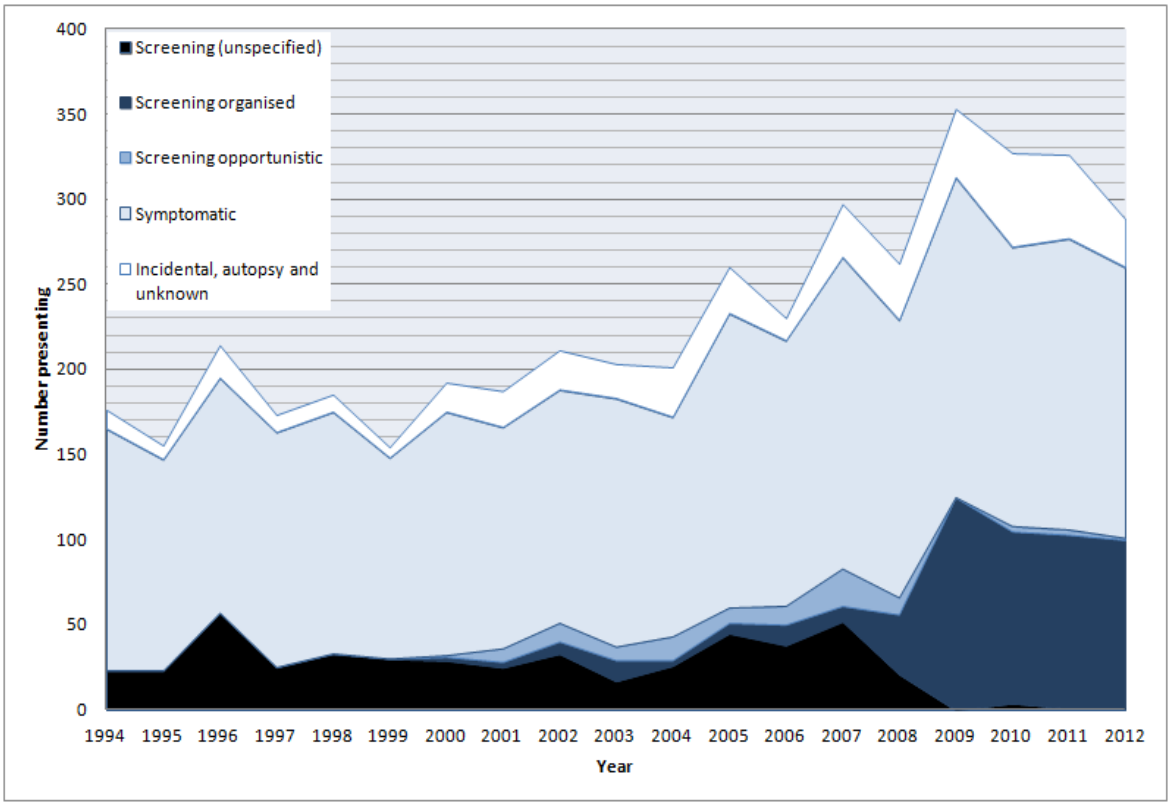
Figure 3.8 Number of cervical carcinoma *in situ* * by reason for presentation, 1994 to 2012



Data courtesy of National Cancer Registry, Ireland
* Cervical carcinoma *in situ* corresponds with cervical intraepithelial neoplasia III (CIN 3) and adenocarcinoma in situ (AIS)
Following the introduction of CervicalCheck in September 2008, women outside the ages of 25 to 60 years had open access to CervicalCheck (organised screening). In these women, it is thought that a proportion of cases of cervical carcinoma *in situ* which were classified as detected through 'opportunistic' or 'unspecified' screening were in fact detected through CervicalCheck.

Between 1994 and 2012, the majority of the 4,394 cases of invasive cervical cancer cases presented with symptoms (Figure 3.9). Symptoms included abnormal vaginal bleeding, vaginal discharge, pelvic pain or discomfort during intercourse. The method of presentation was unknown in approximately 8% of cases and a small number of cases (n=5) were detected at autopsy. The number of cases of invasive cervical cancer presenting through screening increased in the year after the implementation of CervicalCheck in 2008 (Figure 3.9).

Figure 3.9 Number of invasive cervical cancers by reason for presentation, 1994 to 2012*



Data courtesy of National Cancer Registry, Ireland
*Following the introduction of CervicalCheck in September 2008, women outside the ages of 25 to 60 years had open access to CervicalCheck (organised screening). In these women, it is thought that a proportion of cases of invasive cervical cancers which were classified as detected through 'opportunistic' or 'unspecified' screening were in fact detected through CervicalCheck.

3.1.4 Stage and grade at presentation

Cervical cancer is staged clinically according to the International Federation of Gynecology and Obstetrics (FIGO) classification system (see Appendix 2). Staging is based mainly on the findings on physical examination and tests such as cystoscopy, sigmoidoscopy and MRI. The stage of cervical cancer depends upon the size of the tumour, invasion of surrounding tissues, lymph node status and metastases. Staging is not based on findings at the time of surgery. The stage of a cervical cancer is important for determining treatment options and indicating prognosis.[108] The findings at surgery may change the treatment plan, but they do not change the staging. Cervical cancer can also be classified using the American Joint Committee on Cancer (AJCC) TNM system classification system. This is based on three factors:

- The extent of the primary **tumour** (T).
- Whether the cancer has spread to nearby lymph **nodes** (N).
- Whether the cancer has **metastasised** to distant parts of the body (M).

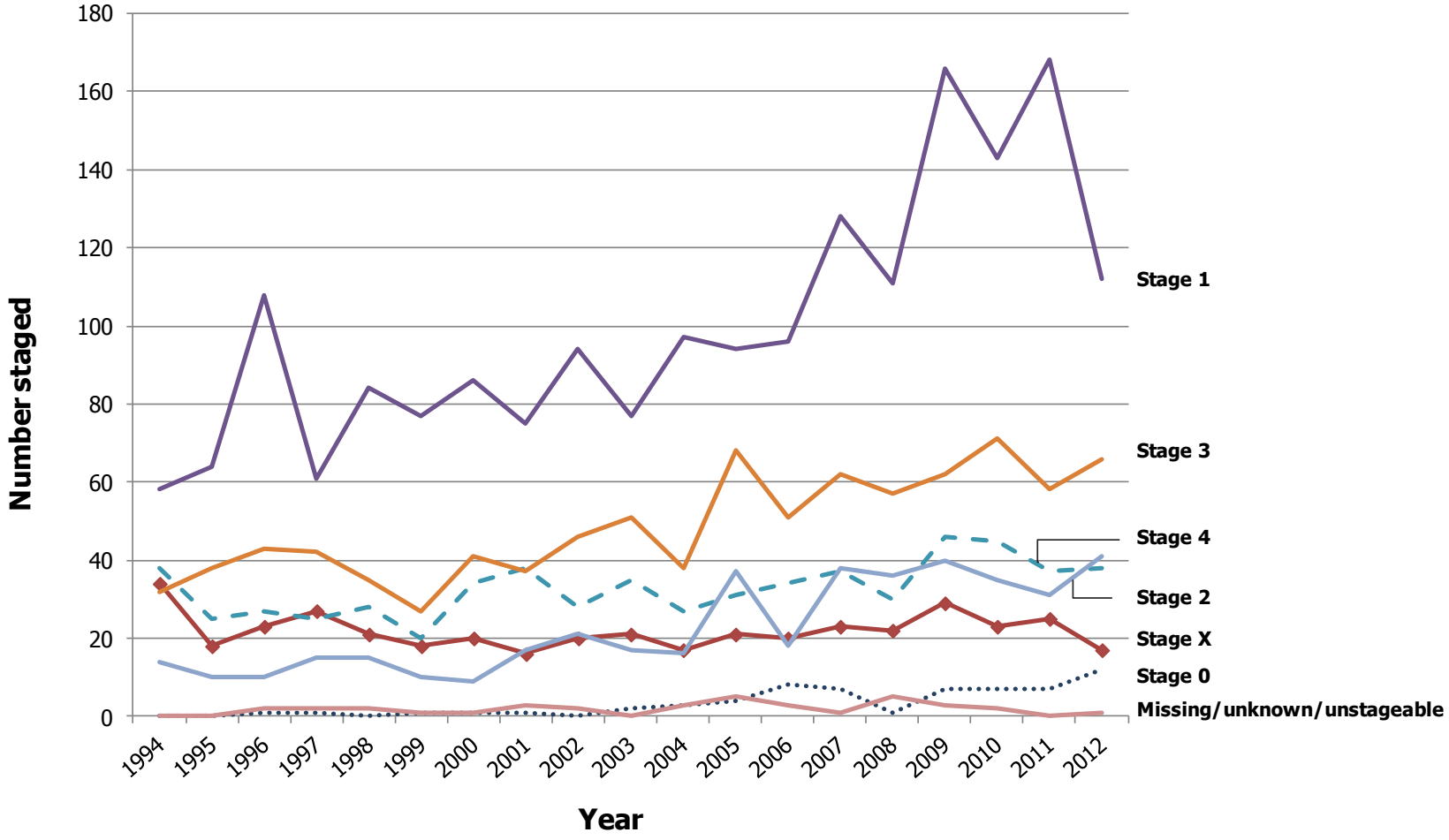
Table 3.1 Cervix uteri cancer staging

FIGO stage	Primary tumour	Nodes	Metastases
Stage 0	Tis*	N0	M0
Stage 1	T1	N0	M0
Stage IA	T1a	N0	M0
Stage IA1	T1a1	N0	M0
Stage IA2	T1a2	N0	M0
Stage IB	T1b	N0	M0
Stage IB1	T1b1	N0	M0
Stage IB2	T1b2	N0	M0
Stage II	T2	N0	M0
Stage IIA	T2a	N0	M0
Stage IIA1	T2a1	N0	M0
Stage IIA2	T2a2	N0	M0
Stage IIB	T2b	N0	M0
Stage III	T3	N0	M0
Stage IIIA	T3a	N0	M0
Stage IIIB	T3b	Any N	M0
	T1-3	N1	MO
Stage IV			
Stage IVA	T4	Any N	M0
Stage IVB	Any T	Any N	M1

Staging key adapted from American Joint Committee on Cancer Staging Manual
*carcinoma *in situ*

In Ireland, between 1994 and 2012, over 43% of invasive cervical cancers were FIGO stage I at diagnosis, 14% were stage II, 21% were stage III and almost 10% were stage IV at diagnosis. The remaining 12% were recorded as unknown, not applicable, no evidence of a primary tumour or the primary tumour could not be assessed (Figure 3.10). Treatment of invasive cervical cancer, particularly in early stages differs with stage and substage. Table 3.2 provides a breakdown of the summary stages of invasive cervical cancer presenting between 1994 and 2012 in Ireland.

Figure 3.10 Staging distribution of invasive cervical cancer in Ireland by year of diagnosis, 1994 to 2012



Data courtesy of National Cancer Registry Ireland

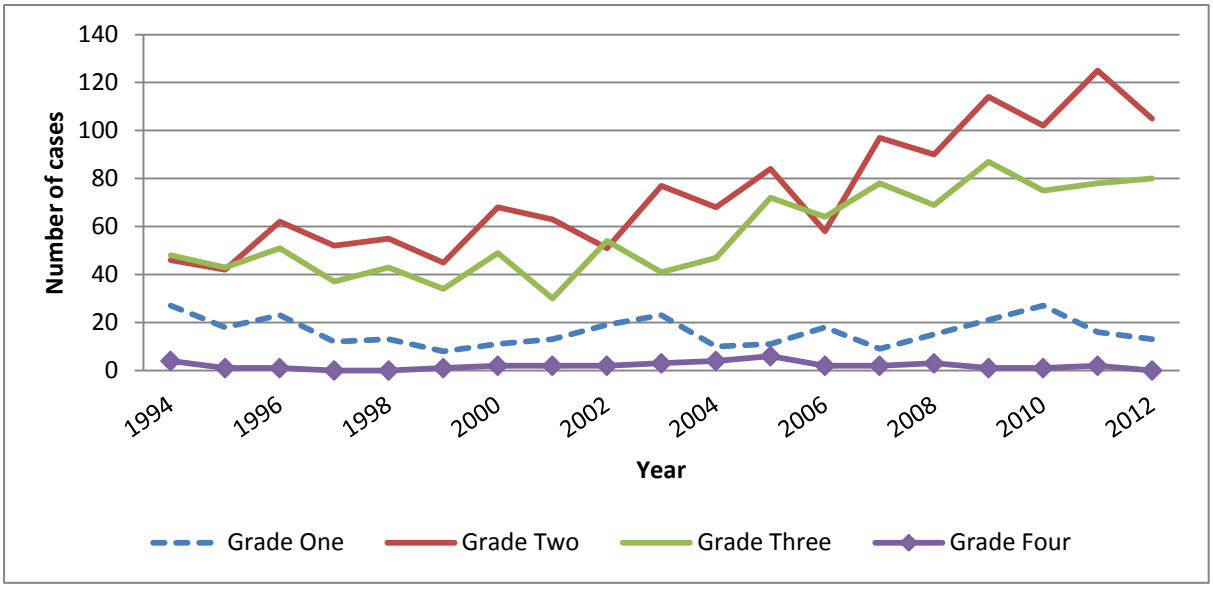
Table 3.2 Staging distribution of invasive cervical cancer cases by year of diagnosis, 1994 to 2012

AJCC Summary Stage	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
X‡	34	18	23	27	21	18	20	16	20	21	17	21	20	23	22	29	23	25	17
0	0	0	1	1	0	1	1	1	0	2	3	4	8	7	1	7	7	7	12
I	15	8	13	5	7	6	1	6	4	3	3	6	4	3	2	6	4	1	0
IA	6	11	9	5	9	9	8	11	17	8	13	12	11	14	19	14	18	15	12
IA1	8	9	21	14	18	13	17	17	19	14	26	27	24	36	26	53	37	57	30
IA2	13	7	18	9	14	18	8	6	7	10	6	7	8	9	7	10	15	10	10
IB	16	29	47	28	36	30	48	30	40	38	46	41	44	58	45	74	60	68	55
IB1	0	0	0	0	0	1	2	2	5	3	3	1	5	5	8	7	4	11	4
IB2	0	0	0	0	0	0	2	3	2	1	0	0	0	3	4	2	3	5	0
II	5	8	7	3	6	2	3	3	1	4	3	1	3	5	3	1	2	4	6
IIA	12	4	7	6	7	4	5	10	6	10	3	8	8	2	6	8	9	5	3
IIB	21	13	13	16	15	14	26	25	21	21	21	22	23	30	21	37	34	28	29
III	6	6	4	6	2	3	7	4	4	3	1	3	2	0	5	4	4	3	2
IIIA	1	2	3	3	5	3	5	1	3	2	2	2	2	6	1	2	4	1	1
IIIB	25	30	36	33	28	21	29	32	39	46	35	63	47	56	50	54	62	53	63
IV	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
IVA	5	5	3	6	7	2	4	5	11	9	3	13	7	11	14	13	11	14	12
IVB	9	5	7	9	8	8	5	12	10	8	13	24	11	26	22	27	24	17	29
Unstagable under AJCC Guidelines	0	0	2	2	2	1	1	3	2	0	3	5	3	1	5	3	2	0	1
Missing / Unknown	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	2	4	2	2

Notes: ‡Stage X – Primary tumour cannot be assessed. Data courtesy of National Cancer Registry Ireland

Tumour grade is a description of the tumour based upon its microscopic appearance and the degree to which the tumour cells are differentiated. Typically tumours are graded into four groups. Grade one is typically well-differentiated with grade four being undifferentiated. During the period 1994 to 2012, the majority of invasive cervical cancers were grade two or three on diagnosis (Figure 3.11).

Figure 3.11 Tumour grading for invasive cervical cancer by year of diagnosis, 1994 to 2012



Data courtesy of National Cancer Registry Ireland

3.2 CervicalCheck service use and burden of precancerous abnormalities

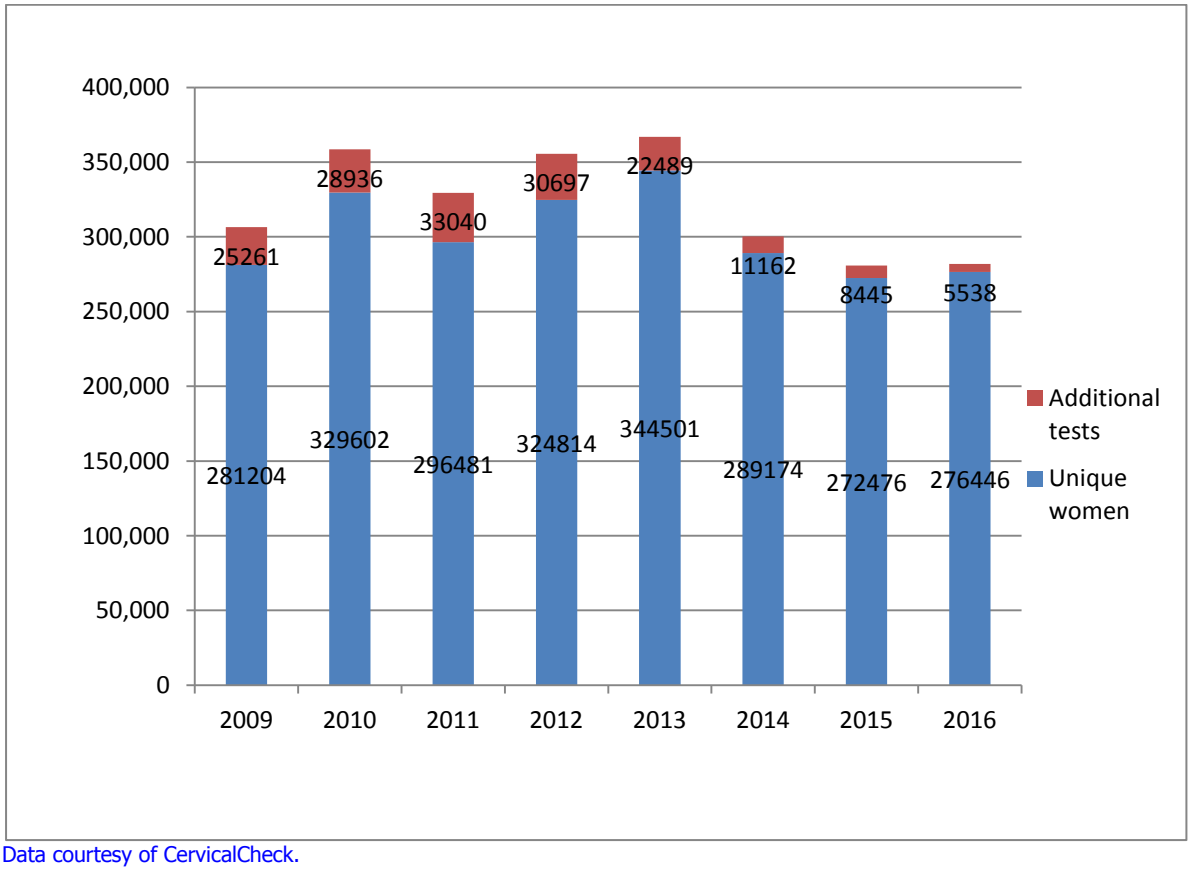
CervicalCheck, Ireland's National Cervical Screening Programme, was introduced in September 2008.

Coverage, a key performance indicator for CervicalCheck, is a measure of the proportion of the target population screened within a period and indicates the effectiveness of the screening programme in reaching the target population. Women who have had a total hysterectomy do not form part of the target population. The objective is to achieve coverage of 80% or more over a five-year period. In the first five years of CervicalCheck to August 2013, 74.7% coverage of the target population was achieved[109]In the five-year period to the end of August 2014 77.0% coverage of the target population was achieved.[56] This increased to 78.7% at the end of August 2015.[110] The five-year coverage to 31 December 2016 was 79.6%, reflecting improving coverage over time with CervicalCheck approaching its goal of 80% or more coverage over a five-year period.[69] Younger women were more likely

to participate in screening: between 2014 and 2015, 85.9% of 25 to 29 year olds screened compared with 68.7% of 55 to 59 year olds.[110]

Figure 3.12 details the number of unique women screened and the number of screening tests (taken in all settings including colposcopy) processed by CervicalCheck between 2009 and 2016. Smear tests are taken in primary care, public gynaecology, STI and GUM services and colposcopy services. The proportion of satisfactory or adequate smear test results (2008 to 2015) ranged from 98.0% to 99.5%.

Figure 3.12 Number of unique women screened and total number of screening tests processed by CervicalCheck* per year, 2009 to 2016



Data courtesy of CervicalCheck.
*Smear tests taken in all settings, including colposcopy

In the early years of CervicalCheck the number of smear tests substantially exceeded the number of women screened. There were a number of reasons for this. Laboratories reported high rates of low-grade cytological abnormalities (>13%) in the early years of CervicalCheck, but reported rates have since declined. Between 2014 and 2016 the combined reported rate for atypical glandular cells of undetermined significance (ASCUS) and low grade squamous intra-epithelial lesion

(LSIL) was 6.1%-6.9% with the AGC (borderline glandular) rate less than 0.2%.[55] The management of these low-grade cytological abnormalities was more conservative between 2008 and 2011 than it is currently. ASCUS or LSIL results were followed up with a repeat smear test in six months. Two successive normal results were required at six-month intervals before return to routine screening.[55] However, CervicalCheck adopted HPV triage (reflex HPV testing) for low-grade cytological abnormalities in May 2015 which allows the expedited referral of HPV-positive women to colposcopy.[111] As noted in Section 2.3.1.1, this use of HPV triage reduces the requirement for repeat tests in women who are HPV-negative and who can be reassured that the cytological abnormalities detected in the smear test are not considered clinically significant. Contributing also to the reduction in the total number of screening tests processed was the introduction in 2012 of HPV testing post treatment in CervicalCheck colposcopy clinics. This allowed HPV-negative women to be discharged to routine screening in three years (rather than returning for annual surveillance tests).

In recent years, the number of smear tests taken in settings other than colposcopy has exceeded the number of women screened by two to three percent.[46] Reasons for this include repeat smear tests because of unsatisfactory or inadequate results.

A breakdown of cytology results from CervicalCheck is given in Table 3.3. When the most recent three screening years are considered (September 2012 to August 2015), of the results reported as satisfactory, on average 90.7% were reported as having 'no abnormality detected', 7.7% of smear tests showed low-grade cytological abnormalities and 1.6% showed high-grade cytological abnormalities. These results included smear tests taken in colposcopy (unrelated to screening).

Table 3.3 Cytology results of satisfactory smear tests, 2008 to 2015

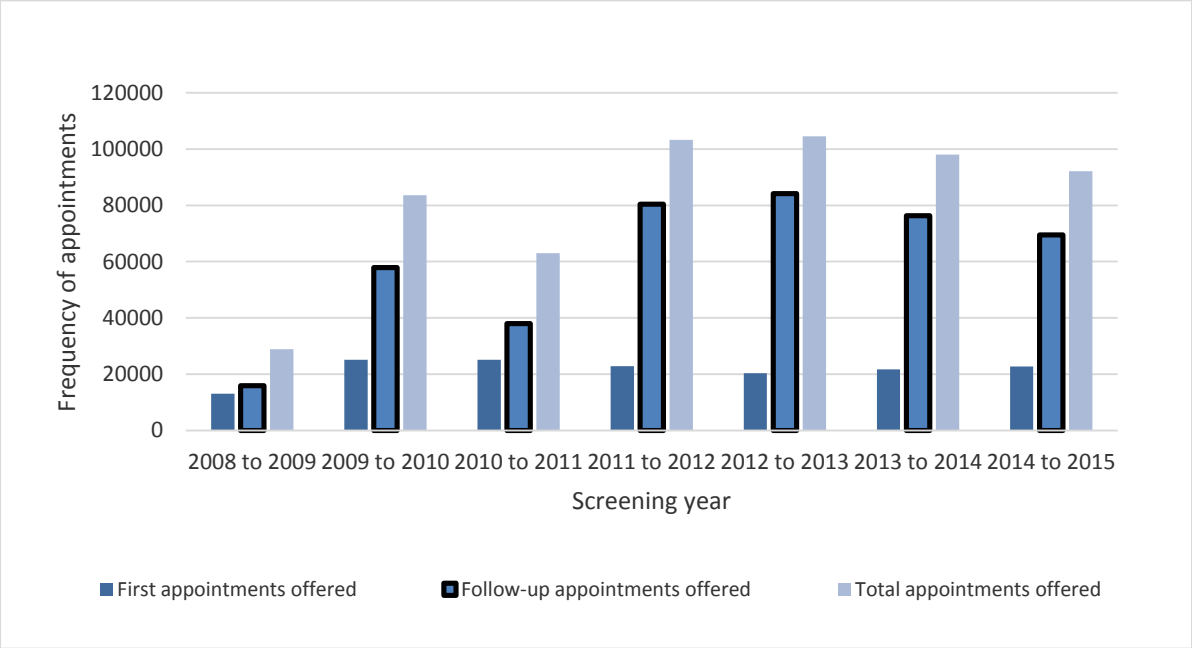
	2008-2009	2009-2010	2010-2011	2011-2012	2012-2013	2013-2014	2014-2015
No abnormality detected	240,074	261,314	282,736	314,476	316,116	284,764	260,748
Low grade							
ASCUS	26,091	27,913	30,964	25,497	12,695	12,619	11,582
AGUS	1,923	-	-	-	-	-	-
AGC (borderline glandular)	-	-	1,239	-	697	719	366
AGC (atypical glandular cells)	28	1,949	-	1,211	-	-	-
LSIL	11,338	10,289	13,102	12,860	10,944	12,048	11,806
High grade							
ASC-H	-	7	2,093	2,026	1,344	1,439	1,290
HSIL (moderate)	2,545	1,737	1,941	1,683	1,559	1,960	1,813
HSIL (severe)	1,460	1,303	2,229	1,870	1,812	1,931	1,780
Query invasive squamous carcinoma	32	23	26	10	32	33	39
AGC (atypical glandular cells-favour neoplastic)	-	4	168	-	-	-	54
Query glandular neoplasia /(AIS)/ adenocarcinoma	-	39	42	26	53	58	49
Total	**283,491**	**304,578**	**334,540**	**359,659**	**345,252**	**315,571**	**289,527**

Data acquired from CervicalCheck annual reports[56, 109, 110, 112-115]
Key: AGC – atypical glandular cells; ASCUS – atypical squamous cells of undetermined significance; AGUS – atypical glandular cells of undetermined significance; AIS – adenocarcinoma in situ; ASC-H – atypical squamous cells, possibly high-grade lesion; HSIL – high-grade squamous intra-epithelial lesion; LSIL – low-grade squamous intra-epithelial lesion.

As previously noted, LBC is the primary screening method currently used by CervicalCheck. Certain types of cytological abnormalities are followed by colposcopy and microscopic evaluation of cervical tissue, as appropriate in order to identify precancerous abnormalities and invasive cervical cancer.[11]

Nationally 15 colposcopy services work within CervicalCheck. Each colposcopy service is delivered by a multidisciplinary team based in a public acute hospital. The number of colposcopy appointments offered per year is shown in Figure 3.13. Between September 2014 and August 2015 a total of 92,153 colposcopy appointments were offered to women.[116] A quarter (n=22,700) of these were first appointments and 72.9% of women attended. In contrast, 56.9% of women offered follow-up appointments attended. Between September 2008 and August 2015, the average attendance at first appointments and follow-up appointments were 72.1% and 54.7%, respectively.

Figure 3.13 Number of colposcopy appointments offered, 2008 to 2015



Data acquired from CervicalCheck annual reports[56, 109, 110, 112-115]

The reduction in the number of follow-up colposcopy appointments seen since 2013-2014 follows the introduction of HPV testing post treatment by CervicalCheck in 2012 (see section 2.3.1.1). This is used in combination with cytology results to identify those who are suitable for discharging to routine screening.

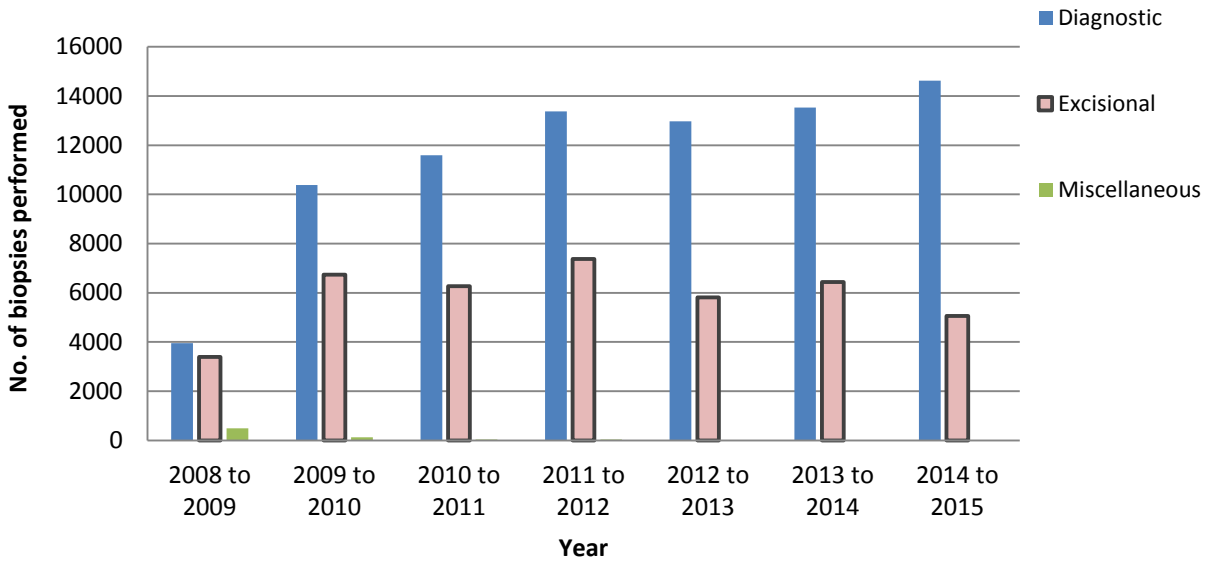
Additional capacity within the colposcopy services contracted to CervicalCheck has been used to support the symptomatic services usually provided by the gynaecology services. The colposcopy services therefore process referrals from both CervicalCheck and the symptomatic services. Referrals for clinical indications include abnormal vaginal bleeding or an anatomical abnormality of the cervix.[56] In the fourth year of CervicalCheck (2011-2012) 17.2% of referrals were for clinical indications[109] increasing to 32.8% in the seventh year (2014-2015).

Colposcopy, which allows microscopic assessment of the cervix, facilitates the management of women with abnormal smear test results. When an abnormality is suspected at colposcopy, it is considered good practice to confirm the diagnosis with biopsy where possible.[56] The 'gold standard' for the diagnosis of precancerous abnormalities and invasive cervical cancer is the histological examination of diagnostic punch or biopsies obtained at colposcopy.

Diagnostic biopsies are used to sample a portion of the abnormal area whereas excisional biopsies remove the abnormal area entirely. Other biopsies may also be performed – for example to excise polyps.

The number of biopsies performed each year is shown in Figure 3.14. These figures are inclusive of those referred for clinical reasons (as explained above) and those who presented through the screening service.

Figure 3.14 Number of biopsies performed, 2008 to 2015

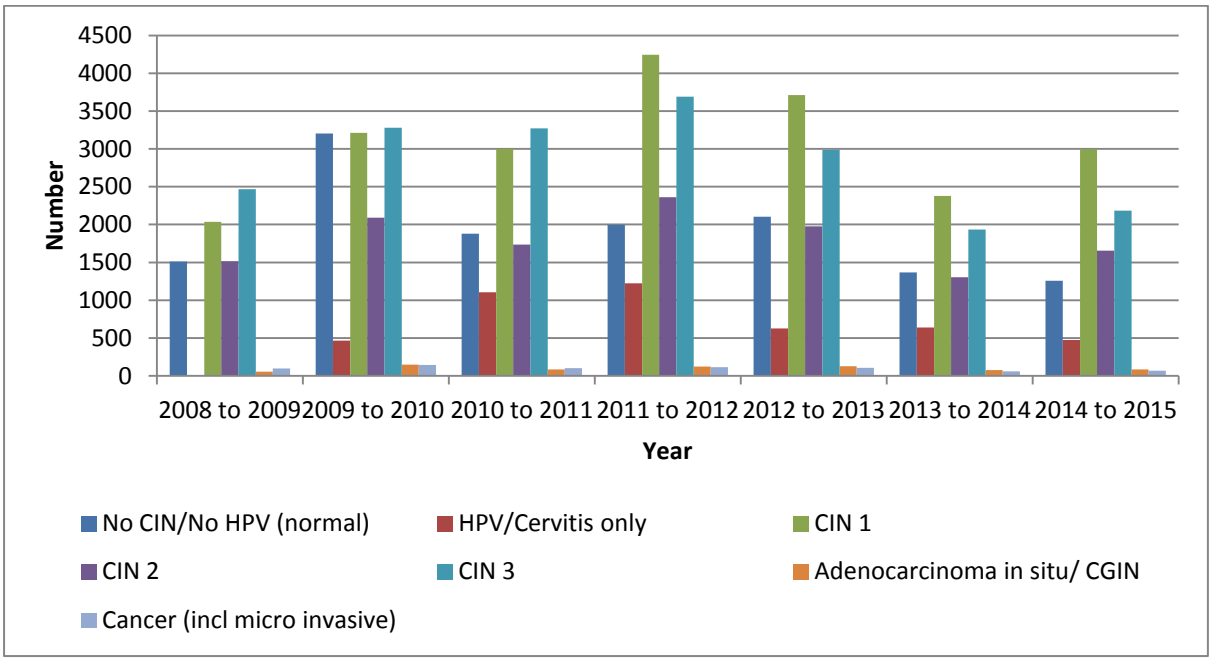


Data acquired from CervicalCheck annual reports[56, 109, 110, 112-115]

Between September 2008 and August 2015 there were 336,916 attendances at colposcopy, 108,094 of which were first appointments. Over 134,000 (134,361) biopsies were performed (first appointments and follow-up appointments). During this period CervicalCheck detected 1,082 invasive cervical cancers, 41,417 high-grade histological abnormalities (for example, CIN 2, CIN 3) and 29,505 low-grade histological abnormalities (for example, CIN 1)[110]

Histology results for those with a satisfactory biopsy at the first visit to colposcopy are shown in Figure 3.15.

Figure 3.15 Histology results for those with a satisfactory biopsy at first visit to colposcopy, 2008 to 2015



Data acquired from CervicalCheck annual reports[56, 109, 110, 112-115]

3.3 Treatment

3.3.1 Treatment of precancerous abnormalities

CervicalCheck aims to detect and treat women with precancerous abnormalities and early stage invasive cervical cancer. As noted in Chapter 2, CervicalCheck classifies histological abnormalities according to CIN terminology (see Chapter 2, Table 2.2). CIN describes squamous cell abnormalities which are classified histologically into low-grade abnormalities (CIN 1) and high-grade abnormalities (CIN 2 and CIN 3). CIN 3 is also called carcinoma in *situ*. CGIN (glandular cervical intraepithelial neoplasia) describe glandular cell abnormalities which are also classified into low-grade abnormalities and high-grade abnormalities; CGIN 3 is also called adenocarcinoma *in situ* (AIS).

Cold coagulation, large loop excision of the transformation zone (LLETZ), needle cone biopsy and cold knife cone biopsy are conservative methods of treatment of high-grade histological abnormalities.[117] LLETZ and cone biopsy completely remove the high-grade abnormality (includes the transformation zone). A cone shaped wedge of cervical tissue is removed at a cone biopsy, hence the name. LLETZ and cold coagulation techniques are usually carried out under local anaesthesia in colposcopy clinics. Cold knife cone biopsy requires general anaesthesia.[117]

Between 2014 and 2015, CervicalCheck treated 5,269 women with LLETZ, 1,224 women with ablation (cold coagulation) and 16 women with cone biopsies. Ninety seven percent of treatments were performed as outpatient procedures under local anaesthetic, exceeding the CervicalCheck target of 90%.

A UK observational study, nested within a RCT, of 751 women who attended colposcopy reported that 53% of women who had a punch biopsy reported pain and 46% reported vaginal discharge.[118] Of women treated by LLETZ, 67% reported pain and 63% reported vaginal discharge. The frequency of bleeding was similar in the biopsy (79%) and LLETZ groups (87%). Women treated by LLETZ reported bleeding and vaginal discharge of significantly longer duration than other women. The duration of pain was similar in both groups. After-effects were also reported by women managed solely by colposcopic examination.[118] Variation in practice regarding administration of local anaesthetic may mean that the findings of this study are not applicable to women treated in CervicalCheck where it is standard of care for local anaesthetic to be administered prior to a biopsy procedure. It is important to ensure that women are fully informed about after-effects. This may help to alleviate anxiety and provide reassurance, thereby minimising the harms of screening.[118]

Referral to colposcopy for evaluation because of an abnormal smear test may be distressing for women. A Dutch prospective study conducted between 2006 and 2008 assessed the effects of colposcopy referral on women's generic health-related quality of life (HRQoL) and anxiety levels.[119] A reference group (n=706) comprising women participating in cervical screening, but who were not referred to colposcopy completed a questionnaire for comparison. The HRQoL and anxiety outcomes of the colposcopy group (n=152) were ascertained from questionnaires completed prior to colposcopy and at one, three and six months after colposcopy. One hundred and thirty women were included in the analysis of which 108 completed all four questionnaires. In the pre-colposcopy questionnaire, there was a significant difference ($p<0.001$) in mental HRQoL and screen-specific anxiety levels compared with the reference group; physical HRQoL scores did not differ. The negative effect on mental health decreased over time and had disappeared by six months after baseline. Overall, HRQoL improved in the colposcopy group and a clinically significant reduction in anxiety ($p<0.001$) occurred over time, irrespective of the grade of CIN detected. The authors concluded that anxiety, not the physical burden of colposcopy and treatment was most bothersome to women and that gynaecological management had a reassuring effect and led to reduced anxiety levels over time.

LLETZ and cold knife biopsy are associated with an increased risk of preterm premature rupture of membranes, preterm birth and low birthweight.[117] These complications are associated with an increased risk of stillbirth and neonatal death.[120] Cold knife conisation is also associated with an increased rate of caesarean section due to cervical stenosis.[117] A case-control study nested in a record linkage cohort study in England reported that the risk of preterm birth appeared to be minimally affected by small excisions. Excisional treatment was defined as LLETZ, laser excision, knife cone biopsy or cone excision not otherwise specified.[121] However, excisions with a depth greater than 15mm were associated with a doubling of the risk of preterm and very preterm births.[121] Laser ablation does not impact on obstetric or neonatal outcomes.[117, 120]

3.3.2 Treatment of invasive cervical cancer

Squamous cell carcinoma is the most common histological type of invasive cervical cancer in Ireland. Between 1994 and 2012, it accounted for over 76% of invasive cervical cancers while adenocarcinoma accounted for just over 15%. Invasive cervical cancer is staged clinically according to the FIGO classification system (see Appendix 2). The stage of cervical cancer depends upon the size of the tumour, invasion of surrounding tissues, lymph node status and metastases. Risk assessment of a tumour incorporates the size of the tumour and depth of its invasion, histological genotype, stage, lymph node status and lymphovascular space involvement.[122] Primary treatment is stage dependent and may consist of surgery, radiotherapy or a combination of chemotherapy and radiotherapy.[122] Management and treatment are recommended by a multidisciplinary team based on the stage, age and general health of the individual woman.

Early stage disease (FIGO stage IA1) may be managed conservatively with cone biopsy. Treatment options for women with FIGO stage IA2 to IVA include surgery, radiotherapy or the combination of chemotherapy and radiotherapy (chemoradiotherapy). Surgical treatment options for women with stage IA2 include radical hysterectomy and pelvic lymphadenectomy, large cone biopsy or radical trachalectomy and pelvic lymphadenectomy. Surgical treatment options for women with stage IB1, IB2 and IIA include radical hysterectomy and pelvic lympadenectomy. Surgery is the preferred treatment option in young women with stage IA2 and IB1 because it confers the benefit of conserving ovarian function, thus avoiding early menopause.[83] Radical trachelectomy is an alternative to radical hysterectomy for women with stage IB1 who wish to preserve fertility. Radical trachelectomy involves vaginal resection of the cervix, the upper vagina and the medial portions of the cardinal and uterosacral ligaments and prophylactic cervical cerclage. Radical hysterectomy involves the en-bloc removal of the uterus, cervix,

parametrial tissues and upper vagina. This is usually combined with pelvic lymphadenectomy.

Women with stages IB2, IIA2 to IVA are generally treated with chemoradiotherapy.[83, 98] Surgery is not offered first-line to women with stage IB2, IIA2 to IVA because of the risk of positive margins and positive lymph nodes, however it may be offered as adjuvant therapy where there is evidence of residual disease.[108, 123] Radiotherapy to the cervix is given by external beam radiotherapy or brachytherapy. Brachytherapy involves delivering short wave radiotherapy into the uterus via the vagina. Women who present with metastatic or recurrent cervical cancer are commonly symptomatic.[122] They are generally offered palliative chemotherapy with or without immunotherapy and or individualised radiotherapy to relieve symptoms and to improve their quality of life.[122] Depending on previous care and the presence of central versus noncentral disease, treatment may include exenteration with or without intraoperative radiotherapy, radical hysterectomy in carefully selected patients or brachytherapy. Complications associated with advanced cervical cancer include pain, lymphoedema, fistulae, thrombosis, haemorrhage and renal failure.[108] Renal failure due to bilateral ureteric obstruction may require nephrostomy or ureteric stent placement.

The types and numbers of treatments performed for precancerous abnormalities and invasive cervical cancer by CervicalCheck between September 2008 and August 2015 are presented in Table 3.4. LLETZ was the most commonly performed treatment each year accounting for over 84% of procedures per annum.

Table 3.4 Treatments offered through CervicalCheck, 2008 to 2015

Treatment	2008-2009	2009-2010	2010-2011	2011-2012	2012-2013	2013-2014	2014-2015
LLETZ	4,326	6,591	6,190	7,236	5,702	5,674	5,269
Ablation	353	893	661	758	910	927	1,224
Cone biopsy	27	32	29	40	42	36	16
Hysterectomy	-	30	52	74	64	80	51
Trachelectomy	-	-	-	1	1	8	-
Total	**4,706**	**7,546**	**6,932**	**8,109**	**6,719**	**6,725**	**6,560**

Data acquired from CervicalCheck annual reports[56, 109, 110, 112-115]
Key: LLETZ - large loop excision of the transformation zone

According to NCRI data, since the year 2000 the proportion of women receiving different forms of treatment for invasive cervical cancer has been relatively stable (Table 3.5). Between 2000 and 2012, 63.3% received tumour-directed surgery, 39.8% received for chemotherapy or immunotherapy and 55.1% received radiotherapy. Of interest are the combinations of therapy used for individual women

with invasive cervical cancer. In the five years from 2008 and 2012, 39.7% of women had surgery alone, 20.2% had chemoradiotherapy and 15.9% had all three therapies.

Table 3.5 Treatment of invasive cervical cancer, 2000 to 2012

Year	Tumour-directed surgery*$	Chemo or immunotherapy*	Radiotherapy*
2000	116	77	103
2001	107	78	106
2002	128	94	117
2003	127	78	128
2004	127	82	101
2005	155	119	152
2006	135	94	130
2007	192	119	155
2008	163	115	150
2009	240	136	182
2010	208	126	183
2011	232	106	170
2012	181	105	161

*Within a year of diagnosis
$ Surgeries for invasive cervical cancer include procedures such as LLETZ and cone biopsies as well as more extensive procedures such as hysterectomies.
Data courtesy of NCRI

According to Hospital Inpatient Enquiry (HIPE) data, between 2005 and 2014 there were 9,658 inpatient admissions and daycases where invasive cervical cancer was the principal diagnosis. This equated to an average of 966 admissions per year. Just over half were for women in the 35 to 55 year age group. St Luke's Hospital and St James's Hospital (and specifically, St Luke's Radiation Oncology Unit in St James's Hospital since 2010) accounted for the largest number, together accounting for over 40% of all admissions and daycases.

Complications of treatment for invasive cervical cancer depend on the treatment modality used. Broadly speaking, complications impacting on quality of life can be categorised as: lymphoedema; bladder dysfunction and other urologic complications; bowel dysfunction and other gastrointestinal problems; sexual dysfunction; and psychosocial problems.[124] Treatment of advanced cervical cancer can lead to bladder dysfunction, detrusor overactivity, fistula, and hydronephrosis.[125] Chemotherapy can result in toxicity-related adverse reactions although these may be short-term. Radiation therapy is associated with haemorrhagic cystitis, ureteric stenosis, low-compliance bladder, and fistula.[125] When multiple treatment

approaches are used in combination, there may be a higher risk of long-term complications.[124]

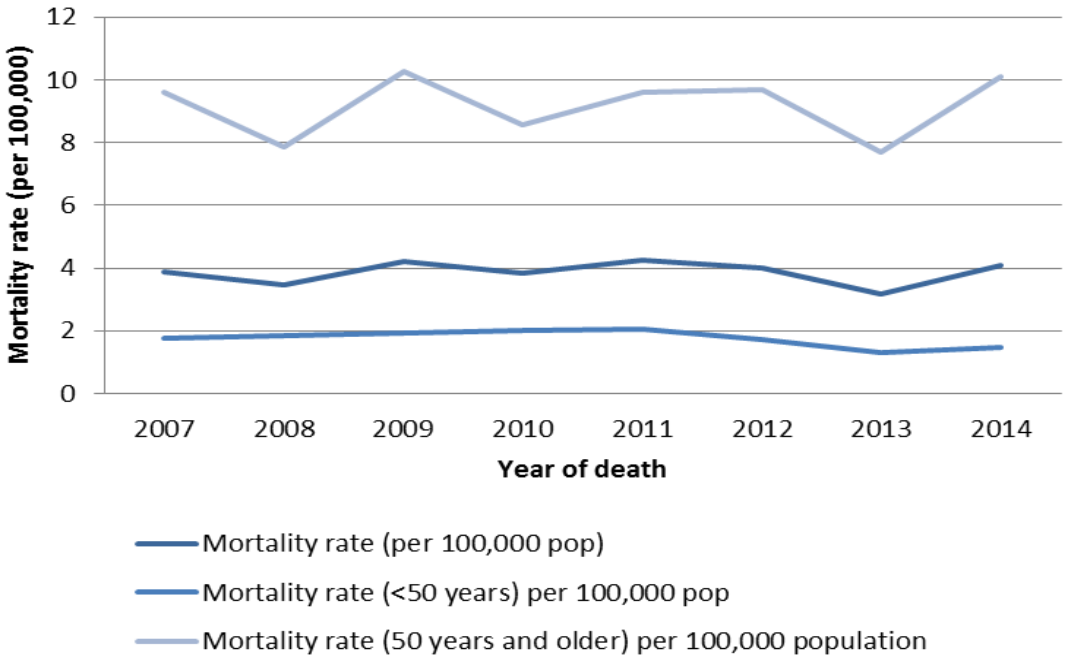
3.4 Mortality

The estimated annual age standardised mortality rate from invasive cervical cancer in 2012 was 4.3 per 100,000 in Ireland.[95] This was higher than the average annual rate for the 27 European Union member states (EU-27) which was 3.7 per 100,000 in 2012. The estimated age-standardised mortality rate from invasive cervical cancer in 40 European countries ranged from 14.2 per 100,000 (Romania) to 0.7 per 100,000 (Iceland) in 2012.[95] Ireland was ranked eighteenth.[95]

According to data from the Central Statistics Office (CSO), between 2007 and 2014, there were 707 deaths in Ireland from invasive cervical cancer, an average of 88 deaths per year. The median age at death from invasive cervical cancer in Ireland is 56 years.[126] The annual number of deaths in women aged less than 50 years ranged from 21 to 35. This represents between 25% and 38% of all deaths from invasive cervical cancer.

Mortality rates for invasive cervical cancer, standardised to the European Standard population (ESP 1976) are shown in Figure 3.16. Although there has been year-on-year fluctuation, there has been no significant change in mortality between 2007 and 2014. Based on data from 2012 to 2014, the cumulative lifetime risk of death due to cervical cancer (to age 74) was 1 in 333 women.

Figure 3.16 Age-standardised mortality rates of invasive cervical cancer per 100,000 population by year of death in Ireland (2007 to 2014)



Data acquired from CSO, standardised to the European Standard Population (1976)

In Ireland, mortality rates from invasive cervical cancer increased in the late 1960s and the early 1970s.[93] Rates subsequently declined somewhat, however average mortality rates for invasive cervical cancer in the last five years are approximately 60% higher than in the early 1950s.[93] Relatively little change in the mortality rate from invasive cervical cancer has been seen in recent years.[93] When stratified by age at time of death, mortality rates are higher in women aged 50 years and over compared with younger women (Figure 3.16).

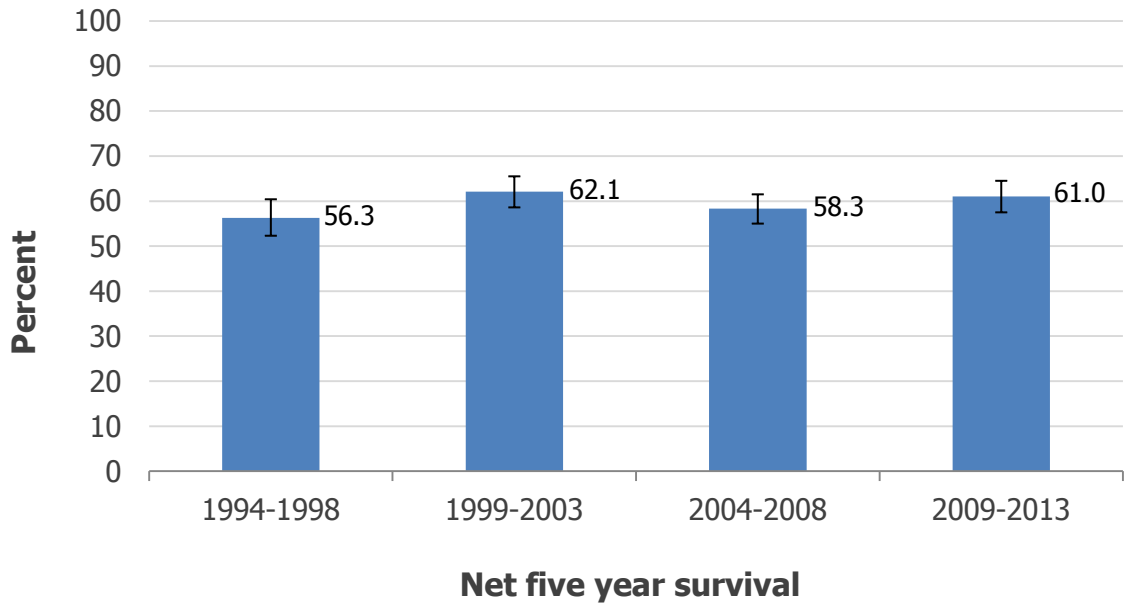
3.5 Survival

Based on data from the EUROCARE-5 study, the five-year relative survival for European women diagnosed with invasive cervical cancer between 2000 and 2007 was 62%.[127] Survival was lowest in Eastern Europe (57%), particularly in Bulgaria and Latvia (51%) and highest in Northern Europe (67%). Norway had the highest five-year relative survival at 71%. Ireland ranked 21st out of 28 countries with a five-year survival of 58.9%.[127] Across Europe, the study reported improvements in the age-standardised five-year relative survival from 61% (in 1999 to 2001) to 65% (in 2005 to 2007), although it noted that exceptions to this trend were observed in Scotland and Ireland where a statistically significant reduction in five-year survival

was observed.[127] In Ireland, five-year relative survival for these two periods were reported as 64% and 55%, respectively.[127]

The NCRI have estimated five-year survival using a cohort method (1994–1998, 1999–2003, 2004–2008) and a hybrid method (2009–2013). While relating to different time periods, in contrast with the EUROCARE-5 study data, five-year survival was estimated to have improved over time in Ireland from 56.3% in 1994 to 1998 to 61.0% in 2009 to 2013 (Figure 3.17).[128] The estimated trends in survival are clearly sensitive to the methodology used which may indicate that net five-year survival has remained largely static over the last 20 years.

Figure 3.17 Age-standardised net five-year survival for invasive cervical cancer in Ireland (1994 to 2013)

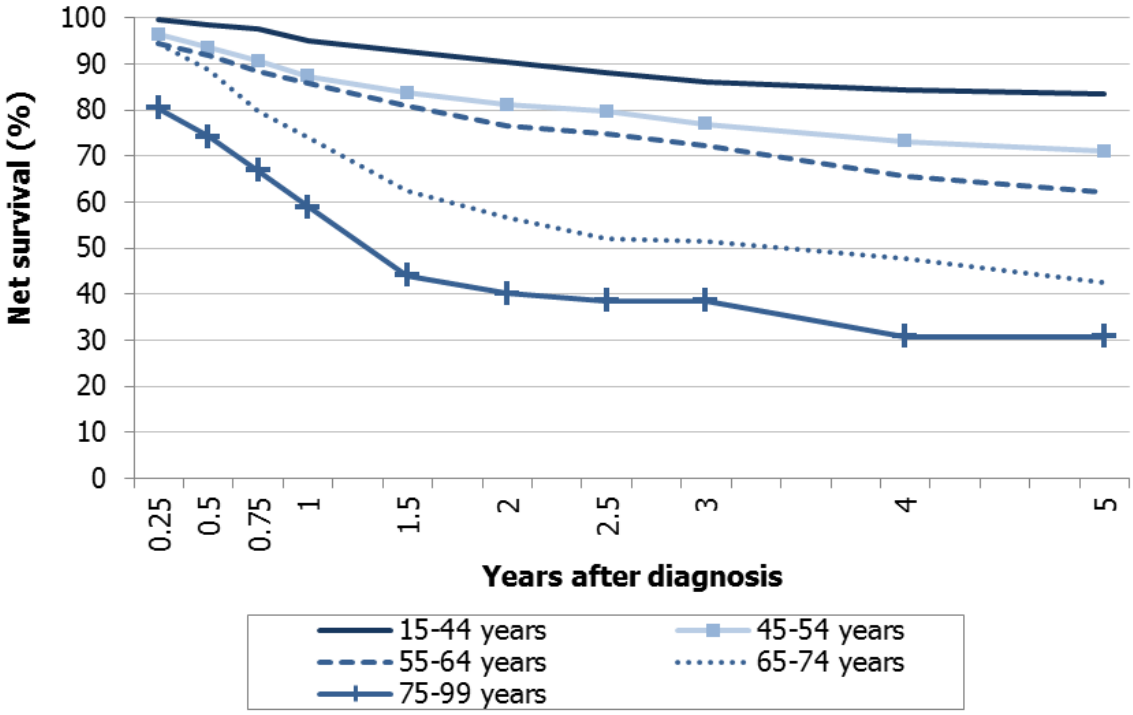


Figures acquired from NCRI , age-standardised

Age-standardised five-year relative survival in European women diagnosed with invasive cervical cancer between 2000 and 2007 reduced with advancing age.[129] Five-year relative survival in 15 to 44 year olds was 81%, but fell to 34% in those women aged 75 years and over at the time of diagnosis.[129]

This pattern was also observed in NCRI-calculated age-specific five-year relative survival for the time period 2008 to 2012 (Figure 3.18).[128] Those in the 15 to 44 year age group had a net five-year survival of 83.5%, whereas those aged 75 years and older at the time of diagnosis had a net five-year survival of 30.7%.

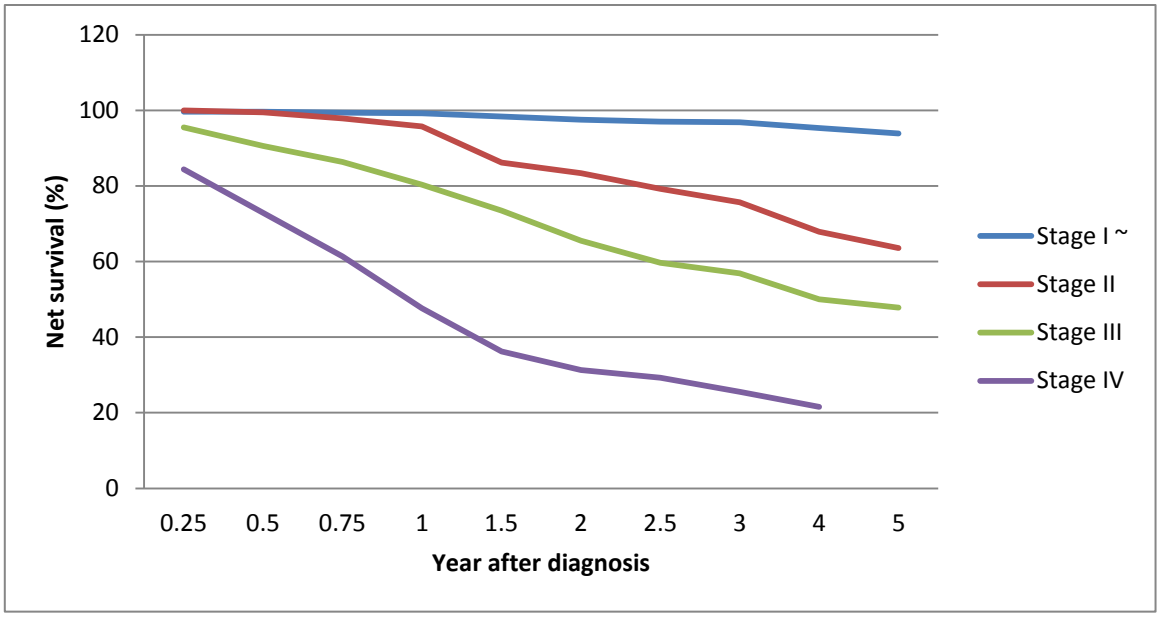
Figure 3.18 Net five-year survival for invasive cervical cancer by age, 2008 to 2012



Figures acquired from NCRI

The reduction in survival rates with increasing stage is well recognised.[25] NCRI age-standardised relative five-year survival calculations for the time period 2008 to 2012 are shown in Figure 3.19.[128] Net five-year survival for those diagnosed at stage II, III and IV disease were 63.6%, 47.8% and 21.6%, respectively. Note age-standardised survival is unavailable for stage I as there were insufficient deaths in some age groups to allow age-standardisation calculations to be made. The five year (un-standardised) survival for stage I disease was 93.9%.

Figure 3.19 Net five-year survival for invasive cervical cancer by stage, 2008 to 2012



Figures acquired from NCRI
~Data are age-standardised, with the exception of Stage I which is not age-standardised due to insufficient cases in some age groups

3.6 Risk factors for cervical cancer

Human papillomaviruses (HPVs) are small non-enveloped DNA viruses which may be classified into cutaneous and mucosal HPVs. There are more than 100 genotypes of HPV – each genotype acts as an independent infection[106] and are designated as low or high risk depending on their propensity to cause cancer (be 'carcinogenic').[130] As noted in Chapter 2.1.1.3, twelve HPV genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59) are considered by the IARC to be carcinogenic (class I) and associated with a higher risk of progression to cancer; these are often referred to by the acronym, 'hrHPV'.[17] Of these, HPV 16 and HPV 18 are responsible for approximately 70% of invasive cervical cancer cases,[131] and when combined with five additional oncogenic genotypes (31, 33, 45, 52, 58) account for approximately 90% of invasive cervical cancer cases.[20] HPV 66 is classified as probably carcinogenic (Group 2A) by the IARC while 12 other genotypes are considered possibly carcinogenic (Group 2B).[17]

HPV is a sexually transmitted infection, with skin-to-skin genital contact sufficient for transmission.[132] Infection is extremely common in young women in their first decade of sexual activity.[106] The majority (more than 90%) clear the infection spontaneously.[133] Cervical cancer arises when HPV is transmitted, the virus persists, persistently infected cells progress to precancerous abnormalities and finally to

invasive cervical cancer.[106] Most cervical infections are cleared or suppressed within one to two years of infection. The half life of HPV infection is estimated to be eight to ten months for high-risk genotypes and approximately half that for infection with low-risk genotypes.[133] Persistent infections and precancerous abnormalities arise from less than 10% of new infections and are usually established within five to ten years.[106]

HPV is necessary for the development of invasive cervical cancer, however other cofactors influence progression from cervical HPV infection to invasive cervical cancer. Established cofactors include co-infection with HIV, tobacco smoking, long-term hormonal contraceptive use, and high parity.[134] Co-infection with herpes simplex virus type-2 (HSV-2), Chlamydia trachomatis, immunosuppression, and certain dietary deficiencies are other probable cofactors.[134] The prevalence of HPV infection is discussed in Section 3.6.1 followed by a description of established cofactors in the development of invasive cervical cancer.

3.6.1 Burden of HPV in women

HPV infection may lead to the development of cervical cytological abnormalities ranging from low-grade cytological abnormalities to high-grade cytological abnormalities to invasive cervical cancer. The prevalence of HPV rises with increasing grade of cytological abnormality. The following three subsections (3.6.1.1 to 3.6.1.3) present more detailed international and national data on the prevalence of HPV (specifically the prevalence of hrHPV) in women with normal (negative) cytology, low-grade abnormalities, high-grade abnormalities and invasive cervical cancer, respectively. Data in subsection 3.6.1.2 and subsection 3.6.1.3 are based on both cytological studies and histological studies. Also included, where available, are data from partial genotyping studies indicating the prevalence of individual hrHPV genotypes.

Although certain HPV genotypes are potentially oncogenic, most women infected with one of these genotypes experience a transient infection and do not develop precancerous abnormalities or invasive cervical cancer.

3.6.1.1 Prevalence of HPV with normal cytology

According to a 2010 report of the Catalan Institute of Oncology, global prevalence of HPV with normal (negative) cytology is estimated to be 11.4% (95% CI: 11.3 to 11.5).[134] Prevalence of HPV is estimated to be higher in developing regions (14.3%) than in developed regions (10.3%). European prevalence of HPV is estimated to be 9.7% (95% CI: 9.6 to 9.9), ranging from 22.3% in Eastern Europe to 7.3% in Western Europe.[134] Prevalence in Northern Europe is 10.8% (95% CI: 10.6 to 11.0).

Prevalence is highest in women under the age of 25 years.[134] A meta-analysis of 194 studies which included just over a million women with normal cytology from 59 countries was published in 2010. [135] Globally, the crude and adjusted prevalence of HPV were estimated to be 7.2% and 11.7% (95% CI: 11.6 to 11.7), respectively Seventeen percent of these studies were population-based surveys, 33.0% were from routine screening programmes, 23.2% were case-controls studies, and 26.2% were other types of cross-sectional studies with convenience sampling. Most women (76.3%) were in routine cervical screening programmes which were not necessarily population-based. [135] In Europe, adjusted prevalence of HPV was estimated to be 14.2% (95% CI: 14.1 to 14.4).[135] Prevalence of HPV was highest in Eastern Europe (21.4%) and lowest in Southern Europe (8.8%).[135] Adjusted prevalence of HPV in Northern Europe, which included studies from Ireland, the UK, Sweden, Norway, Lithuania, Finland and Denmark, was 10.8% (95% CI: 9.8 to 10.2).[135] However, intercountry and intraregional heterogeneity in prevalence of HPV was observed. HPV 16 was the most frequently observed genotype worldwide accounting for over 22% of HPV infections.[135] Worldwide, a peak in HPV infection was observed in women under the age of 25 years. Thereafter, it declined to a plateau.[135] In over half of all regions, a second peak in age distribution was observed at 45 years or older. One hundred and thirty-six studies provided type-specific HPV data. Worldwide, the five most prevalent genotypes were HPV 16 (3.2%), HPV 18 (1.4%), HPV 52 (0.9%), HPV 31 (0.8%), and HPV 58 (0.7%).[135]

Similar trends were found in a large meta-analysis published in 2007.[136] This included 78 published studies of almost 158,000 women with normal cytology, conducted worldwide. Globally, estimated crude and adjusted prevalence of HPV were 10.0% and 10.4% (95% CI: 10.2 to 10.7), respectively.[136] Prevalence of HPV was highest in women under the age of 25 years and decreased thereafter. However in certain regions, of which Europe was one, a second prevalence peak was observed in women aged 45 years and over.[136] Europe was well represented in this analysis, constituting over 44% of study participants. Europe was divided into Eastern (Russia), Northern (Denmark, Sweden and UK) Southern (Greece, Italy and Spain) and Western Europe (Belgium, France, Germany and Netherlands). Adjusted prevalence of HPV decreased with decreasing latitude. It ranged from 29.1% (95% CI: 23.3 to 34.4) in Eastern Europe to 6.8% (95% CI: 5.7 to 7.2) in Southern Europe.[136] The adjusted prevalence of HPV in Northern Europe was estimated to be 7.9% (95% CI: 7.4 to 8.4).[136] Forty-eight studies provided genotype-specific HPV data. HPV 16, 18, 31, 58 and 52 accounted for half of all HPV infections. HPV 16 was the most prevalent genotype, followed by HPV 18.[136]

The UK-based ARTISTIC trial recruited 24,510 women aged 20 to 64 years who presented for routine screening in Greater Manchester.[137] Overall, prevalence of

HPV (13 hrHPV genotypes) was 15.6%. Prevalence of hrHPV in those with normal cytology was 10.4%. HPV positivity rates increased with increasing grade of cytological abnormality.[137]

A population-based study of women aged 20 to 64 years who attended cervical screening in Northern Ireland between February and December 2009, was published in 2013.[138] The crude prevalence of any hrHPV was 18.1%. This increased with increasing grade of cytological abnormality. In those with normal cytology, crude prevalence was 13.2% (95% CI: 12.7 to 13.7). Prevalence of hrHPV in those with normal cytology was 13.2% (95% CI: 12.7 to 13.7). Prevalence of hrHPV was highest in those aged between 20 and 24 years (33.3%) and reduced with age to a prevalence of 5.3% in those aged 55 to 64 years. HPV 16 was the most common genotype identified. The five most common high-risk types were 16, 31, 51, 59 and derived 52.[§] Prevalence of multiple hrHPV genotypes in those with normal cytology was 3.7%.[138] Younger women were more likely to be positive for multiple hrHPV genotypes than older women.

A study of prevalence of HPV in the cervical screening population in the Republic of Ireland was published in 2007.[139] Data were obtained from 996 women aged 16 to 72 years (mean age 35 years) who were opportunistically screened by their general practitioner.[139] Cytological abnormalities were reported in 11.1% of smears tested.[139] The overall prevalence of HPV (all genotypes) was 19.8%. It was 11.4% (101/886) with normal cytology and 100% with moderate (n=9) or severe (n=11) dyskaryosis (BSCC classification, see Chapter 2, Table 2.2).[139] Prevalence of HPV decreased significantly from 31% in women under the age of 25 years to 4% in women over the age of 50 years ($p<0.0001$).[139] High-risk HPV (hrHPV) genotypes accounted for 74% of HPV genotypes detected. HPV 16 (20%) and HPV 18 (12%) were the most prevalent hrHPV genotypes identified, followed by HPV 66, 33, 53, 31 and 58.

Similar, but slightly higher prevalence of HPV was reported by a study which included data from opportunistic and organised screening in Northern Ireland and the Republic of Ireland.[140] Between 2006 and 2009, samples were obtained from sites in Dublin, Galway and Antrim, not all of which were obtained through population-based screening. Following the commencement CervicalCheck in 2008, an additional 1,000 specimens were recruited through the CervicalCheck and The National Cancer Screening Services Board (NCSSB). The study population ranged from 17 to 89 years of age. Crude hrHPV prevalence rate in the study population was 19.2% (614/3193). It was 17.3% (487/2811) in the 25 to 60 year age cohort. The European age-standardised rates for the study population and the 25 to 60 year

[§] The assay used to detect HPV in this study used multiple type probes to detect HPV 52 infection. This limited the test's ability to discriminate HPV status in the presence of HPV 33, 35 and 58. Thus, the genotype is derived as positive if co-infection with HPV 33, 35 and 58 is not present.

age cohort were 19.7% and 15.7%, respectively.[115] Prevalence of HPV was highest in younger age groups (44.4% in women under the age of 25 years and 34.1% in women aged 25 to 29 years). It decreased with increasing age (8.7% in women aged 50 to 54 years).[140]

Prevalence of hrHPV in women with normal cytology was 12.6% (95% CI: 11.6 to 13.6); [140] and was higher in women aged under 30 years (26.5% [95% CI: 23.7 to 29.4]) compared with those aged 30 years and older (8.5% [95% CI: 7.5 to 9.5]) in women 30 years or older.[140] When data were analysed according to the four provinces of Ireland, inter-region differences in prevalence were observed. Ulster (North) had the highest crude prevalence of hrHPV (21.2%). Connaught (West) had the lowest crude prevalence of hrHPV (14.6%). Munster (South) and Leinster (East) had similar crude prevalence of hrHPV (19.4% and 19.2%). HPV genotyping was performed on specimens that tested positive for hrHPV DNA (n=614). Thirty-five genotypes were detected in this study with HPV 16 the most prevalent (29.0%) genotype detected. It was followed by HPV 31/HPV 52 (12.2%), HPV 18 (11.6%), HPV 51 (11.4%) and HPV 39/HPV 66 (9.1%).[140] HPV 16 was the most prevalent genotype identified in each region. Co-infection with low-risk HPV genotypes was identified in 45.3% of hrHPV positive samples; infection with multiple HPV genotypes was found in 56.5 to 58.5% of samples.[140]

The Irish Cervical Screening Research Screening Consortium, CERVIVA, is a multidisciplinary research consortium which focuses its research efforts on addressing some of the key national and international health service and population health challenges relating to cancer of the cervix. An observational study which is currently being conducted by CERVIVA in collaboration with CervicalCheck aims to evaluate and compare different strategies for the triage of women with a hrHPV DNA/HPV mRNA positive primary screening test.[141] The cohort comprises women attending CervicalCheck for a routine smear test. A residue of each smear sample is retained for hrHPV DNA and hrHPV mRNA testing. Baseline population prevalence of hrHPV DNA and hrHPV mRNA will be determined. The study is on-going and the results are yet to be published. However, preliminary data have been released to inform this HTA.[142] To date, 4,500 women aged 23 to 60 years have been recruited (median age 38 years [IQR 32-45 years]). Analysis was conducted on 3,222 samples. The rate of hrHPV mRNA positivity was lower than the rate of hrHPV DNA positivity, but this difference was not significant. For clarity, only the hrHPV DNA results are presented here. The prevalence of hrHPV was 14.6%. The genotype-specific prevalence of hrHPV (cobas® 4800 HPV test) is shown in Table 3.6.

Table 3.6 Genotype specific prevalence of hrHPV by DNA testing[141]

Age (years)	HPV 16 (%)	HPV 18 (%)	hrHPV *(%)
<30	9.2	2.2	20.4
30 to 39	3.5	1.0	10.8
40 to 49	2.0	0.5	5.9
50 years and older	1.5	0.8	5.3
Total	3.6	1.0	14.6

*hrHPV includes a pool of 12 genotypes (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68)

Women under the age of 30 years were significantly ($p<0.0001$) more likely to test positive for hrHPV DNA than women aged 30 years or older. Consistent with the results of other studies, hrHPV DNA positivity rates decreased with increasing age. Women aged 30 to 39 years were at a higher risk of testing positive for hrHPV DNA than women aged 50 years or older. Overall, partial genotyping indicated that 3.6% were positive for HPV 16, 1.0% were positive for HPV 18 and 9.9% were positive for at least one of the 12 other hrHPV genotypes tested. Cytology results were available for 1,973 study participants. Those with normal cytology accounted for 93.9%. The overall prevalence of hrHPV with normal cytology was 8.9% and varied by age, ranging from 21.5% in those aged less than 30 years to 6.9% in women aged 30 years or older.

In summary, currently there are no published national data of prevalence of hrHPV in women aged 25 to 60 years with normal cytology attending organised screening in Ireland. Early data from the CervicalCheck CERVIVA report a prevalence of hrHPV of 8.9% with normal cytology.[142] This is consistent with data from meta-analyses which report that the mean age-adjusted prevalence of hrHPV with normal cytology ranges from 7.9%[136] to 10.8%[135] in Northern European populations. The UK-based ARTISTIC trial, reported a prevalence of hrHPV of 10.4% in women aged between 20 and 64 years with normal cytology.[137] While hrHPV prevalence data for those with normal cytology reported in the aforementioned CERVIVA study are lower than that reported in other Irish studies (which ranged from 11.4% in the Republic of Ireland[139] to 13.2% in Northern Ireland[138]), these data are not directly comparable due to differences in study designs, study age participants and HPV detection methods. Irish data indicate that prevalence of hrHPV in women with normal cytology is highest in those aged less than 30 years, and that it decreases with increasing age.

3.6.1.2 Prevalence of hrHPV in borderline and low-grade abnormalities

This section considers the prevalence of hrHPV in borderline and low-grade abnormalities. Given the propensity of hrHPV to cause invasive cervical cancer, infection with hrHPV genotypes can manifest as abnormal cytological changes in

cervical cells. These early cytological changes, referred to as borderline or low-grade abnormalities may regress spontaneously or persist and develop into high-grade abnormalities which in turn may progress to invasive cervical cancer. Therefore, prevalence of hrHPV would be expected to increase with increasing grade of cytological abnormality.

According to a 2010 report of the Catalan Institute of Oncology, global prevalence of HPV 16 and 18 genotypes in LSIL is estimated to be 24.3% (95% CI: 23.6 to 25.0).[134] European prevalence is estimated to be slightly lower (23.9%) with evidence of regional variation. Prevalence ranges from 32.6% in Eastern Europe to 20.8% in Western Europe. Northern Europe (which includes Ireland) has an estimated prevalence of 30.3% (95% CI: 27.6 to 33.1).[134] HPV 16 and 18 genotypes are estimated to contribute to 16 to 32% of LSIL.[134]

A meta-analysis published in 2009 by Arbyn et al. compared prevalence of hrHPV in ASCUS and LSIL.[143] On average, 43% (95% CI: 40 to 46) of ASCUS (range 23% to 74%) and 76% (95% CI: 71 to 81) of LSIL (range 55% to 89%) were hrHPV positive.[143]

The UK-based ARTISTIC trial, reported rising rates of HPV positivity with increasing grade of cytological abnormality.[137] The ARTISTIC study used the BSCC classification system which classifies ASCUS as a borderline nuclear abnormality and LSIL as mild dyskaryosis (see Chapter 2, Table 2.2). The prevalence of hrHPV in borderline nuclear abnormalities and mild dyskaryosis were 31% and 70%, respectively.[137]

A population-based study of women aged 20 to 64 years who attended cervical screening in Northern Ireland , reported that 7.3% of samples had low-grade abnormalities.[138] Of these, 68.8% were hrHPV positive. HPV 16 was the most prevalent HPV genotype detected in low-grade abnormalities.[138]

A study conducted in the Republic of Ireland of 996 women aged 16 to 72 years who were opportunistically screened by their general practitioner, reported that 11.1% of samples had a cytological abnormality.[139] Just over 87% (96/110) of samples with a cytological abnormality had a positive result for HPV. HPV 16 was the most prevalent genotype in samples with mild, moderate or severe dyskaryosis (BSCC terminology, see Chapter 2, Table 2.2).

A study which included data from opportunistic and organised screening in Northern Ireland and the Republic of Ireland included women between the ages of 17 and 89 years.[140] ASCUS was detected in 5.8% of samples and LSIL was detected in 3.9% of samples.[140] Prevalence of hrHPV in ASCUS samples was 56.8% (95% CI: 50.8% to 62.7%).[140] It was 71.2% in women under the age of 30 years and 47.3% in

women aged 30 years or older.[140] In LSIL samples, the prevalence of hrHPV was 83.2% (95% CI: 77.7% to 88.7%). It was 90.2% in women under the age of 30 years and 76.6% in women aged 30 years or older.[140]

In May 2015 HPV triage testing commenced in CervicalCheck laboratories.[111] Smear test samples reported as ASCUS or LSIL are reflex tested for the presence of hrHPV genotypes. Between 1 June 2015 and 31 July 2016, a total of 278,172 screening tests were carried out in non-colposcopy settings.[144] ASCUS and LSIL were reported in 3.4% (n=9,308) and 2.8% (n=7,813) of samples, respectively.[144] A small number of ASCUS and LSIL samples (n=(6+8)=14) had an indeterminate hrHPV test result or were not tested for hrHPV. The crude prevalence of hrHPV was 38.5% and 71.1% in ASCUS and LSIL samples, respectively. The crude prevalence of hrHPV in ASCUS and LSIL samples was highest in women under the age of 30 years. (Table 3.7).

Table 3.7 Prevalence of hrHPV in ASCUS and LSIL samples in non-colposcopy settings, 1 June 2015 to 31 July 2016

ASCUS			
Age	**Total tested (n)**	**hrHPV +ve (n)**	**(%)**
< 20	3	1	(33.3)
20 - 24	24	18	(75.0)
25 - 29	2,596	1,583	(61.0)
30 - 34	1,807	811	(44.9)
35 - 39	1,631	490	(30.0)
40 - 44	1,372	319	(23.3)
45 - 49	982	177	(18.0)
50 - 54	452	100	(22.1)
55 - 59	253	50	(19.8)
60 - 64	128	27	(21.1)
65 - 69	45	8	(17.8)
70 - 74	12	1	(8.3)
>= 75	3	0	(0.0)
Total	**9,308**	**3,585**	**(38.5)**
LSIL			
Age	**Total tested (n)**	**hrHPV +ve (n)**	**(%)**
< 20	0	0	(0.0)
20 - 24	35	28	(80.0)
25 - 29	3,367	2,733	(81.2)
30 - 34	1,687	1,184	(70.2)
35 - 39	1,120	710	(63.4)
40 - 44	773	466	(60.3)
45 - 49	485	249	(51.3)
50 - 54	193	99	(51.3)
55 - 59	106	59	(55.7)
60 - 64	31	17	(54.8)
65 - 69	13	4	(30.8)
70 - 74	2	2	(100.0)
>= 75	1	1	(100.0)
Total	**7,813**	**5,552**	**(71.1)**

Data provided by CervicalCheck
The number positive are the number with ASCUS or LSIL who tested positive for hrHPV. The % calculation provided in brackets after this is the prevalence of hrHPV within that age band. For example, 1,583, or 61% of the 2,596 25 to 29 year olds with ASCUS were hrHPV positive.

Prevalence of hrHPV shown in Table 3.8 were obtained from screening tests taken in colposcopy settings and are not segregated by test purpose. They include women tested after treatment for high-grade abnormalities and those who are untreated

and typically present with persistent low-grade abnormalities. Smaller numbers of ASCUS and LSIL results were obtained from these tests. Overall crude prevalence of hrHPV in 1,348 ASCUS samples was 44.4% while it was 72.0% in 2,506 LSIL samples. This was similar to the overall crude prevalence of hrHPV in the LSIL samples taken in non-colposcopy settings (71.1%).

Table 3.8 Prevalence of hrHPV in ASCUS and LSIL samples in colposcopy, 1 June 2015 to 31 July 2016

ASCUS			
Age	**Total tested (n)**	**hrHPV +ve (n)**	**(%)**
< 20	2	0	(0.0)
20 - 24	28	9	(32.1)
25 - 29	325	102	(31.4)
30 - 34	306	137	(44.8)
35 - 39	240	123	(51.3)
40 - 44	184	94	(51.1)
45 - 49	111	61	(55.0)
50 - 54	71	36	(50.7)
55 - 59	49	24	(49.0)
60 - 64	21	9	(42.9)
65 - 69	8	1	(12.5)
70 - 74	3	2	(66.7)
>= 75	0	0	(0.0)
Total	**1,348**	**598**	**(44.4)**
LSIL			
Age	**Total tested (n)**	**hrHPV +ve (n)**	**(%)**
< 20	2	2	(0.0)
20 - 24	52	43	(82.7)
25 - 29	609	481	(79.0)
30 - 34	613	449	(73.2)
35 - 39	383	254	(66.3)
40 - 44	294	202	(68.7)
45 - 49	223	149	(66.8)
50 - 54	158	103	(65.2)
55 - 59	105	75	(71.4)
60 - 64	44	31	(70.5)
65 - 69	19	13	(68.4)
70 - 74	4	2	(50.0)
>= 75	0	0	(0.0)
Total	**2,506**	**1,804**	**(72.0)**

Data provided by CervicalCheck

Preliminary data from an observational study being undertaken by CERVIVA in collaboration with CervicalCheck, to evaluate and compare different strategies for the triage of women with HPV/mRNA positive primary screening tests, have been made available to inform this HTA.[142] Cytology results were available for the first

1,973 study participants enrolled in the study. A total of 1.5% and 3.6% of samples were reported to have ASCUS and LSIL, respectively. The prevalence of hrHPV in samples with ASCUS and LSIL was 56.7% and 70.4%, respectively. It was higher in women under the age of 30 years than it was in older women. Of note, as this study is nested within CervicalCheck, these data are also captured within the triage data reported above. Partial genotyping from 1,000 samples indicate that 12.5% (95% CI: 1.6 to 38.3) of ASCUS samples (2/16) were positive for HPV 16, none (95% CI: 0 to 20.6) were positive for HPV 18 (0/16) and 44% (95% CI: 19.8 to 70.1) were positive for other hrHPV genotypes (7/16). Partial genotyping of LSIL samples that were positive for HPV DNA indicated that 20% (95% CI: 8.4 to 36.9) were positive for HPV 16 (7/35), 2.9% (95% CI: 0.1 to 14.9) were positive for HPV 18 (1/35), and 43% (95% CI: 26.3 to 60.6) were positive for other hrHPV genotypes (15/35). At this point, the number in the cohort with ASCUS and LSIL is small (16 and 35, respectively) and the estimates are subject to substantial imprecision.

A prospective study conducted by CERVIVA in collaboration with CervicalCheck, between October 2008 and July 2011 investigated hrHPV DNA testing and $p16^{INK4a}$/Ki-67 staining in the detection of CIN 2+ in women referred to colposcopy with repeat ASCUS and LSIL.[145] The study comprised 471 women who attended their first colposcopy visit at a Dublin centre. HPV DNA was positive in 50.5% of ASCUS referrals and 71.7% of LSIL referrals.[145]

A population based study conducted in Northern Ireland which was published in 2015, aimed to identify the HPV genotypes predominating in histological precancerous abnormalities and invasive cervical cancers in women attending screening services.[146] Of the 1,830 eligible samples, 68.0% tested positive for HPV, 95.2% of which tested positive for hrHPV. The prevalence of hrHPV in CIN 1 samples was 48.1%.

In summary, triage data from CervicalCheck, indicate a crude prevalence of hrHPV of 38.5% with ASCUS.[144] This prevalence is lower than that observed in two published Irish studies, however these are not directly comparable due to differences in the study populations. Preliminary data from CERVIVA in collaboration with CervicalCheck, indicate a crude prevalence of hrHPV of 56.7%. However, ASCUS was reported in only 30 smear tests. The Irish data indicate a higher prevalence that the UK-based ARTISTIC trial which reported a prevalence of hrHPV of 31% with borderline nuclear abnormalities (see Chapter 2, Table 2.2). The UK data were based on women aged 20 to 64 years. The difference in prevalence of HPV persisted when Irish data were restricted to women aged 20 to 64 years. The data are not directly comparable due to differences in HPV detection methods and classification systems.

Published Irish hrHPV prevalence data for LSIL ranges from 71.1% to 83.2%. Data from CervicalCheck, comprising triage date for women with LSIL identified from primary LBC-based screening indicate a crude prevalence of hrHPV of 71.1%. This is consistent also with the preliminary data from the CERVIVA study which is nested in CervicalCheck and which reports a crude prevalence of 70.4% (based on small numbers). These data are also broadly consistent with prevalence of hrHPV reported by the UK-based ARTISTIC trial[137] and the meta-analysis published by Arbyn et al. in 2009.[143]

3.6.1.3 Prevalence of hrHPV with high-grade abnormalities and invasive cervical cancer

This section considers the prevalence of hrHPV in high grade abnormalities and invasive cervical cancer. According to a 2010 report of the Catalan Institute of Oncology, global prevalence of HPV 16 and 18 genotypes in high-grade abnormalities and invasive cervical cancer is estimated to be 51.1% (95% CI: 50.3 to 51.9) and 70.9% (95% CI: 70.3 to 71.5), respectively.[134] European prevalence of HPV 16 and 18 in high-grade abnormalities and invasive cervical cancer is estimated to be 53% (95% CI: 51.9 to 54.1) and 74.5% (95% CI: 73.4 to 75.5), respectively.[134] HPV 16 and 18 are estimated to contribute to between 41% and 67% of high-grade abnormalities.[134]

The UK-based ARTISTIC trial reported prevalence of hrHPV of 86% and 96% for moderate and severe dyskaryosis (BSCC classification, see Chapter 2, Table 2.2), respectively.[137]

A population-based study of women aged 20 to 64 years who attended cervical screening in Northern Ireland reported that1.3% of samples had high-grade abnormalities.[138] Of these, 68.8% were hrHPV positive.[138] HPV 16 was the most prevalent HPV genotype detected in high-grade abnormalities.

Preliminary data from an observational study by CERVIVA in collaboration with CervicalCheck, which is currently in progress, reported HSIL in 0.9% (95% CI: 0.5 to 1.4) of cytological samples.[142] hrHPV positivity rate in HSIL samples was 83.3% (CI 58.6 to 96.4). However, this prevalence estimate must be viewed with caution given the small numbers (n=15).

A study to examine the effect of age on genotype-specific risk of high-grade histological abnormality was conducted in Northern Ireland.[147] The study population consisted of 18,416 women aged between 18 and 65 years who attended for routine screening in the Western Health and Social Care Trust area between February and October 2011. A total of 866 women underwent HPV triage because of borderline

nuclear abnormalities or mild dyskaryosis (see Chapter 2, Table 2.2). Overall, 60.5% were positive for hrHPV.[147] The prevalence fell from 82.1% in women aged less than 25 years to 33.9% in women aged 45 years or older.[147] Of the 60.5% who were hrHPV positive on testing, HPV 16 was the most prevalent genotype detected (27.7%), followed by HPV 18 (9%) with twelve other hrHPV accounting for 63.4%.[147] Regardless of age, the relative risk of CIN 2+ on histology was significantly greater in women with HPV 16 and or HPV 18 infection (2.23) compared with women without HPV 16 and or HPV 18 infection (0.45). In women under the age of 30 years, the risk of CIN 2+ associated with HPV16 infection was significantly greater than the risk of CIN 2+ associated with HPV18 infection and the non-HPV16/18 genotypes (1.74 versus 1.03 and 0.58, respectively). In women aged 30 years or older, HPV18 infection presented the greatest risk of CIN 2+ (3.03).

A population based study conducted in Northern Ireland aimed to identify the HPV genotypes predominating in histological precancerous abnormalities and invasive cervical cancers in women attending screening services.[146] Prevalence of hrHPV with CIN 2 was 65.9%. It was 81.3% with CIN 3 and 92.2% with squamous cell carcinoma. The five most prevalent genotypes detected across all histological abnormalities, in descending order were HPV 16, 31, 52, 18 and 33.[146] Prevalence of hrHPV with adenocarcinoma was reported to be 64.3%.[146] However, as only 14 cases of adenocarcinoma were included, the study is likely underpowered to investigate this. The number of genotypes detected decreased with increasing age, with 51% of all HPV infections in women aged 25 to 29 years.[146]

A study of the genotype-specific prevalence of HPV with CIN 3 and invasive cervical cancer was conducted in England, Scotland, Wales and Northern Ireland.[148] Over 2,000 histological specimens of CIN 3 and over 1,200 histological specimens of invasive cervical cancer were tested for HPV. Most (81.6%) invasive cervical cancers with known morphology were squamous cell carcinoma. This was followed by adenocarcinoma (17.2%) and adenosquamous carcinoma.[148] The age and country-weighted prevalence of hrHPV in invasive cervical cancers was 95.8%.[148] Heterogeneity was observed between countries. In women aged 30 years or younger, 90.6% of CIN 3 specimens were positive for at least one hrHPV genotype.[148]

In summary, published data for Ireland are limited to one cytological study conducted in Northern Ireland and one cytological study conducted by CERVIVA in collaboration with CervicalCheck. The former reported a prevalence of hrHPV of 68.8%. Preliminary data from CERVIVA, based on small numbers, indicate a crude prevalence of hrHPV of 83.3% HSIL. The UK-based ARTISTIC trial reported a higher prevalence of HPV (86% in moderate dysplasia and 96% in severe dysplasia (BSCC

classification, see Chapter 2, Table 2.2). However, it is difficult to compare studies which use different cytological classification systems.

3.6.2 Co-factors for cervical cancer

HPV has been established as a worldwide cause of invasive cervical cancer (both squamous cell carcinoma and adenocarcinoma).[149, 150] However, many women who are infected with HPV do not develop invasive cervical cancer suggesting there are other factors at play.[151] HPV is a sexually-acquired infection and factors such as age of sexual debut and lifetime number of partners are linked to the likelihood of becoming infected with HPV.[151] The International Collaboration of Epidemiological Studies of Cervical Cancer combined data from twelve epidemiological studies and found the relative risk of both squamous cell carcinoma and adenocarcinoma increased with increasing number of sexual partners, younger age at first intercourse, increasing parity, younger age at first full term pregnancy, and increasing duration of oral contraceptive use.[107] The IARC define tobacco smoking, in utero exposure to diethylstilbestrol, combined oral contraceptives and HIV-1 as carcinogenic agents in invasive cervical cancer.[152] These are addressed in further detail below.

Current smokers have a significantly increased risk of developing squamous cell carcinoma when compared to women who have never smoked (RR 1.60; 95% CI: 1.48 to 1.73).[153] This risk increases with the number of cigarettes smoked per day and younger age at smoking initiation.[153] A lesser risk has also been observed for women who smoked previously (RR 1.12; 95% CI: 1.01 to 1.25).[153] Women who have ceased smoking for a minimum of ten years have half the risk of developing high-grade abnormalities and squamous cell carcinoma than current smokers.[154] Heavy smoking has also been associated with an increased risk of CIN 3 in women with persistent hrHPV infection.[155] Smoking may also play an independent role in cervical carcinogenesis.[154] Smoking prevalence in Ireland has declined in recent years. In the twelve months to March 2016, prevalence among persons aged 15 years and over was 18.9% compared with an average of 25% in the period from 2002 to 2006. The prevalence is higher in males (21.2%) than females (16.7%), and is highest in those aged 25 to 44 years (23.9%). Rates of smoking increase with increasing levels of deprivation and are highest (22.7%) in those classed as working class (C2 and DE groups).

Among current users of combined oral contraceptives, the risk of invasive cervical cancer increased with increasing duration of use (RR for five or more years' use versus never use, 1.90; 95% CI: 1.69 to 2.13).[156] Risk declined after use ceased, and by ten or more years had returned to that of never users. A similar pattern of risk was seen in women who tested positive for hrHPV.[156]

In utero exposure to diethylstilbestrol (DES), a synthetic oestrogen hormone previously prescribed to prevent complications of pregnancy, has also been linked to several adverse outcomes including increased risks of clear cell adenocarcinoma of the cervix and vagina.[157] It was widely prescribed between 1938 and 1971 before it was banned when its use was linked to cancer.

Invasive cervical cancer is an AIDS-defining condition.[158] The relationship between HIV and HPV, and HIV and invasive cervical cancer is complex.[159] The natural history of HPV infection is altered by HIV, creating a more aggressive phenotype.[159] HPV is reportedly more prevalent and more likely to become a persistent infection in those who are HIV-positive.[160] In a cross-sectional study of 321 HIV-positive women in an Irish setting, 28.7% had cytological abnormalities.[161] Over half (51.1%) were positive for HPV. Those with a CD4 count of less than 200 x 10^6/L were more likely to be positive for hrHPV than those with a higher CD4 count.[161]

3.7 Discussion

The age-standardised incidence of both cervical carcinoma *in situ* and invasive cervical cancer is increasing in Ireland. The increase is more pronounced in the former with a sharp increase seen in the reported incidence of cervical carcinoma *in situ* following the commencement of CervicalCheck in 2008. This peak was observed in those presenting specifically through CervicalCheck. The same degree of increase was not observed in invasive cervical cancer. This was perhaps influenced by the preponderance of women who present symptomatically with invasive cervical cancer. Further increases in numbers of invasive cervical cancer cases, beyond the increases expected due to demographic changes are predicted.

Invasive cervical cancer is a disease of younger women. In Ireland, cervical carcinoma *in situ* is most commonly diagnosed at 25 to 29 years while invasive cervical cancer is most commonly diagnosed at 40 to 44 years. Regional variation in relative risk of invasive cervical cancer exists. The global trend of increased frequency in lower social strata is also demonstrated in the Irish population, with higher proportions of invasive cervical cancer observed in those with a higher deprivation index.

Squamous cell carcinoma is the most common histological type of invasive cervical cancer in Ireland. Between 1994 and 2012, it accounted for over 76% of invasive cervical cancers while adenocarcinoma accounted for just over 15%. This ratio is similar to that seen internationally where squamous cell carcinoma account for approximately 80% of cases.[107] Squamous cell carcinoma account for most cases of invasive cervical cancer in poorly-screened populations.[106] The relative proportion of adenocarcinoma increase when an organised cervical screening programme is in

place because to date organised cervical screening programmes have been better at detecting exocervical than endocervical abnormalities.[106] HPV genotypes detected in adenocarcinoma are the same as those detected in squamous cell carcinoma which suggests that screening for HPV might have a beneficial impact on both histological subtypes of cervical cancer.[150]

Five-year survival rates for invasive cervical cancer in Ireland have changed little in 20 years. Ireland ranks 21st of 28 European countries in terms of survival, with five-year survival rates of 57.7% and 61.3% reported for the periods 1994 to 1999 and 2008 to 2012, respectively.[127] The observed reduction in survival seen in Europe which accompanies advancing stage and age at diagnosis is replicated in Ireland's population.

Preliminary data from the CERVIVA study indicate an overall crude prevalence of hrHPV of 14.6% in those attending organised screening. National and international data on prevalence of HPV are also available by grade of cytological abnormality (normal cytology, low-grade and high-grade abnormalities and invasive cervical cancer). In Europe, there is evidence of regional variation in age-adjusted prevalence of HPV with normal cytology and estimates range from 8.1% to 14.2%.[134, 135] Based on the results of studies from a combination of opportunistic and organised screening, the prevalence of hrHPV with normal cytology in Ireland (including Northern Ireland) is estimated to be 12.6%.[139, 140] Other data suggest that the prevalence of hrHPV in Northern Ireland is slightly higher at 13.2%.[138] Preliminary data from the CERVIVA collaboration indicate a crude prevalence of 8.9% in those with normal cytology. While it is inappropriate to draw direct comparisons, rates are broadly consistent with those from the organised screening service in the UK where the prevalence of hrHPV with normal cytology is estimated to be 10.4%.[137]

Prevalence of hrHPV rises with increasing grade of cytological abnormality. Internationally, hrHPV DNA is detected in half of ASCUS and AGUS abnormalities, in 20 to 50% of low-grade abnormalities and in 70 to 90% of high-grade abnormalities.[133] Published data from the Republic of Ireland and Northern Ireland report prevalences of hrHPV of 38.5%, 50.5% and 56.8% with ASCUS and 71.1% and 83.2% with LSIL.[140, 145, 162] Again, these data are derived from a mixture of opportunistic and organised screening services. Preliminary crude data from CERVIVA indicate a prevalence of hrHPV of 56.7% and 70.4% with ASCUS and LSIL, respectively for women attending routine screening. The prevalence is higher in women aged less than 30 years compared with those aged 30 years or older. Worldwide, HPV 16 is the most prevalent genotype in normal cytology, low-grade abnormalities, high-grade abnormalities and invasive cervical cancer.[134] Data

indicate that HPV 16 is the most prevalent genotype in Ireland.[139, 140] The distribution in Ireland of other prevalent genotypes varied between studies, although similarities were seen. Whilst HPV 18 is the second most prevalent genotype found in invasive cervical cancer in developing regions, it is the fifth most prevalent in high-grade abnormalities, the ninth in low-grade abnormalities and the third in normal cytology.[134] Preliminary partial genotyping data from the CERVIVA study indicate that for women attending routine screening in Ireland, 32% of those testing positive for HPV are positive for HPV 16 and 18. Although study numbers are small, CERVIVA data indicate an increasing prevalence of HPV 16 with increasing grade of cytological abnormality. Crude prevalence of HPV16 increases from 2.3% with normal cytology to 52% with high-grade abnormalities. In summary, while there are no published HPV prevalence data in women attending CervicalCheck, limited data are available from a number of sources including triage data from CervicalCheck and data from CERVIVA. These data are broadly consistent with the prevalence data reported in the UK-based ARTISTIC trial.

As noted in Chapter 2, in September 2010, quadrivalent HPV vaccination against HPV 6, 11, 16 and 18 was introduced to the national immunisation schedule for all girls in first year of second level school or age equivalent with a catch-up programme the following year. Although the first vaccinated cohort will not be eligible for CervicalCheck until 2018-2019, reductions in the prevalence of HPV 6, 11, 16 and 18 may be expected. In developed countries with a vaccine coverage of at least 50%, meta-analysis reported that the prevalence of HPV 16 and 18 significantly reduced in girls aged 13 to 19 years along with HPV 31, 33 and 45 suggesting some degree of cross-protection.[163]

HPV is a sexually-acquired infection and factors such as age of sexual debut and lifetime number of partners are linked to the likelihood of becoming infected with HPV. Infection is extremely common, with the majority (more than 90%) of infections clearing spontaneously within one to two years of infection. Persistent infection is necessary for the development of invasive cervical cancer, however other cofactors including tobacco smoking, long-term use of combined oral contraceptives, high parity and immunosuppression, including infection with HIV, influence progression from HPV infection to invasive cervical cancer.

3.8 Key messages

- Cervical cancer is the eight most common invasive cancer in women in Ireland. Although year-on-year variation occurs, the incidence rate of invasive cervical cancer in Ireland has increased in the last decade.
- A total of 38,448 cases of cervical carcinoma *in situ* were diagnosed in Ireland between 1994 and 2004. The commonest age at diagnosis was 25 to 29 years. Between 2012 and 2014, there were, on average 2,873 cases of cervical carcinoma *in situ* diagnosed each year.
- Between 1994 and 2014, a total of 4,955 cases of invasive cervical cancer were diagnosed in Ireland. The commonest age at diagnosis was 40 to 44 years. For the period 2012 to 2014, on average, 277 cases of invasive cervical cancer were diagnosed each year.
- There were on average 88 deaths from invasive cervical cancer per year in Ireland between 2007 and 2014. Invasive cervical cancer accounted for 2.3% of cancer-related deaths in women. The median age of death was 56 years.
- On average, CervicalCheck processed approximately 281,000 smear tests per annum in 2015 and 2016, declining from a peak of almost 367,000 tests in 2013.
- CervicalCheck had a five-year coverage of 79.6% (goal ≥ 80%) to the end of December 2016.
- Between 2012 and 2015, on average 7.7% of smear tests each year showed low-grade abnormalities and 1.6% showed high-grade abnormalities.
- Since CervicalCheck commenced in 2008, it has detected 1,082 invasive cervical cancers, 41,417 high-grade histological abnormalities and 29,505 low-grade histological abnormalities (August 2015).
- Prognosis is linked with stage at diagnosis of invasive cervical cancer. In Ireland, between 2008 and 2012 the net five-year age-standardised survival probability for those diagnosed at stage II was 63.6% compared with 21.6% for those diagnosed at stage IV. Five-year survival probability (not age-standardised) for those diagnosed with stage I was 93.9%. Treatment for invasive cervical cancer is stage dependent. On average each year, 162 women undergo surgery for invasive cervical cancer, 102 receive chemotherapy/immunotherapy and 141 are treated with radiotherapy.

- Certain oncogenic strains of HPV (denoted hrHPV) are associated with an increased risk of developing precancerous abnormalities and invasive cervical cancer. Preliminary data from CERVIVA in collaboration with CervicalCheck, indicate a crude hrHPV prevalence of 14.6%. Prevalence is highest under the age of 30 years and decreases with advancing age. Of those testing positive for HPV, partial genotyping data indicate that 32% are positive for HPV subtypes 16 and 18 (the particular subtypes associated with 70% of cervical cancers).

4 Clinical effectiveness and safety

Persistent infection with hrHPV genotypes can lead to the development of invasive cervical cancer. The absence of HPV infection indicates a low risk of developing cervical cancer while the presence of HPV infection is a potentially useful tool in screening for cervical cancer. In line with the agreed scope of the health technology assessment (HTA), this chapter examines the current evidence of effectiveness and safety of using HPV testing as the primary screening test for the prevention of cervical cancer. It also considers the effectiveness of various triage testing strategies for women with a positive HPV test result.

As described in Chapter 2, screening is a form of secondary prevention. Its aim is to reduce the impact of a disease or injury that has already occurred. Cervical screening aims to reduce the incidence, morbidity and mortality from cervical cancer through early detection and treatment of precancerous abnormalities and invasive cervical cancer. Following a positive screening test, women are referred to colposcopy for diagnostic testing. As screening tests are not 100% accurate, there will be some women who, following a positive screening test, will be referred unnecessarily for diagnostic testing as they do not have precancerous abnormalities or invasive cervical cancer. This is called a 'false positive' result. There will also be some women who will receive a negative test result when in fact they do have precancerous abnormalities or invasive cervical cancer; this is called a 'false negative' result.

Diagnostic test accuracy reflects the performance characteristics of a screening test and describes how well the test discriminates between those who do, and do not have the disease. Sensitivity is the ability of a screening test to accurately identify those who have the disease, that is, the proportion of people with the disease who have a positive test result. A more sensitive test will result in fewer women receiving a false negative result. The specificity of a screening test is its ability to correctly identify those who do not have the disease, that is, the proportion of people without the disease who have a negative test result. A test with a high specificity will result in fewer women receiving a false positive result. While it is obviously desirable to have a test that is both highly sensitive and highly specific, usually this is not possible, and there is a trade-off to be made between sensitivity and specificity.

As described in Chapter 3, following persistent infection with oncogenic HPV genotypes, abnormal growth of intraepithelial precancerous cells may occur in the surface layers of the cervix. This is termed cervical intraepithelial neoplasia (CIN). There are three grades of CIN: CIN 1, CIN 2 and CIN 3. If left untreated, CIN can develop into invasive cervical cancer, however it can also regress. It is not possible

to determine which CIN will regress or progress, so currently all CIN 2+ (grade 2 or higher) are treated. Thus CIN 2+ is the clinically relevant point in the development of invasive cervical cancer that a screening test needs to be able to accurately detect.

4.1 Primary screening test

4.1.1 Search strategy

This assessment used two recent systematic reviews by the Belgian Health Care Knowledge Centre, KCE, published in 2015[(164)] as a basis for our systematic reviews of the clinical literature. Their searches were completed in October 2013. The first search compares the accuracy of HPV testing with cytology as the primary screening test for cervical cancer. The second search considers triaging for women identified as HPV-positive in a primary screening test and is presented in Section 4.2.

The systematic literature search comparing primary HPV testing with cytology published by KCE in 2015[(164)] was the latest update in a series of systematic reviews. The original systematic review was published in 2007.[(165)] The KCE search of PubMed and EMBASE was updated to the end of January 2016 using the same search strategy. Full details of the search are provided in Appendix 3. The PICOS (Population, Intervention, Comparator, Outcomes, Study design) analysis used to formulate the search is presented in Table 4.1.

The studies included by KCE and the updated search studies were reviewed according to our inclusion and exclusion criteria. This was carried out independently by two researchers and any disagreements were resolved through discussion. The quality of the included studies (KCE and updated search) was assessed independently by two researchers. Any disagreements were resolved through discussion, using the quality assessment of diagnostic accuracy studies 2 (QUADAS-2) checklist.[(166)] Data extraction from all studies (KCE and updated search) was performed independently by two researchers and any disagreements were resolved through discussion.

Table 4.1 PICOS analysis for identification of relevant studies for primary screening with HPV or cytology testing

Population	Women aged 18 to 70 participating in a cervical screening programme who were not being followed up for previous cytological abnormalities
Intervention	HPV test, Cytology test (conventional or liquid-based) Test thresholds (Cytology- ASCUS or worse, HC2 - ≥1pg/ml)
Comparator	'Gold standard' application of colposcopy and or biopsy on at least all cytology- and HPV-positive samples
Outcomes	Accuracy parameters (sensitivity, specificity, positive predictive value, negative predictive value) Disease threshold (CIN 2+, CIN 3+)
Study design	Observational studies using concomitant cervical cytology and HPV testing RCTs where women were assigned to either cytology testing, HPV testing or both

Key: ASCUS - Atypical squamous cells of undetermined significance; CIN - cervical intraepithelial neoplasia; HC2 - Hybrid Capture 2 HPV assay; HPV – human papillomavirus; RCT – randomised controlled trial.
Note: The test thresholds for cytology-ASCUS or worse and HC2>=1mg are the standard cut-offs and currently in use in the Irish national cervical screening programme, CervicalCheck.
Note: To reduce the complexity of this chapter and aid in clarity, only accuracy results for sensitivity and specificity are presented.

4.1.2 Results

The following section presents the results from the studies identified as part of the updated systematic search along with the original studies. A synthesis of the evidence is presented in Section 4.1.3. For ease of reading, 95% confidence intervals are referred to as confidence intervals (CI) throughout this chapter.

Eleven additional studies were identified in the extension of the systematic review from October 2013 to January 2016. The original KCE systematic review[164] included 60 studies of which nine were randomized controlled trials (RCTs) and 51 were cross-sectional studies. The updated review contains 71 studies.

In the original systematic review, large variation in the sensitivity in studies conducted in developing countries was observed. The inter-study variation was much lower in studies conducted in industrialised countries and non-significant in studies conducted in China. In industrialised countries, the pooled sensitivity of the Hybrid Capture 2 (HC2) HPV assay (Qiagen) in detecting CIN 2+ was 96% (CI: 95-98%, n=18 studies), and the pooled specificity was 91% (CI: 89-91%, n=18 studies), whereas the pooled sensitivity for detecting CIN 2+ across all locations was

91% (CI 89-93%, n=41 studies) and the pooled specificity was 89% (CI 87-90%, n=41 studies). Given this substantial geographic variation, this HTA will consider studies conducted in industrialised countries.

A large number of different HPV tests are currently available, however, the most commonly used test was the Hybrid Capture 2 (HC2) HPV assay (Qiagen), with a smaller number of studies investigating other HPV tests (Cobas® 4800, PreTectTM HPV Proofer, Aptima®, Amplicor®, Linear array®, qPCR HBRT-H14, HPV 9G DNA chipTM). Apart from the HC2, no test was considered in more than four studies. Given the large number of studies within the review, to reduce potential variation between studies, this HTA will further restrict the analysis to studies which considered HC2 only as the HPV test.

Twenty-three of the 71 studies within the review met these additional criteria. The characteristics of these studies are given in Table 4.2. Details of the studies excluded from the review and the reason for their exclusion are provided in Appendix 3.

The included studies comprised 22 cross-sectional studies and one randomised controlled trial (RCT).[167-189] Of the 23 studies, five were conducted in the UK,[172-174, 179, 189] three in Germany,[176, 180, 183] three in France,[170, 171, 181] three were multi-country studies across western and eastern Europe[177, 188] and across Canada and the US,[168] two were conducted in Italy,[185, 186] and one each in Norway,[182] Switzerland,[167] Taiwan,[169] Chile,[175] Japan,[178] Canada[184] and Russia.[187]

Seven of the studies compared HPV testing with liquid-based cytology (LBC),[167, 174, 176, 179, 181, 185, 186] 14 compared HPV testing with conventional cytology,[168, 169, 172, 173, 175, 177, 178, 180, 182-184, 187-189] while the remaining two included subgroups comparing HPV testing with both LBC and conventional cytology.[170, 171]

The total sample size in the included studies ranged from to 231[188] to 25,577.[177]

The majority of the populations included within the studies are representative of routine screening populations. Two studies,[182, 187] considered populations that potentially had a higher risk of cervical cancer. Nygrad et al.[182] included women who had previously received an unsatisfactory cytology result, while the study by Shipitsyna et al.[187] included women who were screened while attending routine gynaecological clinics. The two studies by Ronco et al.[185, 186] reported the results of the same study, but the first only included women aged less than 35 years and the second only included women aged over 35 years. In the evidence synthesis section, these two studies were treated as one study, combining the results. The studies by Ronco et al.[185, 186] included two trial arms, one where samples were tested using

both HPV testing and LBC, and a second arm which used only conventional cytology; only results from the first arm of the trial were included in this analysis.

The reported sensitivity of HC2 ranged from 68.8%[168] to 100%[170, 188, 189] for CIN 2+ and 95.2%[173] to 100%[174, 176, 180, 187, 189] for CIN 3+. This was higher than the reported sensitivity of the cytology tests, which ranged from 34.4%[175] to 100%[185] for CIN 2+ and 38.9%[175] to 100%[185, 187, 189] for CIN 3+. The reported specificity of HC2 ranged from 43.0%[167] to 100%[174] for CIN 2+ and 15.9%[188] to 100%[174] for CIN 3+. The reported specificity of the cytology tests varied widely ranging from 62.0%[184] to 98.7%[175] for CIN 2+, and from 76.6%[188] to 98.6%[175] for CIN 3+.

The prevalence of HPV in screened women varied from 5%[172, 173, 180, 183] to 83%.[188] No relationship was evident between the reported prevalence of HPV in screened women and the resulting sensitivity values. However, studies that reported a high prevalence of HPV had lower specificity values than studies that reported low prevalence of HPV.

The quality of all 23 studies was assessed using the QUADAS-2 checklist (see Table 4.3). Seven studies were assessed as having a low risk of bias across all domains.[170, 171, 175-177, 179, 183] Five were rated at a higher risk of bias regarding patient selection with either the age range not being representative of routine screening populations[173, 185, 186] or the population likely to be at a higher risk of cervical cancer than the general population.[182, 187] Three were assessed as being at a higher risk of bias regarding the reference standard, where the colposcopists were not blinded to the HPV test results.[169, 172, 181] Two studies were rated at a higher risk of bias regarding the reference standard, flow and timing. Specifically, in Nygard et al.[182] the baseline outcomes included any additional women diagnosed with CIN 2+ within three years of follow up. The study by Cuzick et al. which was published in 2013[174] did not consider women with normal (negative) cytology who were HPV negative for further investigation. Overall, the quality of the studies was rated as fair to good.

Table 4.2 Characteristics of studies retrieved from industrialised countries comparing the accuracy of HPV testing using HC2 with the accuracy of cytology-based testing as the primary screening test for cervical cancer.

Study	Country	Study Design (size)	Prevalence of HPV	HPV test (s)	Cytology test (s)	Outcomes reported			
						Sensitivity		Specificity	
						HPV test	Cytology	HPV Test	Cytology
Bigras 2005[167]	Switzerland	cross sectional (n=1,533)	59%	HC2	LBC	CIN 2+: 97.6% CIN 3+: 98.3%	CIN 2+: 58.5% CIN 3+: 57.6%	CIN 2+: 43.0% CIN 3+: 42.4%	CIN 2+: 78.2% CIN 3+: 77.6%
Cardenas-Turanzas 2008[168]	US, Canada	cross sectional (n=835)	8%	HC2	CC	CIN 2+: 68.8%	CIN 2+: 44.0%	CIN 2+: 93.3%	CIN 2+: 94.0%
Chao 2008[169]	Taiwan	cross sectional (n=10,014)	11%	HC2	CC	CIN 2+: 85.1%	CIN 2+: 81.9%	CIN 2+: 89.7%	CIN 2+: 98.6%
Clavel 2001[170]	France	cross sectional (n=2,281)	15%	HC2	CC, LBC	CIN 2+: 100%	CIN 2+: 68.1% CC, 87.8% LBC	CIN 2+: 86.1%	CIN 2+: 95.3% CC, 93.1% LBC
Coste 2003[171]	France	cross sectional (n=1,785)	20%	HC2	CC, LBC	CIN 2+: 96.0%	CIN 2+: 85.4% CC, 78.0% LBC	CIN 2+: 82.0%	CIN 2+: 91.8% CC, 89.5% LBC
Cuzick 2003[172]	UK	cross sectional (n=10,358)	5%	HC2	CC	CIN 2+: 96.7% CIN 3+: 97.1%	CIN 2+: 83.3% CIN 3+: 82.6%	CIN 2+: 95.7% CIN 3+: 95.5%	CIN 2+: 96.7% CIN 3+: 96.5%
Cuzick 2008[173]	UK	cross sectional (n=2,612)	5%	HC2, Sharp	CC	CIN 2+: 85.7% CIN 3+: 95.2%	CIN 2+: 80.9% CIN 3+: 82.4%	CIN 2+: 95.6% CIN 3+: 95.4%	CIN 2+: 95.5% CIN 3+: 95.2%
Cuzick 2013[174]	UK	cross sectional (n=5,984)	15%	HC2, BD HPV, Cobas®, Abbott Realtime, Aptima®,	LBC	CIN 2+: 97.5% CIN 3+: 100%	CIN 2+: 85.4% CIN 3+: 85.2%	CIN 2+: 100% CIN 3+: 100%	CIN 2+: 95.3% CIN 3+: 95.0%

				Proofer					
Ferreccio 2013[175]	Chile	cross sectional (n=8,265)	11%	HC2	CC	CIN 2+: 94.8% CIN 3+: 96.3%	CIN 2+: 34.4% CIN 3+: 38.9%	CIN 2+: 90.3% CIN 3+: 89.9%	CIN 2+: 98.7% CIN 3+: 98.6%
Iftner 2015[176]	Germany	cross sectional (n=9,451)	6%	HC2, AHPV	LBC	CIN 2+: 95.6% CIN 3+: 100%	CIN 2+: 48.9% CIN 3+: 53.5%	CIN 2+: 94.7% CIN 3+: 94.3%	CIN 2+: 98.4% CIN 3+: 98.2%
Ikenberg 2013[177]	Multi (Belgium, France, Germany, Italy, Spain)	cross sectional (n=25,577)	11%	HC2	CC	CIN 2+: 96.1%	CIN 2+: 68.5%	CIN 2+: 89.9%	CIN 2+: 95.4%
Inoue 2006[178]	Japan	cross sectional (n=8,156)	11%	HC2	CC	CIN 2+: 89.8% CIN 3+: 96.7%	CIN 2+: 81.9% CIN 3+: 90.2%	CIN 2+: 90.7% CIN 3+: 90.1%	CIN 2+: 93.9% CIN 3+: 93.4%
Kitchener 2014[179]	UK	RCT (n= 21,910)	13%	HC2	LBC	CIN 2+: 93.4% CIN 3+: 97.0%	CIN 2+: 95.0% CIN 3+: 97.4%	CIN 2+: 88.9% CIN 3+: 88.2%	CIN 2+: 90.3% CIN 3+: 89.6%
Luyten 2009[180]	Germany	cross sectional (n=16,724)	5%	HC2	CC	CIN 3+: 100%	CIN 3+: 50.0%	CIN 3+: 95.2%	CIN 3+: 98.3%
Monsonego 2011[181]	France	cross sectional (n=4,429)	16%	HC2, HPV-AHPV	LBC	CIN 2+: 96.7% CIN 3+: 95.3%	CIN 2+: 69.1% CIN 3+: 73.3%	CIN 2+: 86.4% CIN 3+: 84.9%	CIN 2+: 91.9% CIN 3+: 90.8%
Nygard 2014[182]	Norway	cross sectional (n=19,065)	35%	Amplicor®, HC2, Proofer	CC	CIN 2+: 94.4%	CIN 2+: 69.4%	CIN 2+: 73.1%	CIN 2+: 96.6%
Petry 2003[183]	Germany	cross sectional (n=7,908)	5%	HC2	CC	CIN 2+: 97.8% CIN 3+: 97.3%	CIN 2+: 43.5% CIN 3+: 46.0%	CIN 2+: 95.3% CIN 3+: 95.2%	CIN 2+: 98.0% CIN 3+: 98.0%
Ratnam 2000[184]	Canada	cross sectional (n=407)	45%	HC2	CC	CIN 2+: 85.0%	CIN 2+: 56.0%	CIN 2+: 58.0%	CIN 2+: 62.0%
Ronco 2006a[185]	Italy	cross sectional (n=16,255)	7%	HC2	LBC	CIN 2+: 97.3% CIN 3+: 97.4%	CIN 2+: 73.9% CIN 3+: 81.5%	CIN 2+: 93.2% CIN 3+: 93.0%	CIN 2+: 94.8% CIN 3+: 94.7%

Ronco 2006b[186]	Italy	cross sectional (n=5,860)	14%	HC2	LBC	CIN 2+: 97.7% CIN 3+: 92.8%	CIN 2+: 100% CIN 3+: 100%	CIN 2+: 86.5% CIN 3+: 86.0%	CIN 2+: 91.7% CIN 3+: 91.2%
Shipitsyna 2011[187]	Russia	concomitant testing (n=778)	8%	HC2	CC	CIN 2+: 100% CIN 3+: 100%	CIN 2+: 83.3% CIN 3+: 100%	CIN 2+: 92.6% CIN 3+: 92.4%	CIN 2+: 97.8% CIN 3+: 97.4%
Syrjanen 2002[188]	Russia, Belarus, Latvia	cross sectional (n=231)	83%	HC2	CC	CIN 3+: 96.6%	CIN 3+: 74.2%	CIN 3+: 15.9%	CIN 3+: 76.6%
Szarewski 2007[189]	UK	concomitant testing (n=920)	17%	HC2	CC	CIN 2+: 100% CIN 3+: 100%	CIN 2+: 81.0% CIN 3+: 81.0%	CIN 2+: 84.5% CIN 3+: 85.0%	CIN 2+: 96.2% CIN 3+: 96.0%

Key: AHPV- Aptima® HPV; BD HPV- Becton-Dickinson HPV; CC- conventional cytology; CI- confidence interval; CIN – cervical intraepithelial neoplasia; HBRT-H14-Hybribio Real-time 14 High-risk HPV;HC2 - Hybrid Capture 2 HPV assay; HPV – human papillomavirus; LBC – liquid-based cytology; LSIL- low-grade squamous intraepithelial lesion; RCT- randomised controlled trial.
Note: Studies may have included study arms comparing additional HPV tests, however only HC2 outcomes are shown in the table.
Note: All cytology results presented use the standard threshold of ASCUS+ and all HC2 results presented use the standard threshold of ≥1pg/ml, all extracted data represent the crude values.

Table 4.3 Risk of bias appraisal of the included studies of primary screening tests – QUADAS-2[166]

Study	Domain 1: Patient Selection		Domain 2: Index Test(s)		Domain 3: Reference Standard		Domain 4: Flow and Timing
	A. Risk of Bias	B. Concerns regarding applicability	A. Risk of Bias	B. Concerns regarding applicability	A. Risk of Bias	B. Concerns regarding applicability	A. Risk of Bias
Bigras 2005[167]	Low	Low	Low	Low	Low	Low	Unclear
Cardenas-Tuanzas 2008[168]	Low	Low	Low	Low	Low	Low	Unclear
Chao 2008[169]	Low	Low	Low	Low	High	Low	Low
Clavel 2001[170]	Low	Low	Low	Low	Low	Low	Low
Coste 2003[171]	Low	Low	Low	Low	Low	Low	Low
Cuzick 2003[172]	Low	Low	Low	Low	High	Low	Low
Cuzick 2008[173]	Low	High	Low	Low	Unclear	Low	Low
Cuzick 2013[174]	Low	Low	Low	Low	Low	Low	High
Ferreccio 2013[175]	Low	Low	Low	Low	Low	Low	Low
Iftner 2015[176]	Low	Low	Low	Low	Low	Low	Low

Ikenberg 2013[177]	Low	Low	Low	Low	Low	Low	Low
Inoue 2006[178]	High	Low	Low	Low	Low	Low	Low
Kitchener 2014[179]	Low	Low	Low	Low	Low	Low	Low
Luyten 2009[180]	Low	Low	Low	Low	Unclear	Low	Low
Nygard 2014[182]	High	High	Low	Low	Low	Low	High
Monsonego 2011[181]	Low	Low	Low	Low	High	Low	Low
Petry 2003[183]	Low	Low	Low	Low	Low	Low	Low
Ratnam 2000[184]	Low	Low	Low	Low	Unclear	Low	Unclear
Ronco 2006a[185]	Low	High	Low	Low	Low	Low	Unclear
Ronco 2006b[186]	Low	High	Low	Low	Low	Low	Low
Shipitsyna 2011[187]	High	Low	Low	Low	Unclear	Low	Low
Syrjanen 2002[188]	Low	Low	Low	Low	Unclear	Low	Low
Szarewski 2007[189]	Low	Low	Low	Low	Low	Unclear	Low

Note: The two Ronco studies report results of the same study, but the first only includes women aged less than 35 years and the second only women aged over 35 years.

4.1.3 Evidence synthesis

For the test accuracy for primary screening for CIN 2+ and CIN 3+, the sensitivity and specificity of HC2 and cytology (conventional cytology and LBC) testing were computed using the data from randomized controlled trials (RCTs) or cross-sectional studies where concomitant testing was applied. As previously mentioned, there is evidence to suggest that studies conducted in China and in developing countries are not comparable to those from industrialised countries. As such, only studies conducted in industrialised countries were included in the meta-analyses. For the meta-analyses, a Bayesian bivariate, random effects approach was used.[190] The bivariate random effects model accounts for the bivariate nature of sensitivity and specificity as well as the within-study and between-study variability.[191] Analyses were carried out in Rstudio Version 0.99.893[192] using the bamdit package (version 2.0.1).[193]

Twenty-two studies (n=19 from KCE, n=3 from updated search) were available for inclusion in the meta-analysis of the accuracy of HC2; 20 for CIN 2+ and 15 for CIN 3+. Eight of the included studies compared HC2 HPV testing with LBC (n=8 CIN 2+; n=6 CIN 3+), 16 compared it with conventional cytology (n=14 CIN 2+; n= 9, CIN 3+). Twenty-two studies compared HC2 HPV testing with combined cytology which included LBC and conventional cytology (n=20 CIN 2+; n=15 CIN 3+). Two of the studies included a LBC arm and a conventional cytology arm. The results from these two studies were combined to give overall cytology outcomes. A summary of the results of the meta-analyses are given in Table 4.4. The forest plots of the meta-analyses are shown in Figures 4.1 to 4.8.

The pooled sensitivity of HC2 in detecting CIN 2+ and CIN 3+ was 95.2% (CI 92.5-97.1%) and 98.2% (CI 96.7%-99.1%), respectively. This is significantly higher than the pooled sensitivity of cytology compared with either LBC (CIN 2+: 83.7% [CI 62.2-94.8%]; CIN 3+: 85.0% [CI 53.2%-96.9%]) or conventional cytology (CIN 2+: 70.5% [CI 58.2-80.7%]; CIN 3+: 71.9% [CI 53.6%-85.7%]).

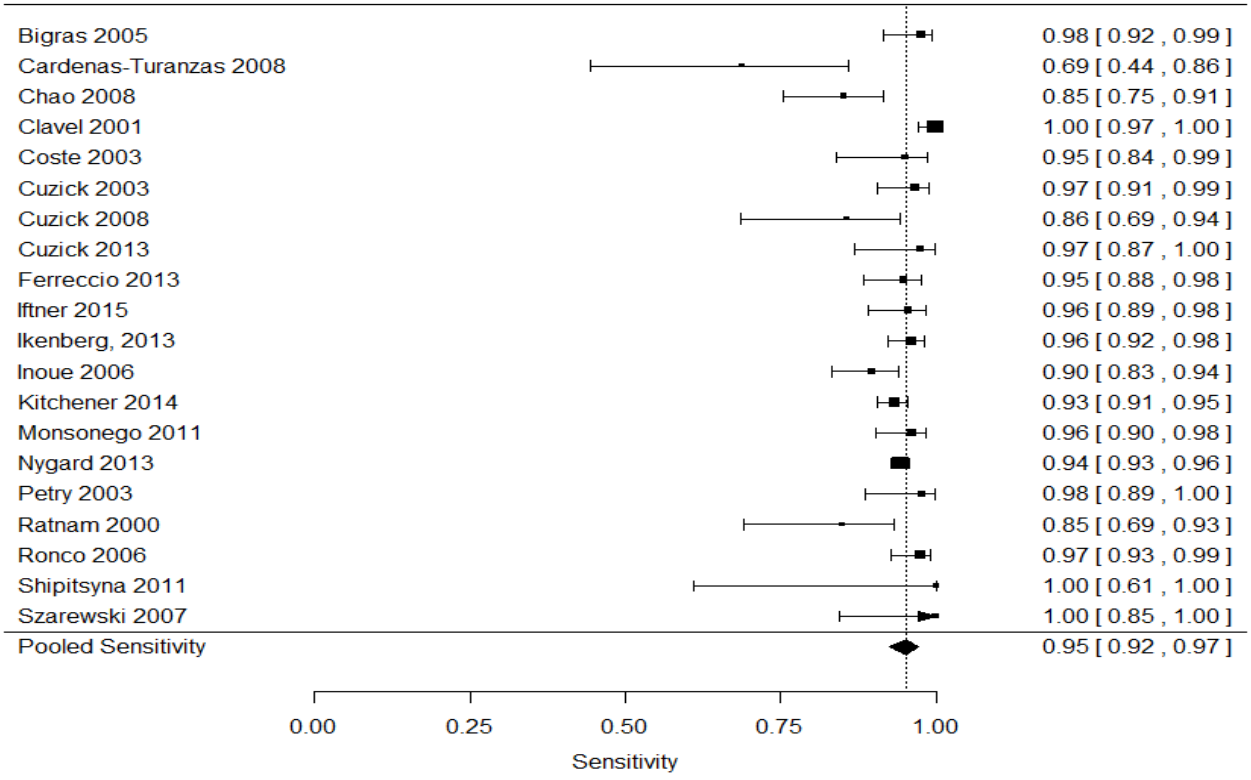
The pooled specificity of HC2 in detecting CIN 2+ was 88.2% (CI 82.9%-92.0%) and CIN 3+ was 87.6% (CI 78.7%-93.2%). This is lower than that of the cytology tests. It is evident from the forest plots (Figure 4.1 and 4.2) for HC2 that two studies in particular, Bigras et al.[167] and Syranen et al.[188] have specificities that are unusually low compared with the other included studies. Exclusion of these studies had only a minor impact on the pooled specificity, indicating that these studies were not particularly influential.

Table 4.4 Results of the meta-analysis

Primary screening test	Outcome	Sensitivity (95% CI)	Specificity (95% CI)	No. of studies
HC2	CIN 2+	95.2% (92.5%-97.1%)	88.2% (82.9%-92.0%)	20
	CIN 3+	98.2% (96.7%-99.1%)	87.6% (78.7%-93.2%)	15
LBC	CIN 2+	83.7% (62.2%-94.8%)	92.9% (83.5%-97.2%)	8
	CIN 3+	85.0% (53.2%-96.9%)	92.6% (75.5%-98.2%)	6
CC	CIN 2+	70.5% (58.2%-80.7%)	95.8% (92.8%-97.6%)	14
	CIN 3+	71.9% (53.6%-85.7%)	96.3% (92.1%-98.2%)	9
Combined cytology (LBC & CC)	CIN 2+	75.0% (64.1%-83.3%)	95.0% (92.2%-96.8%)	20
	CIN 3+	78.0% (63.5%-88.4%)	95.1% (91.6%-97.3%)	15

Key: CC- conventional cytology; CI-confidence interval; CIN – cervical intraepithelial neoplasia; HC2 - Hybrid Capture 2 HPV assay; LBC – liquid-based cytology.

Figure 4.1 Sensitivity and specificity of HC2 in detecting CIN 2+



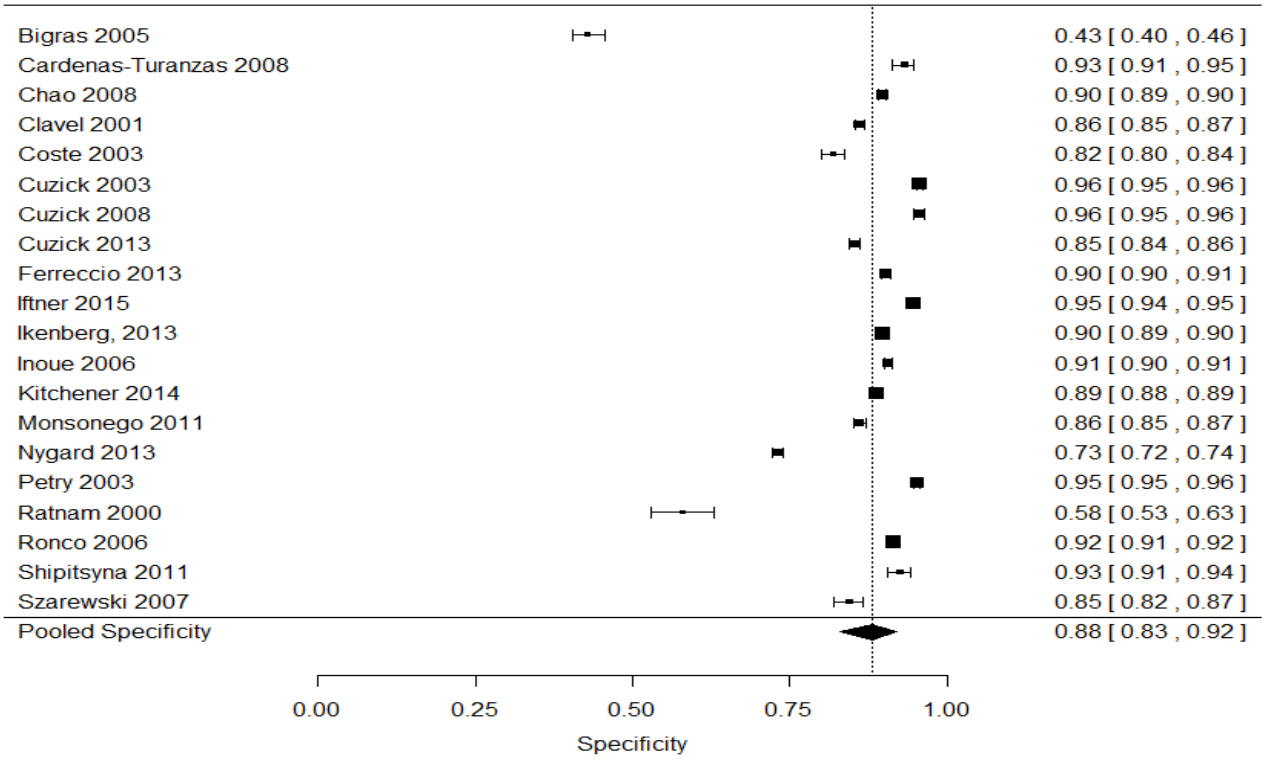
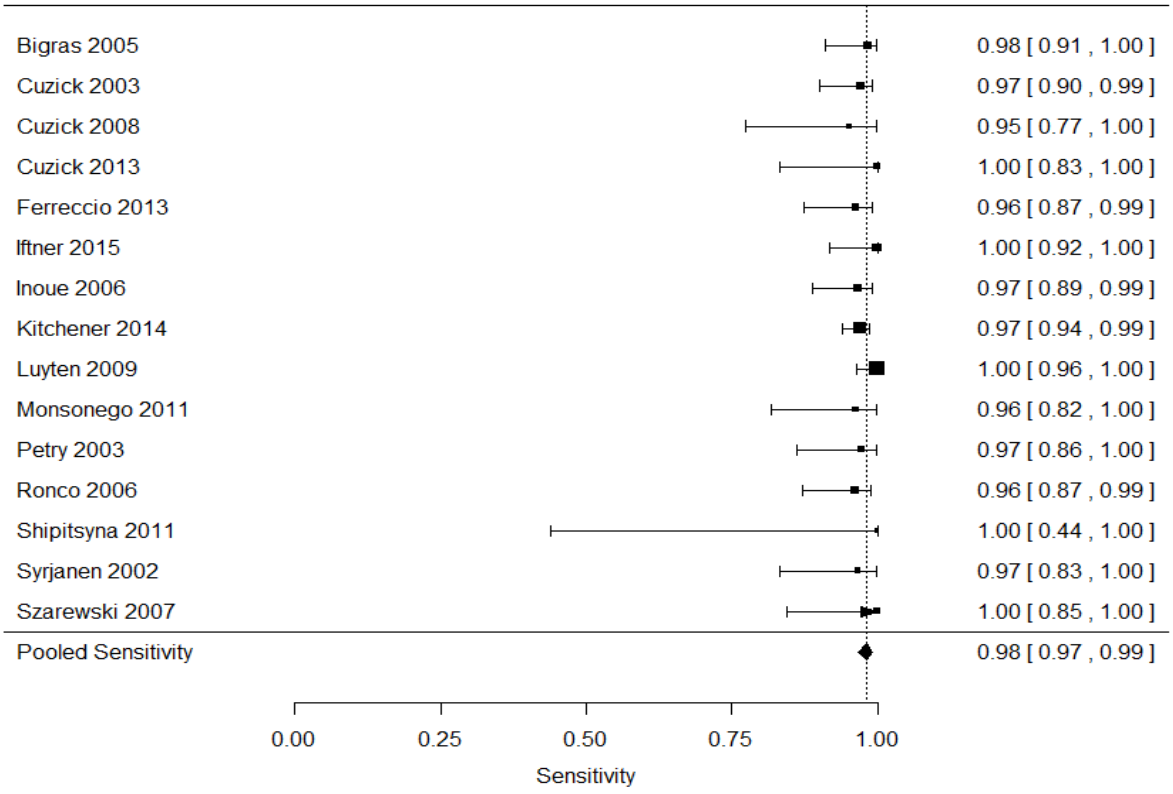


Figure 4.2 Sensitivity and specificity of HC2 in detecting CIN 3+



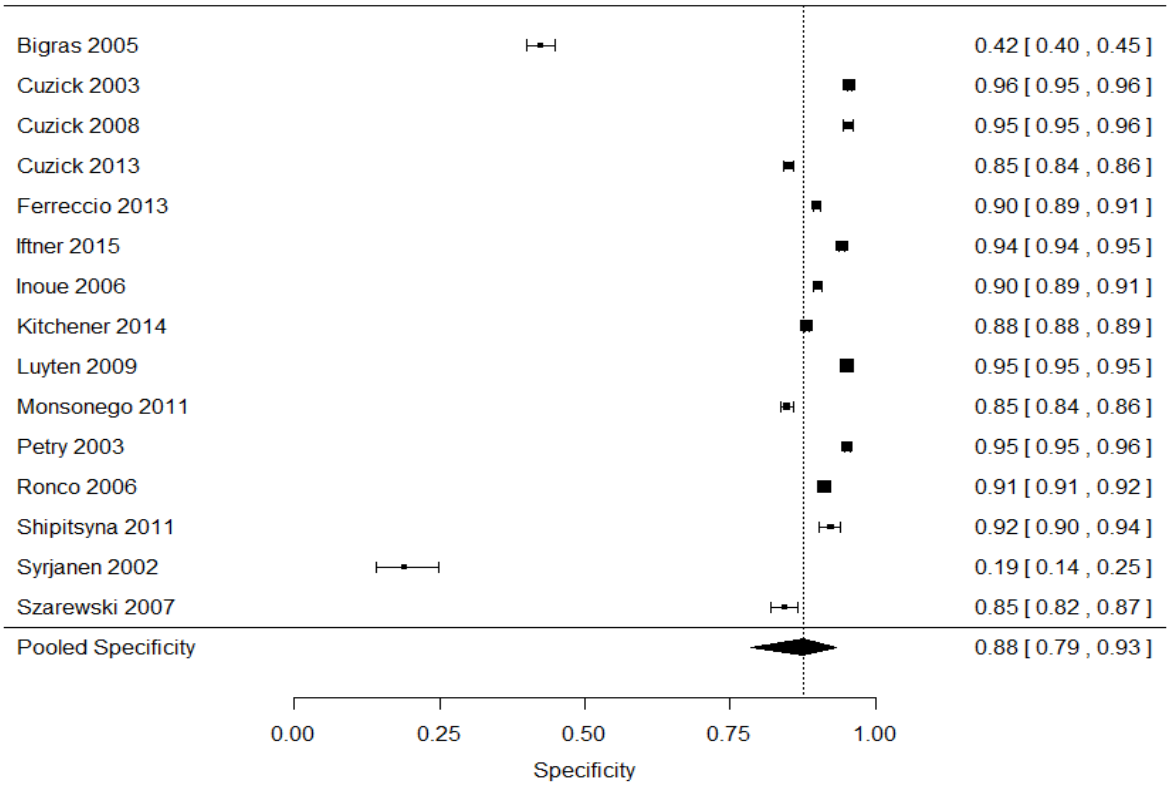
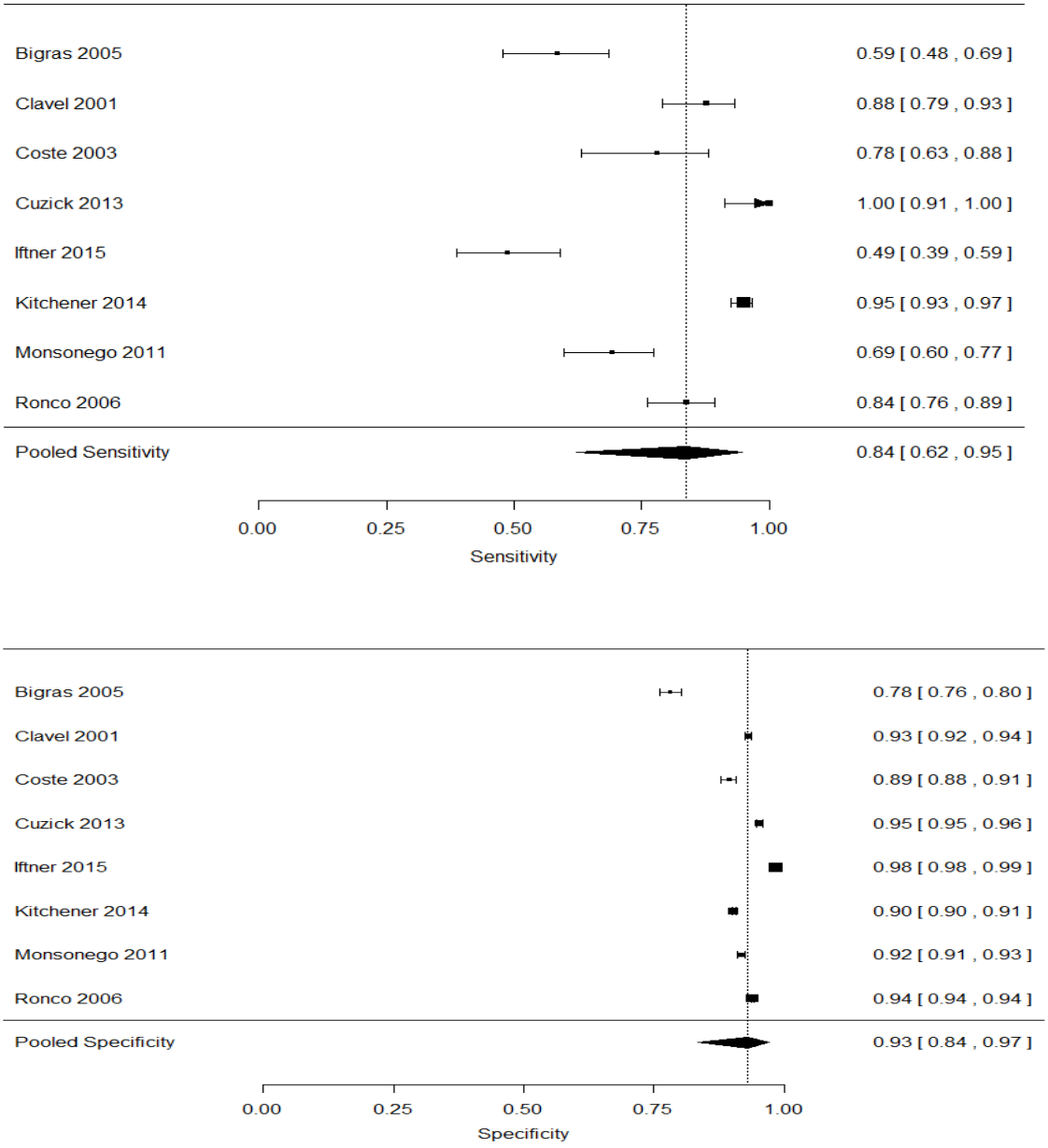
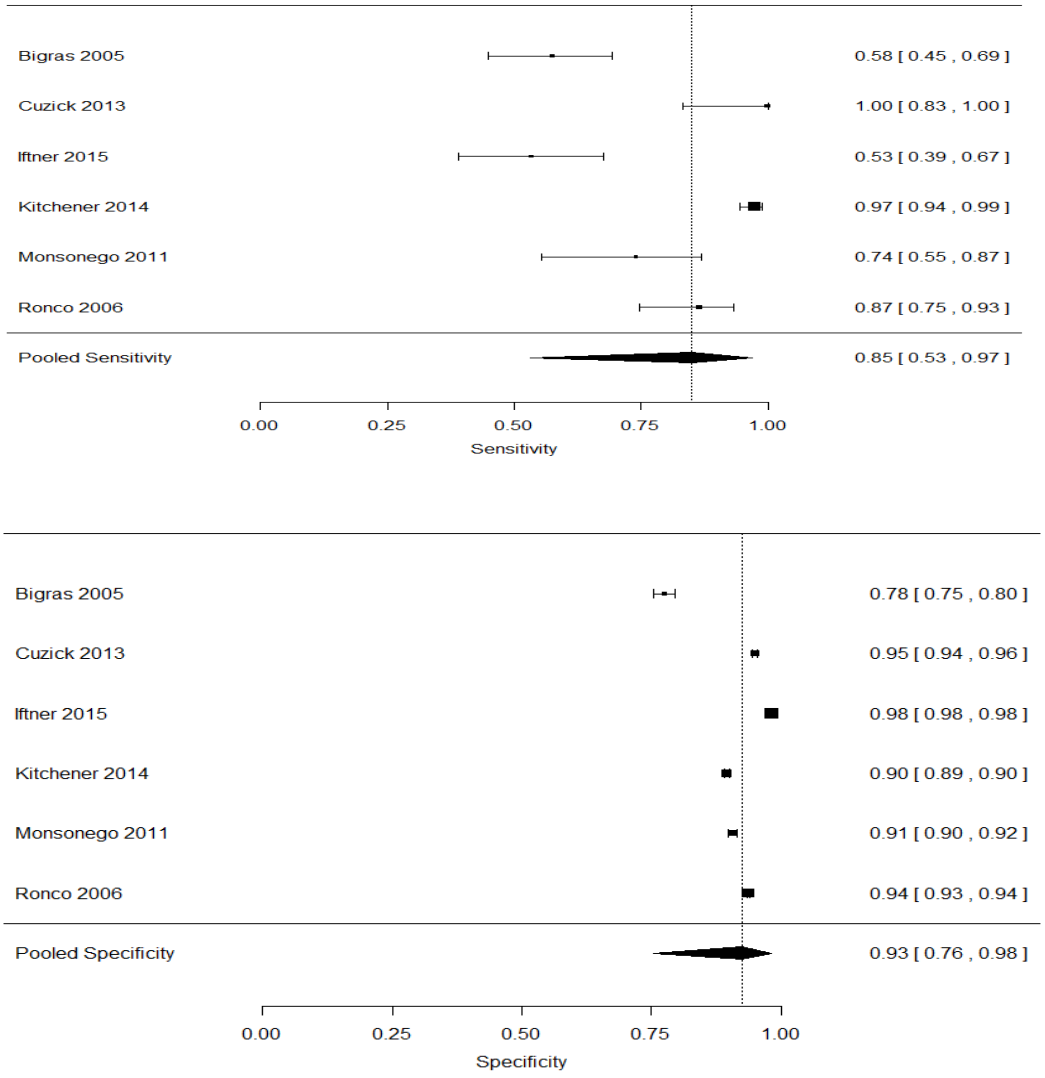


Figure 4.3 Sensitivity and specificity of liquid-based cytology in detecting CIN 2+



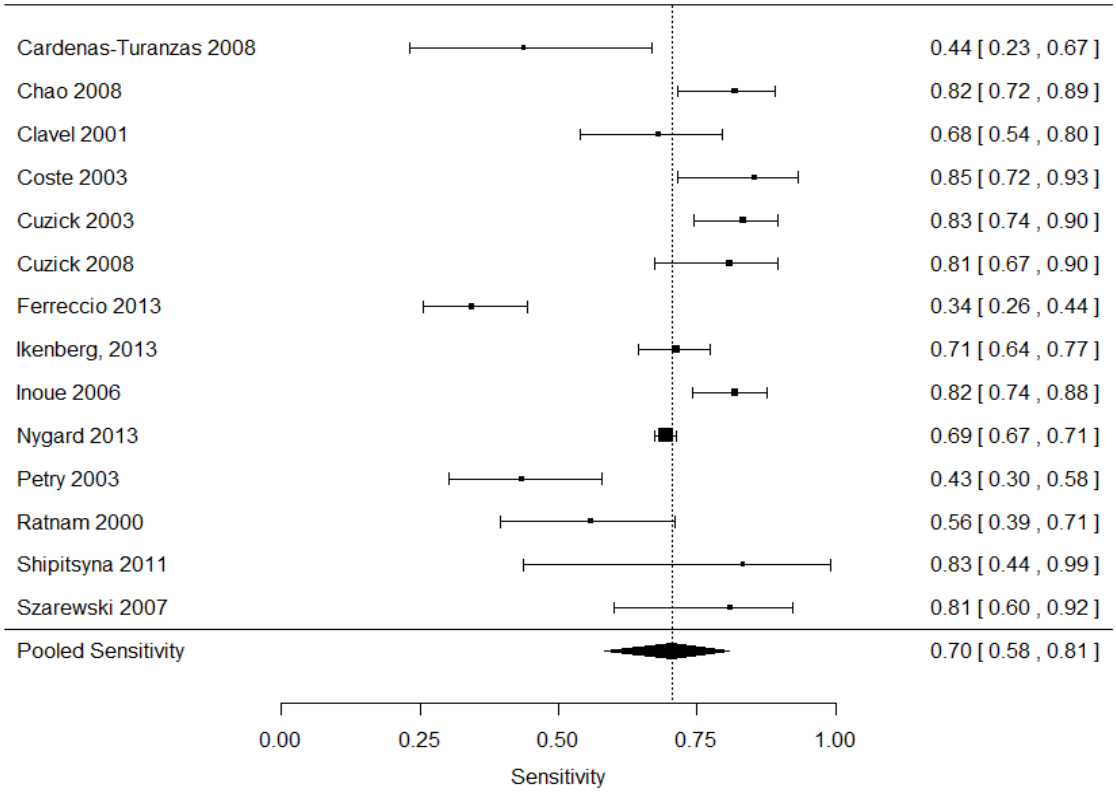
Compared with conventional cytology, the pooled sensitivity of LBC appears higher for both CIN 2+ (83.7% [CI 62.2%-94.8%] versus 70.5% [CI 58.2%-80.7%]), and for CIN 3+ (85.0% [CI 53.2%-86.9%] versus 71.9% [CI 53.6%-85.79%]), although the confidence bounds are wide and overlap. The specificity on the other hand appears lower for LBC compared with conventional cytology for both CIN 2+ (92.9% [CI 83.5%-97.2%] versus 95.8% [CI 92.8%-97.6%]) and CIN 3+ (92.6% [CI 75.5%-98.2%] versus 96.3% [CI 92.1%-98.2%]). For the most part, the LBC studies were conducted more recently than the conventional cytology studies.

Figure 4.4 Sensitivity and specificity of liquid-based cytology in detecting CIN 3+



Two studies in the meta-analysis of conventional cytology, Ferreccio et al.[175] and Ratnam et al.,[184] reported unusual results for the detection of CIN 2+ (Figure 4.5). Ratnam et al.[184] is not an influential study and its exclusion had minimal impact on the pooled specificity. However, Ferreccio et al.[175] reported an unusually low sensitivity (34.4%) in the detection of CIN 2+ and may represent an outlier. Exclusion of this study leads to a significantly higher pooled sensitivity of 73.0% (CI 61.7%-82.2%) for CIN 2+.

Figure 4.5 Sensitivity and specificity of conventional cytology in detecting CIN 2+



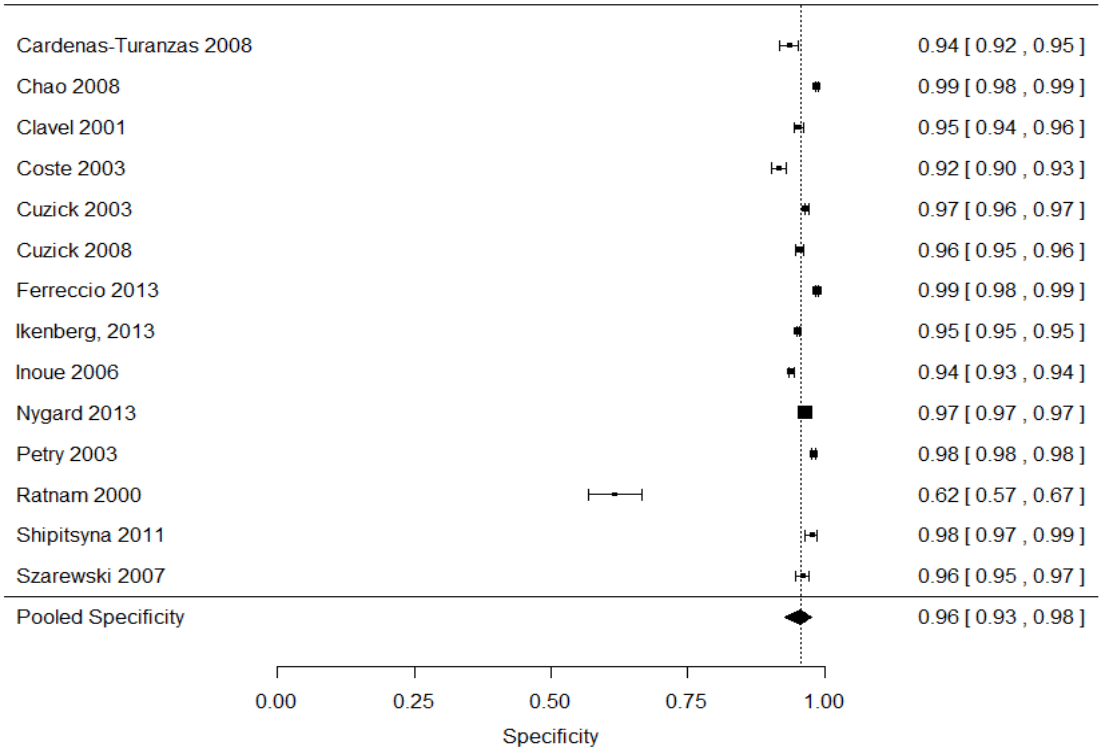
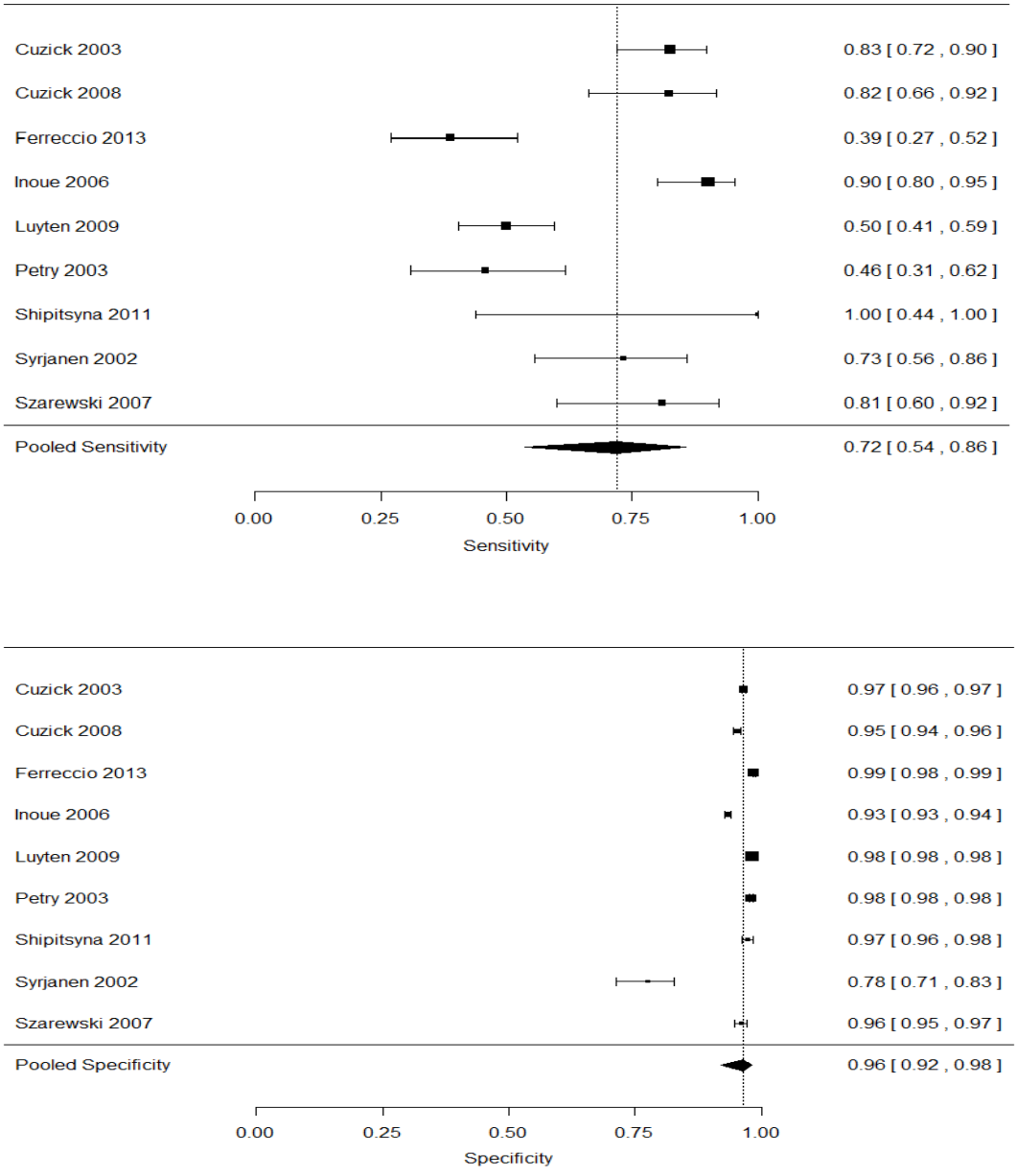


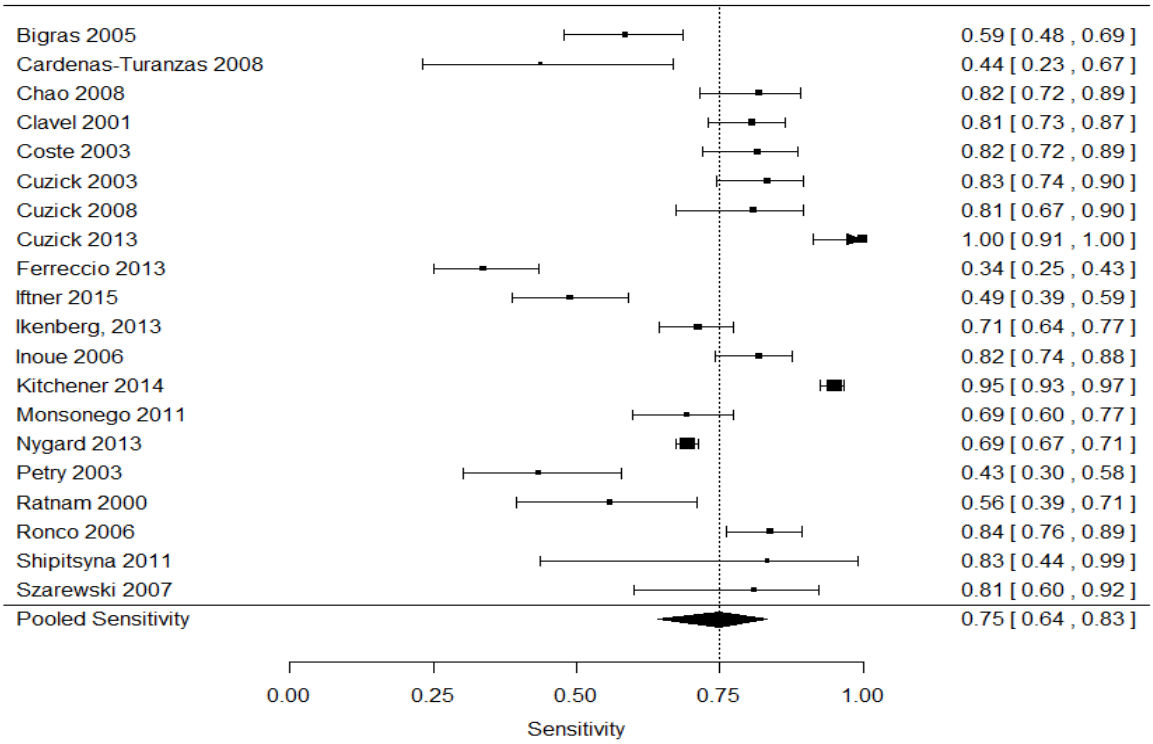
Figure 4.6 Sensitivity and specificity of conventional cytology in detecting CIN 3+



The pooled estimates for sensitivity and specificity of the cytology tests when presented as a combined result lie between those estimated for LBC alone and those estimated for conventional cytology alone (Figure 4.7 and 4.8). The pooled sensitivity was 75.0% (CI 64.1%-83.3%) for CIN 2+ and 78.0% (CI 63.5%-88.4%) for CIN 3+. The pooled specificity was 95.0% (CI 92.2%-96.8%) for CIN 2+ and 95.1% (CI 91.6%-97.3%) for CIN 3+. Similar to the analysis of conventional cytology, the study by Ferreccio et al.[175] reported an unusually low sensitivity in the detection of CIN 2+ (see Figure 4.7) and may represent an outlier. Exclusion of this

study leads to a significantly higher pooled sensitivity of 76.4% (CI 67.1%-84.0%) for CIN 2+.

Figure 4.7 Sensitivity and specificity of cytology (including both liquid-based cytology and conventional cytology) in detecting CIN 2+



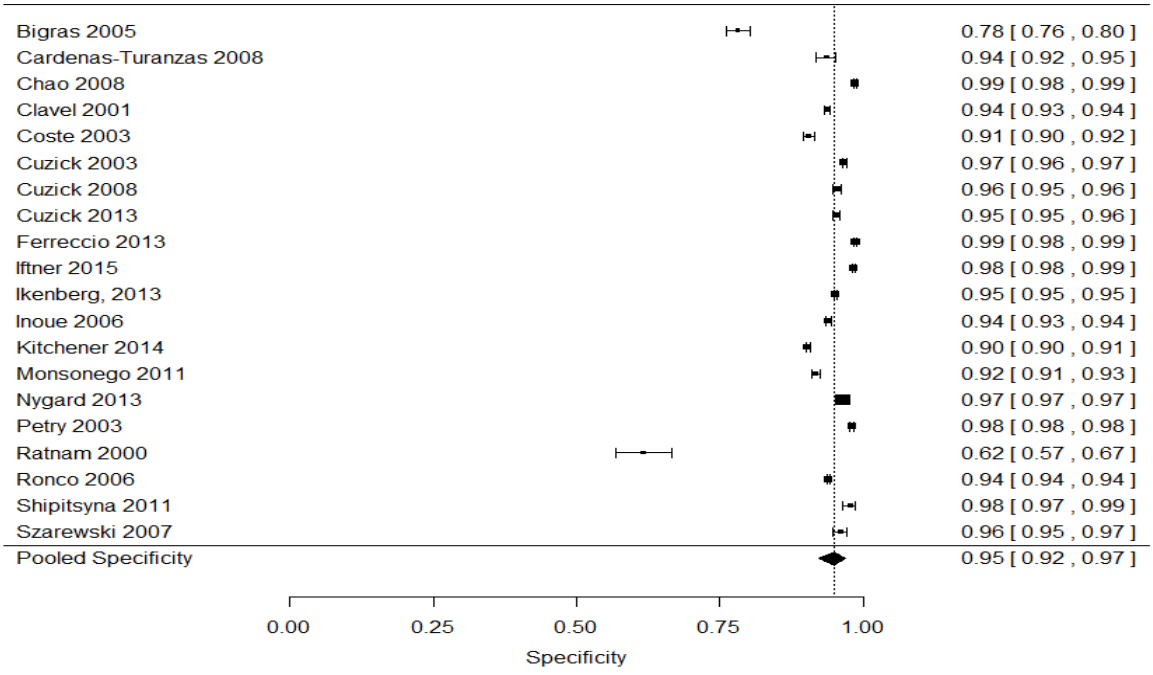
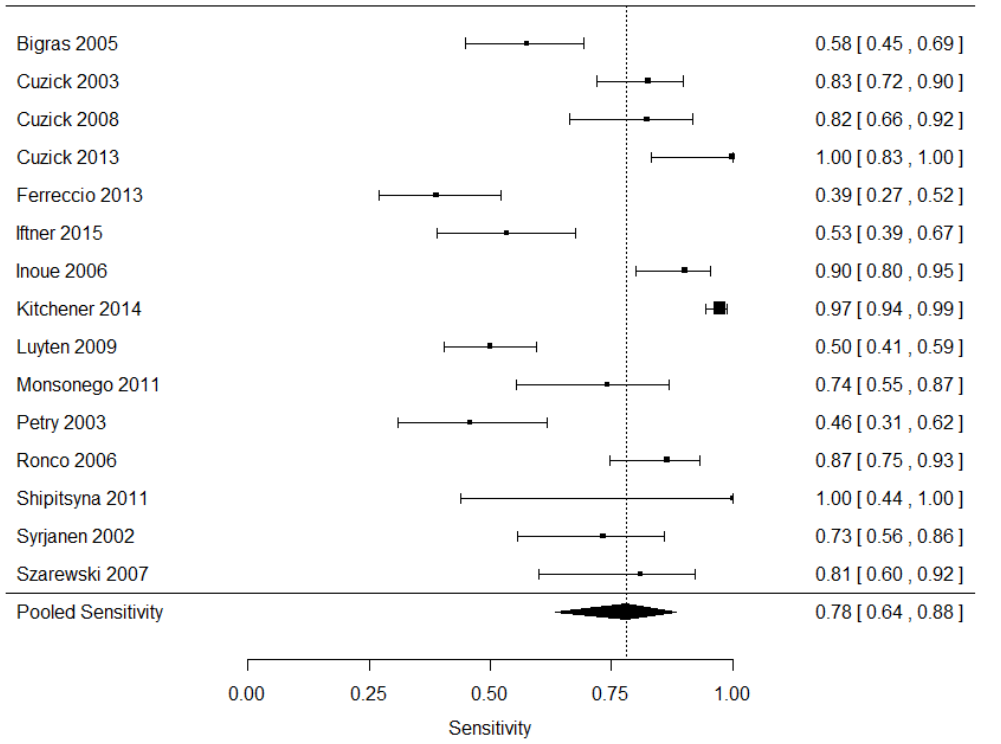
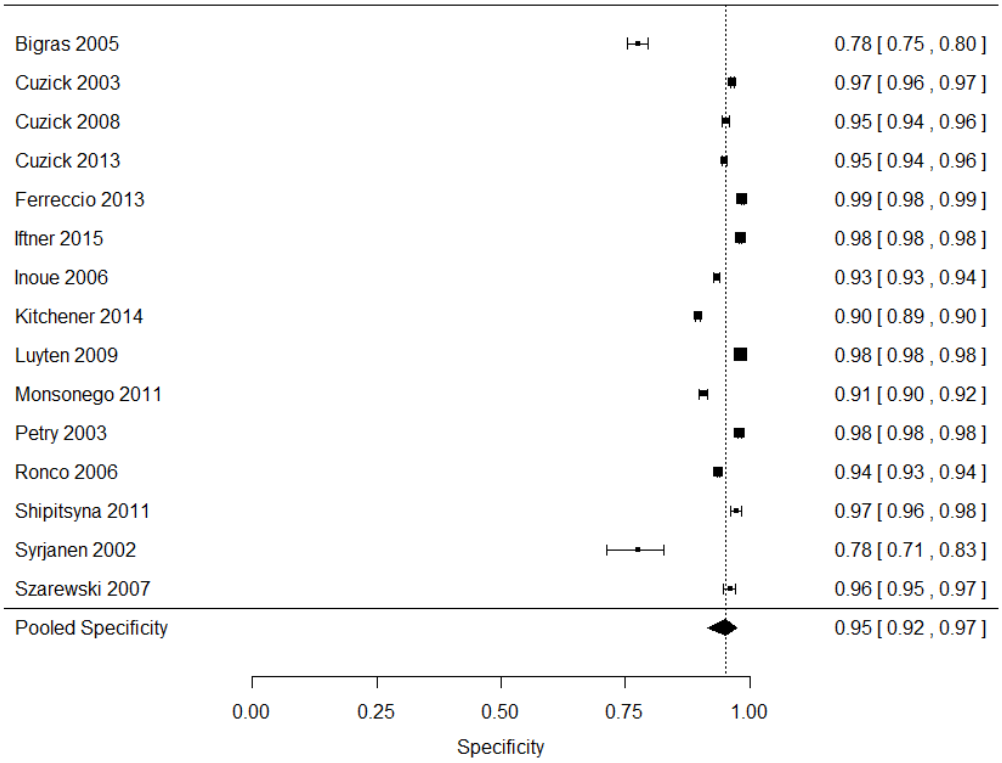


Figure 4.8 Sensitivity and specificity of cytology (including both liquid-based cytology and conventional cytology) in detecting CIN 3+





4.1.4 Applicability of evidence

The results of this meta-analysis confirm that HPV screening is more sensitive than cytology (LBC or conventional cytology) for detecting CIN 2+ and CIN 3+, but is significantly less specific, meaning that there would be more false positive results. This is consistent with the results of previous meta-analyses.[28, 164] With the exception of the sensitivity of the HC2 test in the detection of CIN 3+, all analyses were subject to statistically significant levels of heterogeneity. A random effects approach, which is more appropriate when high level of heterogeneity exist, was therefore used in the analysis.

Across all analyses, the correlation between sensitivity and specificity is not statistically significant in any comparison. This supports the point that the same threshold, that is how the tests define a positive and negative result, is used in all studies. The included studies were all conducted in industrialised countries; the population were representative of general screening populations; and the studies were typically large and of good quality. All cytology performed within CervicalCheck- Ireland's National Cervical Screening Programme uses LBC with all laboratory services centralised to three laboratories. A subgroup analysis using only studies that compared HC2 and LBC resulted in minor changes to the estimated sensitivity and specificity of the HC2 test, and supports the finding that the HC2 test is substantially more sensitive and less specific than LBC for CIN 2+ and CIN 3+.

The HC2 HPV assay was the first to become commercially available and is the most commonly reported assay in the literature. In 2009, an international expert committee proposed criteria for the validation of HPV assays in the context of primary screening for cervical cancer. It required that new tests should be highly reproducible and at least as accurate as HC2.[27] A review in 2015[26] identified five HPV assays (Aptima, Abbott RealTime, BD Onclarity, Cobas 4800, PapilloCheck) that fulfilled these criteria and four (Cervista, GP5+/6+, qPCR, MALDI-TOF) that partially fulfilled these criteria. Since May 2015, CervicalCheck has used the Aptima assay and the Cobas 4800 assay for all HPV testing.[55] As such, there is no evidence to suggest the outcomes reported here would differ from those obtainable in CervicalCheck.

Another way to consider the accuracy of the tests is to look at the positive predictive value (PPV): the proportion of women with a positive test who actually have the disease; and negative predictive value (NPV): the proportion of women with a negative test who are actually free of the disease. These predictive values vary according to the underlying prevalence of the disease; as prevalence of disease in a population approaches zero, the PPV of a test approaches zero. Conversely, as prevalence approaches 100%, the NPV of a test approaches zero (that is all negative

results will be false negatives). The more sensitive a test is, the higher its NPV will be, while the more specific it is, the higher its PPV will be.[191]

Assuming an overall prevalence of 1.6% for CIN 2+ and 1.0% CIN 3+ for women aged 25-60 years in Ireland,[56, 112, 194] the PPV of HC2 for CIN 2+ and CIN 3+ is 11.8% and 7.6%, respectively compared with a PPV of cytology (LBC and cytology) of 19.9% and 14.2% for CIN 2+ and CIN 3+, respectively. The corresponding NPV of HC2 is 99.91% and 99.98% for CIN 2+ and CIN 3+, respectively compared with a NPV for cytology of 99.57% and 99.76% for CIN 2+ and CIN 3+, respectively.

The meta-analysis presents data for a general screening population, without widespread HPV vaccination. There is currently limited evidence about the performance of cytology or HPV testing in vaccinated cohorts. A Scottish study compared the performance of three HPV tests (Abbott RealTime, Aptima, BD Onclarity) in vaccinated and unvaccinated women aged 20 to 21 years.[195] As expected, there was a reduced prevalence of HPV in the vaccinated cohort; however, the overall prevalence of HPV in the vaccinated cohort was significantly lower when estimated using Aptima compared with the two DNA-based assays (RealTime and BD Onclarity). This indicated the performance of the HPV tests may be differentially affected in a vaccinated cohort.[195]

Palmer et al.[196] compared the cytology performance of vaccinated and unvaccinated women aged 20 to 21 years, who had both cytology and histology records, in routine screening in Scotland. As expected, vaccination was associated with a reduction in all grades of cytological abnormalities. The sensitivity and specificities did not differ between the vaccinated and unvaccinated cohorts for either CIN 2+ or CIN 3+. The PPV for CIN 2+ was as expected lower in the vaccinated cohort; however, the PPV for CIN 3+ was similar in both the vaccinated and unvaccinated cohorts.

The systematic review has demonstrated that, at baseline, HPV testing is more sensitive in detecting CIN 2+ and CIN 3+ than cytology. However, this does not necessarily mean there will be a reduction in the incidence of cervical cancer in the long term when compared with cytology-based screening. Evidence from long-term follow up of women with a negative screening result has shown that a negative HPV test carries a lower risk of developing both CIN 3+ and invasive cervical cancer than a negative cytology test result.[28, 197, 198] Arbyn et al.[28] considered the results of the second round of screening in four trials. Despite different follow-up policies for screen-positive women, a consistent reduction in the incidence of CIN 3+ was found among women who had a HPV-negative result compared with those who had a negative cytology result on the first round screening. This suggests there may be earlier detection of CIN 3+ through HPV-based screening.

A European study[198] which included 24,295 women across six countries found the cumulative incidence rate of CIN 3+ after six years among women negative for HPV at baseline to be 0.27% (CI 0.12% to 0.45%). This was considerably lower than among women with negative cytology results (0.97% [CI 0.53% to 1.34%]). Follow up from four European RCTs[197] conducted in Sweden (Swedescreen), the Netherlands (POBASCAM), UK (ARTISTIC), and Italy (NTCC), which included 176,464 women aged 20 to 64 years and who were followed for a median of six and a half years, found the cumulative incidence of invasive cervical cancer in women with negative screening tests at entry was 8.7 per 100,000 (CI 3.3 to 18.6) at five and a half years for women who were screened with HPV-based testing compared with 36.0 per 100,000 (CI 23.2 to 53.5) for women who had cytology-based screening.

4.2 Triage strategies

The systematic review in Section 4.1 has demonstrated that HPV-based screening is more sensitive compared with cytology screening in the detection of CIN 2+ and CIN 3+. However, its low specificity means that using HPV testing as the only screening test would lead to large numbers of women unnecessarily referred to colposcopy clinics. Therefore the triage of women with a HPV-positive screening test result is important. CervicalCheck currently uses LBC as the primary screening test and in May 2015, HPV triage testing commenced for women with a cytology result of ASCUS or LSIL. This section will consider the evidence for triaging strategies for women who screen HPV positive.

4.2.1 Search strategy

A recent systematic review, by the Belgian Health Care Knowledge Centre (KCE) published in 2015[164] was used as the basis for this systematic review of triaging strategies of women with a HPV-positive primary screening test result. The KCE search was completed in October 2013. The Evaluation Team updated this search in PubMed and EMBASE to April 2016 using the same search criteria. Full details of the search strategy are provided in Appendix 3 of this document. The PICOS (Population, Intervention, Comparator, Outcomes, Study design) analysis used to formulate the search is presented in Table 4.5.

Table 4.5 PICOS analysis for identification of relevant studies for triaging women with a HPV-positive screening test

Population	Women participating in a cervical screening programme who had a positive primary HPV screening test result.
Intervention	Reflex testing with cytology, HPV testing, HPV genotyping, $p16^{INK4a}$, $p16^{INK4a}$/Ki-67 immunocytochemistry and or combinations of these.
Comparator	Gold standard application of colposcopy and or biopsy on at least all cytology- and HPV-positive samples.
Outcomes	Cross-sectional and longitudinal accuracy to detect histologically identified disease (CIN 2+, CIN 3+) and referral rate for colposcopy.
Study design	Follow up of randomised controlled trials comparing different triage algorithms for HPV-based primary screening.

Key: CIN – cervical intraepithelial neoplasia; HPV – human papillomavirus.

The KCE-included studies and the updated search studies were reviewed according to the stated inclusion and exclusion criteria. This was carried out by two researchers independently and any disagreements were resolved through discussion. The quality of all studies was assessed independently by two researchers, with disagreements being resolved through discussion, using the quality assessment of diagnostic accuracy studies (QUADAS-2) checklist.[166] Data extraction from all studies (KCE studies and updated search) was performed independently by two researchers, with disagreements being resolved through discussion.

4.2.2 Results

Ten studies were included in the 2015 KCE review. Four additional triage studies were identified in the updated systematic review.[179, 199-201] One additional study from the UK-based ATHENA trial was identified after the completion of the systematic review.[202] Characteristics of these 15 studies are included in Table 4.6. The 15 studies were based on eight RCTs. These RCTs were as follows:

- NCTT (New Technology in Cervical Cancer)[200] trial, conducted in nine population-based cervical screening programmes in Italy, in which women aged 25 to 60 years who were attending for a new routine cervical screening episode were randomly assigned to either conventional cytology, HPV-based screening alone, or HPV-based screening in combination with LBC.

- ARTISTIC (A Randomized Trial In Screening To Improve Cytology)[179] trial, a randomised comparison of combined HPV and LBC testing compared with LBC alone in primary cervical screening. It included 25,410 women aged 20-64 years undergoing routine cervical cytology screening in Greater Manchester.

- ATHENA (Addressing the Need for Advanced HPV Diagnostics)[201] trial was specifically designed to evaluate primary screening with the Cobas® HPV test in women aged 25 years or older in the US and to evaluate different triage strategies for HPV-positive women.

- PROHTECT-3 (PRotection by Offering HPV TEsting on self-sampled Cervico-vaginal specimens Trial-3)[199] trial which recruited 46,001 registered non-attendees of regular cervical screening programme from the year 2007, who lived in four regions of the Netherlands.
- POBASCAM (population-based screening study Amsterdam)[203] trial included 44,938 women aged 29 to 61 years who were randomised to either a conventional cytology–based control arm, or an intervention arm, in which women were managed on the basis of cytology plus the results of HPV tests (both scored blinded for each other).

- Public Health Trial Finland[204] trial invited 108,327 women aged 25 to 65 years for organised cervical screening in nine Finnish municipalities. They were individually randomly assigned to either the primary HPV-testing group, followed by cytology triage or to the primary conventional cytological screening group.

- Swedescreen**[31]** trial, a population-based RCT of primary screening with HPV testing that was conducted within the Swedish organised screening programme. A total of 12,527 women, aged 32 to 38 years, who lived in one of five Swedish cities participated. Women were randomly allocated to either the intervention arm (in which a Pap smear and HPV testing were performed on the baseline screening samples) or the control arm (in which only a Pap smear was performed, and the frozen samples were stored for future use).

- VUSA-screen (Vrije Universiteit Medical Centre-Saltro)[205] trial, a population-based study designed to evaluate the effectiveness of the combination of cytology screening and HPV testing using HC2. The study was carried out in The Netherlands in the setting of the regular Dutch screening programme that invites women aged 30 to 60 years to be screened every five years.

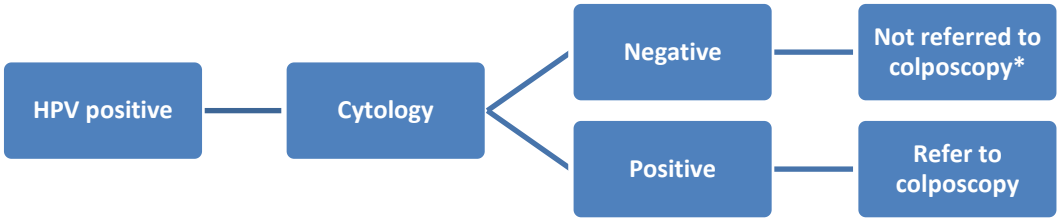
Of these eight RCTs, a number had multiple publications and nested studies that reported outcomes of triaging strategies. The NTCC trial, conducted in Italy, had five publications reporting on three nested substudies as part of this RCT.[35, 185, 186, 200, 206] The ARTISTIC trial, conducted in the UK had two publications, [179, 207] and the ATHENA trial, conducted in the US had three publications.[201, 202, 208] Each of the remaining RCTs, PROHTECT-3, conducted in the Netherlands,[199] Public Health Trial Finland,[204] Swedescreen[31] and VUSA-screen, conducted in the Netherlands,[205] had one publication which reported on the outcomes of triage strategies.

The most commonly used HPV test was the Hybrid Capture 2 (HC2) HPV assay (Qiagen). This was used in four RCTs (NTCC, ARTISTIC, Public Health Trial Finland and VUSA-screen). The GP5+/6+ PCR-enzyme immunoassay was used in three trials

(PROHTECT-3, POBASCAM and Swedescreen). The UK-based ATHENA trial, mostly used the Cobas® HPV test, but a number of other HPV tests were also used. The results were not disaggregated by the HPV test used.

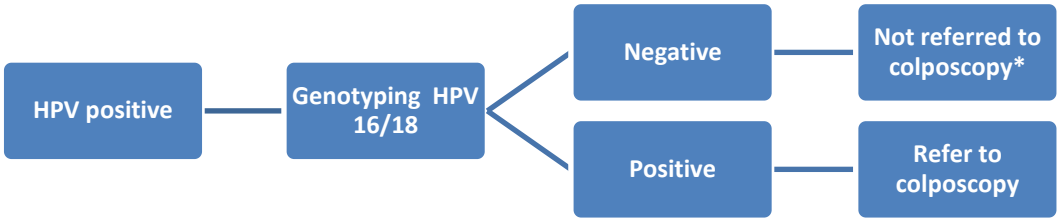
In total, five different triaging strategies of interest are considered within these studies; these are outlined in Figures 4.9 to 4.13. In all strategies, both the primary and subsequent triage tests could be undertaken using the same sample, so only one screening visit was required by the woman. The most common triaging strategy was primary HPV testing followed by cytology triage testing, used in 11 studies.[30, 179, 185, 186, 199, 200, 202-205, 207] Three different triage strategies that used partial genotyping for HPV 16 and HPV 18 were considered. In the first strategy considered in four studies, all women positive for either HPV 16 or HPV 18 were referred to colposcopy;[30, 179, 204, 205] the second variation, which was included in five studies, added an additional triage cytology test where women positive for all three tests were referred to colposcopy;[30, 201, 202, 204, 205] and the final variation considered in four studies was co-testing with partial genotyping for HPV 16 or HPV 18 plus cytology at the triage stage with a positive result on either triage test leading to a colposcopy referral.[30, 202-204] The fifth strategy of interest was the use of $p16^{INK4a}$ or the combined $p16^{INK4a}$/Ki-67 dual stain; this was reported in three papers;[202, 204, 208] however, two of these papers[35, 206] were reporting the same study with longitudinal outcomes reported in the later paper.

Figure 4.9 Strategy 1: Primary HPV testing followed by triage with cytology



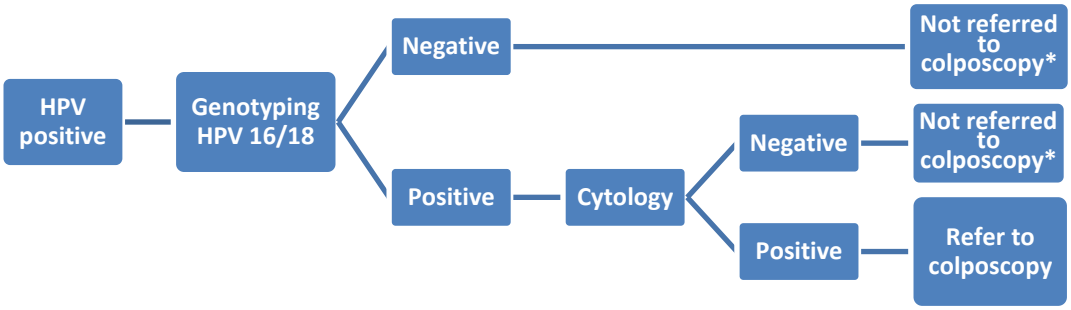
Note: cytology triage may be completed using the same screening sample, so only one screening visit is required by the woman.
Some or all of these women may have undergone colposcopy and biopsy in the included RCTs.

Figure 4.10 Strategy 2: Primary HPV testing followed by triage with partial genotyping for HPV 16 and HPV 18



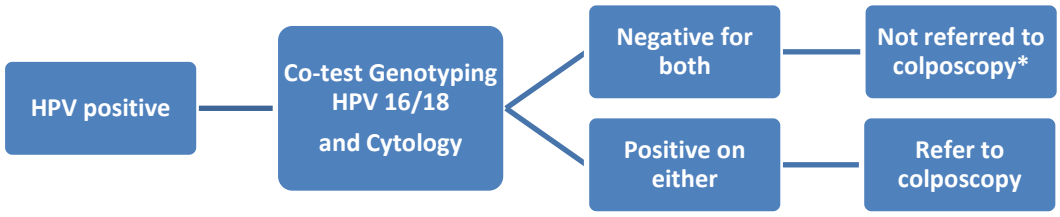
Note: partial genotyping for HPV 16 and HPV 18 may occur concurrently with HPV testing. The diagram represents the decision process leading to referral to colposcopy. Both tests may be completed using the same screening sample, so only one screening visit is required by the woman. Some or all of these women may have undergone colposcopy and biopsy in the included RCTs.

Figure 4.11 Strategy 3: Primary HPV testing followed by triage with sequential partial genotyping for HPV 16 and HPV 18 and cytology



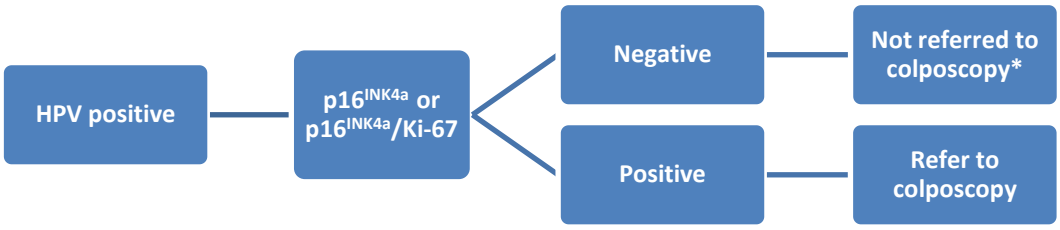
Note: partial genotyping for HPV 16 and HPV 18 may occur concurrently with HPV testing; the diagram represents the decision process leading to referral to colposcopy. Both the primary screening test and the triage tests may be completed using the same screening sample, so only one screening visit is required by the woman.
Some or all of these women may have undergone colposcopy and biopsy in the included RCTs.

Figure 4.12 Strategy 4: HPV primary testing followed by co-testing triage with partial genotyping for HPV 16 and HPV 18 and cytology triage



Note: partial genotyping for HPV 16 and HPV 18 may occur concurrently with HPV testing; the diagram represents the decision process leading to referral to colposcopy. Both the primary screening test and the triage tests may be completed using the same screening sample, so only one screening visit is required by the woman.
Some or all of these women may have undergone colposcopy and biopsy in the included RCTs.

Figure 4.13 Strategy 5: Primary HPV testing followed by $p16^{INK4a}$ or $p16^{INK4a}$/Ki-67 (dual stain) triage



Note: Both the primary screening test and the triage tests may be completed using the same screening sample, so only one screening visit is required by the woman.
Some or all of these women may have undergone colposcopy and biopsy in the included RCTs.

A total of 15 studies were included in the analysis of triage strategies. Sample sizes ranged from 364[199] participants to 40,901.[201] All of these studies included women attending for routine cervical screening. However, the age range of women recruited by Verhoef et al.[199] was higher than the age range in other studies. Verhoef et al.[199]reported a median age of 42 years and an interquartile range of 38 to 48 years. Women recruited by Wright et al.[202] were younger than expected for routine cervical screening. A quarter of the women were between 25 and 29 years. Five studies reported longitudinal outcomes.[186, 199, 201, 203, 205]

Of the 15 studies identified, three [30, 179, 207] were rated at low risk of bias across all four domains (see Table 4.7). Eleven were rated at a higher risk of bias regarding patient selection.[199, 200] [35, 206] [31, 185, 186, 202-205] Blinding of colposcopists to HPV status was not ensured in both Carozzi studies,[35, 206] and in four of the remaining studies it was unclear whether blinding of HPV status was ensured.[199, 203-205] Two studies were at high risk of bias in domain 2 (index test). Verhoef et al.[199] used self-sampling for the primary test, with physician samples taken for triage testing and to confirm the primary test result. Wright et al.[202] included a number of different HPV tests, but disaggregated results were not presented. One study[202] had a high risk of bias in the flow and timing domain as samples were stored for up to five years before testing. Overall, the quality of the studies was rated as fair to good.

Table 4.6 Summary characteristics for studies of HPV triaging strategies

Randomised Control Trial (Country)	Study	Follow-up	HPV-test (s)- primary test, sample size	Relevant triage strategy (ies)
NTCC (Italy)	*Bergeron 2015[200]	Baseline and 3 year	HC2 (n=1,261)	Cytology
	Carozzi 2008[206]	Baseline	HC2 (n=1,137)	$p16^{INK4A}$ (at a threshold of 1+ cells)
	Carozzi 2013[35]	Baseline and 3 year	HC2 (n=1,137)	$p16^{INK4A}$
	Ronco 2006a[185]	Baseline	HC2 (n=16,255)	LBC
	Ronco 2006b[186]	Baseline and 1 year	HC2 (n=5,924)	LBC
ARTISTIC (UK)	Kitchener 2009[207]	Baseline	HC2 (n=18,386)	Cytology
	*Kitchener 2014[179]	Baseline	HC2 (n=21,910)	1. LBC
				2. Partial genotyping for HPV 16/18
ATHENA (US)	Castle 2011[30]	Baseline	Amplicor, Linear Array and Cobas (ThinPrep) (n=7,823)	1. Cytology
				2. Partial genotyping for HPV 16/18+
				3. Co-testing (partial genotyping for HPV 16/18 plus cytology) with referral if positive for either triage test
				4. Co-testing (partial genotyping for HPV 16/18 plus cytology) with referral only if positive for both triage tests
	*Wright 2015[201]	3 year	Mostly Cobas, but other HPV tests used as well (n=40,901)	Co-testing (partial genotyping HPV for 16/18 & LBC)
	*Wright 2016[202]	Baseline	Cobas (n=7,727)	1. LBC
				2. $p16^{INK4a}$/Ki-67 (at a threshold of 1+ cells)
				3. Co-testing (LBC plus partial genotyping for HPV 16/18)

				with referral only if positive for both tests
				4. Co-testing (LBC plus partial genotyping for HPV 16/18) with referral if positive for either test
				5. Co-testing ($p16^{INK4a}$/Ki-67 and partial genotyping for HPV 16/18) with referral only if positive for both tests
				6. Co-testing ($p16^{INK4a}$/Ki-67 and partial genotyping for HPV 16/18) with referral if positive for either test
PROHTECT-3 (The Netherlands)	*Verhoef 2015[199]	1-2 years	HPV (GP5+/6+) (n=364)	Cytology
POBASCAM (The Netherlands)	Dijkstra 2013[203]	4 year	GP5+/6+-PCR EIA (n=1,100)	1. Conventional cytology
				2. Co-testing (conventional cytology plus partial genotyping for HPV 16/18)
Public health Trial Finland (Finland)	Leinonen 2013[204]	Baseline	HC2 (n=2,574)	1. Cytology
				2. HPV partial genotyping for HPV 16/18
				3. Co-testing (cytology and partial genotyping for HPV 16/18) with referral only if positive for both tests
				4. Co-testing (cytology and partial genotyping for HPV 16/18) with referral if positive for either test
Swedescreen (Sweden)	Naucler 2009[31]	Baseline	PCR GP5+/GP6+ (n=6,089)	No relevant strategy combinations
VUSA-screen (The Netherlands)	Rijkaart 2012[205]	3 year	HC2 (n=1,303)	1. Cytology
				2. Partial genotyping for HPV 16/18
				3. Co-testing (cytology & partial genotyping for HPV 16/18)

*Studies identified in the updated search. Note the cross sectional outcomes for Carozzi 2013 are the same as Carozzi 2008.
Note: The Kitchener 2014 paper is an update of Kitchener 2009 with the same cohort of women, thus only Kitchener 2014 values are used in the evidence synthesis.
Note: Test thresholds were: Cytology- ASCUS or worse; HC2 - ≥1pg/ml; p16INK4A - 1+ cells.
Key: CC- conventional cytology; CIN – cervical intraepithelial neoplasia; HC2 - Hybrid Capture 2 HPV assay; HPV – human papillomavirus, LBC- liquid-based cytology.

Table 4.7 Risk of bias assessment of the included triage studies– QUADAS-2[166]

Study	Domain 1: Patient Selection		Domain 2: Index Test(s)		Domain 3: Reference Standard		Domain 4: Flow and Timing
	A. Risk of bias	B. Concerns regarding applicability	A. Risk of Bias	B. Concerns regarding applicability	A. Risk of bias	B. Concerns regarding applicability	A. Risk of bias
*Bergeron 2015[200]	Low	High	Low	Low	Low	Low	Low
Carozzi 2008[206]	Low	High	Low	Low	High	Low	Low
Carozzi 2013[35]	Low	High	Low	Low	High	Low	Low
Castle 2011[30]	Low	Low	Low	Low	Low	Low	Low
Dijkstra 2013[203]	Low	High	Low	Low	Unclear	Low	Low
Kitchener 2009[207]	Low	Low	Low	Low	Low	Low	Low
*Kitchener 2014[179]	Low	Low	Low	Low	Low	Low	Low
Leinonen 2013[204]	Low	High	Low	Low	Unclear	Low	Low
Naucler 2009[31]	Low	High	Low	Low	Low	Low	Low
Rijkaart 2012[205]	Low	High	Low	Low	Unclear	Low	Low
Ronco 2006a[185]	Low	High	Low	Low	Low	Low	Unclear
Ronco 2006b[186]	Low	High	Low	Low	Low	Low	Low
*Verhoef 2015[199]	Low	High	High	Low	Unclear	Low	Low
*Wright 2015[201]	Low	Low	Low	High	Low	Low	Low
*Wright 2016[202]	Low	High	Low	Low	Low	Low	High

*Studies identified in the updated literature search.

4.2.3 Evidence synthesis

All retrieved studies assessed triage strategies for women who underwent a primary HPV screening test. However, seven of the studies[35, 199, 200, 203-206] only included women who had a positive primary HPV test result. The reported sensitivity and specificity of these studies can be considered as the conditional outcomes given a positive primary HPV test result. For the remaining studies,[30, 31, 179, 185, 186, 201, 202, 207] the reported test accuracies should be considered as the sensitivity and specificity for the whole test strategy (primary test plus triage test). Data for the screening strategy as a whole is preferable as this provides direct evidence for the effectiveness of the particular screening strategy of interest.

Each of the five strategies of interest is considered separately. Baseline and longitudinal outcomes are presented. Where sufficient comparable data were available, a meta-analysis was carried out using the same methodology as described in Section 4.1; that is, a Bayesian bivariate, random effects approach.[190] The bivariate random effects model accounts for the bivariate nature of sensitivity and specificity as well as the within-study and between-study variability.[191] Analyses were carried out in Rstudio Version 0.99.893[192] using the bamdit package (version 2.0.1).[193] Where insufficient (less than three)[191] studies of comparable data were available, a narrative summary of the results is presented.

4.2.4 Baseline outcomes

This section considers the baseline screening accuracy of the five triage strategies of interest. The longitudinal outcomes (over a timeframe of one to four years) of the five triage strategies are considered in Section 4.2.5.

4.2.4.1 Strategy 1: Primary HPV testing followed by triage with cytology

Six randomised controlled trial (RCT) study datasets considered baseline accuracies of primary HPV testing followed by triage with cytology (Table 4.8).[30, 179, 186, 200, 202, 204] However, not all six studies are directly comparable. In two of the studies, only women who had a positive HPV test had their disease status confirmed by the 'gold standard' (histological examination of diagnostic biopsies). In the remaining four studies, all women who had the primary test and the triage test had their disease status confirmed by the 'gold standard'.

The forest plots of the four comparable studies are shown in Figures 4.14 to 4.15. It is clear from the forest plots that the sensitivity and specificity reported by Wright et al. and Castle et al.,[30, 202] both of which are from the US-based ATHENA trial, are

considerably lower than those reported in the other two studies. The likely reasons for this are discussed in Section 4.3. These differences suggest that pooling of these studies is not appropriate.

Table 4.8 Baseline results for primary HPV testing followed by cytology triage

Study	Referral to colposcopy	Outcome	Sensitivity (95% CI)	Specificity(95% CI)
Castle 2011[30]	12.0% of total screened 26.8% of triaged	CIN 2+ Strategy	52.6% (47.6%-57.6%)	90.1% (89.4%-90.7%)
		CIN 3+ Strategy	52.8% (46.6%-58.9%)	89.3% (88.6%-90.0%)
Kitchener 2014[179]	4.9% of total screened 38.7% of triaged	CIN 2+ Strategy	88.4% (85.0%-91.1%)	96.7% (96.5%-97.0%)
		CIN 3+ Strategy	94.3% (90.6%-96.7)	96.0% (95.8%-96.3%)
Ronco 2006 [185] [186]	2.8% of total screened 31.2% of triaged	CIN 2+ Strategy	81.4% (73.4%-87.4%)	97.6% (97.4%-97.8%)
		CIN 3+ Strategy	82.7% (70.3%-90.6%)	97.4% (97.2%-97.6%)
Wright 2016[202]	12.1% of total screened 25.9% of triaged	CIN 2+ Strategy	46.5% (41.7%-51.3%)	89.9% (89.1%-90.6%)
		CIN 3+ Strategy	48.3% (42.3%-54.3%)	89.2% (88.5%-89.9%)
Bergeron 2015[200]	2.8% of total screened 37.7% of triaged	CIN 2+ Conditional	85.6% (76.6%-92.1%)	65.9% (63.1%-68.6%)
		CIN 3+ Conditional	88.1% (74.4%-96.0%)	64.0% (61.2%-66.7%)
Leinonen 2013[204]	NR of total screened 38.5% of triaged	CIN 2+ Conditional	97.6% (94.0%-99.1%)	65.6% (63.6%-67.4%)
		CIN 3+ Conditional	95.2% (86.9%-98.4%)	62.9% (61.0%-64.8%)

Key: CIN – cervical intraepithelial neoplasia; CI-confidence interval.
Note: Strategy refers to the entire screening strategy HPV test followed by the triage test(s) with the reported sensitivity and specificity representing the entire screening population. Conditional outcomes represent the outcomes for the triage test(s) for the population who were screened positive on the primary HPV screening test. All extracted data represent the crude values.

Figure 4.14 Sensitivity and specificity of primary HPV testing followed by cytology triage in detecting CIN 2+

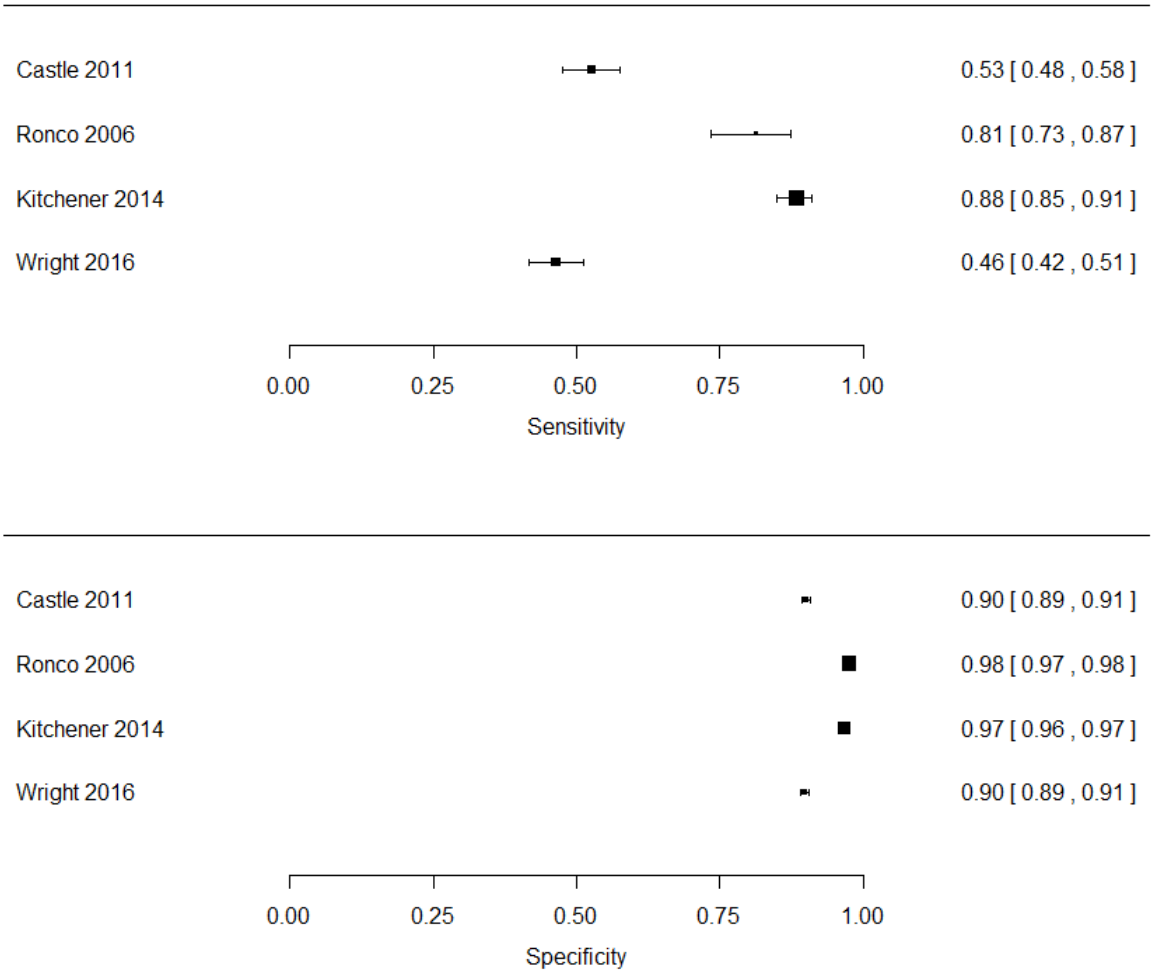
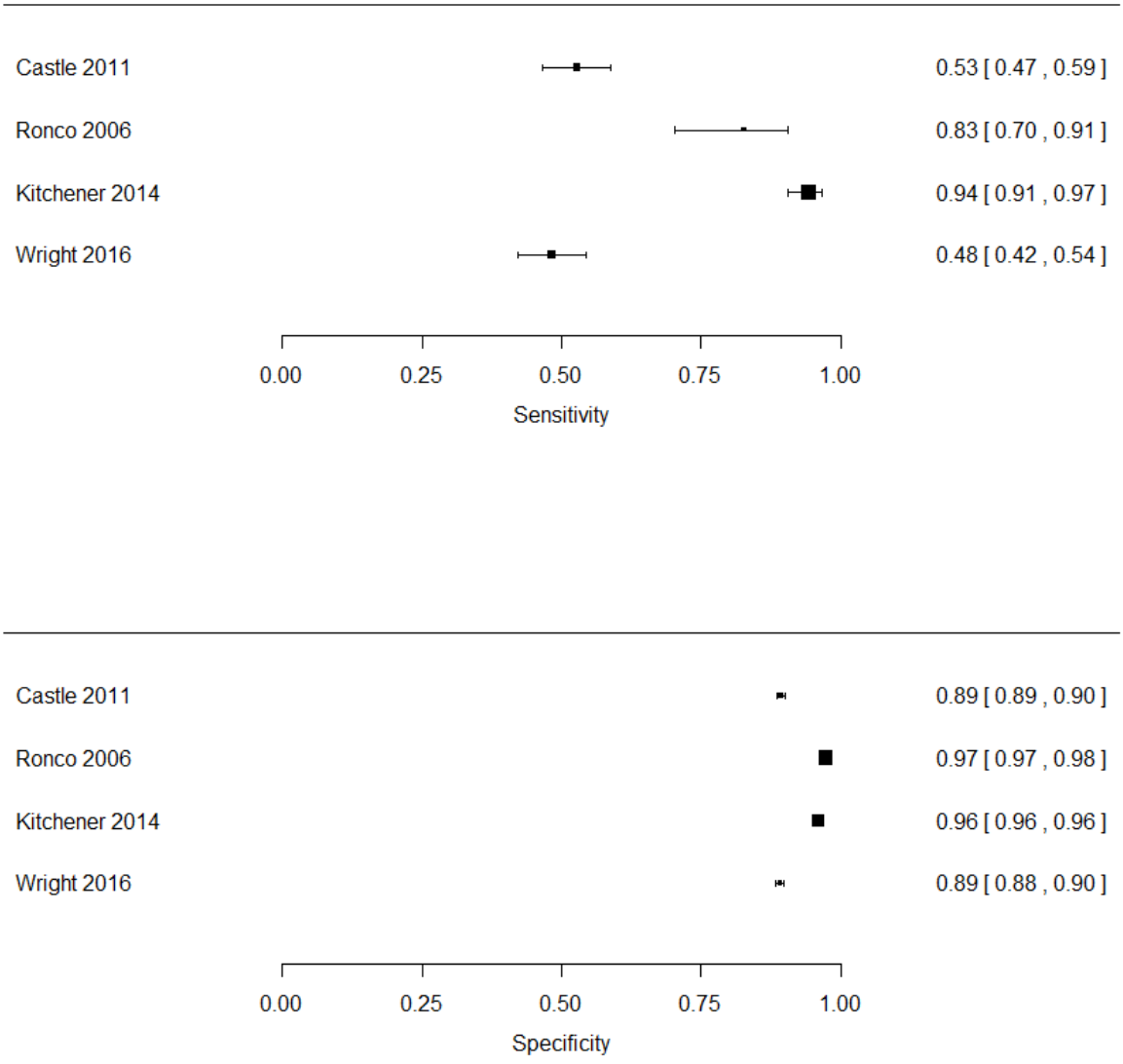


Figure 4.15 Sensitivity and specificity of primary HPV testing followed by cytology triage in detecting CIN 3+



4.2.4.2 Strategy 2: Primary HPV testing followed by triage with partial genotyping for HPV 16 and HPV 18

There were three RCTs which considered the baseline accuracy data for primary HPV testing followed by triage with partial genotyping for HPV 16 and HPV 18, see Table 4.9.[30, 179, 204] In two of the studies, all women received both the primary test and triage test[30, 179], whereas in the other study only women who had a positive HPV test were subjected to the triage test.[204] For the two studies which reported the accuracy estimate for this strategy, the values would suggest that primary HPV testing followed by triage with partial genotyping for HPV 16 and HPV 18 is less sensitive, but more specific than HPV testing followed by cytology triage.[30, 179]

There were insufficient studies (two studies) to conduct a meta-analysis for this strategy.

Table 4.9 Baseline results for primary HPV testing followed by triage with partial genotyping for HPV 16 and HPV 18

Study	Referral to colposcopy	Outcome	Sensitivity (95% CI)	Specificity (95% CI)
Castle 2011[30]	12.3% of total screened 27.6% of triaged	CIN 2+ Strategy	51.8% (46.8%-56.8%)	89.7% (89.0%-90.3%)
		CIN 3+ Strategy	59.5% (53.4%-65.4%)	89.2% (88.5%-89.9%)
Kitchener 2014[179]	4.5% of total screened 28.8% of triaged	CIN 2+ Strategy	56.4% (52.3%-60.3%)	96.8% (96.6%-97.0%)
		CIN 3+ Strategy	67.8% (62.5%-72.8%)	96.3% (96.1%-96.6%)
Leinonen 2013[204]	NR of total screened 70% of triaged	CIN 2+ Conditional	89.8% (84.3%-93.5%)	31.4% (29.6%-33.3%)
		CIN 3+ Conditional	92.1% (82.7%-96.6%)	30.6% (28.8%-32.4%)

Key: CI-confidence interval; CIN – cervical intraepithelial neoplasia; NR – not reported.

Note: Strategy refers to the entire screening strategy HPV test followed by the triage test(s) with the reported sensitivity and specificity representing the entire screening population. Conditional outcomes represent the outcomes for the triage test(s) for the population who were screened positive on the primary HPV screening test. All extracted data represent the crude values.

4.2.4.3 Strategy 3: Primary HPV testing followed by sequential triage with partial genotyping for HPV 16 and HPV 18 and cytology

The first variation on partial genotyping for HPV 16 and HPV 18 used an additional cytology triaging step for those found positive for HPV 16 and HPV 18. Three studies reported baseline outcomes for this strategy; with Castle et al.[30] and Wright et al.[202] reporting the accuracies of the full strategy at baseline. For these studies, the values would suggest that primary HPV testing followed by triage with partial genotyping for HPV 16 and HPV 18 and cytology is less sensitive, but more specific than HPV testing followed by cytology triage. There were insufficient studies providing data on the full strategy (two studies) to conduct a meta-analysis.

Table 4.10 Baseline results for primary HPV testing followed by sequential triage with partial genotyping for HPV 16 and HPV18 and cytology

Study	Referral to colposcopy	Outcome	Sensitivity (95% CI)	Specificity (95% CI)
Castle 2011[30]	4.3% of total screened 9.6% of triaged	CIN 2+ Strategy	30.0% (25.6%-34.8%)	97.0% (96.6%-97.4%)
		CIN 3+ Strategy	34.1% (28.16%-40.2%)	97.8% (97.4%-98.1%)
Wright 2016[202]	4.4% of total screened 9.5% of triaged	CIN 2+ Strategy	26.4% (22.4%-30.9%)	96.9% (96.4%-97.2%)
		CIN 3+ Strategy	31.0% (25.7%-36.9%)	96.5% (96.1%-96.9%)
Leinonen 2013[204]	NR of total screened 31.8% of triaged	CIN 2+ Conditional	87.4% (81.5%-91.6%)	72.1% (70.3%-73.8%)
		CIN 3+ Conditional	87.3% (76.9%-93.4%)	69.6% (67.8%-71.4%)

Key: CI-confidence interval; CIN – cervical intraepithelial neoplasia; NR-not reported.

Note: Strategy refers to the entire screening strategy HPV test followed by the triage test(s) with the reported sensitivity and specificity representing the entire screening population. Conditional outcomes represent the outcomes for the triage test(s) for the population who were screened positive on the primary HPV screening test. All extracted data represent the crude values.

4.2.4.4 Strategy 4: HPV primary testing followed by co-testing triage with partial genotyping for HPV 16 and HPV 18 and cytology

The second variation on partial genotyping for HPV 16 and HPV 18 used co-testing with cytology at the triage stage with a positive result in either triage test leading to a colposcopy referral. This was considered in three studies, see Table 4.11. Baseline results were reported by Castle et al.,[30] Leinonen et al.[204] and Wright et al.[202] For the two studies which reported the accuracy estimate for the strategy, the values would suggest that primary HPV testing followed by triage with partial genotyping for HPV 16 and HPV 18 and cytology has a similar sensitivity, but is less specific than HPV testing followed by cytology triage. Two studies[30, 204] reported baseline outcomes for this strategy also considered the two other partial genotyping strategies, that is partial genotyping for HPV 16 and HPV 18 only as a triage test, and sequential triage testing with partial genotyping for HPV 16 and HPV 18 followed by cytology triage for those found to be positive for HPV 16 or HPV 18. There were insufficient studies providing data on the full strategy (two studies) to conduct a meta-analysis. For both studies,

across the three strategies trialled, the highest sensitivity was reported with co-testing (women with a positive result for either triage test being referred to colposcopy) and the highest specificity for sequential testing (women with a positive cytology result who were initially found to be positive for HPV 16 or HPV 18 referred for colposcopy).

Table 4.11 Baseline results for primary HPV testing followed by co-testing triage with partial genotyping for HPV 16 and HPV 18 and cytology

Study	Referral to colposcopy	Outcome	Sensitivity (95% CI)	Specificity(95% CI)
Castle 2011[30]	20.1% of total screened 44.8% of triaged	CIN 2+ Strategy	74.5% (69.9%-78.6%)	82.7% (81.8%-83.6%)
		CIN 3+ Strategy	78.2% (72.7%-82.8%)	81.9% (81.0%-82.7%)
Wright 2016[202]	20.2% of total screened 43.3% of triaged	CIN 2+ Strategy	66.7% (62.0%-71.1%)	82.5% (81.6%-83.3%)
		CIN 3+ Strategy	72.8% (67.1%-77.8%)	81.7% (80.8%-82.5%)
Leinonen 2013[204]	NR of total screened 76.7% of triaged	CIN 2+ Conditional	100% (97.8%-100%)	24.9% (23.2%-26.7%)
		CIN 3+ Conditional	100% (94.3%-100%)	23.9% (22.2%-25.6%)

Key: CI-confidence interval; CIN – cervical intraepithelial neoplasia; HPV – human papillomavirus; NR-not reported

Note: In this strategy a positive result in either test warranted a referral to colposcopy.

Note: Strategy refers to the entire screening strategy HPV test followed by the triage test(s) with the reported sensitivity and specificity representing the entire screening population. Conditional outcomes represent the outcomes for the triage test(s) for the population who were screened positive on the primary HPV screening test. All extracted data represent the crude values

4.2.4.5 Strategy 5: Primary HPV testing followed by $p16^{INK4a}$ or $p16^{INK4a}$/Ki-67 (dual stain) triage

The fifth strategy of interest was the use of $p16^{INK4a}$ or $p16^{INK4a}$/Ki-67. The baseline screening results for this were reported in two papers. [202, 206] Wright et al.[202] considered $p16^{INK4a}$/Ki-67 dual stain while Carozzi et al.[206] considered $p16^{INK4a}$ testing only. It is important to note that the study by Carozzi et al[206] which considered $p16^{INK4a}$ did not use the current commercially available test, CINtec PLUS, which allows for dual staining for the proliferation marker, Ki-67, the processing of which can be automated. Therefore, it may be difficult to apply the evidence for $p16^{INK4a}$ to the Irish screening programme or to compare it with the evidence for $p16^{INK4a}$/Ki-67 dual stain.

Only one study considered triaging with p16^{INK4a}/Ki-67. Wright et al. considered three different options for triaging with p16^{INK4a}/Ki-67, that is where it was considered:

1) on its own
2) with partial genotyping for HPV 16 and HPV 18 where women were referred to colposcopy only when both triage tests were positive
3) with partial genotyping for HPV 16 and HPV 18 where women were referred to colposcopy when either triage test was positive.

The lowest sensitivity was reported for the second option with a sensitivity of just 35.5% (95% CI: 31.0% to 40.2%) for detection of CIN 2+ and 44.4% (95% CI: 38.5% to 50.5%) for CIN 3+, with the highest sensitivity reported for the third option that is a sensitivity of 74.3% (95% CI: 69.9% to 78.3%) for the detection of CIN 2+ and 80.8% (95% CI: 75.6% to 85.2%) for CIN 3+.

Table 4.12 Baseline results for primary HPV testing followed by p16^{INK4a} /Ki-67 triage

Study	Strategy	Referral to colposcopy	Outcome	Sensitivity (95% CI)	Specificity (95% CI)
Wright 2016[202]	p16^{INK4a}/Ki-67	12.1% of total screened 28.4% of triaged	CIN 2+ Strategy	63.1% (58.3%-67.6%)	89.6% (88.9%-90.3%)
			CIN 3+ Strategy	69.7% (63.9%-75.0%)	88.8% (88.0%-89.5%)
Wright 2016[202]	Co-testing with HPV 16/18 referral only if positive for both tests	5.2% of total screened 11.1% triaged	CIN 2+ Strategy	35.5% (31.0%-40.2%)	96.6% (96.1%-97.0%)
			CIN 3+ Strategy	44.4% (38.5%-50.5%)	96.3% (95.8%-96.7%)
Wright 2016[202]	Co-testing with HPV 16/18 referral if positive for either test	20.6% of total screened 44.1% of triaged	CIN 2+ Strategy	74.3% (69.9%-78.3%)	82.5% (81.6%-83.4%)
			CIN 3+ Strategy	80.8% (75.6%-85.2%)	81.6% (80.7%-82.5%)

Key: CI-confidence interval; CIN – cervical intraepithelial neoplasia; HPV – human papillomavirus.

Note: Strategy refers to the entire screening strategy HPV test followed by the triage test(s) with the reported sensitivity and specificity representing the entire screening population. All extracted data represent the crude values.

Carozzi et al.[206] reported outcomes for the use of $p16^{INK4a}$, see Table 4.13. The baseline sensitivity for detection of CIN 2+ was 88% (CI 80%-94%) and for CIN 3+ was 91% (CI 77%-97%) with a specificity of 61% (CI 57%-64%) for CIN 2+ and 59% (CI 55%-63%) for CIN 3+. The study only included women with a positive primary HPV test. Thus, the accuracies reported reflect the use of $p16^{INK4a}$ as a triage test of women who screened HPV positive.

Table 4.13 Baseline results for primary HPV testing followed by p16INK4a triage

Study	Referral to colposcopy	Outcome	Sensitivity (95% CI)	Specificity (95% CI)
Carozzi 2008[206]	NR of total screened 43.4% of triaged	CIN 2+ Conditional	88% (80%-94%)	61% (57%-64%
		CIN 3+ Conditional	91% (77%-97%)	59% (55%-63%)

Key: CI-confidence interval; CIN – cervical intraepithelial neoplasia; HPV – human papillomavirus; NR-not reported.

Note: Conditional outcomes represent the outcomes for the triage test(s) for the population who were screened positive on the primary HPV screening test. All extracted data represent the crude values.

4.2.5 Longitudinal outcomes

The longitudinal outcomes for all five strategies have been considered in a number of studies, see Table 4.14. Five studies report the longitudinal accuracy of HPV testing followed by cytology triage (Strategy 1) over a timeframe ranging from one to four years. While these included differing methods, overall the longitudinal outcomes suggest that the accuracy of this strategy remains high compared with baseline screening (see Table 4.8 for baseline values), with a high sensitivity and high specificity maintained for both CIN 2+ and CIN 3+ over a typical screening interval.

Only the study by Rijkaart et al.[205] considered the longitudinal outcomes of HPV primary testing followed by triage with partial genotyping for HPV 16 and HPV 18 at three years (Strategy 2). Comparing these with the baseline outcomes reported by Leinonen et al.[204] in Table 4.9 (which also only considered those with a positive primary HPV test result), the longitudinal sensitivity is significantly lower, but the specificity is significantly higher.

For Strategy 3, HPV testing followed by sequential triage with partial genotyping for HPV 16 and HPV 18 and then cytology, the three-year sensitivity outcomes reported by Wright et al.[201] are significantly higher than the baseline outcomes reported by both Castle et al.[30] and Wright et al. (2015) in Table 4.10.[201] As all three studies are from the ATHENA trial, the sensitivity would be expected to be lower at follow up, as it includes cases diagnosed within the three years following baseline screening. In contrast, three year follow-up data reported by Rijkaart et al.

(2012)[205] indicate a slight reduction in both sensitivity and specificity compared with the baseline screening results reported by Leinonen et al. (2013).[204]

The four year follow-up outcomes for HPV primary testing followed by co-testing triage with partial genotyping for HPV 16 and 18 plus cytology were considered by Dijkstra et al. (Strategy 4).[203] Comparing these outcomes to Leinonen et al.[204] (Table 4.11) the longitudinal sensitivity is lower; however, the specificity is higher.

For the fifth strategy, longitudinal outcomes were only available for $p16^{INK4a}$ .These are the three-year follow up to the Carozzi et al. 2008 paper.[206] For both CIN 2+ and CIN 3+, there was a reduction in the sensitivity value compared with baseline (Table 4.13), indicating disease development in women with a negative triage test at baseline.

Table 4.14 Longitudinal results by triage strategy for primary HPV testing

Study	Length of follow up	Outcome	Sensitivity (95% CI)	Specificity (95% CI)
Strategy 1: Primary HPV testing followed by cytology triage				
Ronco 2006b[186]	1 year	CIN 2+ Strategy	80.0% (67.6%-88.4%)	95.3% (94.7%-95.8%)
		CIN 3+ Strategy	81.2% (57.0%-93.4%)	94.8% (94.2%-95.3%)
Bergeron 2015[200]	3 years	CIN 2+ Conditional	67.4% (52.5%-80.1%)	68.0% (65.1%-70.9%)
		CIN 3+ Conditional	61.5% (40.6%-79.8%)	67.1% (64.1%-69.9%)
Dijkstra 2013[203]	4 years	CIN 2+ Conditional	66.0% (59.6%-71.9%)	81.4% (78.0%-84.4%)
		CIN 3+ Conditional	75.4% (67.9%-81.7%)	78.0% (74.6%-81.1%)
Rijkaart 2012[205]	3 years	CIN 2+ Conditional	62.7% (56.2%-68.8%)	89.1% (86.4%-91.4%)
		CIN 3+ Conditional	70.6% (62.7%-77.4%)	85.6% (82.8%-88.1%)
Verhoef 2015[199]	1-2 years	CIN 2+ Conditional	75.6% (66.7%-84.4%)	78.5% (73.6%-83.3%)
		CIN 3+ Conditional	77.4% (67.0%-87.8%)	73.8% (68.9%-78.8%)

Strategy 2: Primary HPV testing followed by triage with partial genotyping for HPV16 and 18				
Rijkaart 2012[205]	3 years	CIN 2+ Conditional	58.6% (52.1%-64.9%)	74.5% (70.8%-77.8%)
		CIN 3+ Conditional	65.4% (57.4%-72.7%)	72.5% (69.0%-75.8%)
Strategy 3: Primary HPV testing followed by sequential triage with partial genotyping for HPV 16 and 18 and then cytology				
Wright 2015[201]	3 year	CIN 2+ Strategy	69.1% (63.7%-74.4%)	94.0% (93.8%-94.3%)
		CIN 3+ Strategy	76.1% (70.3%-81.8%)	93.5% (93.3%-93.8%)
Rijkaart 2012[205]	3 years	CIN 2+ Conditional	81.5% (75.9%-86.1%)	66.6% (62.8%-70.3%)
		CIN 3+ Conditional	87.4% (81.1%-91.9%)	63.2% (59.5%-66.7%)
Strategy 4: HPV primary testing followed by co-testing triage with partial genotyping for HPV 16 and 18 plus cytology				
Dijkstra 2013[203]	4 years	CIN 2+ Conditional	90.3% (85.7%-93.5%)	57.6% (53.3%-61.7%)
		CIN 3+ Conditional	96.6% (92.3%-98.5%)	53.6% (49.7%-57.5%)
Strategy 5: Primary HPV testing followed by p16^{INK4a} triage				
Carozzi 2013[35]	3 years	CIN 2+Conditional	75.6% (63.5-87.7)	61.8% (58.7%-64.7%)
		CIN 3+Conditional	82.4% (67.8-97.0)	59.1% (56.2%-62.0%)

Key: CIN – cervical intraepithelial neoplasia; CI-confidence interval; HPV – human papillomavirus. ; NR-Not Reported

Note: Strategy refers to the entire screening strategy HPV test followed by the triage test(s) with the reported sensitivity and specificity representing the entire screening population. Conditional outcomes represent the outcomes for the triage test(s) for the population who were screened positive on the primary HPV screening test. All extracted data represent the crude values.

4.2.6 Applicability of the evidence

The question of how best to manage women who screen HPV positive has been considered in a number of large-scale, good-quality randomised controlled trials (RCTs). These have been conducted within routine population screening programmes in settings similar to that of CervicalCheck - Ireland's National Cervical Screening Programme. Baseline outcomes and follow up of up to four years have also been reported for the triage strategies.

Five triage strategies of interest were considered:

1) cytology;
2) partial genotyping (HPV 16 and 18) only;
3) partial genotyping (HPV 16 and 18) followed by cytology as a second triage test;
4) co-testing with partial genotyping (HPV 16 and HPV 18) plus cytology;
5) and, testing for the $p16^{INK4a}$ protein alone or in combination with Ki-67 protein (dual stain) which have been identified as surrogate markers of transforming infections.

No one study compared all five triage strategies, and apart from those studies that used cytology alone as a triage test, there were insufficient studies to allow for a meta-analysis of the results.

Four studies reported comparable sensitivity and specificity values for the detection of CIN 2+ and CIN 3+ following primary HPV testing with cytology triage testing. However, the sensitivity values varied widely with two studies by Castle et al.[30] and Wright et al.[202] reporting much lower sensitivity than that reported by either Kitchener et al.[179] or Ronco et al..[185, 186]

Both Castle et al.[30] and Wright et al.[202] were nested sub-studies of the US-based ATHENA trial. The reported sensitivity of cytology when used as a standalone primary test at 51.5% (CI 46.8% -56.2%) for the detection of CIN 2+ and 53.3% (CI 46.8% -56.2%) for the detection of CIN 3+ was substantially lower in the study by Castle et al.[30] than would be expected in Ireland. For the study by Wright et al.,[202] cytology was only applied as a triage test so it is not possible to investigate its accuracy as a primary screening test, although the Evaluation Team acknowledge that the sensitivity values for cytology when used a triage test are indeed lower than observed elsewhere.

Longitudinal outcomes at three years for the ATHENA trial were reported by Wright et al. 2016.[202] The baseline accuracy for cytology as a primary test was reported as 49.9% for CIN 2+ and 52.2% for CIN 3+ across the 40,901 eligible samples. It is not clear why the cytology sensitivity values are so low in the ATHENA trial. Austin et al.[209] discussed possible reasons for this and noted that when comparing the laboratory performance to other US laboratories, the ratio of atypical squamous cell to squamous intraepithelial lesion (ASC/SIL) would indicate a suboptimal screening sensitivity and speculated that this may be due to cytotechnologist workload.

Computer-assisted imaging for LBC was not used in the ATHENA trial,[202] which relied instead on manual reading of LBC images. The implications of this on the test sensitivity are unclear with a systematic review[10] finding conflicting evidence on the

effect of computer-assisted imaging on the accuracy estimates. As the cytology results in the ATHENA trial are considerably lower than those expected in Ireland, with evidence of suboptimal laboratory performance, data on triage options from this study, which included cytology, were not used to inform the estimates in the economic model.

For the remaining strategies, the available evidence is limited, and in some cases is restricted to one or two studies. The evidence was not sufficient for comparison across studies and also did not allow for comparisons between strategies. Longitudinal outcomes were available for all triage strategies apart from triaging with $p16^{INK4a}$/Ki-67 but, as with the baseline results, there were insufficient studies available for a meta-analysis. The question of which of these triage strategies is optimal from a clinical perspective remains unclear.

CervicalCheck - Ireland's National Cervical Screening Programme currently uses primary testing with LBC followed by HPV triage testing. A 2013 Cochrane review[210] reported a sensitivity of HC2 in the triage of ASCUS or worse cytology results of 90.4% (CI 88.1% -92.3%) for the detection of CIN 2+ and 93.7% (CI 90.4% - 95.9%) for CIN 3+. They found a specificity of 58.3% (CI 53.6% -62.9%) for the detection of CIN 2+ and 52.3% (CI 45.7% -58.7%) for CIN 3+.

Ireland has a nationally funded, school-based, girls-only HPV vaccination programme that commenced in 2010. The current vaccination programme is based on the quadrivalent vaccine that protects against HPV 16 and 18, thereby protecting against approximately 70% of cervical cancer cases. The first cohort of vaccinated girls will be eligible for CervicalCheck in 2018-2019, and uptake rates for the vaccination programme have been high (86.9% in 2014 to 2015, although unofficial figures indicate a reduced uptake of approximately 70% in 2015 to 2016). Early indications are that the current uptake rate for 2016 to 2017 is also low relative to historical uptake rates in Ireland. In the context of a reducing background risk of disease, due to a reduction in the prevalence of HPV, HPV-based screening programmes may be more efficient.

4.3 Safety

In making any screening decision, the benefits and risks must be considered. Cervical screening cannot prevent all cervical cancers, however it is considered effective at reducing the incidence of and morbidity and mortality from cervical cancer. For example, evidence of reduction in mortality is available from the National Health Service (NHS) Cervical Screening Programme in England. In a case-control study published in 2016, screening records were used to compare mortality from cervical cancer over a 15-year timeframe in women who were regularly screened by

the programme with unscreened or minimally screened matched controls. Based on existing uptake, screening was estimated to prevent 70% of all cervical cancer deaths; however, it was noted that if everyone attended screening regularly, 83% of deaths could be prevented.[66].

Harms related to the primary screening test itself are considered minimal. HPV testing uses the same procedure for collecting cervical cell samples as that used in the current screening programme. Some women may experience discomfort or minor bleeding following a smear test, but these resolve spontaneously. Women may also suffer anxiety while waiting for a repeated smear test in the case of an inadequate sample. Other potential harms include the worry and anxiety that some women may experience with the knowledge of a HPV-positive status, although this distress typically does not persist.[211] An Irish qualitative study questioned women in a colposcopy clinic who had recently been tested for HPV (both HPV-positive and negative test results) following treatment for CIN or a diagnosis of low-grade cytological abnormalities.[212] This study concluded that in such a setting, the emotional impact of HPV testing was modest. Ethical issues are discussed further in Chapter 6.

For women who have precancerous abnormalities or invasive cervical cancer, the effects of screening are primarily positive. This includes the potential for improved clinical outcomes and fertility sparing for women in whom invasive cervical cancer is detected at an early stage. Treatment of precancerous abnormalities is less invasive than treatment of invasive cervical cancer and results in fewer side effects. As primary HPV testing has been shown to lead to a reduced incidence of invasive cervical cancer, switching to primary HPV testing has the potential to improve these benefits. However, there is also a potential for adverse consequences.

For women who do not have precancerous abnormalities or invasive cervical cancer, the benefits of screening are limited to a sense of reassurance that they are at low risk of disease. The negative effects of screening are particularly associated with false positive test results and referrals to colposcopy clinics. A false positive test occurs when a women without precancerous abnormalities or invasive cervical cancer has a positive result and is referred to colposcopy. This can lead to worry and distress associated with additional unnecessary diagnostic procedures required to confirm an initial positive HPV test result. Colposcopy is associated with adverse effects such as pain, bleeding and vaginal discharge. Higher rates of all these adverse effects are reported in women who require a biopsy at colposcopy compared with women who require colposcopic examination only.[118]

Large-scale screening programmes carry the risk of overdiagnosis and unnecessary treatment, which can occur when a detected precancerous abnormality lacks the

potential to progress to invasive cervical cancer or when death from other causes occurs before the cervical cancer presents clinically. In both instances, overdiagnosis would occur and the woman would be treated with no survival benefit.

It is not currently possible to discriminate between high-grade abnormalities that will develop into invasive cervical cancer and those that would regress if undetected. Finding the former may extend some women's lives, but finding the latter will increase the number of women who are overdiagnosed and receive unnecessary treatment. The harms associated with unnecessary treatment include both the risks from the treatment procedure and the potential longer-term risks of treatment. As noted in Section 3.3, cold coagulation, large loop excision of the transformation zone (LLETZ), laser cone biopsy and cold knife cone biopsy are conservative methods of treatment of high-grade abnormalities. LLETZ and cold knife biopsy are associated with an increased risk of preterm pre-labour rupture of membranes, preterm birth and low birth weight.[117] These complications are associated with an increased risk of stillbirth and neonatal death.[120] Cold knife conisation is also associated with an increased rate of caesarean section due to cervical stenosis.[117]

A case-control study nested in a record linkage cohort study in England reported that the risk of preterm birth appeared to be minimally affected by small excisions. Excisional treatment was defined as LLETZ, laser excision, knife cone biopsy or cone excision not otherwise specified.[121] However, excisions with a depth greater than 15mm were associated with a doubling of the risk of preterm and very preterm births.[121] Cold coagulation[120] and laser ablation[117, 120] do not impact on obstetric or neonatal outcomes.

As HPV testing is more sensitive than cytology, it results in more positive screening results, with strategies that include HPV testing compared with strategies that use cytology alone. As a result, strategies that include HPV testing are likely to lead to increased surveillance and overdiagnosis. However, combining a primary HPV test with cytology triage increases the specificity and avoids some of the excess false positive results. It is worth noting that women aged less than 30 years are potentially at a higher risk of adverse harms from HPV-based screening. As the prevalence of HPV is much higher in women in this age group, the potential for precancerous abnormalities to regress is higher, and women within this age group are more likely to be affected by adverse pregnancy outcomes compared with those over 30 years.

A false negative result occurs when precancerous abnormalities or invasive cervical cancer are present but the test result is reported to be normal. This leads to false reassurance. Of note, it is recognised and accepted that false negative results will occur even as part of an organised cervical screening programme. As the sensitivity

of HPV testing is higher than cytology testing, switching to a primary HPV test is likely to lead to a decrease in the number of false negative results, potentially reducing the false negative rate and improving safety in this regard.

4.4 Discussion

This chapter reviewed the evidence for the clinical effectiveness and safety of HPV testing as a primary screening method for the prevention of cervical cancer. It also considered the evidence for possible triaging strategies for women with a positive primary HPV screening test result.

This systematic review updated a 2015 publication by the Belgian Health Care Knowledge Centre (KCE) which identified 60 relevant studies comparing primary HPV screening with cytology testing. The updated review retrieved an additional 11 studies. When restricted to those studies conducted in industrialised countries and that used HC2 as the HPV test, a meta-analysis of 23 studies found higher sensitivity for HPV testing, but lower specificity compared with both LBC and conventional cytology. Evidence from long-term follow up of women with either a negative cytology test result or a negative HPV screening test result has shown that a negative HPV test result carries a lower risk of developing both CIN 3+ and invasive cervical cancer over six years.[198]

The low specificity of HPV testing means that using it as a standalone screening test would lead to large numbers of women unnecessarily referred to colposcopy clinics. Use of a triage test is necessary to ensure efficiency and to minimise adverse effects by reducing the numbers of unnecessary referrals. Despite the high sensitivity of HPV testing, a small number of women who develop CIN 3+ may receive a false negative result when tested with a HPV test, who could have received a positive result if tested using cytology screening.[213]

Another way to consider the accuracy of the tests is to look at the positive predictive value (PPV) and negative predictive value (NPV); that is the proportion of women with a positive test who actually have the disease, and the proportion of women with a negative test who are actually free of the disease. These predictive values vary according to the underlying prevalence of the disease, as prevalence of disease in a population approaches zero, the positive predictive value (PPV) of a test also approaches zero. Conversely, as prevalence approaches 100%, negative predictive values (NPV) approach zero (that is, all negative results will be false negatives). The more sensitive a test is, the higher its NPV will be, while the more specific it is, the higher its PPV will be.[191]

Assuming an overall prevalence of 1.6% for CIN 2+ and 1.0% CIN 3+, for women aged 25 to 60 years in Ireland,[56, 112, 194] the PPV of HC2 for CIN 2+ and CIN 3+ is 11.8% and 7.6%, respectively compared with a PPV for cytology (LBC and conventional cytology) of 19.9% and 14.2% for CIN 2+ and CIN 3+, respectively. The corresponding NPV for HC2 is 99.91% and 99.98% for CIN 2+ and CIN 3+, respectively compared with a NPV for cytology of 99.57% and 99.76% for CIN 2+ and CIN 3+, respectively. The higher NPV for HPV testing means that there is a greater confidence that a negative screen means an individual does not have the disease, however the lower PPV means that a triage test must be used to avoid over-referral. In the context of increasing numbers of women vaccinated the prevalence of CIN 2+ and CIN 3 + will decrease leading to a decreasing PPV and higher NPV values for both tests.

The 2015 systematic review by KCE identified 10 relevant studies that compared strategies for triaging women identified as HPV-positive during primary screening. Our updated review retrieved an additional five studies. Fifteen studies, based on eight RCTs, were included. Five triage strategies of interest were considered: cytology; partial genotyping (HPV 16 and 18) only; partial genotyping (HPV 16 and 18) followed by cytology as a second triage test; co-testing with partial genotyping (HPV 16 and 18) plus cytology; and testing for the $p16^{INK4a}$ protein alone or in combination with Ki-67 protein (dual stain).

For all strategies, there were few comparable trials available; however, all were high-quality RCTs conducted within large-scale screening programmes and, with the exception of the ATHENA trial, all trial results would be considered clinically applicable to CervicalCheck – Ireland's National Cervical Screening Programme. Some of these strategies appear to be advantageous over primary screening with HPV testing only and longitudinal outcomes would suggest they can be safely used in a typical screening interval of three to five years. Only triaging options where all tests are performed on a single screening sample were considered. More complex triaging strategies involving reflex testing, requiring women to return for a repeat screening sample, were not considered.

Harms related to the primary screening test itself are mild, and most adverse effects in a cervical screening programme will be due to those from overdiagnosis and over treatment. Women under 30 years of age are potentially at a greater risk of harm due to the higher prevalence of HPV within this age group. The optimal screening strategy for these women may be different to that for women aged 30 years or older.

The evidence collated within this chapter on the diagnostic test accuracies for both the primary screening test and triage screening tests were used, where deemed

sufficiently applicable, to underpin the economic modelling in Chapter 5 which evaluates the relative cost-effectiveness and resource implications of a range of cervical screening strategies for both unvaccinated and vaccinated cohorts.

4.5 Key messages

- A systematic review was undertaken to identify relevant studies of the diagnostic accuracy of HPV and cytology (LBC and conventional cytology) testing for the prevention of cervical cancer, considering both primary screening and triage screening for HPV-positive women.
- Twenty-three studies were included in the evidence synthesis of the diagnostic accuracy of HPV testing as a primary screening test.
- Based on evidence from industrialised countries only, the pooled sensitivity of the Hybrid Capture 2 (HC2) HPV assay in detecting CIN 2+ and CIN 3+ were 95.2% (CI 92.5-97.1%) and 98.2% (CI 96.7%-99.1%), respectively. This is significantly higher than cytology (LBC and conventional cytology) where the pooled sensitivity was 75.0% (CI 64.1%-83.3%) for CIN 2+ and 78.0% (CI 63.5%-88.4%) for CIN 3+. Thus, using HC2 as a primary screening test would result in fewer women receiving a false negative result, compared with cytology-based testing.
- The pooled specificity of HC2 was significantly lower in detecting CIN 2+ and CIN 3+ at 88.2% (CI 82.9%-92.0) and 87.5% (CI 78.7%-93.2%), respectively, compared with cytology with a pooled specificity of 95.0% (CI 92.2%-96.8%) for CIN 2+ and 95.1% (CI 91.6%-97.3%) for CIN 3+. Thus, using HC2 as a primary screening test would result in more women receiving a false positive result, compared with using cytology-based testing.
- Assuming an overall prevalence of 1.6% for CIN 2+ and 1.0% CIN 3+ for women aged 25 to 60 years in Ireland, the positive predictive value (PPV) of HC2 is 11.8% for CIN 2+ and 7.6% for CIN 3+. This compares with a PPV of 19.9% for CIN 2+ and 14.2% for CIN 3+ with cytology (LBC and conventional cytology). The corresponding negative predictive value (NPV) for HC2 is 99.91% for CIN 2+ and 99.98% for CIN 3+ compared with a NPV for cytology of 99.57% for CIN 2+ and 99.76% for CIN 3+.
- Fifteen studies across eight RCTs were included in the evidence synthesis of the diagnostic accuracy of different triage strategies following primary screening with HPV testing. The RCTs were typically large-scale trials conducted within population screening programmes with seven of the eight RCTs conducted in Europe.
- Five triage strategies of interest were considered: 1) cytology; 2) partial genotyping (HPV 16/18); 3) co-testing with partial genotyping (HPV 16/18) plus cytology; 4) partial genotyping (HPV 16/18) followed by cytology as a second triage test; and 5) testing for the $p16^{INK4a}$ protein alone or in combination with Ki-67 protein which have been identified as surrogate markers of transforming

infections.

- For all strategies, few comparable trials were available. Some of these strategies appear to be advantageous and longitudinal outcomes would suggest they can be safely used within a typical screening interval.
- The question of which strategy is optimal in the Irish context (particularly in light of the HPV vaccination programme which will lead to a reduction in the prevalence of HPV and a reducing background risk of disease) still remains.
- No cervical screening programme can prevent all cancers. Harms related to obtaining the screening test itself are minimal and short term. Most adverse effects of a cervical screening programme relate to false negative test results, false positive test results and overdiagnosis. False negative test results lead to false reassurance and potentially missed or delayed opportunities to intervene in those with treatable precancerous abnormalities or early invasive cancer. False positive test results lead to unnecessary colposcopic examination. Overdiagnosis refers to identification of abnormalities that would not otherwise become clinically significant. Overdiagnosis may lead to increased surveillance, potentially increasing stress and anxiety, and or unnecessary treatment.

5 Economic evaluation

As determined in the review of clinical effectiveness, human papillomavirus (HPV)-based screening programmes can offer advantages over cytology-based screening programmes. This chapter reviews the existing evidence on the cost-effectiveness of HPV testing as a primary screening method to prevent cervical cancer and describes an economic model to assess the cost-effectiveness of a number of potential different screening strategies in Ireland.

5.1 Review of published literature

A systematic review was carried out to assess the available cost-effectiveness evidence for HPV testing as the primary screening method for cervical cancer and to inform the economic analysis of a cervical screening programme in Ireland. Studies were included in the review if they compared the costs and consequences of using HPV testing with liquid-based cytology (LBC) as the primary screening method in an organised screening programme. A total of six relevant studies were identified.

5.1.1 Search strategy

A number of systematic reviews of the economic literature on HPV testing as a primary screening method have recently been published. However, none of these were considered to adequately address the terms of reference for this HTA. It was considered more appropriate to create a new search rather than to update any of the existing reviews. A search was carried out to identify published economic analyses evaluating HPV testing as a primary screening method for prevention of cervical cancer. The search for economic evaluations was carried out in MEDLINE, EMBASE, and the health technology assessment (HTA) database maintained by the National Health Service (NHS) Centre for Reviews and Dissemination. The review was carried out in accordance with national guidelines on the retrieval and interpretation of economic evaluations of health technologies.[214]

Studies were included if they evaluated HPV screening as the primary test with LBC as the triage test in either vaccinated or unvaccinated cohorts within an organised screening programme. Studies that did not include a comparison of LBC with HPV triage testing were excluded, along with studies that assessed HPV vaccination alone, at risk populations (HIV-infected or immunosuppressed), or only conventional cytology. The search strategy was applied from 2008 (as studies conducted prior to this time period would be of limited applicability to the current Irish situation) to the end of January 2016. Two additional studies, which were published following completion of the systematic review, were identified prior to completion of the HTA.

Both related to changes to national cervical screening programmes and were thus highly relevant to this HTA. The findings of these studies were added to the review.

5.1.2 Results

A total of eight relevant studies were identified (see Table 5.1).[10, 164, 179, 215-219] In the following section, costs reflect those quoted in the original studies with 2015 Irish Euro equivalent prices reported in parentheses. The quality of the cost-effectiveness studies were assessed using the International Society for Pharmacoeconomics and Outcomes Research questionnaire to assess the relevance and credibility of modelling studies.[220] All eight studies included were found to be of good quality.

Table 5.1 Economic evaluations of HPV testing as a primary screening test in cervical screening programmes

Study	Screening Strategies	Population	Analysis Details	Clinical & QALY Outcomes	Costs	Results
(Alberta) IHE 2009	1) CC (base case) 2) CC with HPV triage 3) As for 2, but no HPV triage if <30 4) LBC with HPV triage 5) As for 4, but no HPV triage if <30 6) HPV with LBC triage 7) If age <30, LBC no triage, if ≥30 HPV and LBC triage Screening intervals 1, 2 & 3 years; 21 strategies in total.	Cohort of girls aged 12, followed until 80 years of age. Does not include vaccinated cohort.	**Country:** Canada (Alberta) **Model Type:** Markov cohort simulation model **Perspective:** Payer **Discount rate**: 5% costs, 3% benefits **Time Horizon:** Life time (80 years old)	*LBC with HPV triage:* Total QALYs per woman (discounted) 26.484 1Yr, 26.480 2Yr, 26.479 3Yr. *LBC with HPV triage (no HPV triage <30):* Total QALYs per woman (discounted) 26.481 1Yr, 26.478 2Yr, 26.477 3Yr *HPV with LBC triage: Total* QALYs per woman (discounted) 26.423 1Yr, 26.422 2Yr, 26.421 3Yr *If <30 LBC no triage, if ≥30 HPV and LBC triage:* Total QALYs per woman (discounted) 26.442 1Yr, 26.440 2Yr, 26.437 3Yr HPV tests considered	Costs included screening, diagnosis, treatment and palliative care. LBC: $22.00, HPV test: $40.76 *LBC with HPV triage, total lifetime cost per woman :* $2,071 1Yr, $1,884 2Yr $1,754 3Yr *LBC with HPV triage (not HPV triage <30) total lifetime cost per woman:* $1,877 1Yr, $1,715 2Yr, $1,601 3Yr *HPV with LBC triage total lifetime cost per woman:* $2,028 1Yr, $1,932 2Yr, $1,862 3Yr *If <30 LBC no triage, if ≥30 HPV and LBC triage total lifetime cost per woman:* $1,438 1Yr,	Switching from annual CC to annual LBC with HPV triage would cost $127,076/QALY. The economic analysis indicated that a strategy of 3-yearly screening with CC of women aged 18 to 69 years with HPV triage for women aged ≥ 30 years, (option 3) provided the best value for money, and would save $16,078 per additional QALY saved compared with annual CC. Additional effectiveness can be achieved by employing LBC as the primary screening test. However the additional costs were considered too expensive and not good value for money.

				(HC2 & AMPLICOR)	$1,362 2Yr, $1,303 3Yr (CAN $ 2007, discounted)	
KCE 2015	1) Cytology with HPV triage 3 yrs (current practice) 2) HPV with cytology triage 5 yrs Cytology includes the current mix of LBC and CC testing; this varies per region in Belgium - mainly LBC, but some conventional cytology.	Cohort modeled from age 30 to 104. Note: Flemish region is the only region with a formal screening strategy in Belgium (women aged 25-64 years).	**Country:** Belgium **Model Type:** Markov **Perspective:** Health care payer **Discount rate:** 3% cost, 1.5% health outcomes **Time Horizon:** Lifetime	A change to primary HPV screening at 5-year intervals would lead to 2,878 (discounted) additional life years gained, a reduction of 95 cervical cancer deaths and 240 cancer cases prevented.	Switching to HPV testing would lead to a cost saving of €14 million. This is mainly due to the extension of the screening interval from 3 years to 5 years. Base case analysis cost of HPV test: €35. Cytology cost: €50.35 (primary or follow-up test) Costs do not include additional cost for LBC as this is charged to the patient. (Belgium € 2014)	HPV as a primary test dominates in the base case as it is both more effective and less costly.
MSAC 2013 Lew 2017*	1) CC with IARC age range and intervals (3-yearly in women age 25-49 years, 5-yearly in women aged 50-64 years); 2) Manually-read LBC with IARC age range and intervals; 3) Automated image-	Vaccinated and unvaccinated cohorts included, from age 10.	**Country:** Australia **Model Type:** Dynamic transmission and Markov models **Perspective:** Health services **Discount rate**: 5% for costs and effects **Time Horizon:**	LBC (including manual and automated)-strategies could be either more or less effective than current practice with strategies for unvaccinated ranging from a 7% increase to 14% decrease in cancer mortality, and	LBC (including manual and automated)-unvaccinated strategies lead to a range of $10.3 million increase to $50.2 million cost saving, vaccinated $8.5 million increase to $47.8 million cost saving, compared to current practice, for the	All HPV strategies found to be more effective and cost-effective than CC. HPV strategies predicted an 8-18% decrease in cervical cancer mortality and $33.8M-$52.8M health system saving. Primary HPV testing with either cytology triage or partial genotyping

	read LBC with IARC age range and intervals; 4) HPV primary testing with LBC triage 5) HPV primary testing with partial HPV genotyping 6) Co-testing HPV with LBC Current practice: 18-20 to 69 years screened every 2 years using conventional cytology, with no HPV triage. All strategies were varied by: -invitation system -slower and faster uptake at 25 -alternative HPV triage algorithms -exiting testing -5 and 6 yearly screening for HPV strategies 132 strategies considered in total.		to 84 years	vaccinated strategies ranging from a 6% increase to 14% decrease. Strategies that increased effectiveness generally involved HPV triage testing. HPV - all strategies involving 5-yearly screen (25-64 yrs) predicted to be more effective than current practice; - unvaccinated strategies led to a range of 8%-36% decrease in cancer mortality, vaccinated 8% to 29% decrease compared to current practice. LYS were considered a more valid outcome measure as there were issues with QALY estimates; the outcomes for the main analysis were expressed in LYS.	female Australian population in 2015. All manual read strategies were cost saving. Strategy variants without HPV triage for women with low-grade cytology were predicted to be most cost saving (3-23% and 3-26% in unvaccinated and vaccinated). Primary HPV + cytology triage: Cost savings compared to current practice ranged from $39.3M to $58.5M, and from $44.2M to $60.6M, in unvaccinated and vaccinated. Primary HPV + partial genotyping: Cost savings compared to current practice ranged from $33.8M to $52.8M, and $41.7M to $58.5M, in unvaccinated and vaccinated. Primary HPV + cytology co-testing:	associated with both the most effective and least costly strategies overall' Overall, for cost saving strategies, relative cost savings compared with current practice were predicted to be slightly higher in vaccinated compared with unvaccinated cohort, varying from 1-30% (saving of $1.2-66.8M pa) in unvaccinated and from 1-36% (saving of $1.4-65.8M p.a.) in vaccinated cohort. Cost savings of $50M pa for a strategy of 5-yearly HPV screening with partial genotyping within current programme were estimated for a cohort offered vaccination, and $41M for an unvaccinated cohort.

					Cost differential compared to current practice ranged from a $2.3M increase to $23.6M decrease, and $1.4M decrease to $24.7M decrease, in unvaccinated and vaccinated. ($AUS 2013)	
Kitchener (NIHR) 2014	1) Current practice: LBC with HPV triage (3 yrs 25-49, 5yrs 50-64) 2) HPV with LBC triage (3 alternative triaging follow-up strategies) 3) Co-test LBC and HPV Three screening intervals: 1) 5yrs 2) 6 yrs 3) 6 yrs 25-49 & 10 yrs 50-64 Two age variations for options 1 & 2 (1 follow-up strategy only) 1) Primary LBC 25-29, primary HPV	Vaccinated and unvaccinated cohorts. Modelled cohort representative of ARTISTIC trial population at enrolment: women aged 20–64 years.	**Country:** UK **Model Type:** Three components: dynamic model of HPV transmission and vaccination, 'natural history model' of CIN and invasive cervical cancer - Markov multicohort model of cervical screening. **Perspective:** Health services **Discount rate:** 3.5% costs and effects **Time Horizon:** Lifetime	Unvaccinated cohort (total discounted LYS): 1) 26.2307 2) 26.2302-26.2323 3) 26.2309-26.2322 Vaccinated cohort (total discounted LYS): 1) 26.2366 2) 26.2362-26.2369 3) 26.2364-26.2370 LYS main outcome, QALYs secondary outcome Effectiveness data based on ARTISTIC trial LBC versus LBC + HPV test (RCT). Evaluated over 2 screening rounds, 3 years apart.	Unvaccinated cohort lifetime cost per woman: 1) £159 2) £128-£161 3) £144-£167 Vaccinated cohort life time cost per woman: 1) £129 2) £97-£118 3) £110-£128 (UK £ discounted, 2010 Financial year)	Primary HPV screening more effective and cost saving compared with current practice for a number of potential strategies in both unvaccinated and vaccinated cohorts. Most of the primary HPV strategies examined where HPV was used as the sole primary test were cost saving in both unvaccinated and vaccinated cohorts under baseline cost assumptions, with a 7–18% reduction in annual screening-associated costs in unvaccinated cohorts and a 9–22% reduction for vaccinated cohorts.

	>30 2) Primary LBC 25-34, primary HPV >35			HC2 test only.		
van Rosmalen 2012	1) Cytology testing with cytology triage 2) HPV testing with cytology triage 3) Cytology testing with HPV triage For each of these 3 strategies a varied number of screening rounds (3-10 per lifetime), time intervals (3-10yrs), age at screening (starting at age 25,27,30,32) and cytology test type (LBC or CC) were modelled. Strategies 1 & 2 both included 4 alternative triaging algorithms.	Women who have not been invited for HPV vaccination	**Country:** The Netherlands **Model Type:** Markov **Perspective:** Societal **Discount rate:** 3% costs and effects **Time Horizon:** Lifetime	For the programmes which are considered efficient, QALY gains for HPV followed by CC ranged from 695 to 1,006, per 100,000 for CC followed by HPV they ranged from 501 to 618 per 100,000 QALYS (discounted). Base-case analysis assumed sensitivity and specificity were the same for CC and LBC.	For the programmes which are considered efficient, the costs ranged from €3.1million to €14.6million for HPV followed by CC. For CC followed by HPV they ranged from €1.8million to €2.4million. Lab costs of LBC €33.72, HPV lab test costs: €33.87. Results were sensitive to the costs of the HPV test. (Dutch Euros 2010)	The efficient screening programmes using primary HPV screening with CC triage, ICERs range from €9,558 to €122,508/QALY comparing consecutive programmes on the efficient frontier. Primary CC screening with HPV triage was only cost-effective with a threshold below €7,000 per QALY gained. For women aged 32 years or younger, primary cytology screening is more cost-effective than primary HPV testing. All cost-effective programmes used CC instead of LBC. Increasing the interval between screening rounds and changing to HPV as the primary test can improve the

						effectiveness and decrease the costs of cervical cancer screening.
Vijayaraghavan 2010	1) LBC 2) LBC + HPV triage 3) HPV + LBC triage 4) Cotesting (simultaneous HPV + LBC) 5) Cotesting (HPV + LBC)+ HPV 16/18 genotyping triage 6) HPV + HPV 16/18 genotyping triage Screening interval: 2-yearly if LBC primary test (Strategies 1&2); 3-yearly if included HPV test as primary test (strategies 3-6) Strategies only apply to over 30, under 30 biennial LBC.	Cohort aged 13 followed for their lifetime. HPV vaccination was not considered.	**Country:** US **Model Type:** Markov **Perspective:** Payer **Discount rate:** Not stated **Time Horizon:** Lifetime	Total outcomes per strategy: 1) 28.6623 Quality-adjusted life expectancy (QALE) 2) 28.6651 QALE 3) 28.6670 QALE 4) 28.6714 QALE 5) 28.6725 QALE 6) 28.6745 QALE HPV genotyping strategies prevented 51–73 deaths per 100,000 women screened compared to LBC followed by HPV triage and 4–26 deaths compared to co-screening with LBC and high-risk HPV.	Total costs per strategy: 1) $88,162 2) $88,221 3) $88,226 4) $88,303 5) $88,340 6) $88,407 (US $ 2007)	ICER per QALY relative to no screening/previous strategy 1) $19,321 2) $19,376/$21,304 3) $18,980/$2,618 4) $18,903/$17,204 5) $19,092/$34,074 6) $19,420/$33,807 Use of HPV genotyping to triage all high-risk HPV-positive women every 3 years had an ICER of $34,074 per QALY gained compared to HPV and LBC co-screening.
Lew 2016	Current practice (CP): LBC (+ HPV triage for age 30+) 3 yearly age 20-69 16 alternative strategies including	Unvaccinated cohort and cohort offered vaccination (54%	**Country:** New Zealand **Model Type:** Dynamic transmission and Markov models	12 out of 16 primary HPV strategies predicted a decrease (of 2–20% in cervical cancer incidence and mortality compared	Compared to CP, primary HPV testing with cytology triage predicted a 3–12% decrease in costs. Strategies based on	As the majority of options considered were both cost-saving and more effective, ICERs were not presented. The authors concluded that

	four main options: 1) HPV + LBC 2) HPV genotyping with LBC triage 3) Co-testing LBC and HPV, no triage 4) Co-testing LBC and HPV with HPV genotyping triage Each with 4 variations 1) 5-yearly 25-69, immediate risk (HPV positive and LBC negative or positive for non HPV 16/18 HPV type, but positive for low-grade cytology) co-test at 12 months 2) 5-yearly 25-69, immediate risk colposcopy referral 3) 3-yearly LBC <30, immediate risk co-test at 12 months 4) 3-yearly LBC age <30, immediate risk colposcopy referral.	uptake), aged 20-84	**Perspective:** Health services **Discount rate:** 3.5% **Time Horizon:** until 84 years	with CP. Partial genotyping strategies were associated with a (1–16%) relative decrease in cancer incidence and mortality compared with non-partial genotyping strategies. Co-testing strategies were associated with a (<1–3%) relative decrease compared with non-co-testing strategies.	HPV and cytology co-testing predicted a 12–26% increase in costs. (New Zealand $ 2017/18)	primary HPV screening with partial genotyping would be more effective and less costly than the current cytology-based screening programme, in both unvaccinated women and cohorts offered vaccination.

Abbreviations: CC – conventional cytology; CEA - cost-effectiveness analysis; HPV – human papillomavirus; IARC – International Agency for Research on Cancer; ICER – incremental cost-effectiveness ratio; LBC – liquid-based cytology; LYS – life years saved; QALE – quality-adjusted life expectancy; QALY - quality-adjusted life year; US – United States.
*The economic evaluation in MASC 2013[10] was subsequently amended and published by Lew et al. in 2017[219]

5.1.3 Overview of studies

A 2009 Canadian HTA report compared six alternative screening strategies with their current standard of annual conventional cytology for women aged 18 to 69 years. The six alternatives included:

1. conventional cytology with HPV test as triage;
2. conventional cytology with HPV test as triage for those aged over 30 years only;
3. LBC with HPV triage;
4. HPV with LBC triage for those aged over 30 years only;
5. HPV with LBC triage;
6. and age-dependent testing comprising primary test of LBC with no triage for those aged under 30 years and a primary test of HPV with LBC as a triage for those aged over 30.[217]

Each of these strategies was considered over one-, two- or three-yearly screening rounds; with a total of 21 strategies considered. The study estimated the cost and quality-adjusted life years (QALYs) gained for each of the 21 different strategies. The effects of vaccination for HPV were not included.

Uptake of screening varied by age and was estimated as ranging from 58% to 65% for annual screening, based on uptake data from the existing programme. It was assumed that uptake rates would increase if screening intervals were lengthened; with coverage rates for three-yearly screening ranging from 73% to 87%. A discount rate of 5% for costs and 3% for benefits was applied and the analysis was undertaken from the payer perspective. The costs per screening test were CAN$22 (€17.01) for LBC and CAN$40.76 (€31.51) for HPV, respectively and included processing costs (labour, equipment and supplies), but not administration of the tests. Costs included in the analysis covered screening, diagnosis, treatment and palliative care. Switching from the current strategy of annual screening with conventional cytology to LBC with HPV triage was estimated to cost an additional CAN$127,076 (€98,249) per QALY gained.

The authors concluded that a strategy of three-yearly screening of women aged 18 to 69 years with conventional cytology, and HPV triage test for women aged over 30 years with atypical squamous cells of undetermined significance (ASCUS) detected on cytology provided best value for money as it was both less costly and more effective than the current practice. Although additional effectiveness could be achieved by employing LBC as the primary screening test, the additional costs over conventional cytology were considered too expensive. As of 2011, the current practice in Alberta is LBC with HPV triage.[221] Women are screened annually for their first three screening tests, and if these are clear then the frequency changes to

three-yearly screening. Women are recommended to start screening at age 21 or three years after becoming sexually active (whichever is later) and to continue screening until age 69.[222]

A 2015 Belgian HTA compared primary HPV testing every five years with cytology triage with existing standard of care (cytology as a primary screening test every three years with HPV triage).[164] A time-dependent state transition model was developed following a cohort of women from age 30 for their remaining lifetime. The model was used to estimate the cost per life year gained. A discount rate of 3% was applied to costs and 1.5% to benefits and the study was undertaken from the perspective of the healthcare system. The effects of vaccination for HPV were not included. The coverage rate for screening was assumed to be 60% in the base case. Cytology comprised the current mix of conventional cytology and LBC, which varied by region and mostly comprised LBC; however, only the cost of conventional cytology was included in the model. The cost for analysing the cytological screening test was €50.35 (€52.87) as per the current reimbursement value; the cost of performing the primary HPV test was assumed to be €35 (€36.75). The analysis concluded that HPV as the primary screening test dominates as it would avoid more cervical cancer deaths and be less costly than the existing standard of care. Screening strategies in Belgium vary by region, with only the Flemish region having an organised screening programme.

In 2013, the Medical Services Advisory Committee in Australia published an extensive evaluation of cervical screening strategies including a total of 132 different strategies.[10, 219] The base case comparator used was the current practice of two-yearly screening with conventional cytology starting at age 18 to 20 years until exiting screening at age 69 years. The main strategies considered were the current strategy, but using the recommended International Agency for Research on Cancer (IARC) age and screening intervals (three-yearly screening age 25-49, five-yearly screening age 50-64 years), LBC (manual or automated) with IARC age range and screening intervals, HPV testing with LBC triage (five-yearly age 25-64), HPV testing with partial HPV genotyping, and co-testing with HPV and LBC (five-yearly age 25-64). Variations on the strategies included changes to the invitation system, slower and faster rate of uptake at age 25, alternative HPV triage algorithms and exit testing. All strategies were considered in both vaccinated and unvaccinated cohorts. A discount rate of 5% was applied to both costs and benefits. They considered a range of uptake rates, with variations incorporated due to two different reminder systems, two different call-recall scenarios and slow and fast uptake of initial screening. Uptake rates varied by age and were based on the current uptake rates in Australia. LBC (including manual and automated)-strategies were found to be both more or less effective than current practice, depending on the strategies included in

the model, with strategies for unvaccinated women ranging from a 7% increase to 14% decrease in cervical cancer mortality, and strategies for vaccinated women ranging from a 6% increase to 14% decrease in mortality. Strategies that increased effectiveness generally involved HPV triage testing. All HPV testing strategies involving five-yearly screening were predicted to be more effective than current practice. Compared with current practice, strategies in the unvaccinated cohort lead to an 8% to 36% decrease in cervical cancer mortality and strategies in a vaccinated cohort lead to an 8% to 29% decrease in cancer, and leading to a $33.8M to $52.8M (€21.8M to €34.1M) health system saving overall. Overall, for cost saving strategies, relative cost savings compared with current practice were predicted to be slightly higher in vaccinated compared with unvaccinated cohorts. On the basis of the recommendations in this report, the Australian government has announced plans to change its screening programme. Women aged 25 to 74 years (both vaccinated and unvaccinated) will be invited for screening at five-year intervals with HPV testing used as the primary screening test and LBC as triage.[131]

Kitchener et al. evaluated the cost-effectiveness of a number of different screening strategies for the prevention of cervical cancer focusing on combinations of LBC and HPV primary testing in a 2014 UK National Institute for Health Research (NIHR) report.[179] The base case comparator of current practice was LBC with HPV triage, with women screened three-yearly from ages 25 to 49 and five-yearly from aged 50 to 64 years. The main strategies considered were primary screening with HPV with LBC triage, and co-testing with LBC and HPV. Three different alternative triaging and follow-up strategies were considered for the primary HPV with LBC triage option, including partial genotyping. Additional variations to the strategies were also considered, with three alternative screening intervals (five-yearly, six-yearly and six-yearly from age 25 to 49 and 10-yearly from age 50 to 64) and two age variations to the strategies where women aged less than 30 or 35 years had primary testing with LBC rather than HPV for the strategies with a primary screening test of HPV. Both vaccinated and unvaccinated cohorts were considered. The analysis used a combination of a dynamic model of HPV transmission and vaccination, a 'natural history model' of cervical intraepithelial neoplasia (CIN) and cervical cancer, with a Markov multi-cohort model of cervical screening. The study was conducted from the perspective of the publicly funded healthcare system and a discount rate of 3.5% was used for both costs and outcomes. The model includes age- and interval-specific uptake rates for screening based on registry data. Compared with current practice most of the HPV screening strategies predicted an equivalent or small improvement in cervical cancer incidence or mortality. Most of the primary HPV strategies examined where HPV testing was used as the sole primary test were cost saving in both unvaccinated and vaccinated cohorts. Under baseline cost assumptions they resulted in a 7 to 18% reduction in annual screening-associated costs in

unvaccinated cohorts and a 9 to 22% reduction for vaccinated cohorts. In January 2016, the UK National Screening Committee (NSC) recommended that the UK should adopt HPV testing as the primary screening test.[223]

A 2012 report by Van Rosmalen et al. evaluated the cost-effectiveness of three main cervical screening strategies in the Netherlands:

1. cytology with cytology triage;
2. HPV testing with cytology triage;
3. and cytology with HPV triage.

Both LBC and conventional cytology were considered separately for each strategy.[215] A large number of alternatives were considered: the number of screening rounds was varied from three to 10 per lifetime; the time interval was varied from three to 10 years; four different ages were considered for starting screening (25, 27, 30 and 32 years); and four alternative triaging algorithms were considered. The effect of HPV vaccination was not considered. The analysis used a Markov model (MISCAN). Costs were from the societal perspective and a discount rate of 3% was applied to costs and benefits. A screening uptake rate of 80% was assumed. For the programmes that were considered efficient, QALY gains for primary HPV testing followed by conventional cytology triage ranged from 695 to 1,006 QALYs, and for primary conventional cytology testing followed by HPV triage they ranged from 501 to 618 QALYs gained. For the programmes that were considered efficient, the programme costs ranged from €3.1 million (€4 million) to €14.6 million (€19 million) for primary HPV testing followed by conventional cytology triage. For primary conventional cytology testing followed by HPV triage, the costs ranged from €1.8 million (€2.3 million) to €2.4 million (€3.1 million). Laboratory costs were assumed to be €33.72 (€43.78) for LBC and €33.87 (€43.97) for HPV; results were sensitive to the costs of the HPV test. All cost-effective programmes used conventional cytology instead of LBC. The authors concluded that increasing the interval between screening rounds and changing to HPV as the primary test can improve the effectiveness and decrease the costs of cervical screening.

A 2010 report by Vijayaraghavan et al. evaluated the cost-effectiveness of six main screening strategies compared with no screening in the US.[216] In all six strategies, women aged less than 30 years received biennial LBC. For women aged 30 years and over, the following options were considered: LBC every two years; LBC with HPV triage every two years; HPV with LBC triage every three years; co-testing with LBC plus HPV every three years; co-testing with LBC plus HPV every three years with HPV 16 and HPV 18 partial genotyping triage; and HPV every three years with HPV 16 and HPV 18 partial genotyping as a triage test. The effect of HPV vaccination was not considered. The analysis used a Markov model. Costs were from the payer

perspective and it was unclear what discount rate or screening uptake was used. All options were considered cost-effective compared with no screening. The authors considered HPV 16 and HPV 18 partial genotyping strategies to be the most effective, preventing between 51 and 73 deaths per 100,000 women screened when compared with LBC followed by HPV triage, and preventing between four and 26 deaths when compared with co-testing with LBC and HPV. When compared with primary HPV and LBC co-testing, use of HPV partial genotyping to triage all women every three years positive for high-risk HPV (hrHPV) resulted in an ICER of $34,074 (€36,744) per QALY gained.

A 2016 New Zealand study compared 16 alternative screening strategies with their current standard of three-yearly liquid-based cytology with HPV triage (triage applied only to women over 30) for women aged 20 to 69 years. The 16 alternatives included: HPV with LBC test as triage; HPV partial genotyping with LBC a triage test; co-testing with LBC and HPV with no triage and co-testing with HPV with LBC with partial genotyping as a triage test.[218] Each strategy considered four alternatives:

1. five-yearly screening from age 25 to 69 with co-testing in 12 months for women at intermediate risk (HPV positive and LBC negative or positive for non-HPV 16 and 18 HPV type and positive for low-grade cytology);
2. five-yearly screening from age 25 to 69 with immediate referral to colposcopy for women at intermediate risk;
3. three-yearly screening from age 20 to 30 and five-yearly screening until age 69 with co-testing in 12 months for women at intermediate risk;
4. and three-yearly screening from age 20 to 30 and five-yearly screening until age 69 with immediate referral to colposcopy for women at intermediate risk.

This gave a total of 16 alternative strategies considered. All strategies were considered for both an unvaccinated cohort and a cohort who had been offered vaccination. The study estimated the cost, life years gained and cancer incidence and mortality for each of the 16 different strategies. Screening uptake varied by age and ranging from around 55% to 85% for three-year coverage, based on uptake data from the existing programme, it was assumed that lengthening the screening intervals would increase coverage. A discount rate of 3.5% for costs and benefits was applied and the analysis was undertaken from the payer's perspective. The costs per screening test were NZ$31.10 (€18.34) for LBC and NZ$35.00 (€20.64) for HPV, respectively. Costs included in the analysis covered screening, diagnosis, treatment and palliative care. Switching from the current strategy (three-yearly LBC with HPV triage [triage applied only to women over 30] for women aged 20 to 69 years) to five-yearly HPV partial genotyping with LBC triage and co-testing at 12 months for women at intermediate risk was estimated to save NZ$1.3million (€0.77million) per annum and to lead to a 15% reduction in cancer mortality in

unvaccinated women. In a cohort offered vaccination it was estimated to lead to a saving of NZ$3.2million (€1.89million) per annum and to lead to a 12% reduction in cancer mortality. The authors concluded that a primary HPV screening with partial genotyping would be more effective and less costly than the current cytology-based programme in both unvaccinated women and cohorts offered vaccination.

5.1.4 Quality of included studies

The cost-effectiveness studies were assessed using the International Society for Pharmacoeconomics and Outcomes Research questionnaire to assess the relevance and credibility of modelling studies.[220] Relevance was assessed on the grounds of the study population, characteristics of the intervention, outcomes measured and the overall study context. The credibility of the results was considered using criteria related to the design, validation and analysis methods, the quality of the data used, as well as how the results were reported and interpreted, and whether the authors had any conflicts of interest. All eight included studies were found to be of good quality. Reporting was generally adequate and considered to be fair and balanced.

5.1.5 Applicability of the evidence

Consistent evidence was found in all eight economic evaluation studies that using HPV testing as the primary screening test with cytology triage is cost-effective (or in some cases cost saving) compared with use of cytology as the primary screening test in the prevention of cervical cancer. There was no consistency however in what the optimal screening strategy should look like, with variation in the triaging options, screening frequency and age intervals between studies. This is consistent with the findings in the broader economic literature of HPV testing. In 2015, a systematic review of model-based cervical screening evaluations was published by Mendes et al.[15] Although the primary objective of the review was to assess the type of models used in the economic evaluations, they did note that 15 of the 17 studies, that compared HPV to cytology-based testing as a primary screening test, considered HPV testing to be a cost-effective alternative.

In the 2009 Canadian study, none of the options considered reflect the current practice in Ireland of five-yearly screening for women aged between 45 and 60 years; the maximum screening interval assessed was three-yearly.[217] It is difficult to interpret how these findings would relate to the Irish screening service. The effect of strategies on vaccinated cohorts was also not considered.

In contrast to the other studies included in this review of the economic literature, the 2015 study by the Belgian HTA agency, KCE, evaluated a limited number of alternative strategies.[164] One of the key difficulties in applying the evidence from this study to Ireland is the cytology comparator. The cytology comparator used in

the base case included a mix of both conventional cytology and LBC, representing current standard of care in Belgium, rather than LBC only as is used in Ireland. The costs of cytology were not readily available and a number of assumptions about the costs of the LBC test were made which may have led to an underestimate of the true LBC costs. Furthermore, there is currently no national screening programme in place in Belgium with organised screening only in the Flemish region, where there is a policy of three-yearly cytology screening for women aged 25 to 64 year. In other regions screening is opportunistic.

The 2013 Australian study included a large number of comparisons and considered the effects in both vaccinated and unvaccinated cohorts.[10] The base case comparator of two-yearly screening using conventional cytology for women aged 18 to 69 years is not however a strategy that would be considered in the Irish context. The current screening programme in Ireland is considerably less intensive than the base case considered in the Australian study and comprises three-yearly screening from ages 25 to 44 years and then five-yearly screening from age 45 to 60 years. The International Agency for Research on Cancer (IARC) recommended frequencies and age intervals of three-yearly screening from ages 25 to 49 years and five-yearly screening from age 50 to 64 years were evaluated in this report. These frequencies and intervals are also marginally more intensive than what is currently in place in Ireland and would result in approximately two or three additional screenings over each woman's lifetime. For these reasons, the comparisons in this study are not reflective of the situation and comparators of interest in Ireland.

The 2014 study by Kitchener et al. for the National Institute for Health Research in the UK[179] included a large number of comparisons and the strategies considered were similar to those in place and being considered in Ireland. Similar to Ireland, the UK has an organised call-recall screening programme and universal HPV vaccination of 12 year old girls; uptake of both screening and vaccination are similar for the two countries. The discount rate for costs and health outcomes was 3.5%, which is lower than the 5% rate that is used in Ireland. Using a lower discount rate is likely to overestimate the benefits and costs, thus making it difficult to anticipate the effect this would have on the cost-effectiveness in the Irish settings. Also, similar to the Australian study the age ranges for the screening intervals are from 25 to 49 years and 50 to 64 years in contrast to the age ranges in Ireland of three-yearly from 25 to 44 years and then five-yearly from 45 to 60 years.

The 2012 Dutch study by Van Rosalmen et al.[215] was conducted from a societal perspective and used a discount rate of 3%. A HPV-vaccinated cohort was not considered in this model and it is unclear whether the current Irish strategy was considered, as although they adjusted the number of screening rounds, it is not

clear how this was done. For example, whether screening rounds were always evenly distributed or whether, as is the case in Ireland, shorter intervals could be followed by longer intervals. Thus the results from this study are difficult to apply to the Irish setting.

The 2010 study by Vijayaraghavan et al. compared a number of LBC and HPV screening options in the US.[216] The frequency of screening in all options considered was at most three-yearly, which is shorter than that currently used in Ireland. The effect of vaccination was not considered and the study was not considered in the context of an organised call-recall screening programme. The discount rate was not stated and it appears that discounting was not applied to the analysis. Also it was difficult to rule out bias due to conflicts of interest as all authors received fees from one of the test manufacturers. For these reasons the results from this study are not applicable to the Irish setting.

The 2016 New Zealand study[218] considered alternative screening strategies similar to those being considered in Ireland. However, the current screening programme in Ireland is less intensive than the base case considered in the New Zealand study, which comprises three-yearly liquid-based cytology with HPV triage (triage applied only to women over 30) for women aged 20 to 69 years. Combined with the lower discount rate used (3.5% versus 5% in Ireland), the findings of the study may not be applicable to the Irish setting.

There has been no published cost-effectiveness literature on HPV testing as a primary screening strategy in Ireland. In 2015, Agapova et al.[224] considered the long-term costs of introducing HPV testing in the surveillance of women post treatment for cervical cancer in Ireland. Co-testing with HPV and LBC was found to be cost saving over a 12-year period, compared with LBC only.

5.1.6 Conclusions

Few economic evaluations comparing primary HPV screening with primary LBC screening for prevention of cervical cancer have been published. While consistent evidence was found that cervical screening programmes using HPV testing as the primary screening test are cost-effective and potentially cost saving when compared with programmes using cytology as the primary screening test, it is not possible to determine the optimal screening strategy from the available literature. The identified economic evaluations are quite heterogeneous in terms of the strategies considered, the inclusion of vaccinated cohorts and discount rates used. The variation in strategies considered is particularly important, as no study that considered a strategy which reflects the current cervical screening programme in place in Ireland

was found. Ireland has already adopted LBC testing and has a less intensive screening programme than many of the alternatives considered in the literature.

Given differences in healthcare delivery costs and screening programmes considered, it was not possible to determine the optimal screening strategy for Ireland based on the available literature. A de novo economic evaluation was therefore required to inform decision-making.

5.2 Health-economic analysis

In the absence of applicable published cost-effectiveness evidence from another setting, an economic model was developed specific to the Irish setting.

5.2.1 Overview of the economic model

A decision analysis model was built to compare the costs and benefits associated with different HPV-based primary screening strategies for the prevention of cervical cancer compared with the current strategy of primary LBC followed by triage with HPV in Ireland. The objective of the economic evaluation was to aid decision-making by estimating the total net costs and benefits of each of the different HPV-based primary screening strategies compared with both the current strategy and alternative LBC-based screening strategies.

5.2.2 Study objective

The purpose of this HTA was to examine the cost-effectiveness and budget impact of changing from LBC to HPV testing as the primary screening test for prevention of cervical cancer in Ireland. As part of the HTA, we also considered potential changes to the screening interval, age ranges and test sequencing compared with the current screening programme. Specifically, strategy options included different combinations of two primary screening tests (HPV and LBC), four triage tests (HPV, LBC, partial genotyping for HPV 16 and HPV 18, and $p16^{INK4a}$/Ki-67 dual staining), two screening intervals and two different screening age ranges. The options were all considered in the context of both women vaccinated against HPV (Ireland's current HPV vaccination programme) and unvaccinated women.

5.2.3 Type of economic evaluation

A cost-utility analysis was undertaken in which effectiveness was measured as quality-adjusted life years (QALYs) gained for each of the potential cervical screening strategies and compared across competing alternatives. Cervical screening strategies were also compared in terms of additional outcomes such as, life years gained and cervical cancer mortality.

5.2.4 Study perspective

Costs and benefits were assessed from the perspective of the publicly-funded health and social care system. Only direct medical costs were included. Indirect costs such as decreased productivity associated with morbidity, treatment or death, or out-of pocket expenses incurred by women attending screening or diagnostic testing were excluded. Adoption of this perspective is consistent with national guidelines.[225]

5.2.5 Technology

The assessed technology was screening strategies which included HPV as a primary screening method for the prevention of cervical cancer as part of a national screening programme. See Chapter 2 for a more detailed description of the technology.

5.2.6 Choice of comparators

Currently, CervicalCheck - Ireland's National Cervical Screening Programme, uses LBC as the primary screening test for the prevention of cervical cancer. Screening is offered at three-year intervals for those aged 25 to 44 years, and at five-year intervals for those aged 45 to 60 years. The LBC test is followed by a HPV triage test if low-grade cytological abnormalities (ASCUS or LSIL) are detected on the cytology specimen. As noted, the purpose of this HTA was to examine the potential impact of changing from LBC to HPV testing as the primary screening test, and to also consider potential changes to the screening interval, age ranges and test sequencing.

To include all potential options was not feasible for this HTA as the number of strategies would run into the thousands. It was important that the subset modeled included the most relevant and important options necessary to inform decision-making in relation to the national programme, CervicalCheck. This section lists the 32 included strategies in the economic modelling, along with a brief rationale for the included and excluded options.

5.2.6.1 Rationale for included options

The absence of HPV infection has been shown to be a valuable marker of a low risk of disease. As documented in Chapter 4, HPV testing is more sensitive than cytology as a primary screening method, with evidence also that following a negative primary HPV screening test there is a low risk of developing cervical carcinoma in situ or invasive cervical cancer (CIN 3+) in the next six years. Extending the screening interval to a five-yearly screening interval for all ages was considered in the evaluation.

The current cervical screening programme includes women aged 25 to 60 years. The International Agency for Research on Cancer (IARC) recommended age intervals include women up to the age of 65 years.[9] Extending the screening age in-line with the IARC recommendations was also considered in this evaluation.

As documented in Chapter 3, the prevalence of HPV and abnormal cytology are very high in the 25 to 29 age group. However, in the majority of cases, the infection will clear spontaneously, and in the absence of persistent infection, cytological abnormalities will typically regress. Use of a HPV test in such a group may lead to unnecessary colposcopy referrals, psychological distress and the possibility of overdiagnosis and treatment. To allow for a different testing strategy for younger women, a strategy that offers LBC primary testing to those aged less than 30 years and HPV primary testing to those aged 30 years and over was included.

In 2010, the HSE began a HPV school immunisation programme for girls in their first year of secondary school (age 12-13 years), with a catch-up programme offered from 2011 to 2013 for those in 6th year. This latter cohort will enter CervicalCheck in 2018-2019. The current vaccine immunises against HPV 16 and HPV 18. Worldwide, these strains contribute to 16% to 32% of low-grade abnormalities, 41% to 67% of high-grade abnormalities, and 70% of cervical cancer. It is expected that these vaccinated women will have a lower prevalence of HPV at all ages. Data from the CERVIVA collaboration estimates that, across all age groups, approximately 70% of women who are infected with any of the 14 oncogenic HPV genotypes detected by the commercially available HPV test kits are infected with at least one of the 12 other high-risk HPV (hrHPV) types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68).[141] Therefore, use of HPV tests in vaccinated women aged less than 30 years is not anticipated to lead to excessive or potentially inappropriate referrals.

Currently the primary screening test in Ireland is LBC followed by a HPV triage test. When changing the primary test to HPV it becomes necessary to change the triage test. Chapter 4 of this report considers the available clinical evidence to support alternative triaging strategies. Evidence was available to support seven triaging strategies, that is, HPV primary testing followed by:

1. LBC;
2. partial genotyping for HPV 16 and 18;
3. sequential testing of partial genotyping for HPV 16 and 18 followed, if positive, by LBC;
4. co-testing with partial genotyping for HPV 16 and 18 plus LBC;
5. $p16^{INK4a}$/Ki-67;
6. sequential testing of partial genotyping for HPV 16 and 18 followed, if positive, by $p16^{INK4a}$/Ki-67;

7. and co-testing with partial genotyping HPV 16 and 18 plus p16^{INK4a}/Ki-67.

Table 5.2 includes a summary of the strategies that were included in the economic model.

Table 5.2 Summary of strategies included in the economic modelling

	Strategy	No.
Current strategy	LBC followed by HPV triage for (ASCUS or LSIL) every 3 years ages 25-44, every 5 years ages 45-60	1
Changing primary screening test	HPV followed by LBC triage for (HPV positive) every 3 years ages 25-44, every 5 years ages 45-60	2
	HPV followed by partial genotyping 16/18 triage for (HPV positive) every 3 years ages 25-44, every 5 years ages 45-60	3
	HPV followed, if positive, by sequential testing of partial genotyping for HPV 16/18 followed, if positive, by LBC every 3 years ages 25-44, every 5 years ages 45-60	4
	HPV followed, if positive, by co-testing partial genotyping 16/18 and LBC, every 3 years ages 25-44, every 5 years ages 45-60	5
	HPV followed by p16 ^{NK4a}/Ki-67 triage for (HPV positive) every 3 years ages 25-44, every 5 years ages 45-60	6
	HPV followed, if positive, by sequential testing of partial genotyping for HPV 16/18 followed, if positive, by p16 ^{NK4a}/Ki-67 every 3 years ages 25-44, every 5 years ages 45-60	7
	HPV followed, if positive, by co-testing partial genotyping 16/18 and p16 ^{NK4a}/Ki-67, every 3 years ages 25-44, every 5 years ages 45-60	8
Changing to five-yearly screening interval	HPV followed by LBC triage for (HPV positive) every 5 years ages 25-60	9
	HPV followed by partial genotyping 16/18 triage for (HPV positive) every 5 years ages 25-60	10
	HPV followed, if positive, by sequential testing of partial genotyping for HPV 16/18 followed, if positive, by LBC, every 5 years ages 25-60	11
	HPV followed, if positive, by co-testing partial genotyping 16/18 and LBC, every 5 years ages 25-60	12
	HPV followed by p16^{INK4a}/Ki-67 triage for (HPV positive) every 5 years ages 25-60	13
	HPV followed, if positive, by sequential testing of partial genotyping for HPV 16/18 followed, if positive, by p16^{INK4a}/Ki-67 every 5 years ages	14

	25-60	
	HPV followed, if positive, by co-testing partial genotyping 16/18 and $p16^{INK4a}$/Ki-67, every 5 years ages 25-60	15
Option for differential strategy by age	Under age 30: LBC followed by HPV triage for (ASCUS or LSIL); 30 years and over: HPV followed by LBC triage for (HPV positive), every 3 years age 25-44, every 5 years age 45-60	16
Extending to age 65	Extending to age 65: all options 1-16 with upper age-limit extended to age 65	17-32

Note: All options were considered for both vaccinated and unvaccinated cohorts.
Key: ASCUS – atypical squamous cells of undetermined significance; HPV – human papillomavirus; LBC – liquid-based cytology; LSIL – low-grade squamous intraepithelial lesion.

5.2.6.2 Rationale for excluded options

Conventional cytology is not currently in use in Ireland; all primary screening currently performed uses liquid-based cytology (LBC). The sensitivity and specificity of conventional cytology and LBC are comparable.[14] LBC, however, offers benefits including fewer unsatisfactory cytology samples, uniform spread of epithelial cells in a thin layer facilitating microscopic interpretation, availability of residual material for molecular testing, and potential for automation including automated image analysis. Switching back to conventional cytology was not considered a strategy of interest in Ireland.

Self-sampling as a screening method has been shown to be effective in settings where there is not easy access to an organised screening programme,[226] as an alternative for women who do not regularly attend screening,[189] or as a strategy to improve low-uptake rates.[227] However, where resources are available, the benefits are limited. Given Ireland already has an organised population-level screening programme with a high-uptake rate, there is likely to be little benefit to reorganising the screening programme to be based around self-sampling.

Co-testing using both LBC and HPV as the primary screening test would have benefits in potentially increasing the sensitivity compared with using either test alone. These would be offset by the considerable increase in resources required and a reduction in specificity. As both tests have been shown to be effective as a primary screening test, the increases gained in co-testing are likely to be small relative to the increase in resources required. When comparing it with the list of proposed strategies, co-testing was deemed not to be a feasible strategy for implementation.

There are a number of molecular surrogate markers, which have been suggested as potential options for use as a triage test. The research into these is currently limited with few high-quality studies that consider the longer term outcomes of their use.

There is evidence that following a negative screening test, the screening interval for HPV-based screening programmes can be safely extended to six-yearly intervals,[(197)] with further evidence emerging of the safety of extending even further (up to 10 years) in women aged over 40.[(4)] Given that CervicalCheck commenced in September 2008, and is still relatively new, extending beyond five-yearly intervals was considered to be unacceptable at this point. However, given that CervicalCheck already uses a comprehensive linked screening registry and call-recall based invitation system, adoption of further risk-based screening tailored to the individual's risk and screening history is something that can be adopted in the future. This is particularly important as further evidence emerges of the applicability of the international data in the Irish setting and the long-term safety of HPV-based strategies.

In a partly vaccinated cohort, overall prevalence of HPV 16 and HPV 18 infections is lower than in a pre-vaccination cohort. Therefore unvaccinated women in a partly vaccinated cohort are at a lower risk of acquiring HPV infection due to herd immunity. This indirect protective effect of vaccination will be limited at first, but is expected to rise over time. Within the context of a vaccinated cohort, it may be appropriate to delay the commencement of organised screening. Although the uptake rate of HPV vaccine has been historically high in Ireland (86.9% in 2014 to 2015), the latest figures indicate a reduced uptake rate of 72.3% in 2015 to 2016.[(228)] Early indications suggest that the uptake rate for 2016 to 2017 has declined further. In the context of an uncertain vaccination rate, it was considered not appropriate to consider delaying the screening age from 25 to 30 for all women.

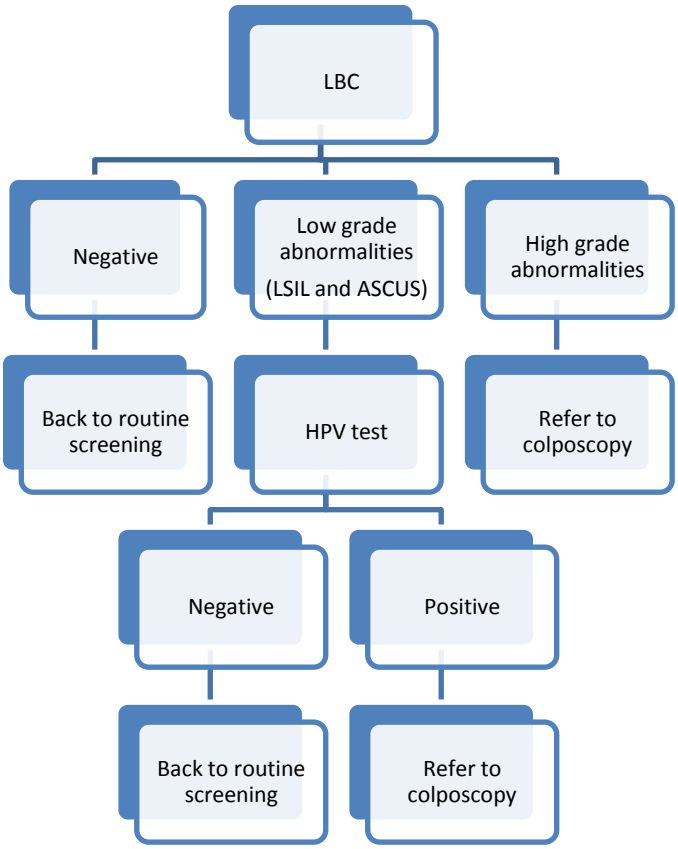
Basic triaging algorithms are mapped out in Figures 5.1 to 5.8. These pathways only include those aspects that differed between strategy options. It was assumed that once referred to colposcopy, there were no changes to the current pathways and current practice for inadequate samples would not change.

Primary HPV screening allows women to be stratified according to risk, based on the presence or absence of HPV infection (Figures 5.2 to 5.8). In the pathway, only women with a positive primary HPV test undergo triage. As outlined in Figures 5.2 to 5.8, women with a positive triage test (or in the case of strategies with sequential triage tests, women whose final triage test is positive) are referred to colposcopy. Women whose triage test is negative are recalled in one year for a repeat HPV test. It is assumed that two positive HPV tests taken one year apart are suggestive of

persistent infection. Women with evidence of persistent HPV infection are referred to colposcopy, irrespective of the triage test findings.

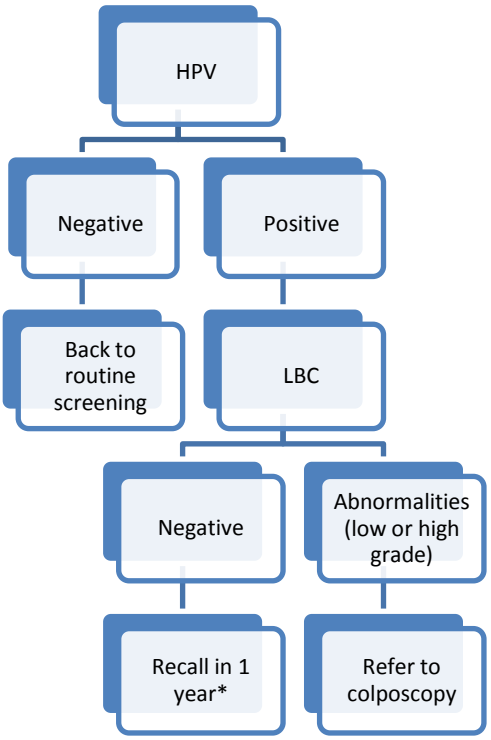
While the pathways reflect the process as a series of sequential steps, in practice some of the steps occur simultaneously. For example, both primary and triage testing can be applied to a single sample based on one screening visit. Therefore, in the event of the initial test being positive, there is no need for the woman to return for a second test to be collected. Likewise, as outlined in Chapter 2, certain HPV test kits with the capacity for partial genotyping can be used to report HPV findings in aggregate (pooled positive or negative finding for all hrHPV) and to specifically identify HPV 16 and 18, while reporting the presence or absence of the additional hrHPV genotypes as a pooled result.

Figure 5.1 Pathway for current screening practice



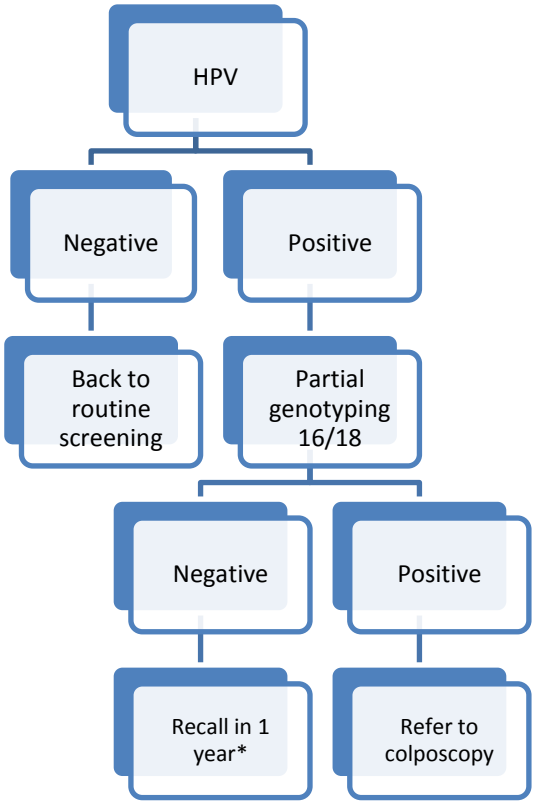
Both primary and triage testing is applied to a sample based on one screening visit.

Figure 5.2 Pathway for primary HPV testing followed by triage with LBC



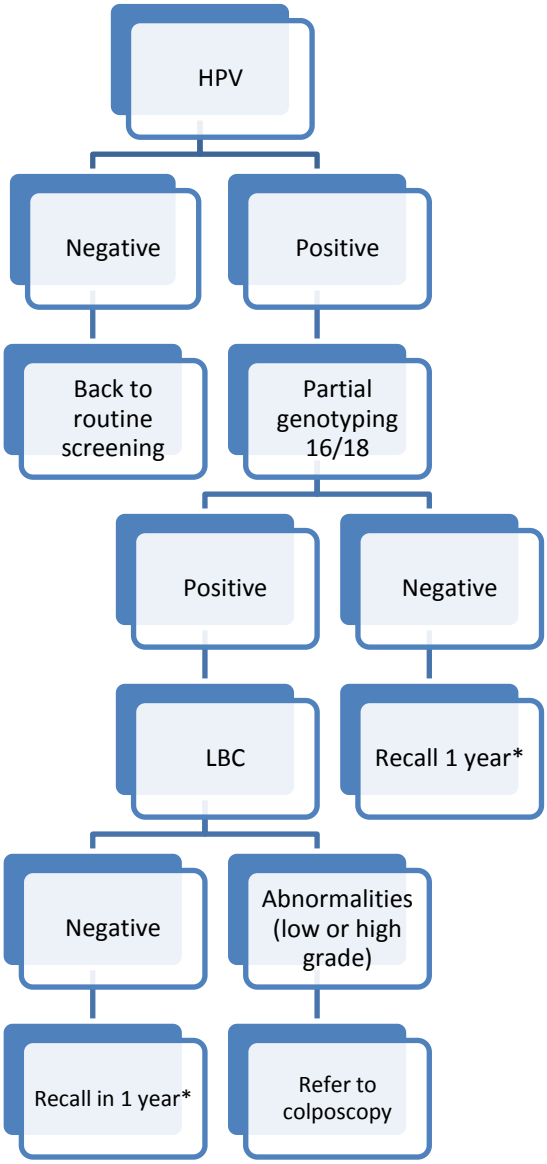
Both primary and triage testing is applied to a sample based on one screening visit.
* If HPV positive at one-year follow-up, refer to colposcopy, irrespective of the triage test results.

Figure 5.3 Pathway for primary HPV testing followed by triage with partial genotyping for HPV16/18



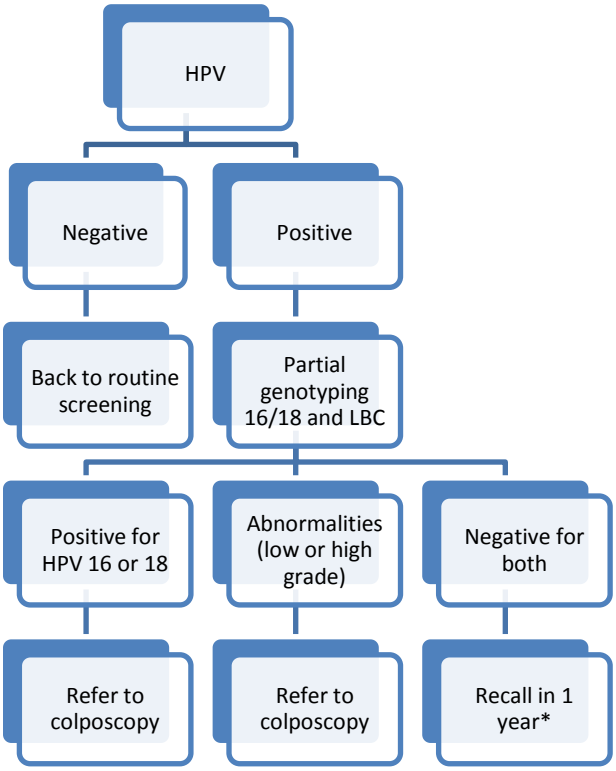
Both primary and triage testing is applied to a sample based on one screening visit.
* If HPV positive at one-year follow-up, refer to colposcopy, irrespective of the triage test results.

Figure 5.4 Pathway for primary HPV testing followed by triage with sequential testing of partial genotyping HPV 16/18 and, if positive, LBC



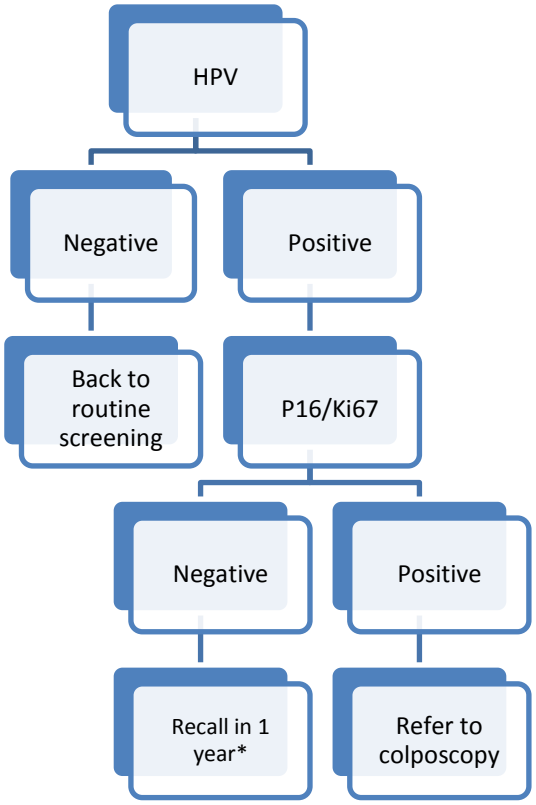
Both primary and triage testing is applied to a sample based on one screening visit.
* If HPV positive at one-year follow-up, refer to colposcopy, irrespective of the triage test results.

Figure 5.5 Pathway for primary HPV testing followed by co-testing with partial genotyping and LBC triage



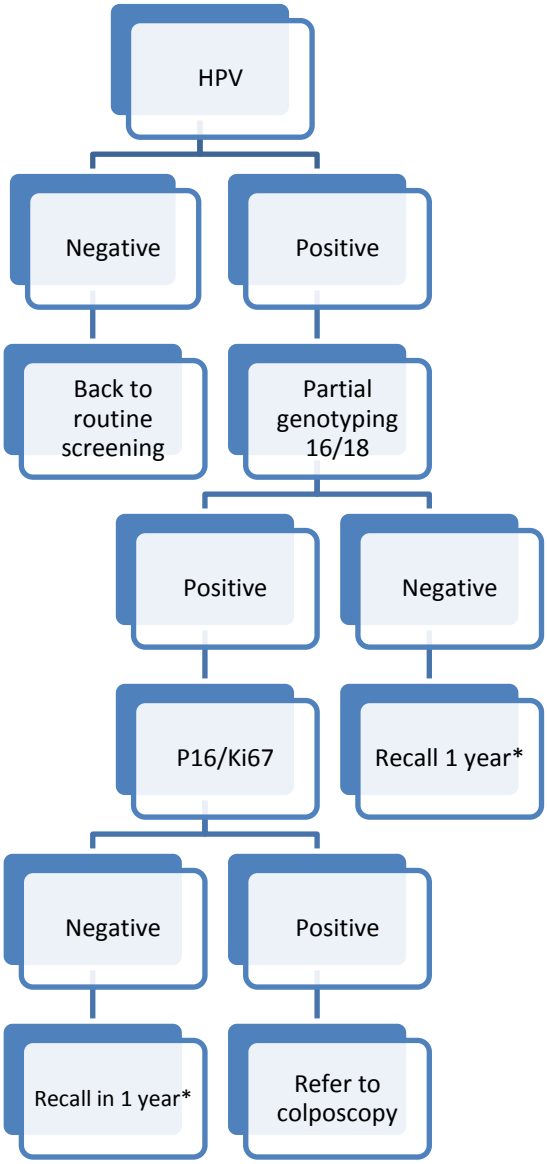
Both primary and triage testing is applied to a sample based on one screening visit.
* If HPV positive at one-year follow-up, refer to colposcopy, irrespective of the triage test results.

Figure 5.6 Pathway for primary HPV testing followed by triage with p16^{INK4a}/Ki-67



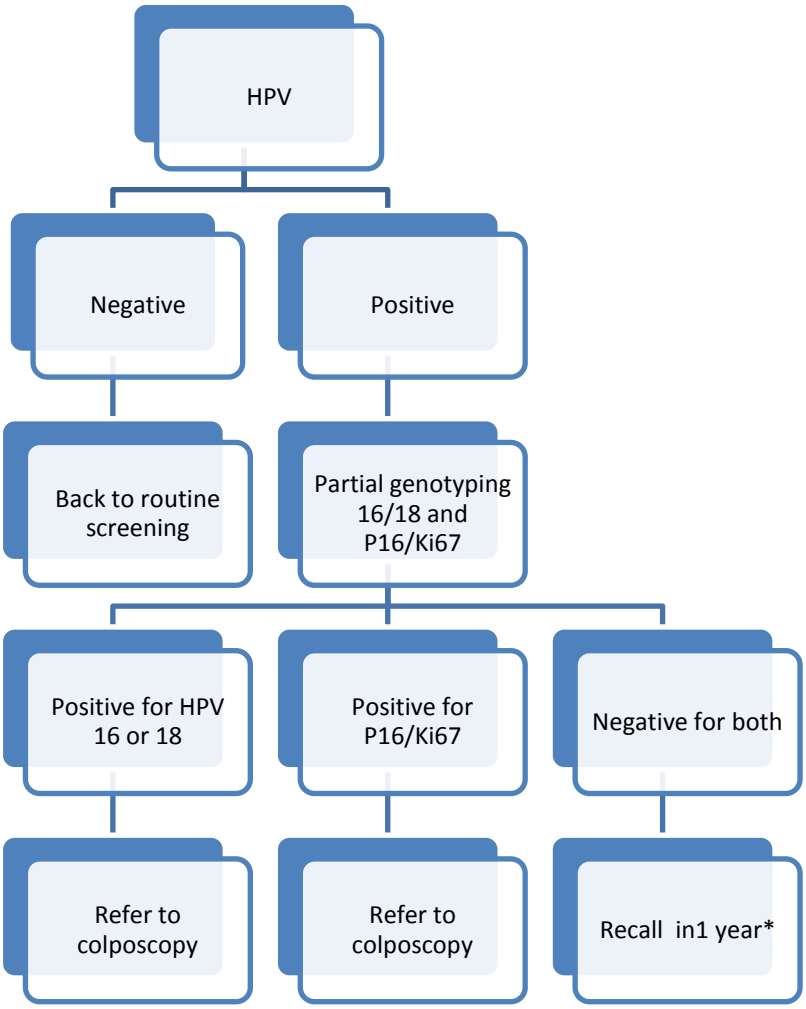
Both primary and triage testing is applied to a sample based on one screening visit.
* If HPV positive at one-year follow-up, refer to colposcopy, irrespective of the triage test results.

Figure 5.7 Pathway for primary HPV testing followed by triage with sequential testing of partial genotyping HPV 16/18 and, if positive, p16^{INK4a}/Ki-67



Both primary and triage testing is applied to a sample based on one screening visit.
* If HPV positive at one-year follow-up, refer to colposcopy, irrespective of the triage test results.

Figure 5.8 Pathway for primary HPV testing followed by co-testing with partial genotyping and p16^{INK4a}/Ki-67 triage



Both primary and triage testing is applied to a sample based on one screening visit.
* If HPV positive at one-year follow-up, refer to colposcopy, irrespective of the triage test results.

5.2.7 Target population

The target population of a cervical screening programme in these pathways was all women (both vaccinated for HPV and unvaccinated) aged 25 to 65 years in Ireland with an intact cervix (that is, who have not undergone hysterectomy). Screening for women who are at increased risk (due to renal failure, renal dialysis, HIV-positive or pre and post organ transplant) was not considered within this evaluation.

5.2.8 Time horizon

The average cost and clinical benefit per woman for each of the screening strategies was estimated by modelling one year's cohort from age 25 years to end of life.

5.2.9 Outline of the model structure

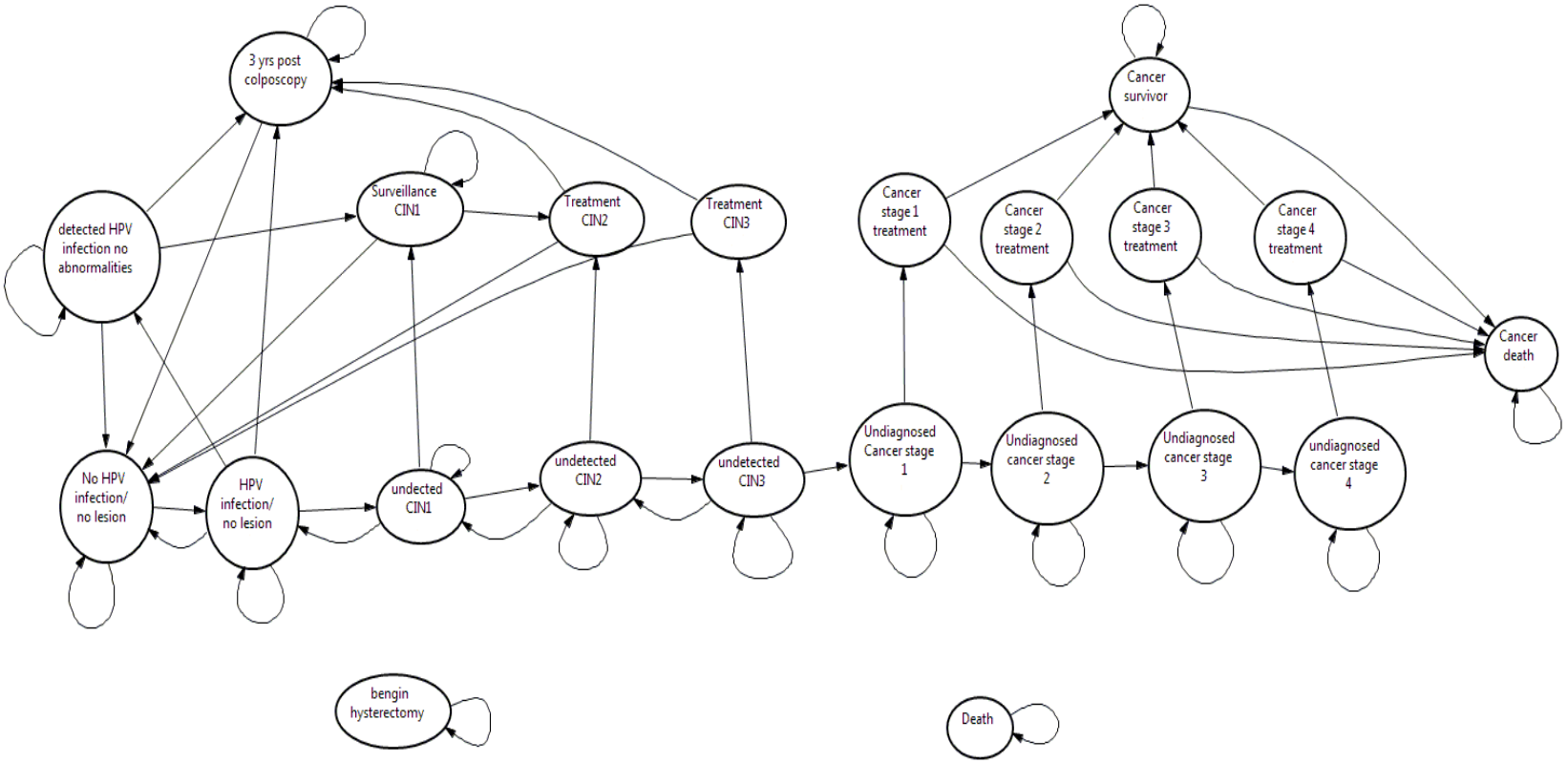
A Markov model structure was developed based on the natural history of cervical cancer. In a Markov model it is assumed that a woman is always in one of a finite number of distinct health states. All events are represented as transitions between states with transition probabilities dictating the likelihood of moving from one state to another in a specified time (cycle length). The model structure was based on the German cervical screening model.[229] The model structure was adapted to match Irish epidemiology, clinical practice and screening patterns, and to enable greater flexibility in setting screening strategies. An outline of the model is given in Figure 5.9.

The model considered a cohort of women who moved in annual cycles through the different health states. The possible states included healthy individuals, those with HPV, with CIN 1, CIN 2, CIN 3, cervical cancer (separated into FIGO stage I, stage II, stage III and stage IV) and death (cancer-related and all-cause). States were also included to represent women undergoing treatment (CIN 2, CIN 3, FIGO stage I, stage II, stage III and stage IV), women under increased surveillance (HPV positive, CIN 1 or post treatment for CIN 2 or CIN 3) and women who were no longer part of the routine screening programme (post hysterectomy for non-cervical cancer and cervical cancer survivors) (see Figure 5.9). Separate states were not included for subtypes of HPV (HPV 16-positive, HPV 18-positive, positive for other high-risk HPV), or cervical cancer subtypes (squamous cell carcinoma, adenocarcinoma). The model instead considers the average pathway through the CIN states (or low and high-grade lesions) from HPV infection through to the development of invasive cervical cancer. During any cycle women could transition from any state to the deceased state due to other causes (that is, all cause mortality), and women could transition from any state where they did not have cervical cancer to the non-cervical cancer hysterectomy state (benign hysterectomy).

Vaccinated women were modeled separately, where the lower transition probabilities from no HPV infection to HPV infection reflected their reduced risk of developing HPV and cervical cancer. Following treatment of precancerous abnormalities, women return to the healthy state and were considered at risk of further HPV infection; it was assumed that there was no reduced risk, or immunity, to developing HPV infection following clearance of HPV.

We assumed that precancerous CIN states were only detectable through screening, but that cancer FIGO stages I to IV could be detected both through the onset of symptoms and screening.

Figure 5.9 Diagram of model structure



Note: This is a simplified version, and for readability not all possible transitions have shown. A table outlining all possible transitions is included in Appendix 6.

The cohort was modelled from age 25 to death. Transitions between states were defined by annual transition probabilities derived from the literature and calibrated to fit Irish data on both age-specific cancer incidence from the National Cancer Registry Ireland (NCRI) and age-specific prevalence of HPV from CERVIVA, in collaboration with CervicalCheck. The initial transition probabilities used were taken from the literature of previously calibrated models of the natural history of cervical cancer. Goodness-of-fit was measured using a least squares method to both the estimate of prevalence of HPV and incidence of cervical cancer. Transition probabilities were adjusted individually, and allowed to vary within age groups. The final set was chosen to ensure the best fit balancing between the overall fit to both parameters and the age-specific fit. The full model was developed in TreeAge Pro Version 2016 and validated using a basic model developed in Microsoft Excel 2010.

Quality-adjusted life years (QALYs) from age 25 to death were based on age-specific quality of life for a healthy population, and reduced quality of life by using temporary disutilities for women under surveillance for CIN 1, in treatment for CIN 2, CIN 3, and cervical cancer and for women post-treatment for cervical cancer. Death was assumed to have zero QALYs.

5.2.10 Model outputs

The outputs of the model included the number of screens, colposcopy referrals, cancer cases, cancer deaths, total costs, life years and quality-adjusted life years (QALYs) for each of the strategies modelled. Summary measures included the discounted incremental cost-effectiveness ratio (ICER), and plots of the cost-effectiveness plane, cost-effectiveness acceptability curve and the expected value of perfect information.

The discounted ICER presents the additional costs divided by the additional benefits of one intervention relative to another. The ICER is typically considered in the context of a willingness-to-pay threshold, which represents the maximum a decision-maker is willing to pay for a unit benefit, such as a life year gained or a quality-adjusted life year gained. With the exception of a current agreement for pharmaceuticals,[230] there is no stated threshold in Ireland below which a technology is automatically considered cost-effective and reimbursed. In previous evaluations, willingness-to-pay thresholds of between €20,000 and €45,000 per QALY gained have typically been used as reference points, per national HTA guidelines.[225] Willingness-to-pay thresholds above €100,000 per life year gained were not evaluated in this study.

Cost-effectiveness acceptability curves (CEACs) are used as a method for summarising information on parameter uncertainty in cost-effectiveness analyses. A

CEAC shows the probability that an intervention is cost-effective compared with the modelled alternatives for a range of willingness-to-pay thresholds.[231]

The expected value of perfect information (EVPI) represents the amount a decision-maker should be willing to pay to eliminate uncertainty about which intervention is the best option.[232] As with the CEAC, the EVPI is calculated for a range of willingness-to-pay thresholds. The EVPI is an evaluation of how much the decision maker should be prepared to pay for perfect information, that is, to eliminate decision uncertainty.

5.2.11 Sensitivity analysis

A probabilistic model of 10,000 iterations was used that explicitly took into account the uncertainty in the model parameters, which were varied simultaneously within the model. All of the key parameters were varied within plausible ranges of values. Where possible, ranges were derived from published evidence. If published evidence was limited or unavailable, plausible ranges were derived with the support of the Expert Advisory Group. As the structure of the economic model presented here is inherently stochastic, the outputs were equivalent to a multivariate probabilistic sensitivity analysis.

A univariate sensitivity analysis shows how influential each parameter is by itself and how sensitive the results are to fluctuations in each parameter value. Given the uncertainty around the parameters themselves, it is important to understand how this translates into uncertainty about the results. Deterministic sensitivity analysis was used to examine this, where each parameter in turn was fixed at its upper and lower bounds, while all the other parameters were held constant at their 'best estimate' or baseline value.

5.2.12 Budget impact analysis

The budget impact analysis was conducted from the perspective of the publicly-funded health and social care system. The analysis reports the annual cost of the modelled cervical screening programmes. As with the cost-effectiveness analysis, indirect costs due to decreased productivity associated with disease or death, or out-of pocket expenses incurred by women attending screening or diagnostic testing were not included. Costs used in the budget impact analysis were the same as those used in the economic analysis. A budget impact analysis is inclusive of value-added tax (VAT), where applicable.[225] VAT applies to non-oral medications and to equipment when calculating amortised capital costs. The cost for screening tests therefore includes VAT at 23% on consumables.

5.2 Model parameters

The economic model required a range of input parameters that describe the cervical screening programmes; the risk of developing HPV, CIN and cervical cancer; the diagnostic test accuracy of the screening strategies; the associated costs of screening; further testing and treatment, and the impact this has on outcomes in terms of survival and morbidity. The purpose of this section is to provide details on the values used for the key parameters. As the model was probabilistic, parameters generally have a base-case value and an associated range or distribution of values.

The overall benefits and costs of competing cervical screening programmes were calculated by performing 10,000 model simulations. Randomly sampled individual parameter values were used in each simulation. Summarising across simulations provides an estimate of overall average costs and benefits, as well as the uncertainty associated with these values.

5.3.1 Discount rate

Discounting reflects a societal preference for benefits to be realised in the present and costs to be experienced in the future. Discounting facilitates comparison between costs and benefits that occur at different times. Costs and benefits were discounted at the rate of 5% as set out by the Department of Finance.[225] The discount rate was fixed in the main analysis and varied from 1.5% to 6% in a univariate sensitivity analysis to illustrate the impact of discounting.

5.3.2 Epidemiological measures

A variety of epidemiological parameters were required to model the incidence of HPV infection, progression and regression to CIN, incidence of cervical cancer, efficacy of the various screening strategies, and outcomes for those with cervical cancer.

Natural history parameters for the infection of HPV, and progression and regression of CIN 1, CIN 2, CIN 3 and cervical cancer were defined by annual transition probabilities derived from the literature and calibrated to Irish data from the NCRI and CERVIVA, in collaboration with CervicalCheck (Table 5.3). The current vaccine immunises against HPV 16 and 18. Worldwide these strains contribute to 16% to 32% of low-grade abnormalities, 41% to 67% of high-grade abnormalities, and 70% of cervical cancer. Thus, it was assumed that not only is the incidence of HPV different in HPV-vaccinated women, but also progression to pre-cancerous lesions and from pre-cancerous lesions to invasive cervical cancer.

Table 5.3 Natural history model parameters

Transition		Point Estimate (95% CI) [age range]		Reference
From	To	Unvaccinated cohort	Vaccinated cohort	
No lesion, HPV-negative	No lesion, HPV-positive	0.0382 (0.005-0.101) [24-29] 0.012 (0.001-0.031)[30-39] 0.009 (0.001-0.025)[40-44] 0.016 (0.002-0.042) [45-49] 0.022 (0-0.06) [55+]	0.0115 (0.0015-0.0303) [24-29] 0.0036 (0.0003-0.0009)[30-39] 0.0027 (0.0003-0.0075)[40-44] 0.0048 (0.0006-0.0126) [45-49] 0.0066 (0-0.018) [55+]	(229, 233, 234)
No lesion, HPV-positive	No lesion, HPV negative	0.126 (0.068-0.197)[all ages]	0.088 (0.048-0.138) [all ages]	(217)
	CIN 1	0.045 (0.013-0.092)[all ages]	0.018 (0.0052-0.0368)[all ages]	(217)
	CIN 2	0.0057 (0.0003-0.017) [25-34] 0.0145 (0.001-0.045)[35+]	0.0057 (0.0003-0.017) [25-34] 0.0145 (0.001-0.045)[35+]	(217)
CIN 1	No lesion, HPV-negative	0.325 (0.237-0.42) [all ages]	0.13 (0.095-0.168) [all ages]	(217)
	No lesion, HPV-positive	0.112 (0.058-0.181)[all ages]	0.034 (0.017-0.054)[all ages]	(217)
	CIN 2	0.1 (0.05-0.165) [all ages]	0.04 (0.02-0.066) [all ages]	(217)
CIN 2	No lesion, HPV-negative	0.12 (0.064-0.191) [all ages]	0.036 (0.019-0.057) [all ages]	(233)
	No lesion, HPV-positive	0.13 (0.073-0.202)[all ages]	0.039 (0.022-0.061) [all ages]	(233)
	CIN 1	0.15 (0.087-0.226) [all ages]	0.045 (0.026-0.068) [all ages]	(233)
	CIN 3	0.3 (0.215-0.391) [all ages]	0.090 (0.065-0.117) [all ages]	(233)
CIN 3	No lesion, HPV-negative	0.002 (0-0.015) [all ages]	0.001 (0-0.009) [all ages]	(217)
	No lesion, HPV-positive	0.05 (0.017-0.1) [all ages]	0.03 (0.01-0.06) [all ages]	(235)
	CIN 1	0.069 (0.029-0.126) [all ages]	0.041 (0.017-0.076) [all ages]	(235)
	CIN 2	0.069 (0.029-0.126) [all ages]	0.041 (0.017-0.076) [all ages]	(235)
	Cancer FIGO I	0.034 (0.008-0.077) [all ages]	0.02 (0.005-0.046) [all ages]	(233)
Cancer FIGO I	Cancer FIGO II	0.148 (0.03-0.33) [all ages]	No change	(217)
Cancer FIGO II	Cancer FIGO III	0.293 (0.09-0.55) [all ages]		(217)
Cancer FIGO III	Cancer FIGO IV	0.397 (0.16-0.67) [all ages]		(217)
Non symptomatic	Symptomatic			
Cancer FIGO I	Cancer FIGO I	0.09 (0.04-0.15) [all ages]	No change	(233)

Cancer FIGO II	Cancer FIGO II	0.14 (0.03-0.31) [all ages]		(233)
Cancer FIGO III	Cancer FIGO III	0.37 (0.16-0.67) [all ages]		(233)
Cancer FIGO IV	Cancer FIGO IV	0.56 (0.42-0.69) [all ages]		(233)

Key: CIN – cervical intraepithelial neoplasia; FIGO – Féderation International de Gynecologie et d'Obstetrique; HPV – human papillomavirus.

As the model follows a hypothetical cohort of women aged 25 years moving through different health states, the baseline rates in a number health states were required. It was assumed at the start of the model that women were only in one of nine states (no HPV infection, HPV infection, undetected CIN 1, undetected CIN 2, undetected CIN 3, undiagnosed cancer stage I, undiagnosed cancer stage II, undiagnosed cancer stage III and undiagnosed stage IV). These values were derived from the literature using observed Irish data, where available, and adjusted within plausible ranges when calibrating the model (Table 5.4). The effect of changes in the baseline rates was considered in the univariate sensitivity analysis where the baseline values were varied according to the confidence intervals specified in Table 5.4.

Table 5.4 Baseline model parameters

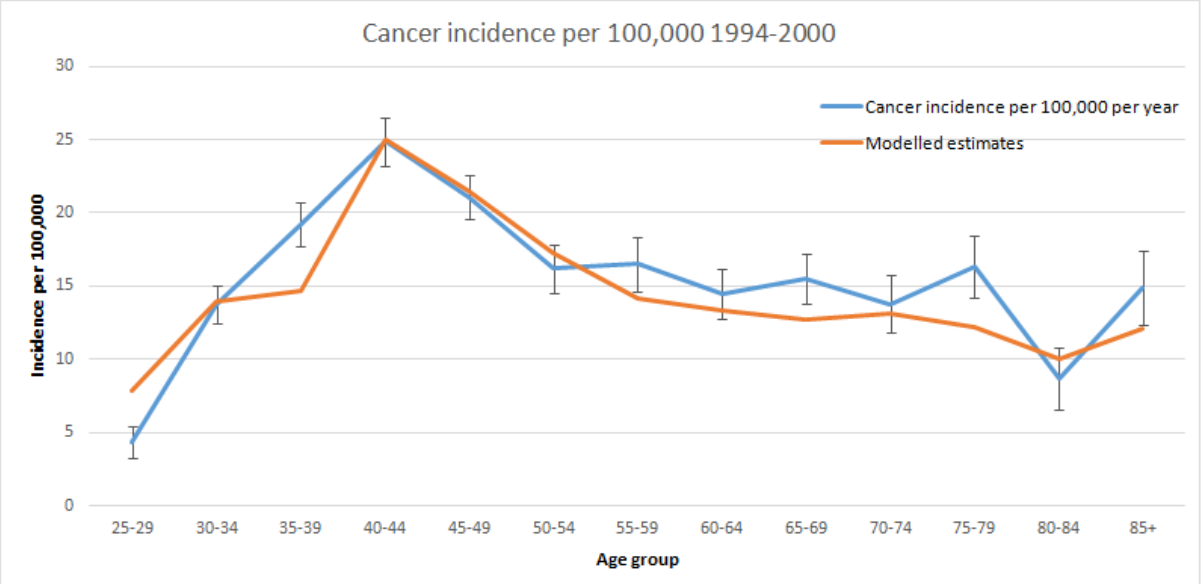
Start prevalence for women aged 25	Point estimate Unvaccinated cohort (95% CI)	Point estimate Vaccinated cohort (95% CI)	Reference
HPV infection	0.35 (0.279-0.36)	0.23 (0.184-0.238)	CERVIVA
Undetected CIN 1	0.03604 (0.018-0.079)	0.024 (0.012-0.052)	(236)
Undetected CIN 2	0.0103 (0.006-0.022)	0.007 (0.004-0.014)	(236)
Undetected CIN 3	0.0062 (0.004-0.026)	0.004 (0.003-0.017)	(236)
Undiagnosed FIGO stage I	0.0001 (0.00001-0.00012)	0.000066 (0.000008-0.000082)	NCRI
Undiagnosed FIGO stage II	0.000006 (0.0000007-0.000007)	0.000004 (0.0000005-0.0000046)	NCRI
Undiagnosed FIGO stage III	0.00002 (0.000003-0.000026)	0.000014 (0.000002-0.000017)	NCRI
Undiagnosed FIGO stage IV	0.000005 (0.000006-0.0000056)	0.000003 (0.0000004-0.000004)	NCRI

Key: CIN – cervical intraepithelial neoplasia; FIGO – Féderation International de Gynecologie et d'Obstetrique; HPV – human papillomavirus; NCRI – National Cancer Registry Ireland.

Figure 5.10 and Figure 5.11 show how the estimated values from the model compared with the observed incidence of cervical cancer and prevalence of HPV in Ireland in 1994-2000. This was before the introduction of organised screening; however when calibrating the model, this HTA assumed that on average 10% of the population were availing of opportunistic screening. Comparing the observed cancer incidence rates to those estimated from the model, and using the current female population numbers, the model underestimates the total numbers of cancer cases by 5% (14 cases) and the total HPV-infected cohort by 7% (11,000 women). However as is shown in Figures 5.10 and 5.11, the estimated prevalence of HPV for all age groups is within the confidence limits. For the incidence of cervical cancer, the most variation was seen between the observed and modelled values in the cohort of women under the age of 40 years, with an overestimate in the 25 to 29 year old group and an underestimate in the 35 to 39 year old group. The model also appears

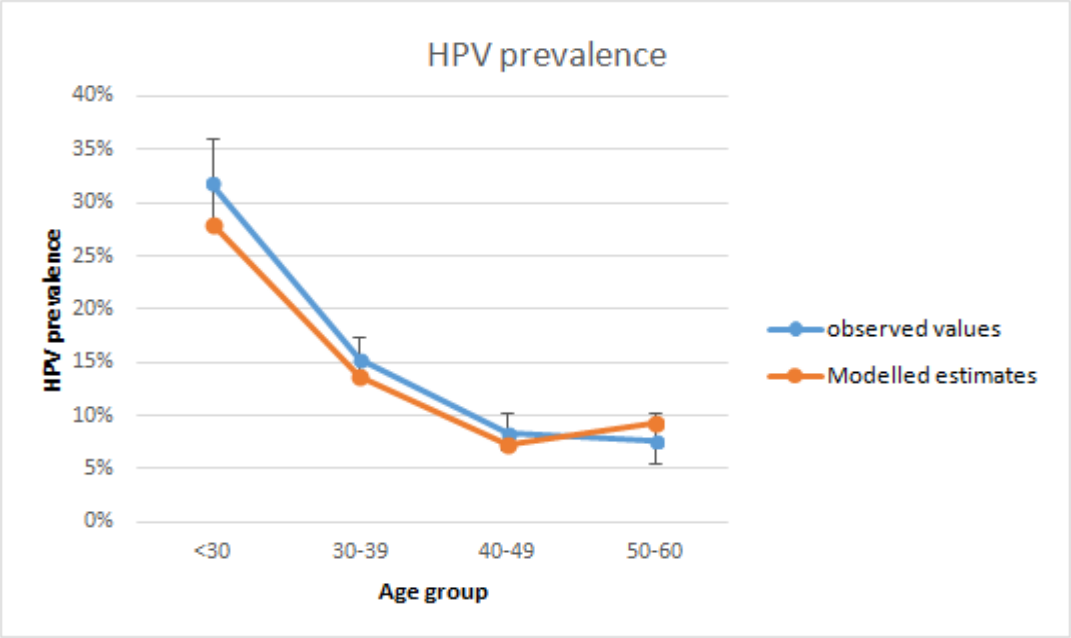
to underestimate incidence of cervical cancer in women aged over 55. Figure 5.12 and Figure 5.13 show the fit for the vaccinated cohort. For the incidence of cervical cancer, the model was calibrated to estimate a drop of 70% in the observed incidence of cervical cancer and a drop of approximately a third in the prevalence of HPV compared with an unvaccinated cohort.

Figure 5.10 Comparison of modeled estimates and observed cancer incidence for an unvaccinated cohort



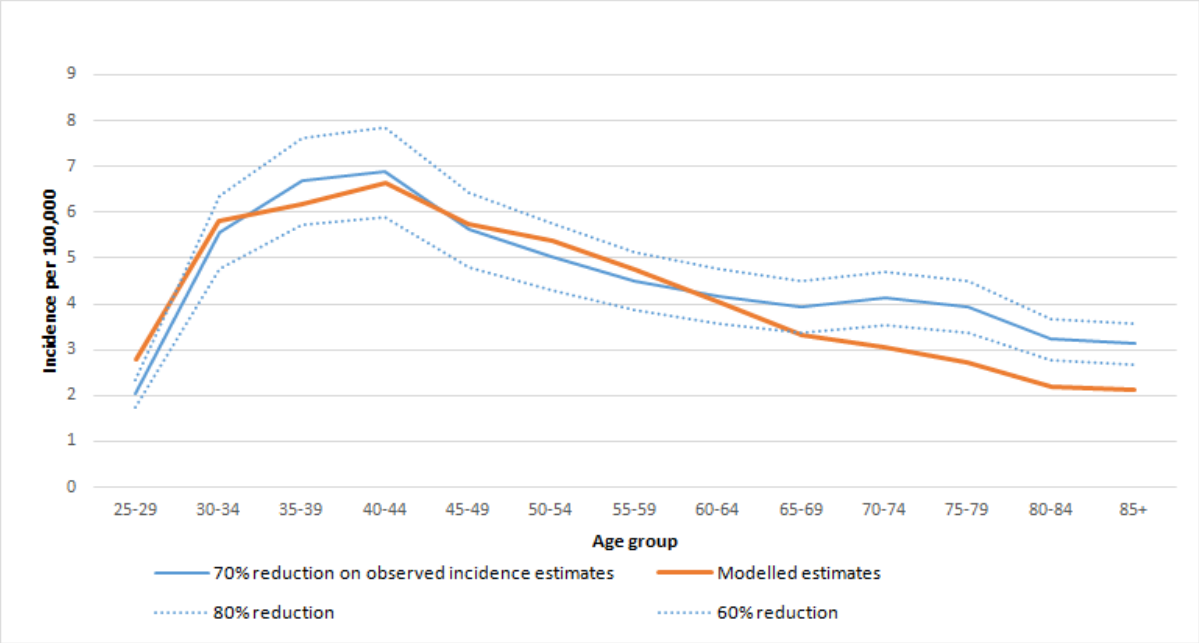
* Incidence data (1994-2000) courtesy of the NCRI.

Figure 5.11 Comparison of modeled estimates and observed HPV incidence for an unvaccinated cohort



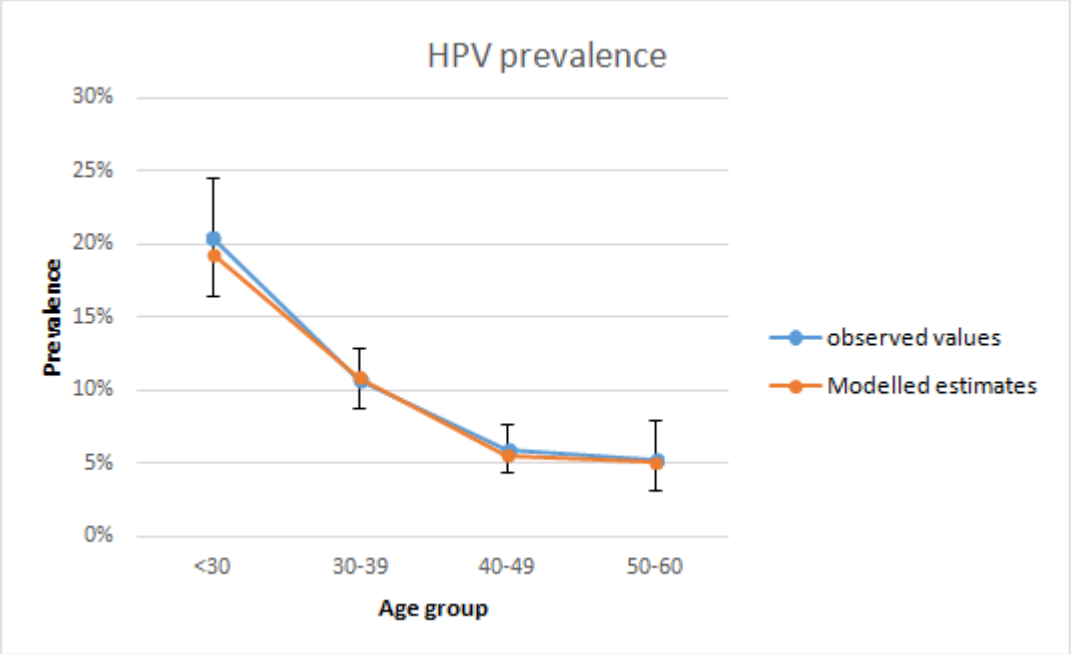
* HPV prevalence based on preliminary data from the CERVIVA collaboration in combination with CervicalCheck. Data for those aged <30 years comprise those aged 23 to 29.

Figure 5.12 Comparison of modeled estimates and an estimated 70% reduction in cancer incidence for a vaccinated cohort



* Incidence data (1994-2000) courtesy of the NCRI.

Figure 5.13 Comparison of modeled estimates and observed prevalence of HPV excluding HPV 16 and HPV 18, for a vaccinated cohort



* HPV prevalence based on a 30% reduction on the preliminary data from the CERVIVA collaboration in combination with CervicalCheck. Data for those aged <30 years comprise those aged 23 to 29.

Women with abnormal pathology who are referred for colposcopy have a higher risk of developing cervical abnormalities again following discharge from colposcopy. To account for this increased risk, the observed prevalence of HPV by age group from women discharged from colposcopy (which was higher than that predicted by the model) was used as the prevalence of HPV for the first year after discharge from colposcopy. These were then included as a subgroup within the calibration model with the prevalence of HPV following discharge from colposcopy, dependent on age, where transitions beyond the first year were the same as in the entire population. As these were then built into the calibration model, any change to the transitions probabilities when investigating the fit automatically adjusted the transition probabilities following discharge from colposcopy. Once the model was calibrated, these were then extracted.

Mortality was modelled based on both mortality from cervical cancer and mortality from all other causes. Cervical cancer mortality by stage at diagnosis was based on the survival data reported by the NCRI for the 2008-2012 cohort of cervical cancer patients (Table 5.5). These were converted into annual mortality rates and applied in each annual cycle of the model. Due to the small number of deaths from cervical cancer in a number of age groups beyond the first year, the data were not robust enough to reliably estimate age-specific mortality rates by cancer stage beyond the first year. For all other causes of mortality, data were taken from the Irish life tables.

All-cause mortality was assumed to be comparable to mortality from all causes other than cervical cancer. Age-specific hysterectomy rates for women without cervical cancer were based on 2014 rates from HIPE.

Table 5.5 One-year cervical cancer mortality by age and stage at diagnosis, and overall cervical cancer mortality at years two to five

	25-44	45-55	55-65	65-74	75+
FIGO I (1 year mortality)	0.006	0.016	0.011	0.011	0.011
FIGO II (1 year mortality)	0.017	0.045	0.070	0.115	0.115
FIGO III (1 year mortality)	0.106	0.139	0.222	0.309	0.254
FIGO IV (1 year mortality)	0.448	0.538	0.345	0.618	0.793
Overall					
2 year mortality	0.045	0.062	0.092	0.173	0.188
3 year mortality	0.093	0.169	0.185	0.313	0.427
4 year mortality	0.064	0.100	0.160	0.210	0.266
5 year mortality	0.101	0.190	0.219	0.366	0.427

Source: National Cancer Registry Ireland data.

Data from the clinical effectiveness review in Chapter 4 were used to define the diagnostic test accuracy of the different strategies. A summary of the parameters used in the model is provided in Table 5.6. As colposcopy plus biopsy when indicated is the 'gold standard diagnostic test, it was assumed that all women referred to colposcopy would be correctly diagnosed. It was also assumed that all women referred to colposcopy would attend and consent to treatment if required. The age-specific uptake rates for screening were based on the observed rates seen in CervicalCheck - Ireland's National Cervical Screening Programme (Table 5.7). A linear regression line was fitted to this data, which was used to provide estimated uptake rates in the model. It was assumed that uptake rates in HPV vaccinated women would be similar to those seen in the current unvaccinated population.

Table 5.6 Diagnostic test accuracies

	Test Accuracy	
Primary test		
LBC	Sensitivity CIN 2	80.37% (95% CI 45.4%- 96.08%)
	Sensitivity CIN 3 +	84.99% (95% CI 51.85%-97.39%)
	Specificity CIN 2+	92.87% (95% CI 83.83%- 96.99%)
HPV	Sensitivity CIN 2	92.83% (95% CI 86.60%-96.82%)
	Sensitivity CIN 3 +	98.17% (95% CI 96.44%-99.41%)
	Specificity CIN 2+	88.19% (95% CI 82.89%-91.90%)
Triage test		
LBC	Sensitivity CIN 2	91.2% (95% CI 82.69%- 97.03%)
	Sensitivity CIN3 +	93.2% (95% CI 85.96%-97.94%)
	Specificity CIN 2+	68.5% (95% CI 61.13%- 75.43%)
HPV	Sensitivity CIN 2	90.4% (95% CI 88.15%-92.45%)
	Sensitivity CIN 3 +	93.70% (95% CI 90.48%-96.37%)
	Specificity CIN 2+	58.3% (95% CI 53.45%-62.76%)
HPV 16/18	Sensitivity CIN 2	60.4% (95% CI 34.17%- 84.01%)
	Sensitivity CIN 3 +	82.0% (95% CI 60.72%-96.22%)
	Specificity CIN 2+	55.20% (95% CI 30.16%- 78.84%)
$p16^{INK4a}$/Ki-67	Sensitivity CIN 2	61.29% (95% CI 34.70%-84.63%)
	Sensitivity CIN 3 +	74.90% (95% CI 52.78%-91.67%)
	Specificity CIN 2+	75.60% (95% CI 47.17%-95.03%)

Key: CI – confidence interval; CIN – cervical intraepithelial neoplasia; HPV – human papillomavirus; LBC – liquid-based cytology.

Table 5.7 Age-specific screening uptake rates

Age	Uptake rate
25-29	80.4% (95% CI 76.5%-84.3%)
30-34	78.6% (95% CI 74.0%-83.1%)
35-39	76.8% (95% CI 71.5%-82.1%)
40-44	75.0% (95% CI 69.0%-81.0%)
45-49	73.2% (95% CI 66.4%-79.9%)
50-54	71.4% (95% CI 63.9%-78.8%)
55-59	69.6% (95% CI 61.4%-77.6%)
60-64	67.8% (95% CI 58.9%-76.7%)

Source: Observed CervicalCheck screening uptake rates.

5.3.3 Health-related quality of life (HRQoL)

HRQoL was expressed as utility values and used to compute quality-adjusted life years (QALYs). QALYs can range from zero (death) to one (perfect health). QALYs were estimated for healthy individuals; women under surveillance for CIN 1, in treatment for CIN 2, CIN 3 and cervical cancer (by FIGO stage); and for survivors of

cervical cancer. QALYs by single year of age for a healthy population were derived from the Health Survey for England data.[237] According to these data, QALYs for women decline from 0.9448 at age 25 to 0.6142 at age 100. It was assumed that these data were applicable to the Irish population.

Disutilities for women under surveillance for CIN 1 and in treatment for CIN 2 and CIN 3 were applied for six weeks; this was assumed to be the average length of time women could experience both treatment and post treatment complications. Disutilities for women in treatment for cervical cancer were applied for one year (Table 5.8). Disutilites for survivors of cervical cancer were applied for five years. No disutilities were assumed for attendance at screening or colposcopy; although there may be a disutility associated with these events, in the context of an organised screening programme with documented adherence to timely notification of results and further referrals where appropriate, they were considered to be minor and short lived. For these reasons, there was also no disutility applied to those women with false positive results. No disutility was applied to false negatives under the assumption that if disease was sufficiently advanced to cause disutility, then it would be detected as a consequence of medical examination. All HRQoL parameters were defined using beta distributions with the alpha and beta parameters selected to reflect the reported mean QALY and disutilities were applied using a multiplicative model.

Table 5.8 Disutilities associated with surveillance and treatment for CIN and cervical cancer

	Point estimate	(95% CI)	Reference
Surveillance for CIN 1	0.91	(0.88-0.93)	(238)
Treatment for CIN 2	0.87	(0.84-0.89)	(238)
Treatment for CIN 3	0.87	(0.84-0.89)	(238)
Treatment for FIGO stage 1	0.76	(0.58-0.90)	(238)
Treatment for FIGO stage 2	0.67	(0.50-0.81)	(238)
Treatment for FIGO stage 3	0.67	(0.50-0.81)	(238)
Treatment for FIGO stage 4	0.48	(0.36-0.60)	(238)
Cervical Cancer survivor	0.84	(0.65-0.96)	(239)

Key: CI – confidence interval; CIN – cervical intraepithelial neoplasia;. FIGO – Féderation International de Gynecologie et d'Obstetrique.

5.3.4 Estimates of cost

Costs were associated with delivery of the screening programme, treatments costs, and follow-up costs. The costs of screening (diagnosis, analysis and communication) and costs for CIN 1, CIN 2 and CIN 3 associated with colposcopy, histology, treatment

within the colposcopy clinic, and communication with patients were provided by CervicalCheck - Ireland's National Cervical Screening Programme.[55]

For FIGO Stage I to Stage IV disease, the time and resources required for diagnosis and treatment planning were provided by expert opinion from senior clinicians identified by the National Cancer Control Programme (NCCP) as being routinely involved in the diagnosis and management of cervical cancer in Ireland. Treatment pathways were informed by the American Society of Clinical Oncology(ASCO) guidelines (2016)[123] and endorsed or modified as appropriate to current standard of care in Ireland as identified by the NCCP nominated experts. Follow-up requirements after successful treatment were informed by the current standard of care in Ireland as described by the NCCP nominated experts. Rare complications associated with treatment were informed by the SIGN guidelines.[240]

Costs associated with treatment were mainly obtained from the Healthcare Pricing Office (HPO) for 2014. Additional costs were identified from previous HTAs and, where relevant, were updated by applying the consumer price index for health to reflect inflation. Palliative care costs were included based on a recent study in Ireland which determined these costs for the last year of life.[241] All costs were varied by ±20% to reflect uncertainty in the point estimates. The cost parameters are outlined in Table 5.9. Full details of the costs used are provided in Appendix 5.

Table 5.9 Cost parameters – average per-person cost of care

Parameter	Cost per patient
Primary screen – LBC	Disaggregated costs are not included due to the commercial sensitivity of the screening test costs.
Primary screen – HPV	
Triage test – LBC	
Triage test – HPV	
Triage test – partial genotyping HPV 16/18	
Triage test – p16^{INK4a}/Ki-67	
No CIN	€322.23
CIN 1 detection and surveillance	€350.51
CIN 2 /3 detection and treatment	€469.32
FIGO stage I	€20,870.45
FIGO stage II	€40,907.38
FIGO stage III	€63,155.30
FIGO stage IV	€41,879.90
Palliative care, last year of life	€38,112.84

Abbreviations: CIN - Cervical intraepithelial neoplasia; HPV – human papillomavirus; LBC – liquid-based cytology.

5.4 Results of the economic analysis

The model was run separately for a vaccinated and unvaccinated population. The screening strategies as outlined in Section 5.2.6.1 were modelled for both populations. The results of the comparison of each of the proposed screening strategies compared with current practice (base case) are provided separately for effectiveness outcomes (life years gained, diagnosed cases of cervical cancer, cervical cancer mortality) and utility outcomes (quality-adjusted life years gained). Each strategy was evaluated over 10,000 model simulations during which all of the main parameters were varied.

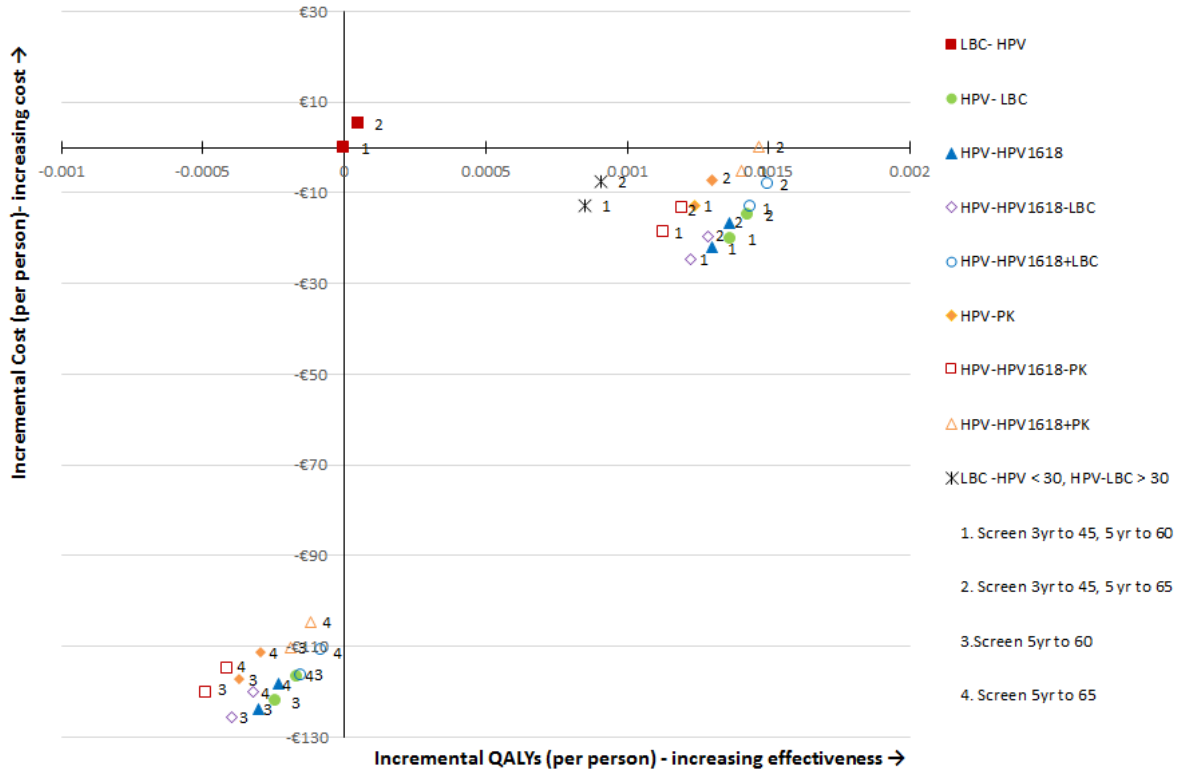
The cost-effectiveness plane is also presented for both unvaccinated and vaccinated cohorts. In the cost-effectiveness plane, strategies are plotted according to their incremental benefit on the horizontal axis (in QALYs) and incremental cost (on the vertical axis) relative to a common comparator, in this case the current practice. If an intervention is less costly and more effective than a comparator, then it is considered to dominate the comparator and would be the preferred option. A strategy that is more costly and less effective than the comparator is said to be dominated and would not be considered a cost-effective strategy. The cost-effectiveness frontier identifies the strategies that are considered to be cost-effective at different values of the cost-effectiveness threshold. Strategies not lying on the frontier are not cost-effective at any value of the cost-effectiveness threshold.

Cost-effectiveness acceptability curves (CEACs) are also presented. These plots show the probability that a strategy is cost-effective for a given willingness-to-pay threshold. The willingness-to-pay threshold represents the amount society may be willing to pay for a benefit, in this case QALYs. For a given threshold, the CEAC indicates which strategy has the highest probability of delivering the greatest net benefit.

5.4.1 Unvaccinated cohort

Figure 5.14 shows where each comparator lies on the cost-effectiveness plane when outcomes are measured in quality-adjusted life years gained (QALYs) and current practice is used as the base case. Current practice of LBC followed by HPV testing has higher costs and fewer QALYs gained compared with a number of other strategies and is therefore dominated. Two strategies are more effective, but more costly: the current strategy where the screening age is extended to 65 years and HPV testing followed by triage comprising co-testing with partial genotyping and $p16^{INK4a}$/Ki-67 with screening extended to age 65.

Figure 5.14 Cost-effectiveness plane (QALYs) for unvaccinated cohort, with current practice as base case



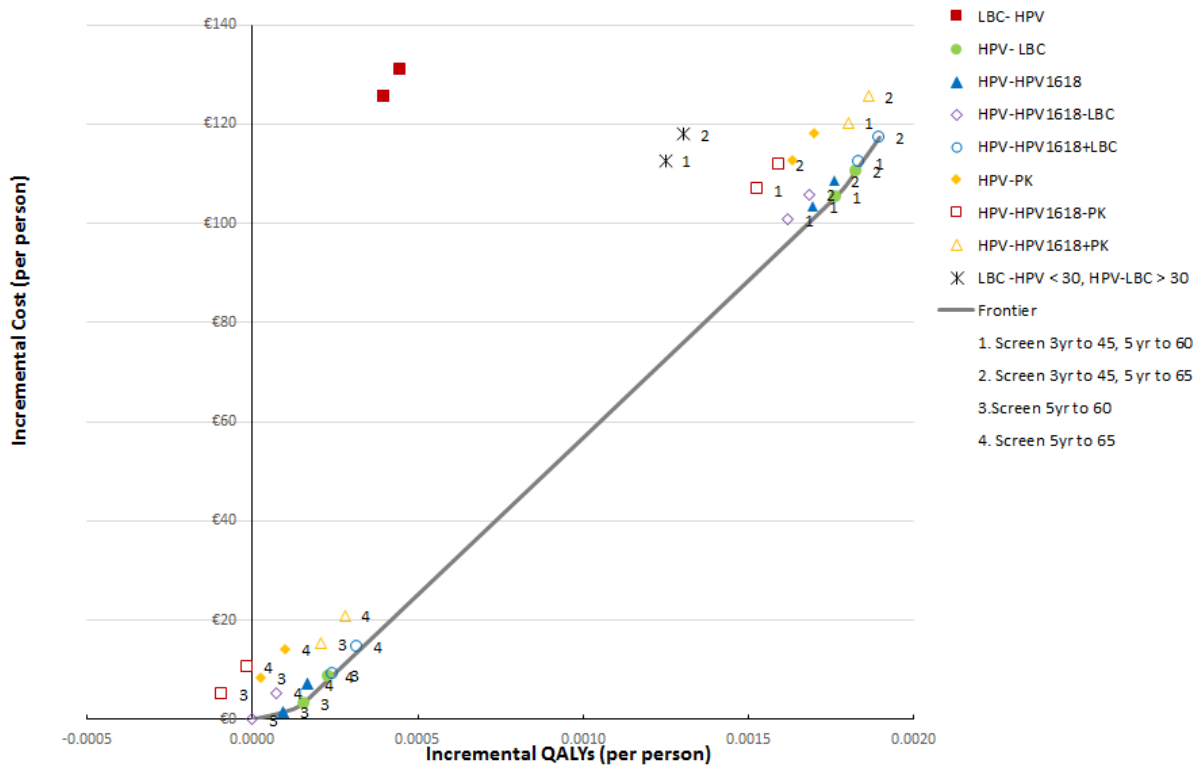
Key: LBC-HPV denotes LBC primary testing followed by HPV triage; HPV-LBC denotes HPV primary testing followed by LBC triage; HPV-1618 denote HPV primary testing followed by partial genotyping of HPV 16 and HVP18; HPV-PK denotes HPV primary testing followed by p16INK4a/Ki-67 triage; HPV-1618-LBC denotes HPV primary testing followed by triage testing with partial genotyping of HPV 16 and HVP18 and if positive a further triage test of LBC; HPV-1618+LBC denotes HPV primary testing followed by triage testing with a co-test of partial genotyping of HPV 16 and HVP18 and LBC; ; HPV-1618-PK denotes HPV primary testing followed by triage testing with partial genotyping of HPV 16 and HVP18 and if positive a further triage test of p16INK4a/Ki-67; HPV-1618+PK denotes HPV primary testing followed by triage testing with a co-test of partial genotyping of HPV 16 and HPV 18 and p16INK4a/Ki-67; LBC-HPV<30, HPV-LBC≥30 denotes primary HPV testing with LBC triage for women under 30 and primary LBC testing with HPV triage testing for women aged r 30 and over.

With current practice dominated by almost all alternative strategies, to aid in presentation the graph has been re-presented with the least costly option as the base case. Figure 5.15 therefore shows where each comparator lies on the cost-effectiveness plane when the least costly option, primary HPV screening followed by sequential triage with partial genotyping and LBC at five-yearly intervals from age 25 to 60, is used as the base case.

It is clear from Figure 5.15 that the difference in QALYs between the current strategy and the HPV-based primary screening strategies, where screening is offered five-yearly throughout, is minimal ranging from 0.0005 to 0.0001. There is also considerable overlap in the confidence intervals for the effectiveness of these strategies and current practice. Given the uncertainty in the estimates and the

minimal difference in the point estimates, these strategies can be considered to have comparable effectiveness.

Figure 5.15 Cost-effectiveness plane (QALYs) for unvaccinated cohort, with least costly option (HPV followed by sequential triage with partial genotyping and LBC, five yearly from 25 to 60) as the base case



Key: LBC-HPV denotes LBC primary testing followed by HPV triage; HPV-LBC denotes HPV primary testing followed by LBC triage; HPV-1618 denote HPV primary testing followed by partial genotyping of HPV 16 and HVP18; HPV-PK denotes HPV primary testing followed by p16INK4a/Ki-67 triage; HPV-1618-LBC denotes HPV primary testing followed by triage testing with partial genotyping of HPV 16 and HVP18 and if positive a further triage test of LBC; HPV-1618+LBC denotes HPV primary testing followed by triage testing with a co-test of partial genotyping of HPV 16 and HVP18 and LBC; ; HPV-1618-PK denotes HPV primary testing followed by triage testing with partial genotyping of HPV 16 and HVP18 and if positive a further triage test of p16INK4a/Ki-67; HPV-1618+PK denotes HPV primary testing followed by triage testing with a co-test of partial genotyping of HPV 16 and HPV 18 and p16INK4a/Ki-67; LBC-HPV<30, HPV-LBC≥30 denotes primary HPV testing with LBC triage for women under 30 and primary LBC testing with HPV triage testing for women aged 30 and over.

Table 5.10 shows the incremental cost-effectiveness ratios (ICERs) per QALY for each comparator relative to the next best option for an unvaccinated cohort. Strategies are rank ordered in terms of effectiveness (QALYs) and then dominated strategies are excluded. This indicates that primary HPV testing followed by LBC triage testing at five-yearly intervals to age 60 years, which has an ICER of €29,788 per QALY, is cost-effective given willingness-to-pay thresholds in the range of €20,000 to €45,000 per QALY.

Table 5.10 Estimated incremental cost-effectiveness ratios (Euro per QALY) for an unvaccinated cohort

Strategy	Cost (€)	Incremental Cost (€)	Effectiveness (QALYs)	Incremental Effectiveness (QALYs)	ICER (€/ QALYs)
Base case (HPV-HPV1618-LBC screen 5yr to 60)	321		17.37007		
HPV-HPV1618 screen 5yr to 60	323	1	17.37017	0.0001	15,868
HPV- LBC screen 5yr to 60	325	2	17.37023	0.0001	29,788
HPV-HPV1618+LBC screen 5yr to 60	330	6	17.37032	0.0001	63,253
HPV- LBC screen 3yr to 45, 5yr to 60	427	96	17.37184	0.0015	63,391
HPV- LBC screen 3yr to 45, 5yr to 65	432	5	17.37190	0.0001	86,656
HPV-HPV1618+LBC screen 3yr to 45, 5yr to 65	439	7	17.37197	0.0001	94,273

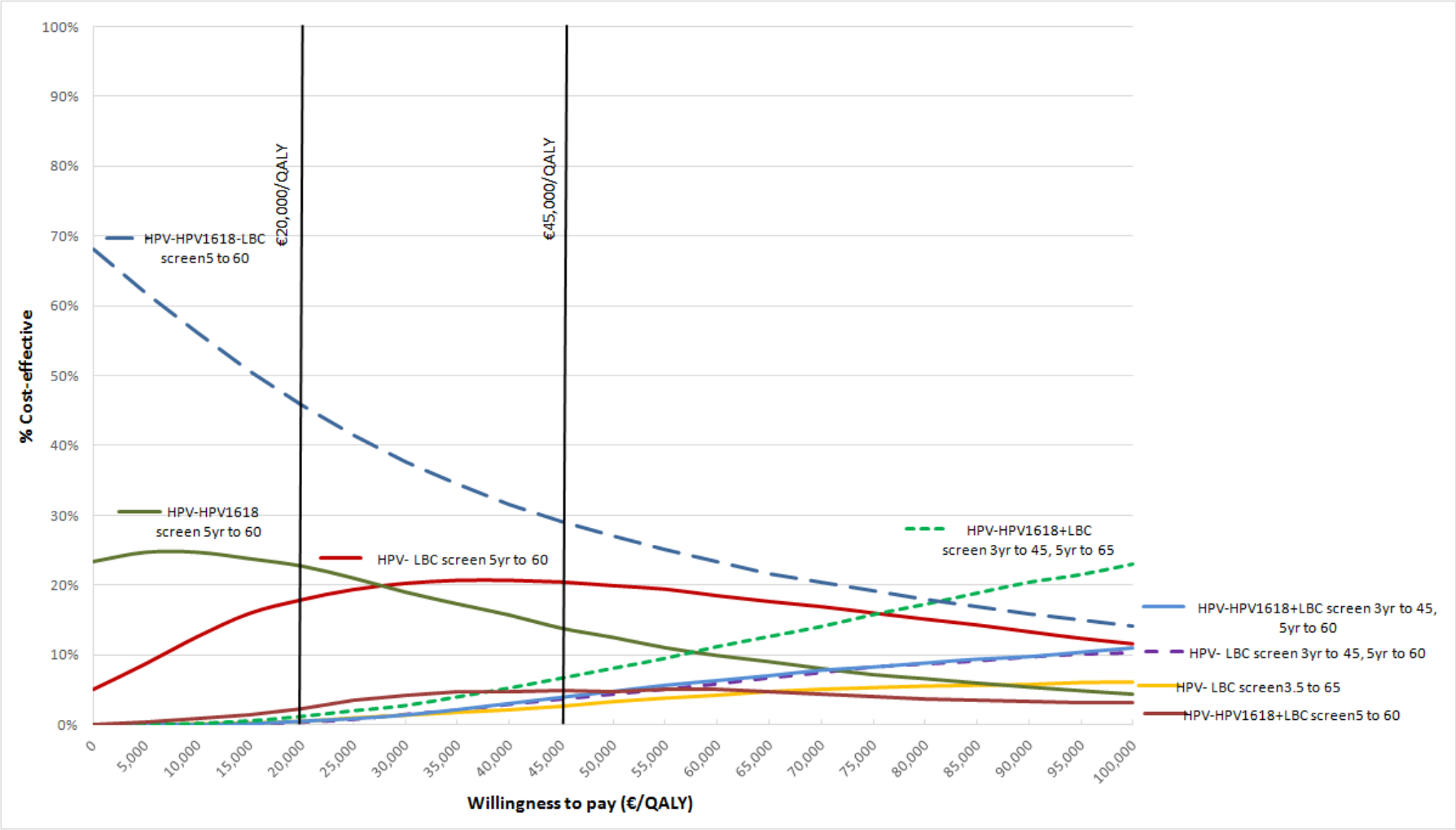
Abbreviations: QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio.
Note all values are discounted.

The degree of uncertainty about the ICER for each intervention can be visualised using cost-effectiveness acceptability curves (CEAC). These show the probability that any of the screening strategies is cost-effective for a given willingness-to-pay threshold (Figure 5.16). To aid in presentation, strategies that had a less than 5% probability of being cost-effective at all thresholds were excluded. At a threshold of €20,000 per QALY, HPV followed by sequential triage with partial genotyping (and if positive LBC every five years to age 60 years) is cost-effective in 46% of simulations. HPV followed by partial genotyping every five years to age 60 years is cost-effective in 23% of simulations, and HPV followed by LBC triage every five years to 60 is cost-effective in 18% of simulations. At a threshold of €45,000 per QALY, HPV followed by sequential triage with partial genotyping (and if positive LBC every five years to age 60 years) is cost-effective in 29% of simulations. HPV followed by LBC triage every five years to 60 is cost-effective in 20% of simulations, and HPV followed by partial genotyping every five years to age 60 years is cost-effective in 14% of simulations.

It is clear from the CEAC that between the willingness-to-pay thresholds of €20,000 per QALY to €45,000 per QALY there is large uncertainty as to which is the cost-effective strategy. Primary HPV screening followed by sequential triage with partial genotyping and, if positive LBC, every five years to age 60 years, has the highest probability of being the most cost-effective strategy at a threshold of €45,000 per

QALY. This differs to the analysis presented in Table 5.10, which is based on the ICER. Although we would typically expect these to agree, in situations where the data are particularly skewed and there are high correlations between interventions compared, as is the case in this analysis, these methods have been shown to disagree.[242] As the CEAC is designed to aid in visualising the uncertainty rather than be used as a decision rule,[242] it is results based on the ICERs which have been used to determine cost-effectiveness.

Figure 5.16 Cost-effectiveness acceptability curve (QALY), unvaccinated cohort



In this analysis, the expected value of perfect information was calculated over the lifetime of an unvaccinated population assuming a steady state of vaccination had been reached at the target rate of 80%, and where a cohort of 20% of the population would remain unvaccinated. At a willingness-to-pay threshold of €45,000 per QALY, the expected value of perfect information is €5.1 million. This rises to a peak of €10 million at a willingness-to-pay threshold of €65,000 per QALY (Figure 5.17). This corresponds with the CEAC, where at a willingness–to-pay threshold of €65,000, the probability that HPV followed by LBC triage at five-yearly intervals from 25 years to 60 years is cost-effective begins to decline and there are a number of other strategies which could be considered cost-effective.

Figure 5.17 Expected value of perfect information (QALY) for an unvaccinated cohort

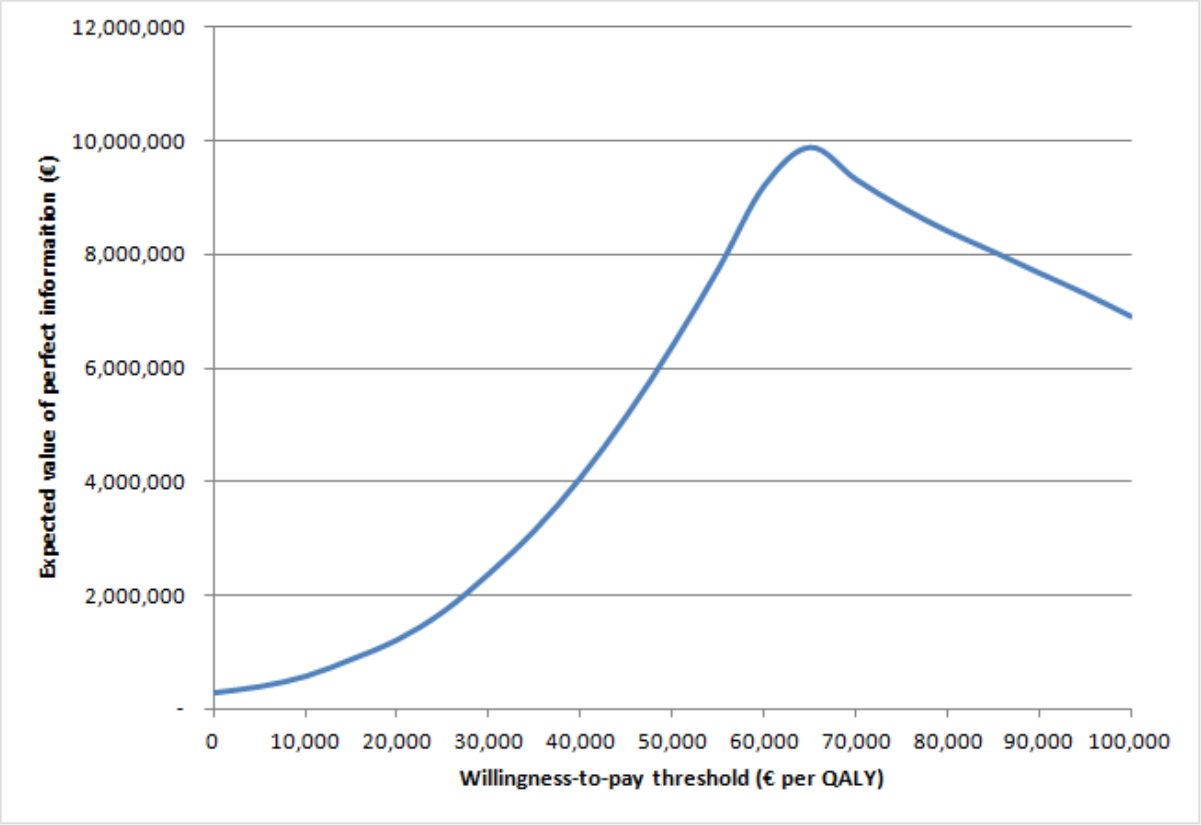


Table 5.11 shows the results for each of the modelled strategies. It presents the average costs and clinical benefits per woman and per 100,000 population for a cohort modelled from age 25 years to end of life. The lowest mortality was for a strategy of primary HPV testing followed by co-testing with HPV 16 and HPV 18 partial genotyping and LBC triage for women with screening at three-yearly interval up to the age of 45 years , and five-yearly to age 65 years. For all strategies, extending the screening age to 65 years leads to a decrease in both the number of

cervical cancer cases and cervical cancer deaths prevented. However, as these benefits occur far into the future, the effect of discounting means that the number of QALYs gained by extending the screening age to 65 is small. In some instances, strategies result in fewer QALYs than other comparator strategies despite generating lower overall mortality. This apparent anomaly is due to the combination of when mortality occurs in each strategy and the effect of discounting.

The number of screens presented in Table 5.11, reflect the average number of lifetime screens for a woman in each of the strategies. They take into account the uptake rate (based on current CervicalCheck uptake rates) as well as any additional screens required due to early recall following either a positive HPV test or surveillance following discharge from colposcopy. The number of colposcopy referrals presented in Table 5.11, reflect the number of new referrals to colposcopy arising from screening over a woman's lifetime. These modelled estimates should not be considered as being indicative of total CervicalCheck coloposcopy activity (which include clinical referrals from symptomatic services) such as that described in Chapter 3). Rather, these modelled estimates provide a useful basis for comparing between the strategies. Compared with current practice, a strategy of primary HPV screening at five-yearly intervals to age 60 years would result in fewer referrals to colposcopy over the lifetime of the cohort (9,484 versus 12,459 per 100,000 population).

Extending the screening age to 65 years leads to an increase of 0.6 lifetime screens on average per woman. Changing to a five-yearly screening strategy for all ages results in an average reduction of two screens per lifetime. Compared with using liquid-based cytology (LBC) as a primary screening test, HPV-based primary screening strategies result in a marginal increase in the average number of lifetime screens. This increase is primarily driven by the recall at one year of women who are HPV-positive, but have a negative triage test.

Table 5.11 Results for the unvaccinated cohort, ordered by decreasing intensity of screening within strategy

Strategy	Per 100,000					
	Cost (€)	QALYs	Average number of lifetime screens	Cervical cancer cases	Cervical cancer deaths	Colposcopy referrals
LBC- HPV screen 3yr to 45, 5yr to 65	452	17.3705	8.6	375	97	13,161
LBC- HPV screen 3yr to 45, 5yr to 60	**447**	**17.3705**	**8.0**	**404**	**110**	**12,459**
HPV- LBC screen 3yr to 45, 5yr to 65	432	17.3719	8.7	313	83	12,670
HPV- LBC screen 3yr to 45, 5yr to 60	427	17.3718	8.1	346	97	11,966
HPV- LBC screen 5yr to 65	330	17.3703	6.5	397	99	10,193
HPV- LBC screen 5yr to 60	325	17.3702	5.9	432	114	9,484
HPV-HPV1618 screen 3yr to 45, 5yr to 65	430	17.3718	8.7	317	85	13,855
HPV-HPV1618 screen 3yr to 45,5yr to 60	425	17.3718	8.1	350	99	13,102
HPV-HPV1618 screen 5yr to 65	328	17.3702	6.5	401	102	11,081
HPV-HPV1618 screen 5yr to 60	323	17.3702	5.9	435	116	10,371
HPV-HPV1618-LBC screen 3yr to 45,5yr to 65	427	17.3718	8.7	326	88	9,918
HPV-HPV1618-LBC screen 3yr to 45, 5yr to 60	422	17.3717	8.2	359	102	9,358
HPV-HPV1618-LBC screen 5yr to 65	327	17.3701	6.5	410	105	8,076
HPV-HPV1618-LBC screen 5yr to 60	321	17.3701	5.9	445	119	7,508
HPV-HPV1618+LBC screen 3yr to 45, 5yr to 65	439	17.3720	8.7	304	81	16,486
HPV-HPV1618+LBC screen 3yr to 45, 5yr to 60	434	17.3719	8.1	337	95	15,597
HPV-HPV1618+LBC screen 5yr to 65	336	17.3704	6.5	387	96	13,160
HPV-HPV1618+LBC screen 5yr to 60	330	17.3703	5.9	422	111	12,257
HPV-PK screen 3yr to 45, 5yr to 65	439	17.3718	8.7	323	87	11,461

HPV-PK screen 3yr to 45, 5yr to 60	434	17.3717	8.2	356	101	10,825
HPV-PK screen 5yr to 65	335	17.3702	6.5	407	104	9,249
HPV-PK screen 5yr to 60	330	17.3701	5.9	442	119	8,604
HPV-HPV1618-PK screen 3yr to 45, 5yr to 65	433	17.3717	8.8	333	91	9,352
HPV-HPV1618-PK screen 3yr to 45,5yr to 60	428	17.3716	8.2	366	105	8,823
HPV-HPV1618-PK screen 5yr to 65	332	17.3701	6.5	418	109	7,627
HPV-HPV1618-PK screen 5yr to 60	326	17.3700	5.9	452	123	7,090
HPV-HPV1618+PK screen 3yr to 45, 5yr to 65	447	17.3719	8.7	307	81	15,866
HPV-HPV1618+PK screen 3yr to 45,5yr to 60	442	17.3719	8.1	340	96	15,009
HPV-HPV1618+PK screen 5yr to 65	342	17.3704	6.5	391	97	12,669
HPV-HPV1618+PK screen 5yr to 60	337	17.3703	5.9	425	112	11,799
LBC -HPV < 30, HPV-LBC ≥ 30 screen 3yr to 45,5yr to 65	439	17.3714	8.7	326	84	13,544
LBC -HPV < 30, HPV-LBC ≥ 30 screen 3yr to 45,5yr to 60	434	17.3713	8.1	365	100	12,800

Abbreviations: QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio.
Cost and QALYs are discounted, whereas cancer cases and cases deaths are undiscounted.
Note the average lifetime number of screens is adjusted for uptake rate, includes any additional screens due to increased surveillance, following either a positive HPV primary test and negative triage test, or discharge from colposcopy clinic.
Key: LBC-HPV denotes LBC primary testing followed by HPV triage; HPV-LBC denotes HPV primary testing followed by LBC triage; HPV-1618 denote HPV primary testing followed by partial genotyping of HPV 16 and HVP18; HPV-PK denotes HPV primary testing followed by p16INK4a/Ki-67 triage; HPV-1618-LBC denotes HPV primary testing followed by triage testing with partial genotyping of HPV 16 and HVP18 and if positive a further triage test of LBC; HPV-1618+LBC denotes HPV primary testing followed by triage testing with a co-test of partial genotyping of HPV 16 and HVP18 and LBC; ; HPV-1618-PK denotes HPV primary testing followed by triage testing with partial genotyping of HPV 16 and HVP18 and if positive a further triage test of p16INK4a/Ki-67; HPV-1618+PK denotes HPV primary testing followed by triage testing with a co-test of partial genotyping of HPV 16 and HPV 18 and p16INK4a/Ki-67; LBC-HPV<30, HPV-LBC≥30 denotes primary HPV testing with LBC triage for women under 30 and primary LBC testing with HPV triage testing for women aged 30 and over.

Table 5.12 shows the incremental cost-effectiveness ratios (ICERs) per life year gained (LYG) for each comparator relative to the next best option for an unvaccinated cohort. Dominated strategies are excluded. The results are broadly consistent with the findings of the analysis based on quality-adjusted life years.

Table 5.12 Estimated incremental cost-effectiveness ratios (€/LYG) for an unvaccinated cohort

Strategy	Cost (€)	Incremental Cost (€)	Effectiveness (LYG)	Incremental Effectiveness (LYG)	ICER (€/LYG)
Base case (HPV-HPV1618-LBC screen 5yr to 60)	321		19.3246		
HPV- LBC screen 5yr to 60	325	3	19.3248	0.0002	16, 607
HPV-HPV1618+LBC screen 5yr to 60	330	6	19.3249	0.0001	58,529
HPV-HPV1618+LBC screen 5yr to 65	336	5	19.3249	0.0001	63,768
HPV-HPV1618+LBC screen 3yr to 45, 5yr to 65	439	103	19.3259	0.0010	107,376

Abbreviations: LYG, life year gained; ICER, incremental cost-effectiveness ratio.
Note all values are discounted.

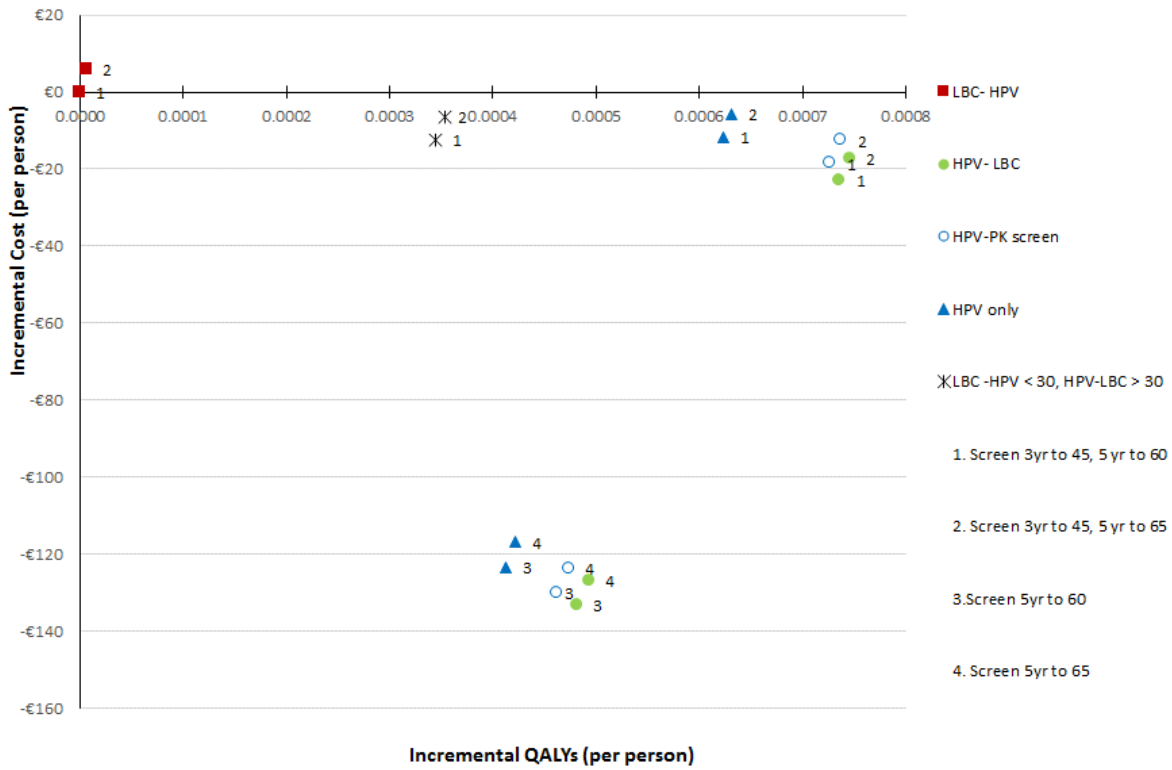
5.4.2 Vaccinated cohort

Figure 5.18 shows where each comparator lies on the cost-effectiveness plane when outcomes are measured in quality-adjusted life years gained (QALYs) and current practice is used as the base case. Current practice of LBC followed by HPV testing is dominated (has higher costs and fewer QALY gains) by all strategies with the exception of extending the screening age for the current screening practice to age 65 years.

We have assumed that vaccination for HPV 16 and 18 is 100% effective. However, it was still considered to be a reasonable triage test to include for a vaccinated cohort, as it would simplify implementation in CervicalCheck if the same test strategy is used across the entire population. Furthermore, the inclusion of partial genotyping for vaccinated women would provide useful information in monitoring the long-term effectiveness of HPV vaccination. Therefore, the inclusion of partial genotype testing for HPV 16 and HPV 18 for the vaccinated cohort adds an additional cost to the strategy, but does not impact on the effectiveness. In other words, the screening test results for partial genotyping do not influence the decision to refer to colposcopy with the effect that where HPV partial genotyping occurs in the pathway,

this step is ignored and women automatically move onto the next step. Thus, HPV primary testing followed by partial genotyping becomes equivalent in effectiveness to a HPV primary testing only strategy. HPV testing followed by sequential testing with partial genotyping (and if positive, LBC testing) becomes equivalent in effectiveness to HPV primary testing followed by LBC triage and equivalent in both costs and effects to HPV primary testing followed by co-testing with partial genotyping and LBC. Similarly, HPV primary testing followed by sequential testing with partial genotyping (and if positive $p16^{INK4a}$/Ki-67) becomes equivalent in effectiveness to HPV primary testing followed by $p16^{INK4a}$/Ki-67 and equivalent in both costs and effectiveness to HPV primary testing followed by co-testing with partial genotyping and $p16^{INK4a}$/Ki-67. To aid in presentation these strategies have therefore been removed from the cost-effectiveness planes.

Figure 5.18 Cost-effectiveness plane (QALYs) for a vaccinated cohort, with current practice as the base case



Key: LBC-HPV denotes LBC primary testing followed by HPV triage; HPV-LBC denotes HPV primary testing followed by LBC triage; HPV only denote HPV primary testing with no triage test; HPV-PK denotes HPV primary testing followed by p16INK4a/Ki-67 triage; LBC-HPV<30, HPV-LBC≥30 denotes primary HPV testing with LBC triage for women under 30 and primary LBC testing with HPV triage testing for women aged 30 and over.

With current practice dominated by almost all alternative strategies, to aid in presentation and to allow for a common comparator we have included a no

screening option. Figure 5.19 shows where each comparator lies on the cost-effectiveness plane when no screening is used as the base case.

Figure 5.19 Cost-effectiveness plane (QALYs) for vaccinated cohort, with no screening as base case

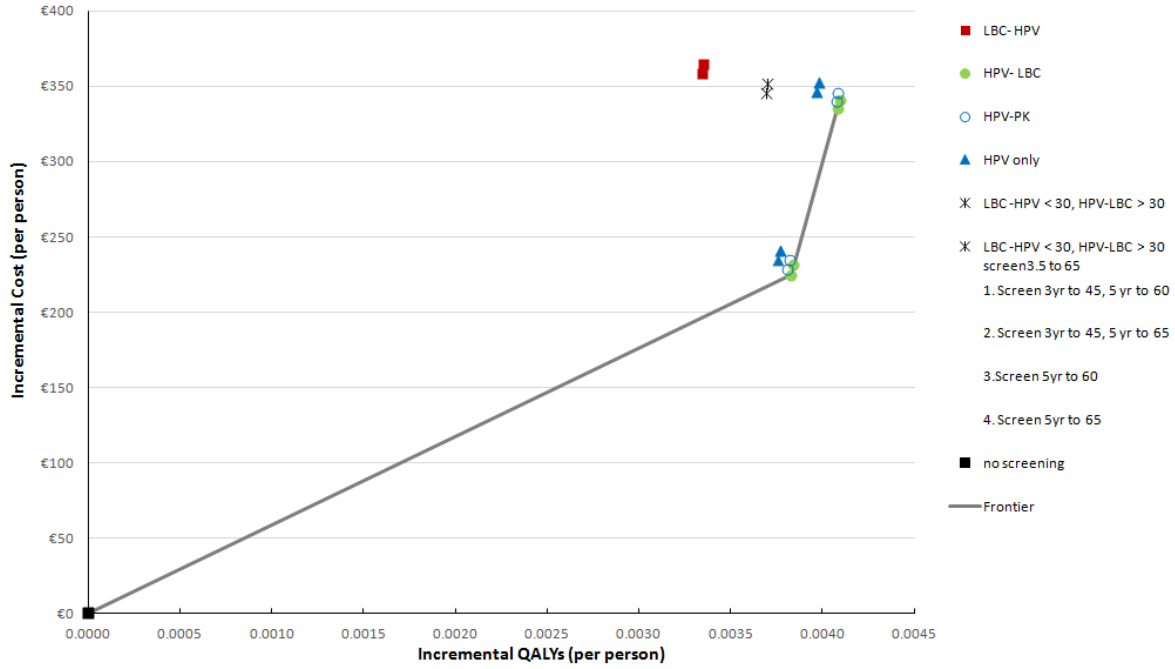


Table 5.13 shows the incremental cost-effectiveness ratios (ICERs) per QALY for each comparator relative to the next best option for a vaccinated cohort. Dominated strategies are excluded. Relative to a policy of no screening, the ICER for primary HPV testing followed by LBC triage testing, at five-yearly intervals to age 60 years is €58,745 per QALY and would not be considered cost-effective under willingness-to-pay thresholds in the range of €20,000 to €45,000 per QALY.

Table 5.13 Estimated incremental cost-effectiveness ratios (€/QALY) for a vaccinated cohort

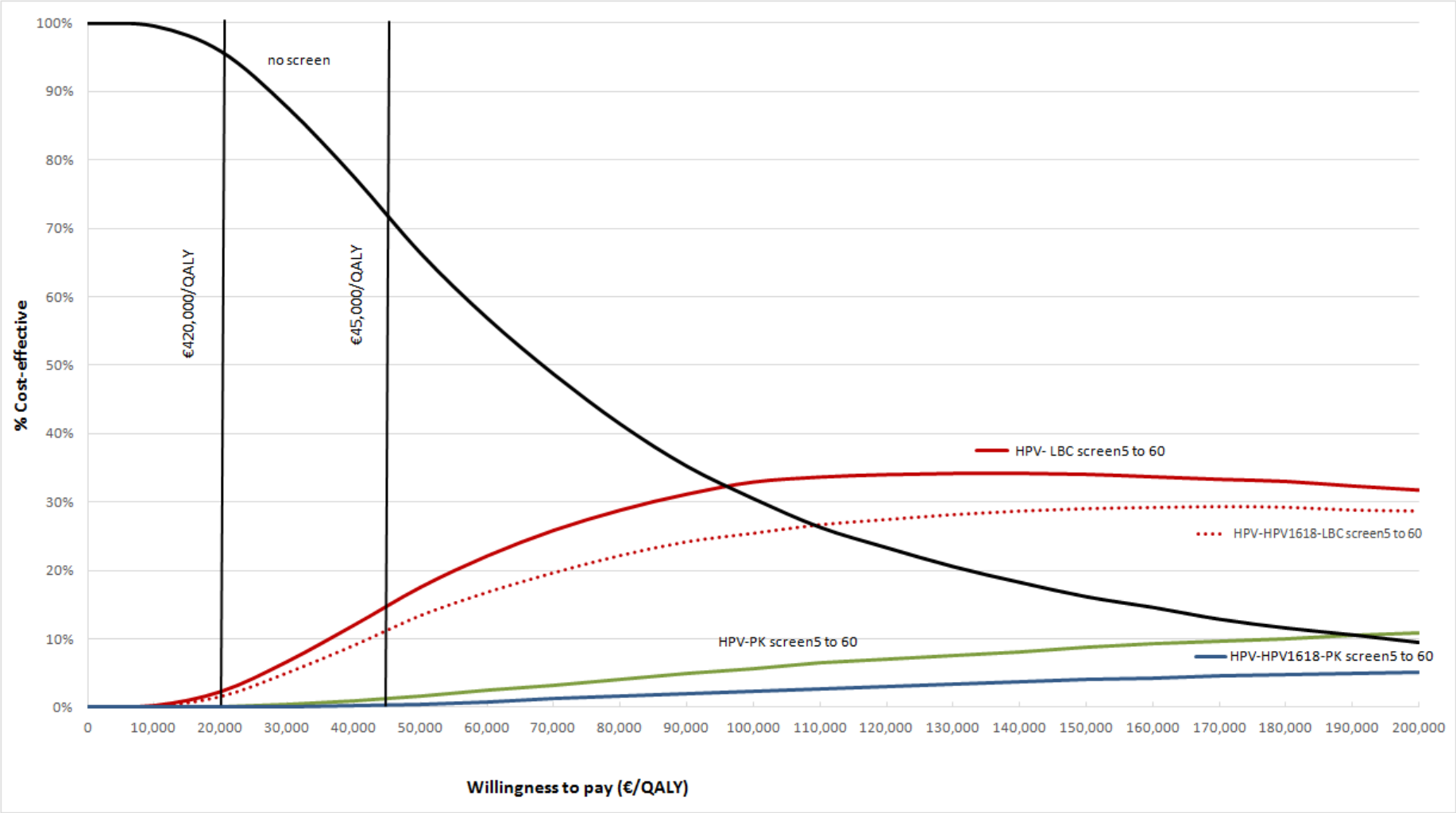
Strategy	Cost (€)	Incremental Cost (€)	Effectiveness (QALYs)	Incremental Effectiveness (QALYs)	ICER (€/QALYs)
Base case (no screening)	51		17.3692		
HPV- LBC screen 5yr to age 60	275	225	17.3730	0.00383	58,745
HPV- LBC screen 3yr to 45, 5yr to age 60	386	110	17.3733	0.00025	432,254
HPV- LBC screen 3yr to 45,5yr to age 65	391	6	17.3733	0.00001	605,759

Abbreviations: QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio.
Note all values are discounted.

The degree of uncertainty about the ICER for each intervention is examined using cost-effectiveness acceptability curves (CEAC). This shows the probability that any of the screening strategies are cost-effective for a given willingness-to-pay threshold (Figure 5.20). Strategies that had a probability of being cost-effective of less than 3% at all thresholds were excluded to improve clarity of presentation. At a threshold of €20,000 per QALY, there is little uncertainty that no screening is cost-effective, being the cost-effective option in 96% of simulations. At a threshold of €45,000 per QALY, HPV primary screening followed by LBC triage every five years to age 60 years is the cost-effective option in 15% of simulations.

For a vaccinated cohort, the strategy of HPV primary testing followed by partial genotyping for HPV 16 and HPV 18 followed, if positive, by LBC for a vaccinated cohort has the same effectiveness as HPV primary testing followed by LBC triage testing (as it was assumed that all those vaccinated against HPV 16 and 18 will test negative for these genotypes and where HPV partial genotyping occurs in the pathway, this step is ignored and the women automatically move onto the next step), but has a higher cost associated with the additional triage step.

Figure 5.20 Cost-effectiveness acceptability curve (QALY), vaccinated cohort



In this analysis the expected value of perfect information (EVPI) was calculated over the lifetime of a vaccinated population, assuming a steady state of vaccination had been reached at the target rate of 80%. Below a willingness-to-pay threshold of €20,000 per QALY (Figure 5.21), the expected value of perfect information is low, as it is clear from the CEAC that below this point there is little uncertainty that no screening is the cost-effective option. At a willingness-to-pay threshold of €60,000 per QALY, the expected value of perfect information rises steadily to a peak of €68 million (Figure 5.21). At this point the probability that no screening is the cost-effective option declines below that of the other options combined. However, there is a high degree of uncertainty as to which of these alternative options is cost-effective, before HPV primary testing followed by LBC triage every five years to age 60 years emerges as the cost-effective option as the willingness-to pay-threshold increases.

Figure 5.21 Expected value of perfect information (QALY) for a vaccinated cohort

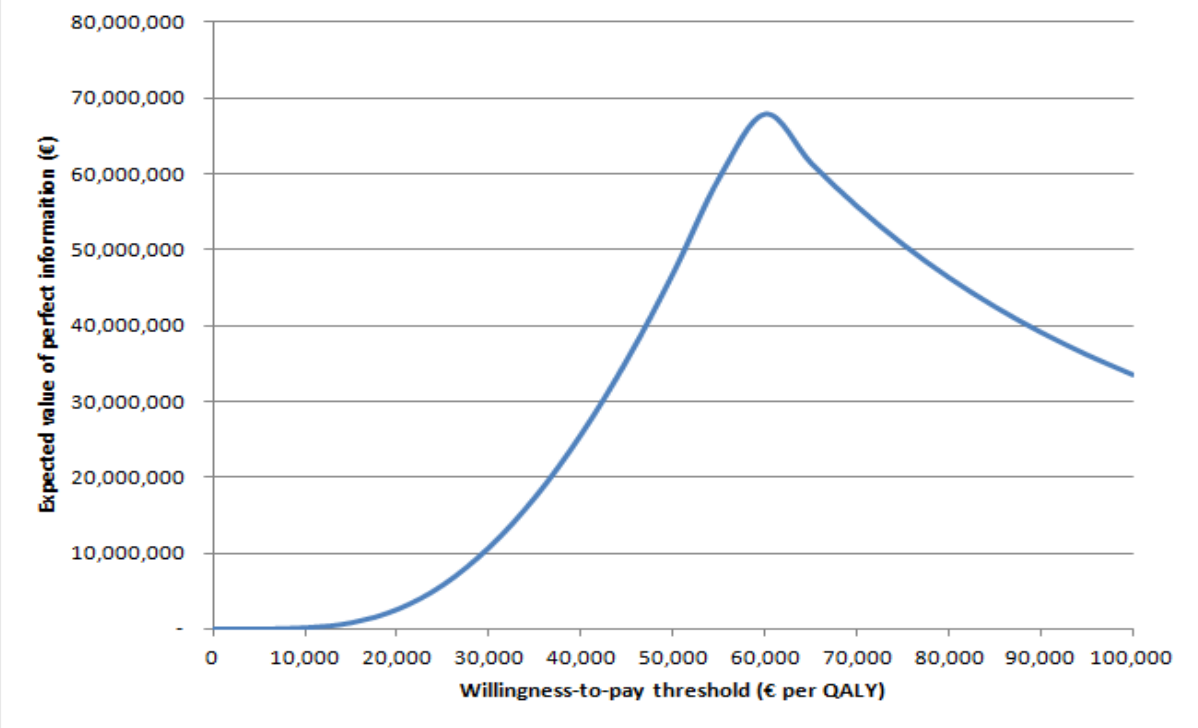


Table 5.14 shows the results for each of the modelled strategies for a vaccinated cohort. No screening would result in the highest mortality. The lowest mortality was estimated for primary HPV testing followed by partial genotyping every three years up to the age of 45 years and five-yearly to age 65 years.

In a situation where there is no cervical screening, the model estimates 348 cervical cancer cases would develop over the lifetime of 100,000 HPV-vaccinated women.

Implementing a strategy of primary HPV testing followed by LBC triage every five years to age 60 years, would prevent 274 of these cervical cancer cases. There were a number of strategies which resulted in fewer QALYs than other comparator strategies despite generating lower overall mortality. This was due to the combination of when mortality occurred in each strategy and the effect of discounting.

For all strategies extending the screening age to 65 years decreases both the number of cervical cancer cases and cervical cancer deaths. However, as these benefits occur far into the future the effect of discounting means that the number of QALYs gained by extending the screening age is small.

Table 5.14 Results for the vaccinated cohort, ordered by decreasing intensity of screening within strategy

Strategy	Per 100,000					
	Cost (€)	QALYs	Average lifetime number of screens	Cervical cancer cases	Cervical cancer deaths	Colposcopy referrals
No screening	51	17.3692	0	348	99	0
LBC- HPV screen 3yr to 45,5yr to 65	415	17.3725	8.6	64	15	8,184
LBC- HPV screen 3yr to 45,5yr to 60	**409**	**17.3725**	**8.0**	**71**	**17**	**7,889**
HPV-HPV1618 screen 3yr to 45,5yr to 65	403	17.3732	8.6	45	11	13,449
HPV-HPV1618 screen 3yr to 45, 5yr to 60	397	17.3732	8.0	52	13	12,954
HPV-HPV1618 screen 5yr to 65	292	17.3730	6.4	62	14	10,738
HPV-HPV1618 screen 5yr to 60	286	17.3730	5.8	69	17	10,227
HPV- LBC screen 3yr to 45, 5yr to 65	391	17.3733	8.7	50	12	7,675
HPV- LBC screen 3yr to 45, 5yr to 60	386	17.3733	8.1	57	15	7,387
HPV- LBC screen 5yr to 65	282	17.3730	6.4	66	15	6,209
HPV- LBC screen 5yr to 60	275	17.3730	5.9	74	18	5,543
HPV-HPV1618-LBC screen 3yr to 45, 5yr to 65	392	17.3733	8.7	50	12	7,675
HPV-HPV1618-LBC screen 3yr to 45,5yr to 60	386	17.3733	8.1	57	15	7,387
HPV-HPV1618-LBC screen 5yr to 65	281	17.3730	6.4	66	15	6,209
HPV-HPV1618-LBC screen 5yr to 60	276	17.3730	5.9	74	18	5,913
HPV-HPV1618+LBC screen 3yr to 45,5yr to 65	392	17.3733	8.7	50	12	7,675
HPV-HPV1618+LBC screen 3yr to 45,5yr to 60	386	17.3733	8.1	57	15	7,387
HPV-HPV1618+LBC screen 5yr to 65	282	17.3730	6.4	66	15	6,209

HPV-HPV1618+LBC screen 5yr to 60	276	17.3730	5.9	74	18	5,913
HPV-PK screen 3yr to 45, 5yr to 65	396	17.3733	8.7	52	13	6,924
HPV-PK screen 3yr to45, 5yr to 60	390	17.3733	8.1	59	15	6,663
HPV-PK screen 5yr to 65	285	17.3730	6.4	69	16	5,634
HPV-PK screen 5yr to 60	279	17.3730	5.9	76	19	5,366
HPV-HPV1618-PK screen 3yr to 45,5yr to 65	397	17.3733	8.7	52	13	6,924
HPV-HPV1618-PK screen 3yr to 45,5yr to 60	391	17.3733	8.1	59	15	6,663
HPV-HPV1618-PK screen 5yr to 65	286	17.3730	6.4	69	16	5,634
HPV-HPV1618-PK screen 5yr to 60	279	17.3730	5.9	76	19	5,366
HPV-HPV1618+PK screen 3yr to 45,5yr to 65	397	17.3733	8.7	52	13	6,924
HPV-HPV1618+PK screen 3yr to 45,5yr to 60	391	17.3733	8.1	59	15	6,663
HPV-HPV1618+PK screen 5yr to 65	286	17.3730	6.4	69	16	5,634
HPV-HPV1618+PK screen 5yr to 60	280	17.3730	5.9	76	19	5,366
LBC -HPV < 30, HPV-LBC≥ 30 screen 3yr to 45,5yr to 65	402	17.3729	8.6	55	13	8,332
LBC -HPV < 30, HPV-LBC ≥ 30 screen 3yr to 45,5yr to 60	396	17.3729	8.1	61	15	8,005

Abbreviations: QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio.
Note the average lifetime number of screens, includes any additional screens due to increased surveillance, following either a positive HPV primary test and negative triage test, or discharge from colposcopy clinic.
Strategies which include the HPV 16/18 partial genotype test increases the cost but all other outcomes remain the same, where the strategy includes a co-test the outcomes of the strategy are then identical to a strategy of both sequential testing and a single triage test.
Key: LBC-HPV denotes LBC primary testing followed by HPV triage; HPV-LBC denotes HPV primary testing followed by LBC triage; HPV-1618 denote HPV primary testing followed by partial genotyping of HPV 16 and HVP18; HPV-PK denotes HPV primary testing followed by p16INK4a/Ki-67 triage; HPV-1618-LBC denotes HPV primary testing followed by triage testing with partial genotyping of HPV 16 and HVP18 and if positive a further triage test of LBC; HPV-1618+LBC denotes HPV primary testing followed by triage testing with a co-test of partial genotyping of HPV 16 and HVP18 and LBC; ; HPV-1618-PK denotes HPV primary testing followed by triage testing with partial genotyping of HPV 16 and HVP18 and if positive a further triage test of p16INK4a/Ki-67; HPV-1618+PK denotes HPV primary testing followed by triage testing with a co-test of partial genotyping of HPV 16 and HPV 18 and p16INK4a/Ki-67; LBC-HPV<30, HPV-LBC≥30 denotes primary HPV testing with LBC triage for women under 30 and primary LBC testing with HPV triage testing for women aged 30 and over.

Table 5.15 shows the incremental cost-effectiveness ratios (ICERs) per life year gained (LYG) for each comparator relative to the next best option for a vaccinated cohort, excluding dominated strategies. As with the ICER based on QALYs, relative to no screening, the next best option was primary HPV testing followed by LBC triage every five years to age 60 years with an ICER of €72,968 per LYG.

Table 5.15 Estimated incremental cost-effectiveness ratios (€/LYG) for a vaccinated cohort relative to no screening

Strategy	Cost (€)	Incremental Cost (€)	Effectiveness (LYG)	Incremental Effectiveness (LYG)	ICER (€/LYG)
No screening	51		19.3223		
HPV- LBC screen 5yr to 60	275	225	19.3253	0.00308	72,968
HPV-HPV1618 screen 5yr to 60	286	10	19.3254	0.00004	289,412
HPV -HPV1618 screen 5yr to 65	292	6	19.3254	0.00001	456,473
HPV -HPV1618 screen 3yr to 45, 5yr to 65	403	€11	19.3256	0.00018	620,119

Abbreviations: LYG, quality adjusted life year; ICER, incremental cost-effectiveness ratio.
Note all values are discounted.

5.4.3 Budget impact analysis (BIA)

A budget impact analysis (BIA) was carried out to estimate the total cost of implementing each of the comparator screening strategies over the next eight years, for both the vaccinated and unvaccinated populations. The HPV vaccine programme commenced in a limited number of schools in May 2010 for first-year girls (age 12-13 years). It was subsequently expanded to girls in first and second year in all schools starting in September 2010. From September 2011 for a period of three years, there was vaccination catch-up programme for those in sixth-year.

Table 5.16 shows the estimated numbers of vaccinated women entering cervical screening over the next eight years. These estimates are based on the uptake rate in the catch-up cohorts from 2011-12 to 2013-14 and the initial cohort of those in first year in 2010-11 to 2012-13.[243] Adjustments were made to reflect that vaccination occurred based on school year of enrolment rather than age of birth and also to reflect that some girls who were out-of-cohort, for example girls aged 19 years who were enrolled in sixth-year, would have been offered vaccination. It was assumed that all women born before 1992 would not have received HPV vaccination.

By 2025, HPV vaccinated women would represent almost 85% of those entering CervicalCheck, and almost 9% of the total CervicalCheck population.

Table 5.16 Estimated numbers of vaccinated women entering CervicalCheck between 2018 and 2022[60, 228, 243]

Entering CervicalCheck	Year of birth	Estimated % vaccinated	Estimated population vaccinated (n)	Estimated population unvaccinated (n)	Total population entering CervicalCheck (n)	% of Total screening population vaccinated
2018	1993	10.73	2,731	22,729	26,436	0.21
2019	1994	30.03	7,023	16,362	24,904	0.75
2020	1995	70.10	15,374	6,557	22,020	1.95
2021	1996	66.02	13,792	7,099	21,409	3.02
2022	1997	69.46	14,871	6,538	20,891	4.18
2023	1998	81.90	18,034	3,986	21,931	5.59
2024	1999	84.30	20,994	3,910	23,385	7.23
2025	2000	84.60	22,365	4,071	25,460	8.96

The model calculates the costs that occur in each year, over the course of eight years, assuming implementation of any new strategy in 2018. It considers only women aged between 18 and 65 years, followed for a total of eight years. Any treatment costs due to a diagnosis of cervical cancer in women outside these age ranges were not included. The model does not include the treatment costs for women who are currently diagnosed with cervical cancer and are in treatment. For this reason, the treatment costs within the budget impact analysis reflect estimated treatment costs for women who will be diagnosed with cervical cancer and receive treatment over the next eight years. The number of colposcopy referrals included in the model reflects the number of new referrals to colposcopy clinics arising from screening over the next eight years. It does not include clinical referrals, (apart from a small number of clinical referrals for women with cervical cancer) which currently account for up to 30% of all new referrals to colposcopy clinics.

Tables 5.17, 5.18 and Figure 5.22 provide the estimated net eight-year budget impact for the vaccinated and unvaccinated populations both separately and combined. The estimated number of screenings and referrals to colposcopy are also shown in these tables for each screening strategy.

Table 5.17 Net budget impact analysis for each strategy for unvaccinated women from 2018 - 2025

Strategy	Total Cost (€)	Screening cost (€)	Treatment cost (€)	Incremental screens (n)	Incremental referrals to colposcopy (n)	Incremental cost (€)
LBC-HPV screen 3yr to 45,5yr to 60	**214,630,250**	**181,613,390**	**33,016,860**			
LBC-HPV screen 3yr to 45,5yr to 65	224,491,806	191,134,273	33,357,533	105,325	1,281	9,861,556
HPV-LBC screen 3yr to 45,5yr to 60	208,202,139	177,436,477	30,765,661	19,617	-1,012	-6,428,111
HPV-LBC screen 3yr to45,5yr to 65	217,841,656	186,777,878	31,063,778	125,676	259	3,211,406
HPV-LBC screen 5yr to 60	**182,841,983**	**50,089,934**	**32,752,048**	**-291,119**	**-4,707**	**-31,788,267**
HPV-LBC screen 5yr to 65	192,494,314	159,431,374	33,062,940	-185,060	-3,436	-22,135,936
HPV-HPV1618 screen 3yr to 45,5 to 60	207,209,178	176,604,202	30,604,976	19,399	1,092	-7,421,072
HPV-HPV1618 screen 3yr to 45,5yr to 65	216,760,485	185,899,905	30,860,580	125,454	2,436	2,130,235
HPV-HPV1618 screen 5yr to 60	181,598,862	149,263,854	32,335,008	-291,063	-3,104	-33,031,388
HPV-HPV1618 screen 5yr to 65	191,150,169	158,559,557	32,590,612	-185,008	-1,760	-23,480,081
HPV-HPV1618-LBC screen 3yr to45,5yr to 60	205,499,038	174,998,826	30,500,213	26,850	-7,321	-9,131,212
HPV-HPV1618-LBC screen 3yrto 45,5yr to 65	214,947,125	184,220,167	30,726,957	133,092	-6,331	316,875
HPV-HPV1618-LBC screen 5yr to 60	179,820,641	147,707,934	32,112,706	-287,649	-10,194	-34,809,609
HPV-HPV1618-LBC screen 5yr to 65	189,268,727	156,929,276	32,339,451	-181,407	-9,204	-25,361,523
HPV-HPV1618+LBC screen 3yr to 45,5yr to 60	211,062,197	180,258,756	30,803,441	12,248	7,293	-3,568,053
HPV-HPV1618+LBC screen 3yr to 45,5yr to 65	220,868,506	189,727,807	31,140,699	118,120	8,918	6,238,256

HPV-HPV1618+LBC screen 5yr to 60	185,648,916	152,736,004	32,912,912	-294,518	2,352	-28,981,334
HPV-HPV1618+LBC screen 5yr to 65	195,455,225	162,205,055	33,250,170	-188,646	3,976	-19,175,025
HPV-PK screen 3yr to 45,5yr to 60	210,146,321	179,713,827	30,432,494	23,965	-4,010	-4,483,929
HPV-PK screen 3yr to45, 5yr to 65	219,783,136	189,134,021	30,649,115	130,134	-2,882	5,152,886
HPV-PK screen 5yr to 60	183,825,023	151,821,247	32,003,775	-288,974	-7,425	-30,805,228
HPV-PK screen 5yr to 65	193,461,838	161,241,441	32,003,775	-182,805	-6,297	-21,168,412
HPV-HPV1618-PK screen 3yr to 45,5yr to 60	206,666,985	176,622,370	30,044,614	29,420	-8,849	-7,963,265
HPV-HPV1618-PK screen 3yr to 45, 5yr to 65	216,088,725	185,900,954	30,187,771	135,726	-7,936	1,458,475
HPV-HPV1618-PK screen 5yr to 60	180,318,678	148,975,740	31,342,938	-286,368	-11,622	-34,311,572
HPV-HPV1618-PK screen 5yr to 65	189,740,419	158,900,954	31,486,094	-180,062	-10,709	-24,889,832
HPV-HPV1618+PK screen 3yr to 45,5yr to 60	213,848,365	183,055,217	30,793,148	14,018	5,831	-781,885
HPV-HPV1618+PK screen 3yr to 45, 5yr to 65	223,752,956	192,637,546	31,115,410	119,936	7,389	9,122,706
HPV-HPV1618+PK screen 5yr to 60	187,916,839	155,089,224	32,827,615	-293,654	1,061	-26,713,411
HPV-HPV1618+PK screen 5yr to 65	197,821,430	164,671,553	33,149,877	-187,737	2,618	-16,808,821
LBC-HPV<30, HPV-LBC≥30 screen 3yr to 45, 5yr to 60	208,333,201	177,494,540	30,838,661	16,282	-869	-6,297,049
LBC-HPV<30, HPV-LBC≥30 screen 3yr to 45, 5yr to 65	217,928,708	186,252,550	31,135,463	122,412	371	3,298,458

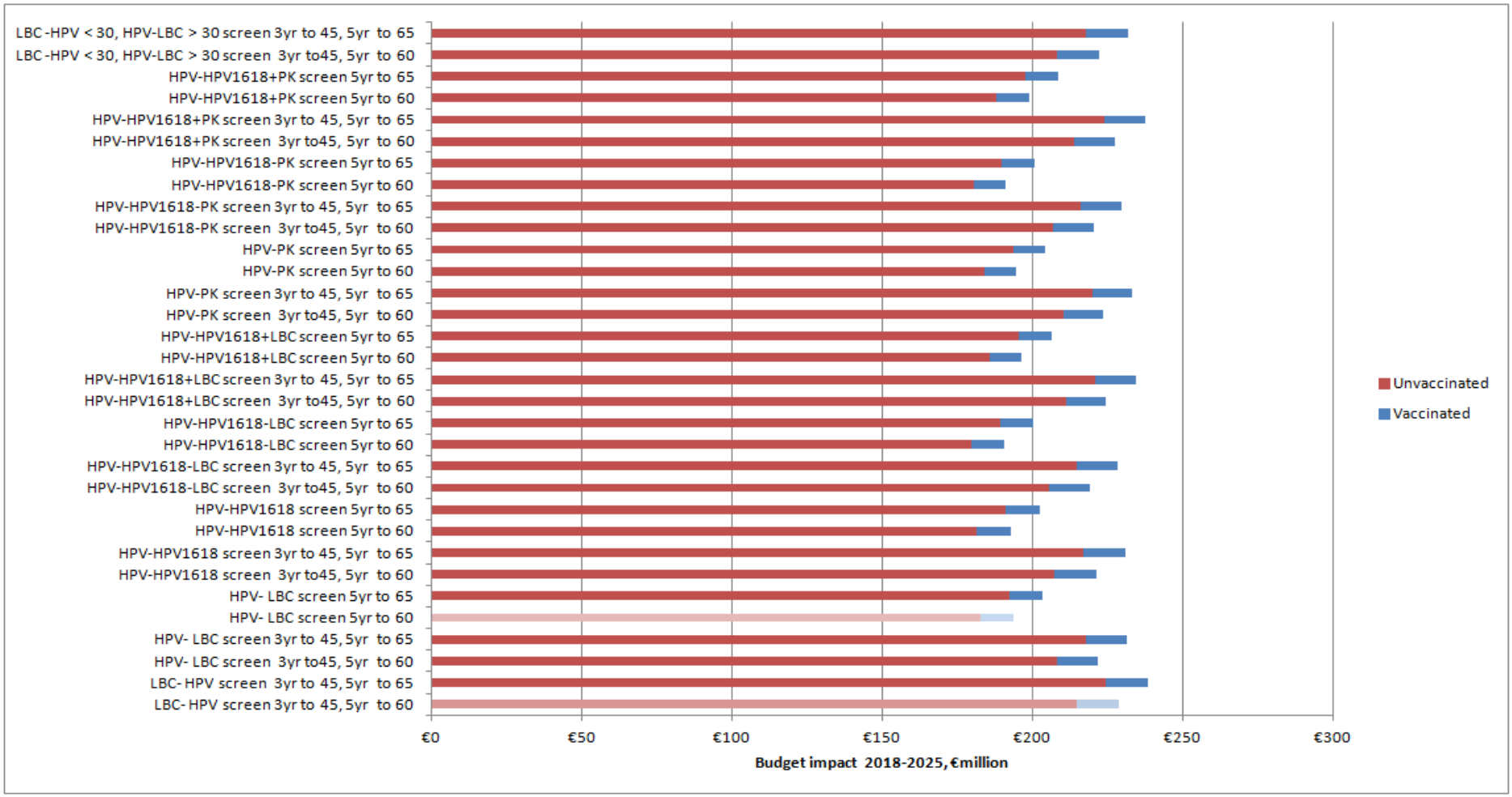
Note the screening cost includes primary and triage screening as well as treatment and follow-up in colposcopy clinics for women without a diagnosis of cervical cancer. The incremental cost is in comparison with the current screening practice of LBC followed by HPV every 3 years to 45, and every five years to 60.
Note the number of screens, includes any additional screens due to increased surveillance, following either a positive HPV primary test and negative triage test, or discharge from colposcopy clinic.
Note: the number of colposcopy referrals is limited to those arising from screening activity and does not include clinical referrals to colposcopy apart from the small number of clinical referrals because of cervical cancer in the screening cohort.

Table 5.18 Net budget impact analysis for each strategy for vaccinated women from 2018-2025

Strategy	Total Cost (€)	Screening cost (€)	Treatment cost (€)	Incremental screens (n)	Incremental referrals to colposcopy (n)	Incremental cost (€)
LBC- HPV screen 3yr to 45, 5yr to 60	**13,937,009**	**13,540,735**	**396,274**			
HPV- LBC screen 3yr to 45, 5yr to 60	13,400,584	13,030,263	370,321	2,017	-285	-536,425
HPV- LBC screen 5yr to 60	**10,784,806**	**10,422,226**	**362,580**	**-28,349**	**-693**	**-3,152,203**
HPV-HPV1618 screen 3yr to 45, 5yr to 60	14,101,372	13,724,908	376,465	101	2,254	164,363
HPV-HPV1618 screen 5yr to 60	11,420,083	11,049,905	370,178	-29,279	1,409	-2,516,926
HPV-HPV1618-LBC screen 3yr to 45, 5yr to 60	13,423,097	13,052,776	370,321	101	2,254	-508,871
HPV-HPV1618-LBC screen 5yr to 60	10,803,723	10,441,143	362,580	-29,279	1,409	-3,133,286
HPV-HPV1618+LBC screen 3yr to 45, 5yr to 60	13,428,138	13,035,196	370,321	2,017	-285	-508,871
HPV-HPV1618+LBC screen 5yr to 60	10,808,171	10,426,129	362,580	-28,349	-693	-3,128,839
HPV-PK screen 3yr to 45, 5yr to 60	13,549,398	13,198,597	350,800	2,017	-285	-387,612
HPV-PK screen 5yr to 60	10,891,140	10,550,580	340,559	-28,349	-693	-3,045,870
HPV-HPV1618-PK screen 3yr to 45, 5yr to 60	13,571,334	13,242,697	350,800	2,398	-663	-365,676
HPV-HPV1618-PK screen 5yr to 60	10,909,140	10,568,909	340,559	-28,138	-1,015	-3,027,541
HPV-HPV1618+PK screen 3yr to 45, 5yr to 60	13,593,498	13,242,697	350,800	2,398	-663	-343,512
HPV-HPV1618+PK screen 5yr to 60	10,928,957	10,588,398	340,559	-28,138	-1,015	-3,008,052
LBC -HPV < 30, HPV-LBC ≥ 30 screen 3yr to 45, 5yr to 60	13,905,252	13,507,565	397,687	2,398	-663	-31,757

Note the screening cost includes primary and triage screening as well as treatment and follow-up in colposcopy clinics for women without a diagnosis of cervical cancer. The incremental cost is in comparison with the current screening practice of LBC followed by HPV every 3 years to 45, and every five years to 60.
Note the number of screens, includes any additional screens due to increased surveillance, following either a positive HPV primary test and negative triage test, or discharge from colposcopy clinic.
As it is anticipated that there will be no women over 65 who are vaccinated over the next eight years, strategies which include extending screening to age 65 for the vaccinated cohort are identical to those with a final screening age of 60, and thus these have been removed from the table.

Figure 5.22 Net budget impact analysis for each strategy for the combined population (unvaccinated and vaccinated) from 2018 to 2025



Note the current screening strategy and the optimal screening strategy identified in the economic evaluation are denoted by the light shaded bars.

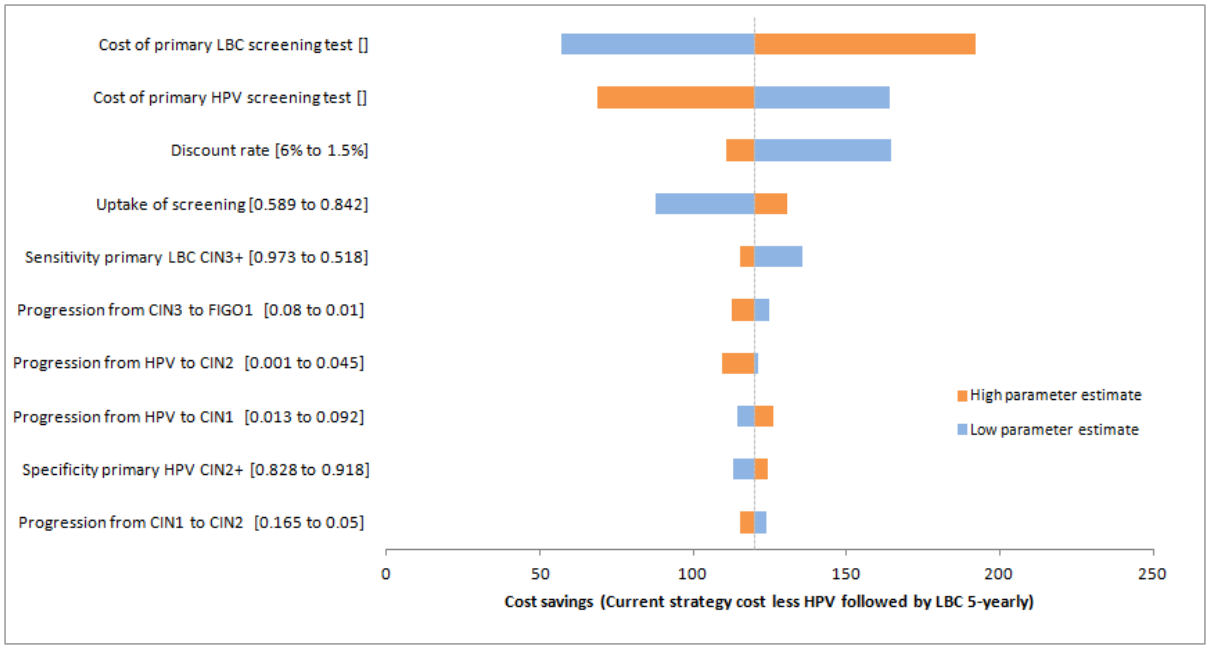
5.5 Sensitivity analyses

A univariate sensitivity analysis was used to assess how sensitive the results were to fluctuations in each parameter, in accordance with the national guidelines.[225] Given the uncertainty around the parameters themselves, the sensitivity analysis shows how this translates into uncertainty about the results.

The results of the sensitivity analyses are presented for the optimal strategy only (that is, primary HPV testing with LBC triage at five-yearly intervals to age 60 years which was identified as the cost-effective strategy given a willingness-to-pay threshold of €20,000 to €45,000 per QALY). These results are presented relative to the current strategy of primary LBC screening with HPV triage at three-yearly intervals from age 25 to 44 years and five-yearly intervals age 45 to 60 years. The results of the sensitivity analysis for all other strategies evaluated are included in Appendix 7.

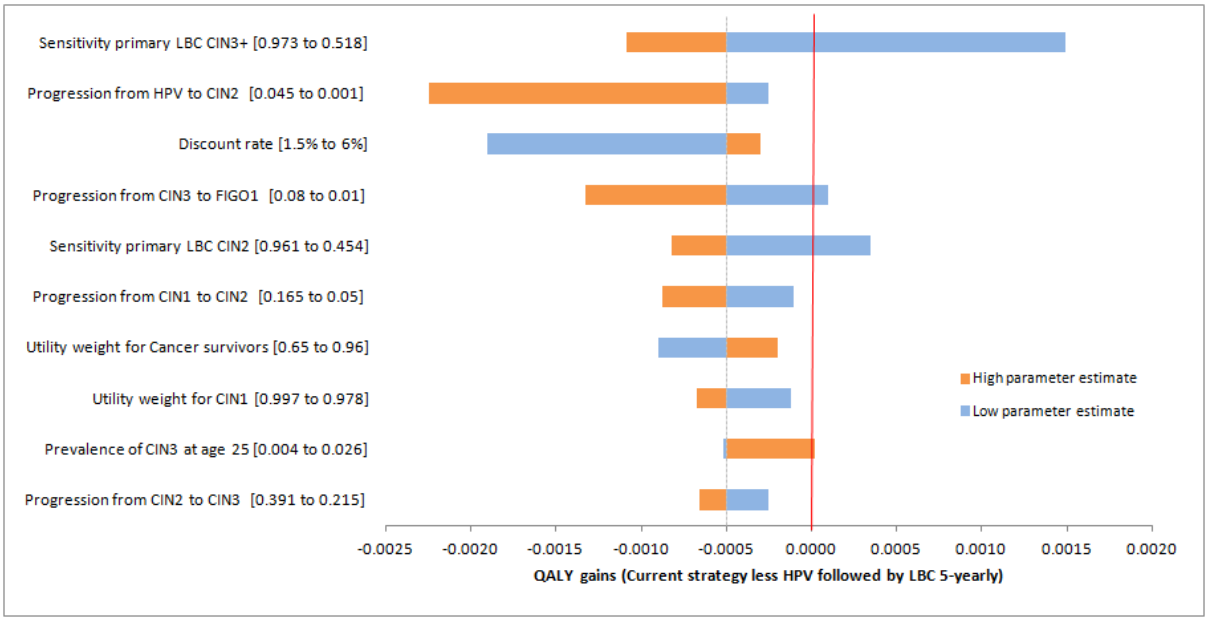
For an unvaccinated cohort, in terms of cost, there were no parameters where the upper or lower bounds resulted in HPV primary screening followed by LBC triage at five-yearly intervals until age 60 years being more costly than current practice (Figure 5.23). In terms of quality-adjusted life years, there were four parameters where the upper or lower bounds resulted in HPV primary screening followed by LBC triage at five-yearly intervals until age 60 years being more effective than current practice. These were: lowering the sensitivity of LBC for CIN 3+ and for CIN 2, reducing the probability of progression from CIN 3 to undiagnosed cervical cancer FIGO stage I, and increasing the prevalence of CIN 3 at age 25 (Figure 5.24).

Figure 5.23 Univariate sensitivity analysis comparing the difference in costs for HPV primary screening followed by LBC triage every 5 years to age 60 relative to current practice, for an unvaccinated cohort



Note: All parameters were varied in the analysis. For legibility, only the ten most influential parameters are included in the tornado plot.

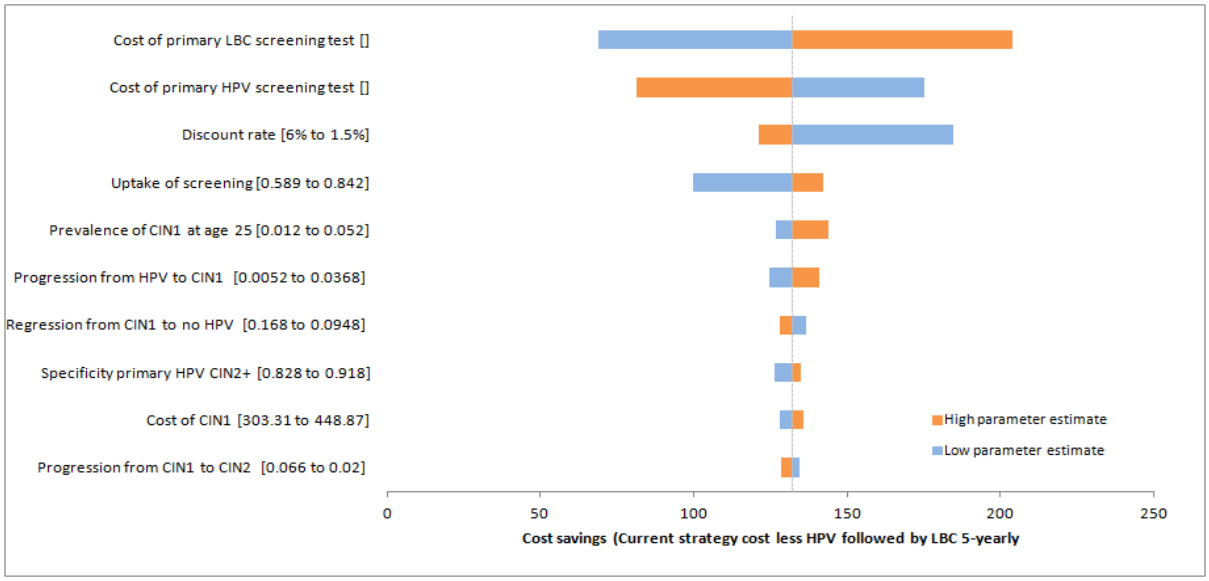
Figure 5.24 Univariate sensitivity analysis comparing the difference in QALYs for HPV primary screening followed by LBC triage every 5 years to age 60 relative to current practice, for an unvaccinated cohort



Note: All parameters were varied in the analysis. For legibility, only the ten most influential parameters are included in the tornado plot.

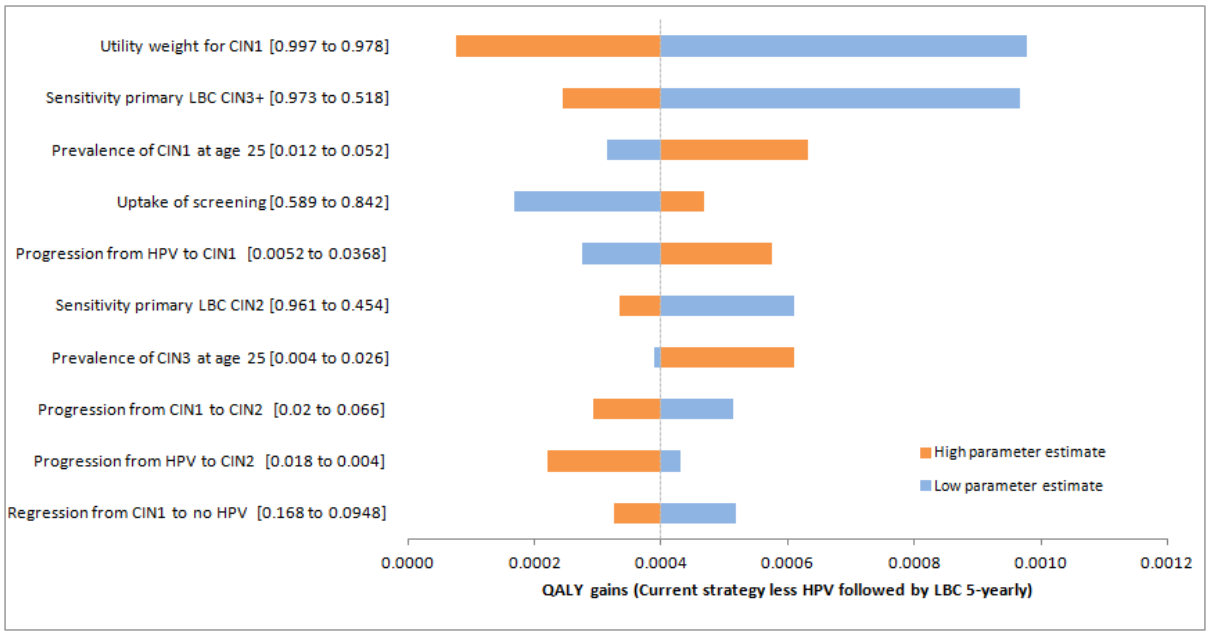
For a vaccinated cohort, in terms of cost, there were no parameters where the upper or lower bounds resulted in HPV primary screening followed by LBC triage at five-yearly intervals until age 60 years being more costly than current practice (Figure 5.25). For a vaccinated cohort, in terms of quality-adjusted life years, there were also no parameters where the upper or lower bounds resulted in HPV primary screening followed by LBC triage at five-yearly intervals until age 60 being less effective than current practice (Figure 5.26). The most influential parameter on the cost estimate was the cost of the primary screening tests. The most influential parameter on the effectiveness estimates was the QALY value for CIN 1.

Figure 5.25 Univariate sensitivity analysis comparing the difference in costs of HPV primary screening followed by LBC triage every 5 years to age 60 with current practice, for a vaccinated cohort



Note: All parameters were varied in the analysis. For legibility, only the ten most influential parameters are included in the tornado plot.

Figure 5.26 Univariate sensitivity analysis comparing the difference in QALYs for HPV primary screening followed by LBC triage every 5 years to age 60 with current practice, for a vaccinated cohort

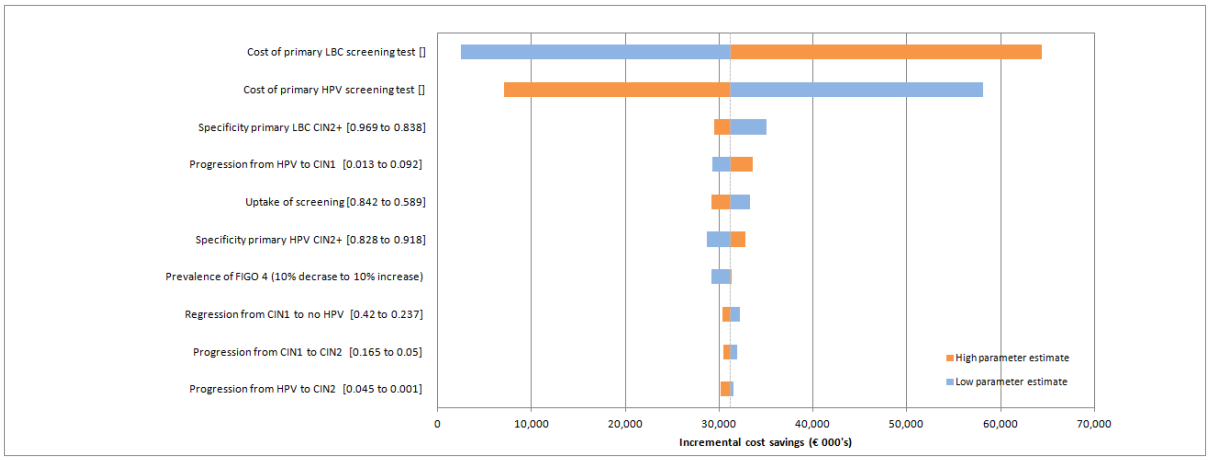


Note: All parameters were varied in the analysis. For legibility, only the ten most influential parameters are included in the tornado plot.

The results of the sensitivity analysis for the budget impact analysis are presented in Figure 5.27. Discounting is not applied in the budget impact analysis, and hence the discount rate is not included in the univariate sensitivity analysis.

In the base case analysis for unvaccinated women, the eight-year budget impact of the optimal strategy (HPV primary screening followed by LBC triage every five years to age 60) was €31,788,267 less than for the current practice (LBC primary screening followed by HPV triage at three-yearly intervals to age 45, and five-yearly intervals to age 60). The incremental budget impact was however very sensitive to variation in the cost of the primary screening test (HPV or LBC) (Figure 5.27). The next two most important parameters were the specificity of primary screening with LBC for CIN 2+ and the progression from HPV to CIN 1, respectively.

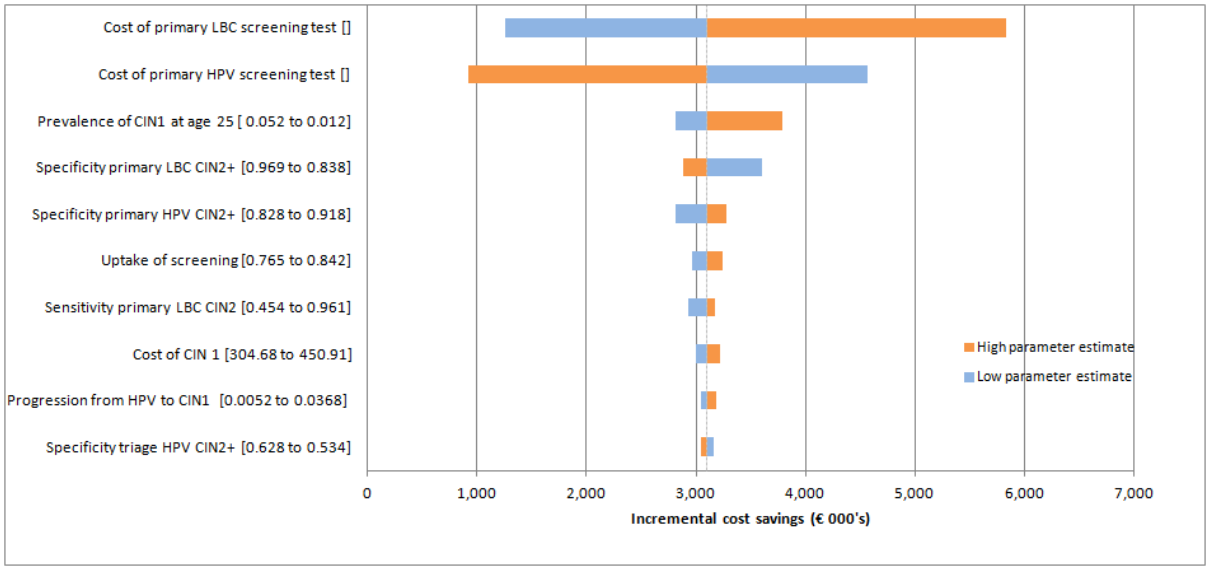
Figure 5.27 Univariate sensitivity analysis for the budget impact analysis of HPV primary screening followed by LBC triage every 5 years to age 60 compared with current practice (LBC primary screening followed by HPV triage 3-yearly to 45, 5-yearly to 60) for an unvaccinated cohort



Note: All parameters were varied in the analysis. For legibility, only the ten most influential parameters are included in the tornado plot.

In vaccinated women, the eight-year budget impact in the base case analysis for the optimal strategy (HPV primary screening followed by LBC triage every five years to age 60) was €3,152,203 less than for the current practice of LBC primary screening followed by HPV triage at three-yearly intervals to age 45, and five-yearly intervals to age 60. The univariate sensitivity analysis indicated that the incremental budget impact was very sensitive to variation in the cost of the primary screening test (HPV or LBC) (Figure 5.28). The next two most important parameters were the prevalence of CIN 1 at age 25 years and the specificity of primary screening with LBC for CIN 2+, respectively.

Figure 5.28 Univariate sensitivity analysis for budget impact analysis of HPV primary screening followed by LBC triage every five years to age 60, with current practice (LBC primary screening followed by HPV triage three-yearly to 45, five-yearly to 60) for a vaccinated cohort



Note: All parameters were varied in the analysis. For legibility, only the ten most influential parameters are included in the tornado plot.

5.6 Subgroup analyses

Two subgroup analyses were defined. The first considers extending the screening exit age from 60 to 65 years in a cohort who have not had the benefit of lifetime access to organised screening from age 25, and who have only been offered access to organised screening since the age of 50 years. The second subgroup analysis considers how best to screen unvaccinated women under age 30 years, in the context of five-yearly HPV primary testing with LBC triage from age 30 onwards.

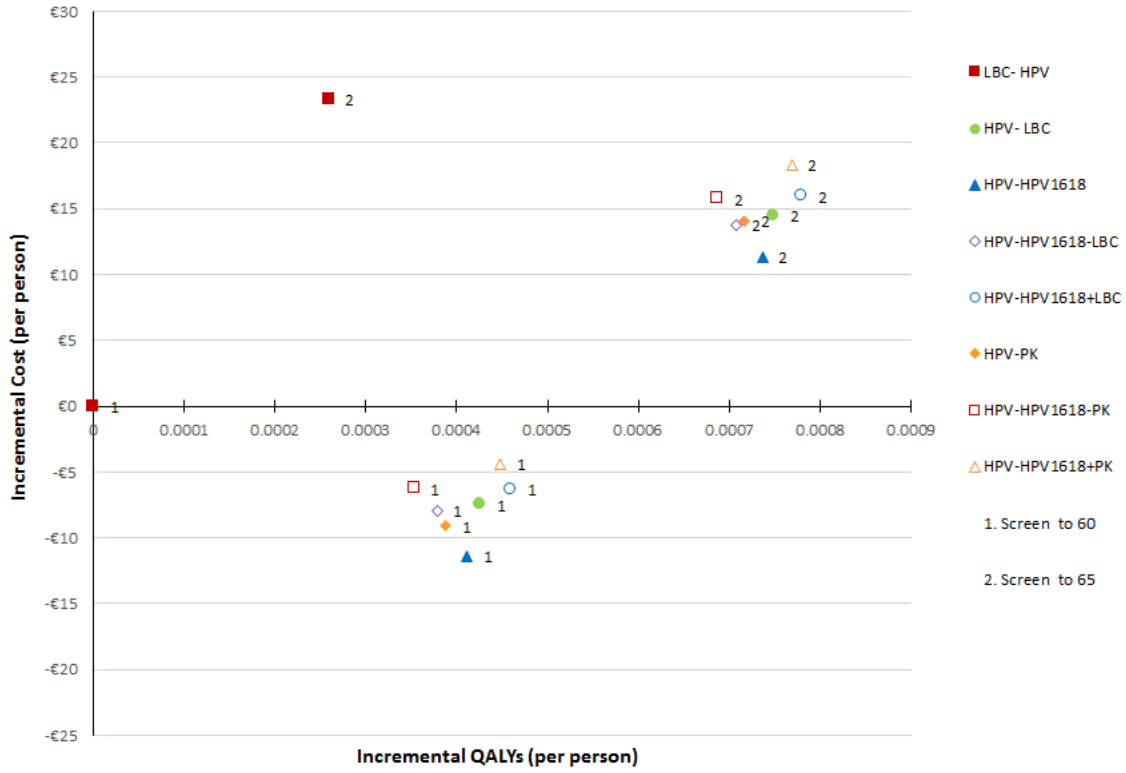
5.6.1 Subgroup analysis 1: cohort only offered organised screening from age 50

The first subgroup analysis considers extending the screening exit age from 60 to 65 years in a cohort who have not had the benefit of lifetime access to organised screening from age 25, but who have only been offered access to organised screening since the age of 50 years. This subgroup is relevant given that CervicalCheck was only established in 2008. For this subgroup, it was assumed that the first time these women were offered access to organised screening they were aged 50. This subgroup analysis was only relevant for an unvaccinated cohort.

Current CervicalCheck policy stipulates that a woman must have two sequential negative tests at three-yearly intervals before moving to five-yearly screening. It also stipulates a woman must have two sequential negative tests before being discharged from screening. Therefore, for this cohort it was assumed in the base case that following the first screening test, the next routine screening test would be offered at three years. As all women within the cohort are aged 50 years or older, all strategies that considered three-yearly screening until age 45 as an option were not included in the subgroup analysis, along with strategies with differential testing for those aged under 30 years. To reflect the ongoing opportunistic screening that existed prior to the introduction of the CervicalCheck, it was assumed that 10% of this cohort would have had opportunistic screening during their lifetime.

Figure 5.29 shows where each comparator lies on the cost-effectiveness plane when outcomes are measured in quality-adjusted life years gained (QALYs). Current practice is used as the base case. Of the strategies that considered an exit age of 60 years, current practice of LBC followed by HPV testing is the least effective and the most costly.

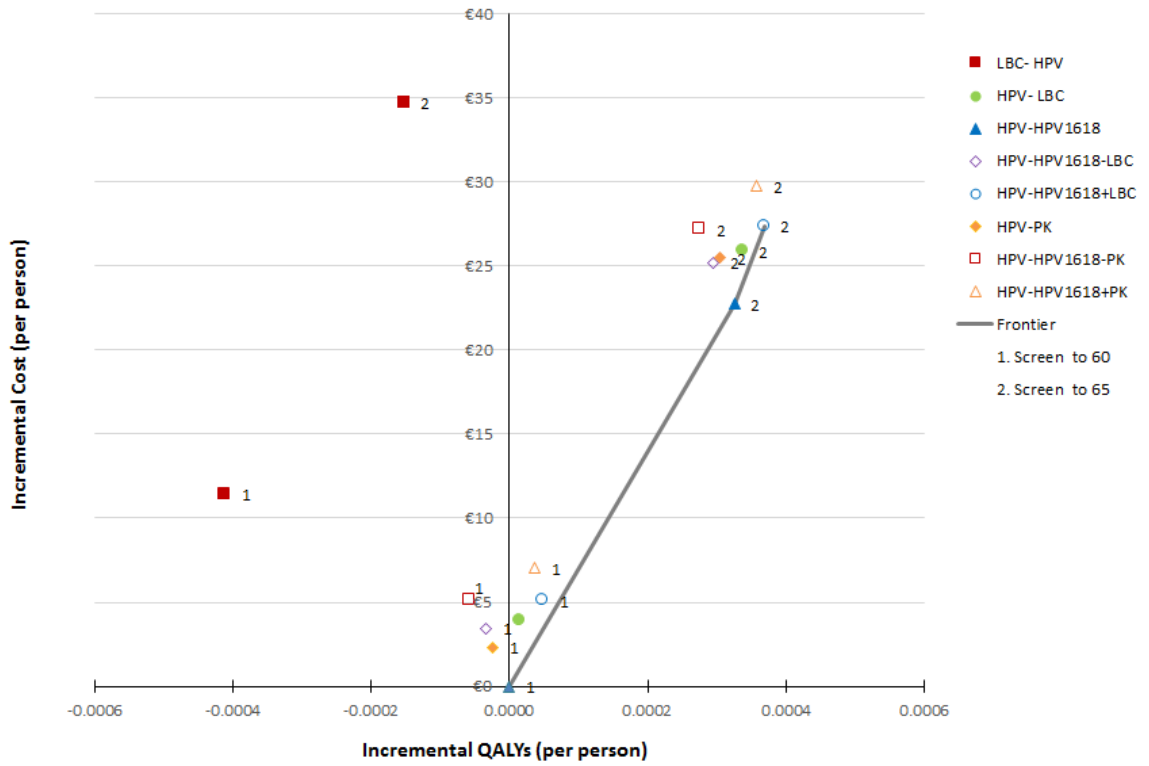
Figure 5.29 Cost-effectiveness plane (QALYs) for an unvaccinated cohort aged 50, with current practice as the base case



Key: LBC-HPV denotes LBC primary testing followed by HPV triage; HPV-LBC denotes HPV primary testing followed by LBC triage; HPV-1618 denote HPV primary testing followed by partial genotyping of HPV 16 and HVP18; HPV-PK denotes HPV primary testing followed by p16INK4a/Ki-67 triage; HPV-1618-LBC denotes HPV primary testing followed by triage testing with partial genotyping of HPV 16 and HVP18 and if positive a further triage test of LBC; HPV-1618+LBC denotes HPV primary testing followed by triage testing with a co-test of partial genotyping of HPV 16 and HVP18 and LBC; HPV-1618-PK denotes HPV primary testing followed by triage testing with partial genotyping of HPV 16 and HVP18 and if positive a further triage test of p16INK4a/Ki-67; HPV-1618+PK denotes HPV primary testing followed by triage testing with a co-test of partial genotyping of HPV 16 and HPV 18 and p16INK4a/Ki-67.

To aid in presentation the graph has been represented with the least costly option as the base case. Figure 5.30 shows where each comparator lies on the cost-effectiveness plane when the least costly option, primary HPV screening followed by partial genotyping triage to 60 years, is used as the base case.

Figure 5.30 Cost-effectiveness plane (QALYs) for an unvaccinated cohort aged 50, with the least costly option (HPV primary screening followed by partial genotyping triage to 60) as the base case



Key: LBC-HPV denotes LBC primary testing followed by HPV triage; HPV-LBC denotes HPV primary testing followed by LBC triage; HPV-1618 denote HPV primary testing followed by partial genotyping of HPV 16 and HVP18; HPV-PK denotes HPV primary testing followed by p16INK4a/Ki-67 triage; HPV-1618-LBC denotes HPV primary testing followed by triage testing with partial genotyping of HPV 16 and HVP18 and if positive a further triage test of LBC; HPV-1618+LBC denotes HPV primary testing followed by triage testing with a co-test of partial genotyping of HPV 16 and HVP18 and LBC; ; HPV-1618-PK denotes HPV primary testing followed by triage testing with partial genotyping of HPV 16 and HVP18 and if positive a further triage test of p16INK4a/Ki-67; HPV-1618+PK denotes HPV primary testing followed by triage testing with a co-test of partial genotyping of HPV 16 and HPV 18 and p16INK4a/Ki-67.

Table 5.19 shows the incremental cost-effectiveness ratios (ICERs) per QALY for each comparator relative to the next best option, excluding dominated strategies. The base case comparator (primary HPV testing followed by HPV partial genotyping, at five-yearly intervals to age 60) was the least costly option. Extending this strategy to 65 years increases the effectiveness, but also increases the cost with an ICER of €69,910 per QALY. This would not be considered cost-effective under willingness-to-pay thresholds in the range of €20,000 to €45,000 per QALY.

Table 5.19 Estimated incremental cost-effectiveness ratios (€/QALY) for an unvaccinated cohort aged over 50

Strategy	Cost (€)	Incremental Cost (€)	Effectiveness (QALYs)	Incremental Effectiveness (QALYs)	ICER (€/QALYs)
Base case (HPV-HPV1618 screen to 60)	199		13.18255		
HPV-HPV1618 screen to 65	222	23	13.18288	0.00033	69,910
HPV-HPV1618+LBC screen to 65	227	5	13.18292	0.00004	106,736

Abbreviations: QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio.
Note all values are discounted.

Table 5.20 Results for the subgroup analysis of an unvaccinated cohort who first access organised screening aged 50, ordered by decreasing intensity of screening within each strategy

Strategy	Per 100,000					
	Cost (€)	QALYs	Average number of screens	Cervical cancer cases (n)	Cervical cancer deaths (n)	Colposcopy referrals (n)
LBC- HPV screen to 65	234	13.1824	2.7	280	94	2,932
LBC- HPV screen to 60	211	13.1821	2.1	314	108	2,171
HPV- LBC screen to 65	225	13.1829	2.7	258	86	2,965
HPV- LBC screen to 60	**203**	**13.1826**	**2.1**	**297**	**103**	**2,202**
HPV-HPV1618 screen to 65	222	13.1829	2.7	259	87	3,200
HPV-HPV1618 screen to 60	199	13.1825	2.1	298	103	2,376
HPV-HPV1618-LBC screen to 65	224	13.1828	2.7	263	89	2,378
HPV-HPV1618-LBC screen to 60	203	13.1825	2.1	301	105	1,769
HPV-HPV1618+LBC screen to 65	227	13.1829	2.7	255	85	3,781
HPV-HPV1618+LBC screen to 60	204	13.1826	2.1	294	101	2,805
HPV-PK screen to 65	225	13.1829	2.7	261	88	2,700
HPV-PK screen to 60	202	13.1825	2.1	300	104	2,006
HPV-HPV1618-PK screen to 65	226	13.1828	2.7	265	90	2,251
HPV-HPV1618-PK screen to 60	204	13.1825	2.1	302	106	1,675
HPV-HPV1618+PK screen to 65	229	13.1829	2.7	256	85	3,644
HPV-HPV1618+PK screen to 60	206	13.1826	2.1	295	102	2,704

Abbreviations: QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio.
Costs and QALYs are discounted, whereas cancer cases and cases deaths are undiscounted.
Key: LBC-HPV denotes LBC primary testing followed by HPV triage; HPV-LBC denotes HPV primary testing followed by LBC triage; HPV-1618 denote HPV primary testing followed by partial genotyping of HPV 16 and HVP18; HPV-PK denotes HPV primary testing followed by p16INK4a/Ki-67 triage; HPV-1618-LBC denotes HPV primary testing followed by triage testing with partial genotyping of HPV 16 and HVP18 and if positive a further triage test of LBC; HPV-1618+LBC denotes HPV primary testing followed by triage testing with a co-test of partial genotyping of HPV 16 and HVP18 and LBC; ; HPV-1618-PK denotes HPV primary testing followed by triage testing with partial genotyping of HPV 16 and HVP18 and if positive a further triage test of p16INK4a/Ki-67; HPV-1618+PK denotes HPV primary testing followed by triage testing with a co-test of partial genotyping of HPV 16 and HPV 18 and p16INK4a/Ki-67.

5.6.2 Subgroup analysis 2: Unvaccinated women under age 30

The second subgroup analysis investigates how best to screen women under the age of 30 years. In the main analysis, a single strategy allowing for a different testing strategy for younger women (LBC primary testing to those aged less than 30 years and HPV primary testing for those aged 30 years and over) was included with all screening at three-yearly intervals from age 25 to 44 years, and at five yearly intervals thereafter. This was not found to be cost-effective. However, in the context of changing to five-yearly HPV primary testing with LBC triage from age 30 onwards, it is unclear what the optimal screening for the subgroup of women aged less than 30 is.

As documented in Chapter 3, rates of both HPV positivity and abnormal cytology are very high in the 25-to-29-years age group. Within this age group, HPV infection is also more likely to clear spontaneously and in the absence of persistent infection, cytological abnormalities will typically regress. As this subgroup has high rates of both HPV infection and abnormalities, it is plausible that continuing with three-yearly screening until they reach 30 years could be beneficial for these women. Therefore, this HTA has considered a number of additional strategies for this age group. In all cases, it is assumed that the optimal strategy of HPV primary testing followed by LBC triage would be used for women over the age of 30.

Five strategies were modeled for an unvaccinated cohort. In all strategies women over 30 years had five-yearly screening with primary HPV followed by a LBC triage test and each strategy was modeled to both 60 and 65 years to create 10 different strategies in total. As in the main analysis, women who have high-grade cytological abnormalities or who are HPV positive and have low-grade cytological abnormalities are referred directly to colposcopy. Women who are HPV positiive, but LBC negative are recalled for screening at 12 months. If still HPV positive at 12 months, this is considered evidence of persistent infection and the woman is referred to colposcopy regardless of the result of the LBC triage test. Given the higher prevalence of HPV in women under 30, one alternative pathway was considered that incorporates HPV 16 and HPV 18 partial genotyping. Those women who are HPV positive, but LBC negative, are only referred to colposcopy if positive on a partial genotyping HPV 16 and HPV 18 triage test. If partial genotyping is negative they would be recalled again in 12 months, and this cycle would repeat until either the woman cleared HPV, developed cytological abnormalities, was positive on partial genotyping or was over 30 (at which point they would be directly referred to colposcopy). Thus, the management of HPV positive, cytology negative women within the five strategies considered was as follows:

1. Five-yearly primary HPV with LBC triage, from age 25 years. All women who have a repeat positive HPV test at 12 months are referred to colposcopy.

2. Three-yearly primary HPV with LBC triage, from ages 25 to 30 years, and five-yearly thereafter. All women who have a repeat positive HPV test at 12 months are referred to colposcopy.

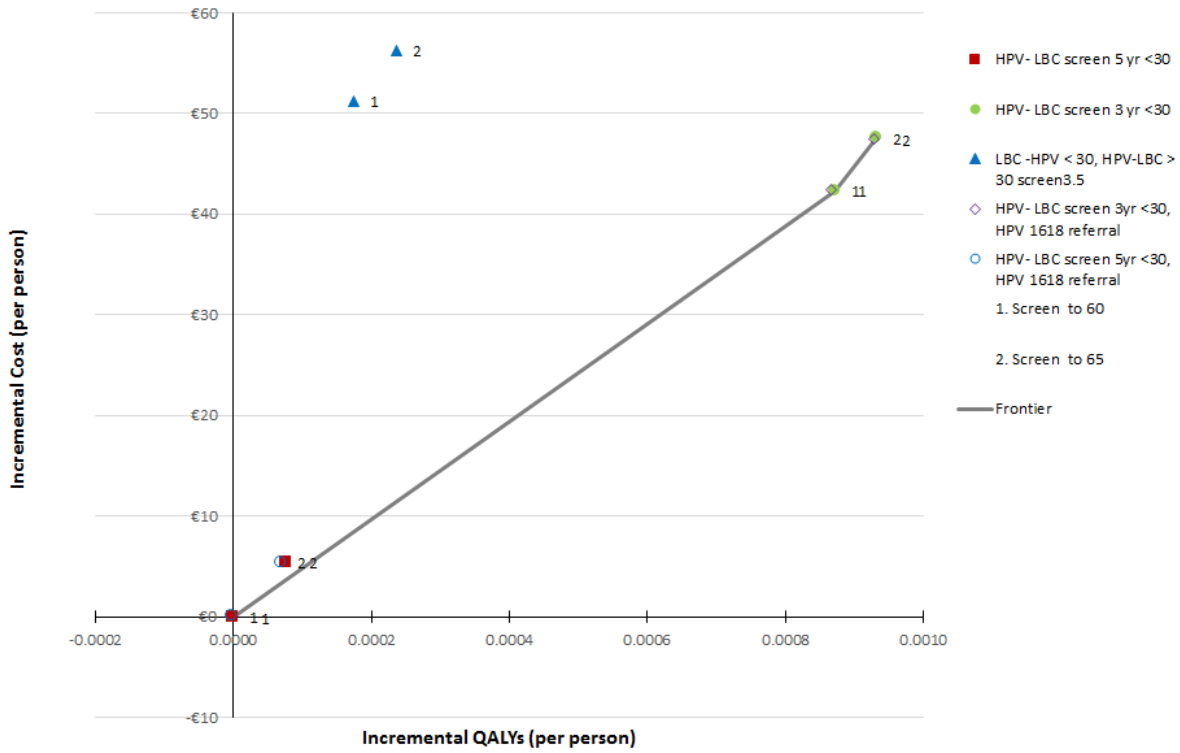
3. Three-yearly primary LBC with HPV triage, from ages 25 to 30 years, and five-yearly primary HPV with LBC triage thereafter. All women who have a repeat positive HPV test at 12 months are referred to colposcopy.

4. Five-yearly primary HPV with LBC triage, from age 25. At 12 months, all cytology-negative women under 30 are required to be positive for both HPV and HPV 16 or 18 to be referred to colposcopy. If HPV positive, but HPV 16 or 18 negative they are recalled again in 12 months. This cycle repeats until they are over the age of 30, at which point if still HPV positive they are referred to colposcopy regardless of the results of the HPV16 or 18 test or the LBC triage test.

5. Three-yearly primary HPV with LBC triage, from ages 25 to 30, but five-yearly thereafter. At 12 months, all cytology-negative women under 30 are required to be positive for both HPV and HPV 16 or 18 to be referred to colposcopy. If HPV positive, but HPV 16 or 18 negative they are recalled again in 12 months. This cycle repeats until they are over the age of 30, at which point, if still HPV positive, they are referred to colposcopy regardless of the results of the HPV 16 or 18 test or the LBC triage test.

It was assumed that all other assumptions and parameters values remained unchanged. Figure 5.31 shows where each comparator lies on the cost-effectiveness plane when outcomes are measured in QALYS and five-yearly primary HPV followed by LBC triage from age 25 to 60 is used as the base case.

Figure 5.31 Cost-effectiveness plane (QALYs) for an unvaccinated cohort, with five-yearly primary HPV followed by LBC triage from age 25 to 60 as the base case with alternative strategies for those under 30



Key: HPV-LBC denotes HPV primary testing followed by LBC triage; LBC-HPV denotes LBC primary testing followed by HPV triage; with referral plus HPV1618<30 denotes the alternative referral pathway where women are required to be positive for both HPV and HPV16/18 at 12 months to be referred to colposcopy, where LBC triage is negative. If HPV positive and LBC triage positive they will be referred to colposcopy. If HPV positive, but HPV 16/18 negative they are recalled again in 12 months. This cycle repeats until they are over the age of 30, at which point, if HPV positive, they are referred to colposcopy regardless of the results of the HPV16/18 test or the LBC triage test.

Table 5.21 shows the incremental cost-effectiveness ratios (ICERs) per QALY for each comparator relative to the next best option, excluding dominated strategies. The base case comparator (primary HPV testing followed by LBC triage, at five-yearly intervals to age 60) was the least costly option. Adding an additional screening for women under 30 years to this strategy (that is three-yearly screening from age 25 then five-yearly screening from age 30), increases the effectiveness, but also increases the cost, with an ICER of €48,501 per QALY. This would not be considered cost-effective under willingness-to-pay thresholds in the range of €20,000 to €45,000 per QALY.

Table 5.21 Estimated incremental cost-effectiveness ratios (€/QALY), of alternative screening strategies for those under 30 in an unvaccinated cohort, with 5 yearly HPV followed by LBC from 25 to 60 as the base case

Strategy	Cost (€)	Incremental Cost (€)	Effectiveness (QALYs)	Incremental Effectiveness (QALYs)	ICER (€/ QALYs)
Base case (HPV- LBC screen 5yr to 60*)	324		17.3685		
HPV- LBC screen 3yr 30, and 5 yr to 60	367	42	17.3694	0.0009	48,501
HPV- LBC screen 3yr 30, and 5 yr to 65	372	5	17.3695	0.0001	86,077

Abbreviations: QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio; LBC, liquid-based cytology.
*Where women at all ages who are HPV positive but cytology negative are recalled at 12 months and referred to colposcopy if HPV positive at 12 months.

Table 5.22 illustrates the average costs and clinical benefits per woman and per 100,000 population for a one-year cohort modelled from age 25 to end of life. Adding an additional screening for women under 30 years (that is three-yearly screening from age 25 then five-yearly screening from age 30), would increase the average lifetime number of screenings and the number of colposcopy referrals. However, it remains unclear how best to manage women who are HPV positive, but cytology negative. The two alternative pathways (referral to colposcopy if HPV positive at 12 months or referral only if positive for HPV 16 and 18 on partial genotyping) modelled are almost identical in terms of costs and clinical effectiveness. Incorporation of HPV 16 and 18 partial genotyping would however lead to fewer colposcopy referrals.

Table 5.22 Results for the subgroup analysis of an unvaccinated cohort under 30, ordered by decreasing intensity of screening within each strategy

Strategy	Per woman			Per 100,000		
	Cost (€)	QALYs	Average number of screens	Cervical cancer cases (n)	Cervical cancer deaths (n)	Colposcopy referrals (n)
HPV- LBC screen3.5 to 65	372	17.3695	7.217	360	92	11,470
HPV- LBC screen3.5 to 60	367	17.3694	6.654	393	106	10,766
HPV- LBC screen5 to 65	330	17.3686	6.478	399	99	10,188
HPV- LBC screen5 to 60	**324**	**17.3685**	**5.907**	**433**	**114**	**9,478**
HPV- LBC screen3.5 to 65, with referral plus HPV1618<30	372	17.3694	7.217	360	92	11,291
HPV- LBC screen3.5 to 60, with referral plus HPV1618<30	367	17.3694	6.656	394	106	10,591
HPV- LBC screen5 to 65, with referral plus HPV1618<30	330	17.3686	6.479	399	99	10,083
HPV- LBC screen5 to 60, with referral plus HPV1618<30	324	17.3685	5.908	434	114	9,374
LBC -HPV < 30, HPV-LBC > 30 screen3.5 to 65	381	17.3688	7.185	376	94	11,709
LBC -HPV < 30, HPV-LBC > 30 screen3.5 to 60	376	17.3687	6.623	409	108	11,009

Abbreviations: QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio; LBC, liquid-based cytology.
Costs and QALYs are discounted, whereas cancer cases and cases deaths are undiscounted.
Women who are HPV positive but cytology negative are recalled at 12 months and referred to colposcopy if HPV positive at 12 months.
Key: HPV-LBC denotes HPV primary testing followed by LBC triage; LBC-HPV denotes LBC primary testing followed by HPV triage; with referral plus HPV1618<30 denotes the alternative referral pathway where women are required to be positive for both HPV and HPV16/18 at 12 months to be referred to colposcopy, where LBC triage is negative. If HPV positive and LBC triage positive they will be referred to colposcopy. If HPV positive, but HPV 16/18 negative they are recalled again in 12 months. This cycle repeats until they are over the age of 30, at which point, if HPV positive, they are referred to colposcopy regardless of the results of the HPV16/18 test or the LBC triage test.

5.7 Discussion

A review of economic evaluations comparing primary HPV screening with primary liquid-based cytology (LBC) screening for the prevention of cervical cancer found consistent evidence that cervical screening programmes using HPV testing as the primary screening test are cost-effective and potentially cost saving when compared with programmes using cytology as the primary screening test. However, it was not possible to determine the optimal screening strategy from the available literature. No study was identified that considered a strategy which reflects the current cervical screening programme in place in Ireland.

An economic model was therefore developed to estimate the cost-effectiveness of 32 alternative screening strategies relative to current screening practice in Ireland, for both a vaccinated and unvaccinated cohort. The parameters used in the model were derived from a wide variety of sources. A Markov model that simulated a cohort from age 25 to death was used to determine the impact of the different screening strategies. Benefits were measured in terms of both life years gained and quality-adjusted life years.

5.7.1 Main findings

The current screening strategy of LBC primary testing followed by HPV triage testing was found to be less effective and more costly than almost all alternatives in both a vaccinated and an unvaccinated cohort.

For an unvaccinated cohort, based on quality-adjusted life years and given a willingness-to-pay threshold in the range of €20,000 to €45,000 per QALY, HPV primary testing followed by LBC triage at five-yearly intervals until age 60 was the cost-effective strategy, with an ICER of €29,788 per QALY. The probability that it was the cost-effective option at a threshold of €45,000 per QALY was 20%.

For a vaccinated cohort, HPV primary testing followed by LBC triage at five-yearly intervals until age 60 was also the cost-effective strategy with an ICER of €58,745 per QALY relative to no screening. The probability that it was the cost-effective option at a threshold €45,000 per QALY was 15%.

Compared with the current screening policy, the net eight-year budget impact of switching to HPV primary testing followed by LBC triage at five-yearly intervals until age 60 was estimated at a saving of up to €3 million for the population vaccinated against HPV 16 and 18, €32 million for the unvaccinated population, and up to €35 million for the entire CervicalCheck population.

Based on the results of the economic evaluation, HPV primary testing followed by LBC triage at five-yearly intervals until age 60 was found to be the optimal strategy, that is, it was the cost-effective strategy given a willingness-to-pay threshold in the range of €20,000 to €45,000 per QALY. However, while having comparable efficacy to current screening practice, it was not the most effective strategy. Using the willingness-to–pay threshold allows for comparison to be made across the entire health service and identifies when interventions can be considered good value for money. Applying the willingness-to-pay threshold to guide the choice in the optimal strategy ensures that where the health gains are small relative to the increase in costs, this is highlighted and consideration can be given to redistributing resources to elsewhere within the health system to maximise the benefit for the entire population.

5.7.2 Sensitivity and subgroup analysis

A univariate sensitivity analysis highlighted that the most influential parameter on the cost difference between the strategies was the cost of the primary screening tests. For differences in effectiveness, the test accuracy of LBC was most influential. Lowering the sensitivity of LBC for CIN 3+ and for CIN 2 would result in five-yearly HPV-primary testing followed by LBC triage being more effective than the more intensive current screening practice (LBC followed by HPV triage three-yearly from 25 to 44 years and five-yearly from 45 to 60 years). The sensitivity analysis also highlighted how variation in the estimates of how HPV infection progresses through CIN 1, CIN 2, CIN 3 and into cervical cancer influences the cost-effectiveness estimates for both a unvaccinated and a vaccinated cohort.

There are a number of different sets of progression and regression probabilities through the CIN states published in the literature which have been calibrated to various national data sets. For the unvaccinated cohort, the base case values for the regression and progression probabilities were chosen by calibration to Irish data, and provided a good fit for both the observed prevalence of HPV and the incidence of cervical cancer. However, it is clear from the sensitivity analysis that variation in these transition probabilities is influential on the cost-effectiveness estimate. Similarly for the vaccinated cohort, the base case values for the probabilities of progressing and regressing from HPV infection to cervical cancer were chosen by calibration to Irish data, and provide a good fit for the observed prevalence of HPV and an estimated reduction in the incidence of cervical cancer of 70% compared with an unvaccinated cohort. As data are not currently available for the incidence of cervical cancer in a vaccinated cohort, there is clearly more uncertainty in the vaccinated cohort model compared with the unvaccinated cohort model.

Two subgroup analyses were defined. The first considers extending the screening exit age from 60 to 65 years in a cohort who have not had the benefit of lifetime access to organised screening from age 25, but who have only been offered access to organised screening since the age of 50. For this cohort, it was assumed that these women were offered screening for the first time women at age 50. The optimal screening strategy for this cohort was found to be primary HPV testing followed by HPV partial genotyping at five-yearly intervals to age 60. Extending this strategy to age 65 years marginally increases its effectiveness. However, due to the additional costs incurred it becomes less cost-effective. With an ICER of €69,910 per QALY, it would not be considered cost-effective under willingness-to-pay thresholds in the range of €20,000 to €45,000 per QALY.

The second subgroup analysis considered how best to screen women under 30 years, in the context of five-yearly HPV primary testing with LBC triage from age 30 onwards. As documented in Chapter 3, rates of both HPV positivity and abnormal cytology are very high in the 25 to 29 age group. However within this age group the infection is also more likely to clear spontaneously and, in the absence of persistent infection, cytological abnormalities will typically regress. The optimal screening strategy for this subgroup of unvaccinated women under the age of 30 years was found to be primary HPV screening followed by LBC triage at five-yearly intervals from age 25 to age 60 years. Providing three-yearly screening in those under 30 (that is, adding one more screening round) increases the effectiveness of this strategy, but also increases the cost with an ICER of €48,501 per QALY. This would not be considered cost-effective under willingness-to-pay thresholds in the range of €20,000 to €45,000 per QALY. It remains unclear how best to manage women in this age group who are HPV positive but cytology negative. The two alternative pathway models were found to be almost identical in terms of costs and clinical effectiveness (as measured with QALYs), with the requirement to be positive for partial genotyping leading to fewer referrals to colposcopy.

5.7.3 Limitations of the economic model

There are important limitations associated with the economic analysis that need to be considered when interpreting the results. These can broadly be assigned to two categories: parameter uncertainty and model uncertainty.

Parameter uncertainty arises where there is a lack of reliable data to inform model inputs, such as the population prevalence of CIN 1, CIN 2 and CIN 3 in both unvaccinated and vaccinated populations. There can also be uncertainty related to parameter variability, since some parameters naturally vary over time even when measured accurately. Model uncertainty (also called structural uncertainty) arises from the choices made regarding the functional form of the model used to represent

the real world. If the model fails to adequately capture the natural history in the progression from HPV infection to cervical cancer, then there can be little expectation of an accurate result even if the true value of all input parameters were known.

There is always a degree of uncertainty surrounding model parameters and standard methods to handle this have been used in the analysis. These include Monte Carlo simulation to quantify the level of confidence around the cost-effectiveness results and univariate deterministic sensitivity analysis to examine the effect of uncertainty associated with individual parameters. In this section, the strengths and weaknesses of the available Irish data on a number of key parameters are discussed further, along with the implications these may have for the model results.

No Irish data on quality of life for women under surveillance for CIN 1, in treatment for CIN 2, CIN 3 and cervical cancer (by FIGO stage) and for survivors of cervical cancer were available. These data were taken from international literature; however, it must be noted that there is no consensus within the literature on the most appropriate set of QALY data to use, and previous economic evaluations have found the cost-effectiveness estimate to be sensitive to the chosen QALY estimates.[10, 218, 219]

In an analysis using QALY outcomes, it is the accuracy of the test, the intensity of screening and the quality of life estimates which determine the entirety of the clinical benefit in the model. This is weighted against the overall cost to calculate the incremental cost-effectiveness of competing strategies. Therefore any differences between Irish and the estimated international QALY outcomes may have important implications for the analysis. However, the analysis was also conducted using life years gained as the primary outcome, and the results were consistent with those based on the QALY analysis. Despite these potential issues with the QALY estimates, the difference in QALY gains is a more valid way to compare the overall effectiveness of the alternative strategies. Consideration of the relative difference in QALYs rather than the relative number of cancer cases and cancer deaths has the advantage in that QALYs account for the differences in the quantity and quality of life. For example, QALYs account for stage at cancer diagnosis - treatment pathways for those diagnosed at FIGO stage 1 versus FIGO stage 4 disease may differ substantially in their impact on quality of life. They also take into account any difference in the duration of survival for those who die from cervical cancer.

QALYs also account for harms due to screening including overdiagnosis. Overdiagnosis refers to the identification of abnormalities that would not otherwise become clinically significant. Overdiagnosis may lead to a loss of quality of life due to increased surveillance of CIN 1 potentially increasing stress and anxiety and unnecessary treatment of CIN 2 and CIN 3 lesions. The QALY estimates have also been discounted

to reflect society's preference for benefits to be realised sooner and undesirable effects to be realised further into the future.

The test accuracy data underpinning the triage tests is based on a small number of high-quality studies. As discussed in Chapter 4, this was deemed sufficiently applicable to be used within the economic model. However, it is worth noting that only one study was available to estimate the accuracy of the $p16^{INK4a}$/Ki-67 dual stain triage strategy. There is therefore greater uncertainty around the strategies that include this option. Along with the uncertainty in the effectiveness of this test there is also greater uncertainty in the estimated costs for $p16^{INK4a}$/Ki-67 as this test is in not currently in widespread use in Ireland. The cost estimates for $p16^{INK4a}$/Ki-67 are based on the current cost. However, this may be an overestimate as it is likely that the cost of this test may drop if subjected to a competitive tendering process for potential adoption as the triage test used by CervicalCheck.

The model was conducted from the perspective of a publicly-funded health and social care system, that is only direct medical costs were included. Adoption of this perspective is consistent with national guidelines.[225] However, it means that any potential reductions in indirect costs were not considered. These would have included increased productivity where cervical cancer cases or deaths are avoided; a reduction in out-of pocket expenses incurred by women attending screening in the less intensive screening strategies and a reduction in out-of pocket expense when attending for diagnostic testing for those strategies with a lower colposcopy referral rate.

Uncertainty in relation to the structure of the model was dealt with by eliciting the input of the Expert Advisory Group and other relevant people to describe both the screening service and the patient pathway through treatment. The model was developed as a natural history model where the progression of HPV infection through to the development of cervical cancer was modelled. The structure of our natural history model was based upon the structure of the German cervical screening model.[229] The model structure was reviewed by the Expert Advisory Group prior to finalisation and is consistent with modelling approaches adopted in previous cost-effectiveness studies within the literature.

For the unvaccinated cohort, the estimated transition probabilities were varied within plausible ranges taken from the literature and calibrated to both Irish prevalence of HPV data and cancer incidence. These calibrated transition probabilities are similar to those used in other natural history models of cervical cancer which have been calibrated in different population settings. However, the model was not calibrated to the Irish prevalence of CIN 1, CIN 2 and CIN 3, and there is thus greater uncertainty around the modelled predictions for these states. Comparing the predicted prevalences in these states (1.46%, 0.46% and 0.66% for CIN 1, CIN 2 and CIN 3,

respectively) to the detected rates seen in CervicalCheck (0.79%, 0.43% and 0.64% for CIN 1, CIN 2 and CIN 3, respectively) shows that the modelled estimates are broadly consistent. However, when these were compared against detected rates in the UK-based ARTISTIC trial[179] (1.2% and 1.27% for CIN 2 and CIN 3, respectively) the modelled estimates appeared to be underestimating the prevalence of CIN 2 and CIN 3. If the prevalence of detected CIN 2 and CIN 3 have been underestimated, then this will directly impact on the reported numbers of colposcopy referrals, which may be underestimated, along with the costs associated with them.

The model was a calibrated model that was fit to observed cancer incidence. However, the model did slightly underestimate the cancer incidence in women aged over 55 years. Although the underestimate was small, it could potentially bias against strategies which target older women, especially if the incidence of cervical cancer in these age groups was to increase.

For the vaccinated cohort, as with the unvaccinated cohort, the model was calibrated to prevalence of HPV and incidence of cervical cancer. Irish data on the prevalence of HPV by genotype was available, however incidence of cervical cancer by genotype was not available. For this reason, the Evaluation Team calibrated the model to see a 70% reduction in the incidence of cervical cancer relative to an unvaccinated cohort, which may not accurately predict the true incidence of cervical cancer in an Irish vaccinated cohort. There is also greater uncertainty around how vaccinated women will progress through the precancerous states from HPV infection to cervical cancer as there is currently a lack of data on the longer term outcomes from HPV vaccination. This HTA assumed that progression would follow a similar but slower pattern than for the unvaccinated cohort. The uncertainty in the progression through the cancerous states will have a number of potential impacts. If the progression is overestimated, this will potentially bias against the less intensive screening options, where the screening interval can be safely extended and gains in effectiveness seen in the more intensive screening strategies may actually be overtreatment of precancerous abnormalities which would not otherwise progress. If alternatively progression is underestimated, the model will predict fewer referrals to colposcopy, with fewer treatments for precancerous abnormalities, and will potentially bias towards the less intensive screening strategies.

For the vaccinated cohort, the proportion of vaccinated women entering CervicalCheck will not stabilise until 2023. However, the HPV vaccination rates observed in the national immunisation programme which remained high and stable from 2011 to 2015 have dropped in the most recent year. Whether uptake will drop further, stabilise at a lower uptake rate or improve back to the previous rate in excess of 80% is unknown. Currently the HPV vaccine offered to girls is the

quadrivalent vaccine which is estimated to reduce the incidence of cervical cancer by 70%. Further innovations in this field may have further implications for the incidence of cervical cancer. For example, a nonavalent vaccine has been licensed that offers protection against nine HPV types and is estimated to reduce the incidence of cervical cancer by 90% when compared with no vaccination. As the risk of cervical cancer in the population eligible for screening decreases, then the cost-effective screening strategy is likely to change and may need to be reconsidered.

The model was a cohort model which followed vaccinated and unvaccinated population cohorts from age 25 years to death. One limitation of this modelling structure in the context of screening is that all women at each screening round (excluding those under higher surveillance) are considered to have the same probability of attending screening. In practice however, we would expect women who are poorly compliant with screening or who have not previously attended for screening to have a lower attendance rate at subsequent screening rounds. As these habitual poor attendees and non-attendees may have a higher risk of cervical cancer,[244] the model will potentially overestimate the effect of screening by considering the average risk for all women. This may be particularly relevant for those strategies where the screening interval is extended to age 65, as the women attending at the final round are more likely to be those who have previously attended screening and thus have a lower cervical cancer risk than the cohort as a whole. The model is thus likely to overestimate the effectiveness in these strategies.

This evaluation considered 32 potential strategies.The chosen strategies were considered based on the available literature and on what could feasibly be delivered by CervicalCheck. However, it is possible that better options exist that were not considered. This is particularly relevant for the vaccinated cohort where none of the modelled strategies were cost-effective relative to no screening at a willingness-to-pay threshold of €45,000 per QALY. Given the reduced risk of cervical cancer in the vaccinated cohort, it is plausible that there are less intensive screening options which would be considered cost-effective for this cohort. However, all of the alternative strategies modelled would potentially offer an improvement in terms of cost-effectiveness compared to current screening practice.

5.7.4 Interpretation of the results

Cervical screening is effective at reducing the incidence of cervical cancer. Moving to a strategy of primary HPV screening is likely to both reduce costs and provide comparable or improved clinical effectiveness compared with a primary liquid-based cytology (LBC) testing strategy. This is the case for both unvaccinated and vaccinated cohorts, with the improved benefits relatively larger in a vaccinated cohort.

Based on cost per quality-adjusted life years for an unvaccinated cohort, HPV primary testing followed by LBC triage testing at five-yearly intervals to age 60 is the most cost-effective strategy and provides comparable clinical efficacy to current practice when measured in terms of QALYs gained. However, based on the parameter values used in this evaluation and willingness-to-pay thresholds of up to €45,000 per QALY, this strategy is not considered cost-effective in a vaccinated population. A switch to HPV primary testing followed by LBC triage testing at five-yearly intervals to age 60, would result in a net budget saving of up to €35 million over eight years relative to the current screening programme.

There was substantial uncertainty regarding a number of the key parameters, all of which were allowed to vary within plausible ranges in the main analysis. For the vaccinated cohort, where longer term data on the development of cervical cancer by these women is not yet available, it is difficult to accurately predict the cost-effectiveness of cervical screening. As such, a policy of continued screening in this cohort may not be unreasonable until further data emerge.

5.8 Key messages

- A review of the evidence of the cost-effectiveness of HPV testing as the primary screening method for cervical cancer identified eight relevant studies. However, given differences in healthcare delivery costs and screening programmes considered, it is not possible to determine the optimal screening strategy for Ireland based on the available literature.
- Thirty-two different screening strategies were modelled in the analysis, including two different primary tests (HPV testing and liquid-based cytology [LBC]), four different triaging tests (HPV testing, LBC, partial genotyping for HPV 16 and HPV 18, and $p16^{INK4a}$/Ki-67), two different screening intervals (three-yearly to 45 and five-yearly throughout) and two different screening exit ages (60 and 65). All strategies were considered for both an unvaccinated and a vaccinated cohort.
- For the unvaccinated cohort:
  - The current strategy of primary LBC testing followed by HPV triage at three-yearly intervals until age 45 and five-yearly intervals until age 60 was more costly and either less or equally effective, when compared with all other options (apart from extending the current strategy to age 65 and primary HPV screening followed by triage comprising co-testing with partial genotyping and $p16^{INK4a}$/Ki-67 with screening extended to age 65).
  - Five-yearly primary HPV testing followed by LBC triage test from age 25 to 60 years was cost-effective with an ICER of €29,788 per QALY given willingness-to-pay thresholds in the region of €45,000 per QALY. While this strategy provides comparable clinical effectiveness to current practice, a number of the other strategies modelled were more effective. Although these strategies were more effective, their incremental gain in effectiveness would not be considered cost-effective for the incremental increase in cost.
  - Subgroup analysis that considered women who only had access to organised screening from age 50 years confirmed that extending the upper screening age limit from 60 to 65 years provides a clinical benefit, but is not cost-effective under willingness-to-pay thresholds in the range of €20,000 to €45,000 per QALY, irrespective of when access to organised screening starts (25 or 50 years).
- In the context of primary HPV screening followed by LBC triage at five-yearly intervals from age 30 years, a subgroup analysis considered alternative screening strategies in unvaccinated women aged under 30 years. Although they provide additional clinical benefit, none of the strategies that considered an additional screening round (that is, three-yearly screening in women aged less than 30 years) were found to be cost-effective under willingness-to-pay thresholds in the range of €20,000 to €45,000 per QALY.

- For the vaccinated cohort:
  - The current strategy was less effective and more costly when compared with all other options (apart from the current strategy extended to age 65).
  - None of the modelled strategies were considered cost-effective compared with no screening at a willingness-to pay threshold of €45,000 per QALY.
  - There is uncertainty around how vaccinated women will progress through the precancerous states from HPV infection to cervical cancer. It was assumed that the risk of developing cervical cancer is 70% lower in vaccinated women. This parameter is very influential on the predicted cases of cervical cancer within the model and thus whether the modelled strategies are cost-effective.
  - As more effective HPV vaccines become available, the risk of vaccinated women developing cervical cancer may reduce even further. Given their lower risk of developing cervical cancer, less intensive screening strategies, which have not been modelled in this evaluation, may be more appropriate.
- Compared with the current screening practice, the net incremental eight-year budget impact for primary HPV screening followed by LBC triage testing at five-yearly intervals from age 25 to 60 resulted in a saving of up to €3 million for the cohort against HPV 16 and 18, €32 million for the unvaccinated cohort, and up to €35 million for the whole CervicalCheck population.

6 Organisational and social implications

This chapter provides a review of the potential organisational implications that the introduction of HPV testing as the primary screening test would have for CervicalCheck - Ireland's National Cervical Screening Programme, as well as potential social implications.

Since its introduction in September 2008, CervicalCheck has used liquid-based cytology (LBC) as its primary screening test. Screening is at three-yearly intervals for women aged 25 to 44 years and at five-yearly intervals for those aged 45 to 60 years. Women with (normal) negative cytology are referred back to routine screening. Women with high-grade cytological abnormalities are referred directly to colposcopy. In May 2015, CervicalCheck adopted HPV testing as a triage test when low-grade cytological abnormalities (ASCUS and LSIL) are detected on LBC. Women with a positive HPV triage test are referred to colposcopy. Women with a negative HPV triage test are referred back to routine screening.

Staff involved in providing CervicalCheck include clinical staff in primary care, public gynaecology, genitourinary medicine (GUM) and STI services, administrative staff, colposcopy staff and laboratory staff. Outside of colposcopy settings, 98.5% of screening tests are undertaken in primary care, predominantly through GP practices. There are 15 colposcopy services currently working with CervicalCheck. Each service is delivered by a multidisciplinary team, based in an acute public hospital. Colposcopy staff include lead clinicians (consultant obstetricians and gynaecologists), nurse colposcopists, colposcopy nurse specialists and administrative staff.

As noted in Chapter 1, over the last decade evidence has emerged to suggest that using human papillomavirus (HPV) testing as the primary screening method has a higher sensitivity for the detection of cervical cancer than liquid-based cytology (LBC). Evidence has also emerged of the potential to increase the screening interval with a HPV-based testing programme. Newer HPV partial genotyping tests and molecular biomarkers have become available that provide additional information regarding the clinical relevance of an HPV infection. The first cohort of schoolgirls vaccinated against HPV through the national vaccination programme will be eligible for CervicalCheck in 2018-2019. Vaccination reduces the risk of cervical cancer and decreases the efficiency of cytology as a screening tool in a HPV-vaccinated cohort. As the number of vaccinated women increases they will represent a growing proportion of those eligible for screening through CervicalCheck. In consideration of all of these factors, this HTA was requested by CervicalCheck to examine potential opportunities to increase the clinical and cost-effectiveness of the existing programme.

An economic evaluation was undertaken to estimate the cost-effectiveness of 32 different screening strategies compared with current screening practice. The evaluation assessed the impact of changing to HPV-based primary testing in addition to changes to the triage test, screening interval, and extending the screening exit age from 60 to 65 years. All strategies were considered separately for both an unvaccinated and a vaccinated cohort. Current practice was found to be dominated by (that is, was less effective and more costly) almost all the alternative strategies considered. In both the unvaccinated and vaccinated cohorts, five-yearly screening using primary HPV testing followed by LBC triage from age 25 to 60 years was found to be the cost-effective strategy given typical willingness-to-pay thresholds used in Ireland (€20,000 to €45,000 per QALY). In addition to the main analysis, two subgroups were identified based on clinical need:

- extending the screening exit age from 60 to 65 years for women who have not had the benefit of lifetime cervical screening from the age of 25 years, but who have only been offered screening since the age of 50 years.
- management of unvaccinated women aged less than 30 years in the context of primary HPV screening and LBC triage at five-yearly intervals being provided once they reach 30 years.

As discussed in Chapter 5, extending screening to age 65 years for women who first obtained access to organised screening at age 50 was not found to be cost-effective; however, consideration could be given to providing this extension in order to reduce the burden of cervical cancer in this underscreened population. It was highlighted that the benefit of extended screening would only be realised if it is combined with an increase in screening uptake rates in those aged over 60 years.

The second subgroup analysis considered how best to screen women under the age of 30 years who are not vaccinated for HPV 16 and 18. These women have a high prevalence of both HPV and cervical abnormalities, and five-yearly screening may lead to an increase in interval cancers within this subgroup. The cost-effectiveness analysis showed that there would be a clinical benefit in offering one additional HPV primary screening test to these women before the age of 30 years, although the increase in cost meant that this was slightly above the higher threshold for cost-effectiveness of €45,000 per QALY. If implemented for clinical reasons, a question remains as to how best manage women aged under 30 years who screen HPV-positive, but cytology negative.

Two alternative referral pathways were considered in Chapter 5. In the first pathway, unvaccinated women aged under 30 years who were HPV-positive at 12 months were referred directly to colposcopy. In the second, only those also positive

for HPV 16 or HPV 18 on partial genotyping test were referred for colposcopy. If negative for HPV 16 and HPV 18, then they would be recalled again for screening in another 12 months. Both pathways lead to similar clinical outcomes. The requirement for a positive partial genotyping test would reduce the number of colposcopy attendances in this age group, but would lead to repeated annual screening and potentially high levels of anxiety for some women. The implementation of partial genotyping in women under the age of 30 years would have logistical implications for CervicalCheck's laboratory services because these women would be on a different process pathway to women aged 30 years or over.

6.1 Organisational implications

Any changes to the current screening programme would have implications for CervicalCheck, for women eligible to avail of CervicalCheck, and for cancer services. This analysis of organisational issues focuses on the potential implications of changing from the current strategy to five-yearly screening based on primary HPV testing with LBC triage for all women. In primary HPV screening, women with negative primary HPV tests are referred back to routine screening. LBC triage is carried out on positive primary HPV tests. Women with abnormalities on LBC testing are referred to colposcopy, while those with negative LBC triage are recalled for a repeat HPV test in one year. Women with a repeat positive HPV test are considered to have persistent HPV infection and are referred to colposcopy regardless of the result of any triage test. Additional implications arising from the implementation of strategies for the two subgroups are also highlighted, where relevant.

6.1.1 Informed consent

Women currently participating in CervicalCheck provide informed consent for HPV triage testing and HPV testing to be carried out following treatment in colposcopy. The introduction of HPV testing as a primary screening test would result in all women being made aware of their current HPV status. Providing information to explain this change and to allow for informed consent would have a greater resource requirement in the initial screening round than in subsequent screening rounds. CervicalCheck information sheets and consent forms would need to updated, however, this would be a once-off piece of work. Changes would need to be made to clinical algorithms. Similarly, if partial genotyping were to be introduced as a triage test, this would also require changes to information sheets and consent forms. The ethical issues relating to primary HPV testing followed by LBC triage are addressed in Chapter 7.

6.1.2 Test taking

The ThinPrep® LBC test currently used by CervicalCheck is also used for triage HPV testing. The collection medium is retained, so that only one clinic visit is required by a woman if triage HPV testing is indicated.

The current sampling method also provides a screening sample that would be suitable for primary HPV testing followed by LBC triage. Only one clinic visit by a woman would be required at each screening round. Therefore, a switch in the order of the primary and triage tests would not have any organisational implications in this regard. Of note, the current sampling method would also provide a screening sample that is suitable for partial-genotyping should additional data become available to support this strategy as being the cost-effective alternative. As outlined in Chapter 2, certain HPV test kits with the capacity for partial genotyping can be used to simultaneously report HPV findings in aggregate (pooled positive or negative finding for all high-risk HPV [hrHPV]) and to specifically identify HPV 16 and 18, while also reporting the presence or absence of the additional hrHPV genotypes as a pooled result.

As noted in Section 2.1.1.3, in contrast to cytology testing, HPV testing could be suitable for self-sampling (that is, where the woman takes the screening test sample herself). Self-sampling could provide an opportunity to increase screening coverage and reduce cervical cancer rates in women who would not otherwise engage with CervicalCheck. This includes eligible women who have never attended CervicalCheck and women who are underscreened because they do not attend CervicalCheck at the recommended screening intervals. However, women with a positive HPV test on self-sampling would require triage with LBC, the sample for which cannot be obtained by self-sampling, so these women would need to engage with primary care services. While not assessed as part of this HTA, it may be a strategy to consider in the future as an initial mechanism to engage with those who have not availed of screening or who are underscreened.

A screening test submitted in an expired vial is not processed by CervicalCheck. The percentage of expired vials would not be expected to change if primary HPV testing were introduced as the method of collection would not change. Currently, key performance indicators around unsatisfactory or inadequate screening tests only apply to LBC. If primary HPV testing is implemented CervicalCheck would need to identify additional key performance measures that ensure the validity of the screening test samples in order to ensure that screening tests reported to be HPV-negative are true negative tests. According to the 2014-2015 CervicalCheck Programme Report, 2.0% (5,827 out of 295,354) of screening tests were unsatisfactory or inadequate.

There would also be no change to the methods of transport and storage of the screening test.

6.1.3 Test processing

Switching to primary HPV testing would be an incremental change for CervicalCheck because it has used HPV testing following treatment in colposcopy since 2012 and HPV triage of low-grade cytological abnormalities since 2015.

A change to the current sequence of tests from primary LBC testing with HPV triage to primary HPV testing with LBC triage would have implications for the laboratory services contracted by CervicalCheck. Currently, CervicalCheck uses three laboratory services (two US companies and Quest Diagnostics). Quest Diagnostics provides cytology services at the Coombe Women and Infants University Hospital as part of a National Cervical Cytology Training Centre. It processes approximately 9% of the total volume of tests per annum. As test processing has already been centralised in a small number of sites by CervicalCheck, these laboratories should continue to have sufficient capacity in the HPV testing platforms to allow high throughput testing while ensuring that there is still sufficient cytology throughput to maintain staff expertise for quality assurance purposes. Changes in laboratory practices and workloads (apart from storage and or preparation prior to transport to the US) would need to be negotiated as part of the routine tendering process and should not otherwise have organisational implications for CervicalCheck.

Should partial genotyping be adopted as a triage option, HPV tests with the capacity for concurrent or reflex partial genotyping, which can distinguish HPV 16 and 18 would be required. Since May 2015 Aptima HPV assay [Hologic] and the cobas® HPV test [Roche Molecular Diagnostics]) are used for all HPV testing in CervicalCheck, both of which have the capacity for partial genotyping.

6.1.4 Volume of screening tests, surveillance tests and colposcopy referrals

Changing to primary HPV testing would facilitate an extension of the screening interval to five-yearly screening and would lead to a reduction in the lifetime number of screening tests. Currently in Ireland, a woman who adheres fully to CervicalCheck and in whom no abnormalities are detected has 11 lifetime screens. Taking account of the fact that not all of the eligible population attend for screening at the recommended times, and that some women may have additional screens due to increased surveillance following discharge from colposcopy clinics or a positive primary HPV screening test, the economic model estimated that on average, based on current CervicalCheck attendance rates, a woman has eight lifetime screens with

the current screening strategy. It is estimated that a change to five-yearly primary HPV testing followed by LBC triage from age 25 to 60 years would reduce this to 5.9 lifetime screens, assuming there is no change in attendance rates in unvaccinated and vaccinated women.

An increase in the screening interval from three to five years in women aged 25 to 44 years would represent an organisational challenge for CervicalCheck. Based on discussions with CervicalCheck, any such change would be done on a phased basis as those women who are currently on a three-year screening interval would remain on that schedule until their next screening visit.

> For example, a 28 year old woman who has a negative screening test in 2017 and is scheduled to re-attend for screening in 2020 will be seen as planned at that time. In the event of a negative HPV screening test, her next scheduled visit would be in 2025.

Therefore, it would take eight years to fully migrate to a five-yearly screening interval. Such a change would require a systems change and development of a phased implementation plan. A transitional phase would be required during which time there would be fluctuations in the numbers of screening tests, colposcopy referrals and treatment procedures. The logistics around this fluctuation would need to be determined to avoid excessively large variations in workload due to a change in the screening interval.

As illustrated in the budget impact analysis in Chapter 5 (Tables 5.15 and 5.16), assuming a transition over an eight-year period from 2018 to 2025, a change to five-yearly primary HPV screening with LBC triage for all women would lead to a reduction in the number of screening tests and in colposcopy referral rates for both unvaccinated and vaccinated women. As the national HPV immunisation programme only commenced in 2010, the vaccinated cohort is relatively small. Relative to continuation with current practice, it is estimated that total screening tests would decrease by 291,119 (15%) in the vaccinated cohort and 29,278 (20%) in the unvaccinated cohorts. In the unvaccinated population, the number of colposcopy referrals would decrease from 30,691 with the current strategy to 25,984, representing a 15% decrease. For the vaccinated cohort it would decrease from 2,980 with the current strategy to 2,287 (23% decrease).

As noted in Chapter 5, extending the screening age to 65 years was not found to be cost-effective for either the unvaccinated or vaccinated cohorts. For each of the strategies considered in the economic evaluation, extending the screening age would increase the lifetime number of screens and would impact on screening test numbers and colposcopy referrals. For example, if five-yearly primary HPV screening with LBC

triage was adopted, extending screening to age 65 would mean that the number of screening tests and colposcopy referrals would only decline by 9.5% and 11%, respectively over an eight-year period in the unvaccinated cohort. This is compared with predicted decreases of 15% in both screening and colposcopy numbers if screening continues to stop at age 60.

A decrease in the number of screening tests could have implications for those registered to provide screening on behalf of CervicalCheck and in particular primary care practices where over 98% of screening tests are currently carried out. Due to a phased introduction, no decrease in screening numbers would occur until at least year four following a change to primary HPV screening. An increase in screening activity is likely in the first three years due to surveillance of the HPV-positive, cytology negative cohort. A decrease in numbers of colposcopy referrals would have funding implications for the colposcopy clinics and would potentially free additional capacity for the management of women attending through symptomatic services. The current waiting time targets for colposcopy appointments are two weeks for an urgent referral, four weeks for high-grade cytological abnormalities and eight weeks for low-grade cytological abnormalities. As of June 2016, all colposcopy services met these targets. No change to these targets is anticipated.

Two subgroups were identified in the economic evaluation based on clinical need. The first considered women who only first obtained access to organised screening from age 50 (that is, women who were 50 years old when CervicalCheck commenced in 2008). While not found to be cost-effective, it was noted that extending the screening exit age to 65 years would provide additional clinical benefit and therefore could be considered in this subgroup given their historic underscreening. Implementing an additional screening round would result in an increase in the number of screening and surveillance tests and colposcopy referrals for CervicalCheck. However, if the age extension is confined to this subgroup, this increase in activity would only apply for a finite period.

A second subgroup analysis considered alternative screening strategies for women under age 30 years who are not vaccinated against HPV 16 and HPV 18. While this was not found to be cost-effective, the provision of three-yearly screening for this subgroup may be considered on clinical grounds. Implementing an additional screening round for unvaccinated women under 30 years would result in an increase in the number of screening and colposcopy referrals. The size of the unvaccinated subgroup will be determined by the uptake of HPV vaccination in the national immunisation programme. By 2023 it is estimated that over 80% of women aged 25 years entering CervicalCheck will be vaccinated against HPV 16 and HPV 18, although it is noted that vaccination uptake has declined in the last two years due to

high-profile negative publicity concerning HPV vaccine safety. If HPV vaccination rates remain high, consistent with international findings, a reduction in the prevalence of HPV 16 and 18 in nonvaccinated women is anticipated due to herd immunity.

There is a prospect that screening intervals for unvaccinated cohorts may increase as more evidence emerges for primary HPV screening based on extended follow-up data from the clinical trials identified in Chapter 4. As highlighted in Chapter 5, screening at five-yearly intervals was not found to be cost-effective in a vaccinated cohort (ICER of €58,745 relative to no screening). Given their lower risk of developing cervical cancer, less intensive screening strategies (which were not modeled in this evaluation) may be more appropriate for vaccinated women. Emerging evidence from post-vaccination surveillance programmes and the adoption of a nonavalent vaccine, which would provide greater protection against cervical cancer, may provide additional evidence to further de-intensify screening. As the vaccinated cohort represents an increasing proportion of the CervicalCheck population, the total number of screening tests and colposcopy referrals that CervicalCheck would be required to provide could decline further.

Changing to primary HPV screening would result in the creation of a new cohort – those women who are HPV positive, but cytology negative. These women do not have treatable abnormalities, but based on clinical trial data are at twice the population-based risk of developing CIN 2+ and cannot be returned to routine screening. The economic model assumed early recall (surveillance) for this cohort at 12 months. A repeat positive HPV test was assumed to be indicative of persistent infection warranting referral to colposcopy regardless of the results of the triage test. Surveillance of this group would necessitate organisational changes for CervicalCheck, including educating providers who take the screening samples in relation to the clinical relevance of these findings. The impact of this cohort on overall CervicalCheck activity (test taking, processing and colposcopy numbers) is accounted for as they are included in the total number of screening tests and colposcopy referrals discussed above. The size of this population can be estimated based on preliminary data from an Irish observational study by CervicalCheck and the CERVIVA collaboration (Chapter 3, Section 3.6.1.1). Results of a primary HPV screening test indicated a baseline population prevalence of high-risk HPV (hrHPV) of 14.6% in women attending for routine screening through CervicalCheck. The prevalence of hrHPV in those with normal cytology was 8.9%, and was higher in those aged less than 30 years (21.5%) than in those aged 30 years and over (6.9%).

As noted in Chapter 5, two alternative surveillance pathways were considered for HPV-positive, LBC(cytology)-negative women in the subgroup analysis that looked at

alternative screening strategies for women under age 30 years who are not vaccinated against HPV 16 and 18. In the first pathway, women who were HPV positive, cytology negative at 12 months were referred directly to colposcopy. In the second pathway, women were only referred to colposcopy if positive on the partial genotyping test for HPV 16 or 18. Both pathways lead to similar clinical outcomes, however the requirement for a positive partial genotyping test would reduce the number of additional colposcopy attendances in this age group. However, it would lead to an increase in the number of surveillance tests as cytology-negative women who are positive for the other HPV genotypes would return for repeat screening after another 12 months. Implementing partial genotyping in women under the age of 30 years would have logistical implications for CervicalCheck's laboratory services because these women would be on a different process pathway to women aged 30 years or over.

A change to the primary screening test and the screening interval would not impact current biopsy and treatment practices. In general, women diagnosed with CIN 1 are not treated and remain under surveillance within colposcopy clinics while those diagnosed with high-grade histological abnormalities (CIN 2 and CIN 3)[245] are treated. The percentage of biopsy specimens suitable for histological diagnosis would also remain the same.

6.1.5 Coverage

It has been speculated that an increase in the screening interval for women between the ages of 25 and 44 years could lead to either a reduction or an improvement in attendance for routine screening. Attendance is known to decrease with advancing age, but it is unclear if this is related to the longer screening interval (five years compared with three years). CervicalCheck provides a quality-assured screening programme with a comprehensive call-recall system: women are sent invitations and reminders for screening visits and there is a facility to track non-responders. As with any screening programme, the success of CervicalCheck relies in part on maximising coverage rates. Five-year coverage in the CervicalCheck programme has steadily improved from 74.7% for the first five years to 79.6% to the end of December 2016. Monitoring of coverage and reporting against established targets (current target is ≥ 80%) will continue to represent an important performance indicator and will allow any change in coverage to be detected in a timely fashion should it occur. As noted in Section 6.1.2, switching to primary HPV screening would allow for self-sampling and may provide an opportunity to improve coverage through an initial engagement with those who have not availed of screening or who are underscreened.

It has been speculated that the perception of cervical cancer risk in women aged 50 and over might change if primary HPV screening is implemented. CERVIVA is currently

conducting a study on the implications of switching to primary HPV screening for women aged 50 years and over. Increasing coverage of older women is particularly important given their lower uptake of screening. This would be particularly relevant in the context of any extension to the screening exit age to 65 years, as any clinical benefit from providing this additional screening round would only be realised if uptake improved in those aged over 60 years.

6.1.6 Evaluation and risk-based screening

Primary HPV testing allows HPV risk-based screening that is tailored to the individual woman's risk and screening history. CervicalCheck uses a comprehensive linked screening registry and call-recall based invitation system. It has an established link to the national HPV vaccination programme, providing access to the vaccination records of those eligible to attend CervicalCheck. These systems will allow CervicalCheck to develop a formal, ongoing evaluation process of HPV risk-based screening should primary HPV screening be adopted. This will be particularly relevant as further evidence emerges of the applicability of the international data in the Irish setting and the long-term safety of HPV-based strategies.

The link to the national HPV vaccination programme will also provide an opportunity to evaluate the effectiveness of the national HPV vaccination programme. The first cohort of schoolgirls vaccinated through this programme will be eligible for CervicalCheck in 2018-2019. By 2023, over 80% of women aged 25 years entering CervicalCheck will be vaccinated against HPV 16 and HPV 18, although it is noted that vaccination uptake has declined in the last two years. If high vaccination rates can be maintained, consistent with international findings, a reduction in the prevalence of HPV 16 and 18 in unvaccinated women is anticipated due to herd immunity. Ongoing evaluation of any alternative screening strategy for unvaccinated women under the age of 30, if implemented, will therefore be required to ensure that the management of these women is optimised.

6.1.6 CervicalCheck processes and quality standards

There may be additional implications of a change in the screening test or screening interval for CervicalCheck processes and quality standards. CervicalCheck has developed quality requirements and quality standards which must be complied with for quality assurance in service delivery. Current quality standards apply to programme coverage, laboratory turnaround time, letters to women and takers of tests advising of results, LBC findings, referral to colposcopy, cytology correlation measures, attendance at colposcopy services, reasons for referral to and waiting times for colposcopy services, biopsy rates, treatment at colposcopy services and histology.

6.2 Social implications

Primary HPV testing may result in increased worry and anxiety for some women. The effect of incorporating primary HPV testing into established screening programmes remains uncertain.[246]

In 2007 and 2008 in Ireland, focus groups were conducted with 59 women recruited through primary care in order to determine their knowledge, attitudes towards and acceptability of cervical screening, HPV testing and HPV vaccination.[246] Women were asked if they were aware of HPV and if so what they knew. Groups were then provided with a brief HPV information sheet which was also read aloud by the facilitator. Following this, the groups discussed HPV. Analysis used a thematic approach and was ongoing and iterative. Women were concerned about the lack of treatment for HPV infection. They reported strong feelings of reliance on existing cervical screening using cytology. Women thought that the way in which HPV was explained to them by healthcare practitioners was very important. Women spoke about fears of testing positive for HPV because of the possible implications for their health and their relationships, as well as fear of the unknown. They were concerned about the worry that may result from waiting for the result of a HPV test. Some women thought that an adequate explanation of results would be of paramount importance in order to minimise negative psychological effects associated with testing positive for HPV. In contrast, other women thought that testing positive for HPV would encourage women to attend for further screening or treatment while testing negative would be reassuring. The results of the study were published in 2014 and may not be applicable as the original research was conducted prior to the introduction of the national HPV immunisation programme in 2010 and HPV-based post-treatment and triage testing by CervicalCheck in 2012 and 2015, respectively. These factors are likely to have increased public awareness of HPV and its association with cervical cancer.

The Irish Screening Research Consortium (CERVIVA) in collaboration with CervicalCheck undertook exploratory, in-depth, semi-structured interviews with 27 women who had HPV testing in a colposcopy clinic in 2011 following treatment of high-grade histological abnormalities (CIN 2 and CIN 3) or as follow up of low-grade cytological abnormalities.[247] The study aimed to explore women's emotional responses to undergoing HPV testing and to identify factors that influence negative emotional responses to HPV testing. A thematic approach was used to analyse interview transcripts. For most women, having a test for high-risk HPV types generated little negative or positive emotional impact. Adverse emotional responses related to HPV infection rather than HPV testing. Most women who reported no negative emotional response to the result of the HPV test had relatively low levels of

knowledge about HPV infection and HPV testing. In contrast, women who experienced negative emotional responses to the result of the HPV test tended to have greater knowledge about HPV infection and HPV testing. CERVIVA also conducted a study on the factors which influenced participants' need for information about HPV.[248] Women expressed fear of testing positive for HPV because of the possible implications for their health, their relationships as well as fear of the unknown. Women were also concerned about the worry that may result from waiting for the result of a HPV test. Women thought that the timing of delivery of information about HPV was key and that this information should be provided in stages rather than altogether.

The provision of adequate and appropriate information about HPV to women is vital in order to ensure that cervical cancer prevention strategies continue to be effective.[246] ATHENS (A Trial of HPV Education and Support) was conducted in Ireland under the umbrella of CERVIVA to develop a theory-based intervention to support primary care practitioners in relation to HPV infection, HPV vaccination and HPV testing. In-depth, semi-structured telephone interviews were conducted with 19 general practitioners (GPs) and 14 practice nurses as the first step in this intervention development process.[249] The study aimed to identify HPV-related clinical behaviours that the intervention will target, to clarify the roles and responsibilities of GPs and practice nurses in these areas, and to determine what influences these behaviours. A framework analysis approach, using the Theoretical Domains Framework, was taken for content analysis. Responsibility for the taking of cervical screening tests was considered to be a predominantly female role but HPV infection was discussed with women by male and female practitioners. Knowledge, emotion, social influences and beliefs about capabilities and consequences were judged to be the most important domains in relation to HPV infection. Beliefs about consequences, social influences, knowledge, environmental context and resources were judged to be the most important domains in relation to HPV vaccination. Knowledge and beliefs about capabilities were judged to be the most important domains in relation to HPV testing. Primary care practitioners saw CervicalCheck as a trusted source of information about HPV.

A randomised web-based survey of a sample representative of Norwegian women was conducted in 2011 in order to determine how primary screening for HPV and the type of information in the invitation letter would affect a woman's intention to attend screening.[250] A total of 3,540 women were randomised to receive one of three invitation letters. The first version of the letter contained text from the current reminder letter about "Pap" smear testing. The second version stated that primary HPV testing would replace "Pap" smear testing and that women would only need to be screened every six years. The third version was identical to the second version,

but it also included information about HPV infection. Women randomised to versions two and three were asked to imagine that the HPV test was positive and that there was evidence of cytological abnormalities. Women randomised to version one were only asked to imagine that they had cytological abnormalities. There was no significant difference between the three groups in women's intent to participate in screening or follow up or in their anxiety level. The study authors noted that prior to the implementation of primary HPV testing in Norway, it is important for policy-makers to gauge the impact this will have on attendance.

It has been speculated that an increase in the screening interval from three years to five years for women between the ages of 25 and 44 years may lead to a reduction in adherence to the screening programme. Rates of adherence are known to decrease with advancing age but it is unclear if this is related to the longer screening interval. Beliefs may take time to change as some women between the ages of 25 and 44 years may not feel reassured by an increase in the screening interval and may opt to have screening tests more frequently in the private system. Currently, CervicalCheck accepts out-of-interval tests and sends the result to the registered doctor or clinic and to the Cervical Screening Register. Currently, around 1.0% - 1.6% of tests annually are not paid for, with this early return being the principle reason. CervicalCheck will only reject screening tests when the 'when is my next test due' online facility for women and primary care practitioners works accurately in greater than or equal to 99% of cases (currently, 95%-96%, with development ongoing). The number of private tests is currently believed to be insignificant.

Women who have been vaccinated against HPV 16 and 18 may consider themselves to be at low risk of developing cervical cancer and may not present for cervical screening.[251] It is essential that CervicalCheck has high population coverage if it is to remain effective in the future. While they have a lower risk of cervical cancer, women who have been vaccinated against HPV 16 and 18 should still participate in screening because the current vaccine offered in the national school-based vaccination programme does not protect against all oncogenic HPV infections. It has been speculated from the outset that vaccinated women will not participate in screening because they (falsely) believe that vaccination has eliminated their risk of developing cervical cancer.[245, 252, 253]

Data from Australia indicate that young vaccinated women have a significantly lower rate of uptake of screening than unvaccinated women.[254] In contrast, emerging evidence from other high-income countries such as Scotland[251] Wales[255], Sweden[256] and the US[257] suggest that the rate of uptake of screening may be higher in vaccinated women, perhaps due to greater health consciousness than in unvaccinated women. Rates of uptake of screening vary in different countries as

they are influenced by the context within each country. They are affected by the organisation, maturity and coverage rates of screening and vaccination programmes as well as the social and cultural attitudes of the population towards vaccination and screening. CERVIVA-VAX will monitor and compare rates of uptake of screening in vaccinated and unvaccinated women within the catch-up cohort in order to provide evidence about the likely impact of vaccination on the coverage rate of screening in Ireland.

On the basis of the above research, it is evident that a communications strategy including a public information campaign would be required to ensure those women eligible for CervicalCheck are aware of the implications of any change in the choice of the primary screening test and the screening interval. CervicalCheck has an established Screening Training Unit and a Communications Department that develop information resources and tools for both screening providers and the general population. As noted, CervicalCheck is seen as a trusted source of information about HPV by primary care practitioners. These units would play an integral role in amending and adapting current CervicalCheck resources to ensure delivery of adequate information at the appropriate time. Together with the healthcare professionals involved in the provision of CervicalCheck, they would play a key role in ensuring informed consent and in the implementation of any changes to the screening strategy.

6.3 Discussion

This chapter reviewed the organisational and social implications of potential changes to CervicalCheck – Ireland's National Cervical Screening Programme. The results of the economic evaluation (Chapter 5) indicated that the current programme was less effective and more costly that almost all of the alternative strategies tested. Primary HPV testing followed by LBC triage at five-yearly intervals between the ages of 25 and 60 years was found to be cost-effective for the unvaccinated cohort. While not cost-effective for the vaccinated cohort, this strategy had the lowest ICER (€58,745 per QALY).

Given that CervicalCheck was only established in 2008, it is a relatively new national cervical screening programme. A potential disadvantage of this is there is not an established culture of cervical screening in Irish women. There is a concern therefore that coverage levels may not be maintained, particularly if screening intervals were to be extended. However, an advantage of the late adoption of organised screening in Ireland is that CervicalCheck was established according to best international practice at that time. Current primary screening is based on liquid-based cytology (LBC) rather than conventional cytology, or a mix of liquid-based cytology and conventional cytology as in other countries with long-established

screening programmes. The current test kit used in Ireland is therefore suitable for primary HPV screening (including partial genotyping should this be adopted) and cytology triage, so there would be no change in the screening experience for either the woman or the provider taking the test sample.

In contrast to countries with annual or biennial (every two years) screening from the age of 18, screening is already broadly consistent with International Agency for Research on Cancer (IARC) recommendations for screening at three-yearly intervals from 25 to 49 years and five-yearly intervals for those aged 50 to 60 years (or 65 in countries where resources permit). Test processing has already been centralised in a small number of sites by CervicalCheck, again minimising any disruption that would be associated with changing from primary LBC screening to primary HPV screening. The contracted laboratories should continue to have sufficient capacity in the HPV testing platforms to allow high throughput testing while ensuring that there is still sufficient cytology throughput to maintain staff expertise for quality assurance purposes. Finally, CervicalCheck already uses a comprehensive linked screening registry and call-recall based invitation system. CervicalCheck is linked to the national HPV vaccination programme and so has access to the vaccination records of those eligible to attend screening. Therefore systems are already in place to facilitate risk-based screening that is tailored to the individual woman's risk and screening history.

A change to primary HPV screening would mean all women who participate in screening will be aware of their HPV status. This will have resource implications particularly in the initial screening rounds following the change. CervicalCheck information sheets and consent forms would need to be updated and additional time would be required by healthcare professionals to explain the new screening strategy to women. More research is required on the type of information about HPV that is required by those eligible for screening and the best way to provide to this information.

Two subgroup analyses were conducted. The first considered extending the screening exit age from 60 to 65 years to represent women who have not had the benefit of lifetime cervical screening from the age of 25 years, but who have only been offered screening since the age of 50 years. While this strategy was not found to be cost-effective at a willingness-to-pay threshold of €20,000 to €45,000 per QALY, it may be considered to reduce the burden of cervical cancer in this subgroup given their historic underscreening. Extension of screening to age 65 would only be required for a finite period as it would only apply to the group of women who were 50 years of age when CervicalCheck commenced in 2008.

The second subgroup analysis considered screening alternatives in unvaccinated women aged less than 30 years in the context of primary HPV screening and LBC triage at five-yearly intervals being provided once they reach 30 years. This subgroup was identified on the basis of its high prevalence of HPV and cytological abnormalities. While not cost-effective, providing an additional screening round (that is, screening at three-yearly intervals for women under the age of 30 who have not been vaccinated against HPV) may be considered on clinical grounds. It is anticipated that, if adopted, such a strategy would only be required for a finite period of time as both size of the unvaccinated cohort and their risk of cervical cancer will be dependent on the HPV vaccination rates achieved through the national immunisation programme. If high HPV vaccination rates can be maintained, fewer women will be unvaccinated and, in those women who are unvaccinated, the prevalence of HPV 16 and 18 infection is expected to decrease, due to protection provided through herd immunity.

A change to primary HPV screening would create a new cohort for surveillance – women who screen HPV positive, but have no cytological abnormalities identified on triage. Due to their increased risk of developing high grade histological abnormalities and early-stage invasive cervical cancer (CIN 2+) compared with the population-based risk, these women cannot be returned to routine screening. In the considered strategies it was assumed that these women would require early recall in one year, with those who have a repeat positive HPV test referred to colposcopy regardless of the result of the triage test.

A change to primary HPV screening and an extension of the screening interval would have implications for the screening programme's workload resources. The number of screening tests and colposcopy referrals would decline over an eight-year period for both the unvaccinated and the vaccinated cohorts. Emerging evidence from post-vaccination surveillance programmes along with the adoption of a nonavalent vaccine, which would provide greater protection against cervical cancer, may provide additional prospects to further de-intensify screening for the vaccinated cohort. As the proportion of the CervicalCheck population that is vaccinated grows, this could lead to a progressive reduction in the workload of the screening programme in time – for providers taking test samples, laboratories, colposcopy units and pathology services.

A change to the screening programme would not be without risk. The goal of organised screening is to reduce the incidence and mortality from cervical cancer while minimising screening-related harms. Ongoing auditing against the performance standards set for adherence to screening policy, programme coverage, and compliance with the recommended triage and management of screen-positive

women will be required with steps taken to try to identify issues, should any emerge.

6.4 Key messages

- Changing to primary HPV screening would represent an incremental change for CervicalCheck. HPV testing following treatment in colposcopy was adopted in 2012 while HPV testing in the triage of low-grade cytological abnormalities was adopted in 2015.
- The test kit currently used by CervicalCheck is suitable for HPV testing (including partial genotyping) and LBC (cytology) testing. Adopting primary HPV screening would therefore not impact the current screening experience for either the woman or the provider taking the test sample, with only one clinic visit required at each screening round.
- CervicalCheck has centralised processing of screening tests in three laboratories. Should primary HPV screening with cytology triage be adopted, these laboratories should continue to have sufficient capacity in the HPV testing platforms to allow high throughput testing while ensuring that there is still sufficient cytology throughput to maintain staff expertise for quality assurance purposes.
- Adopting primary HPV screening with LBC (cytology) triage would identify a new cohort for surveillance. Woman who are HPV-positive, but LBC-negative have twice the population-based risk of developing high grade histological abnormalities and cervical cancer (CIN 2+). It was assumed that these women would be recalled for surveillance in one year. A repeat positive HPV test was assumed to indicate persistent HPV infection, warranting referral to colposcopy regardless of the result of any triage testing. Surveillance of this group would have organisational implications for CervicalCheck, including educating women and the providers collecting the screening sample in relation to the clinical relevance of these findings.
- Adopting primary HPV screening and extending the screening interval to five-yearly screening for all women would lead to a reduction in the number of screening tests a woman requires in their lifetime. Estimates from the economic model indicate that compared with current practice, adopting five-yearly primary HPV screening with LBC (cytology) triage would lead to a reduction of 15% in the total number of screening tests and 16% in colposcopy referrals between 2018 to 2025. A reduction in the number of colposcopy referrals would have potential implications for the funding and resourcing of colposcopy services. Due to phased implementation, no reduction in screening activity would occur until year four. Screening activity would increase in the first three years due to surveillance of women identified as HPV positive, but cytology negative.
- The impact of extending the screening interval from three to five years on

programme coverage is not known, with both speculation that adherence to screening could improve or disimprove. Ongoing audit of programme coverage and tracking of non-responders will allow changes in adherence to be identified in a timely fashion. Switching to primary HPV screening would allow for self-sampling and may provide an opportunity to improve coverage through an initial engagement with those who have not availed of screening or are underscreened.

- A switch to primary HPV screening would result in all women being aware of their current HPV status and may result in increased worry and anxiety for some women. This would have resource implications which would be greater in the initial than in subsequent screening rounds. This would include adaptation of literature and training resources for women and providers collecting the test sample in relation to the implications of positive and negative tests and an increase in the time to explain primary HPV screening, so that women are able to provide informed consent and understand the implications of any positive results.
- CervicalCheck uses a comprehensive linked screening registry and a call-recall based invitation system. It is linked to the national HPV vaccination programme, with access to the HPV vaccination records of the eligible CervicalCheck population. These mechanisms would allow CervicalCheck to develop a formal, ongoing evaluation process of HPV risk-based screening and would allow future screening to be tailored to the individual woman's risk and screening history. It will also provide a mechanism to evaluate the efficacy of the national HPV immunisation programme.

7 Ethical Issues

This health technology assessment (HTA) was carried out to examine the potential impact of changing from liquid-based cytology (LBC) testing to HPV testing as the primary screening test for the prevention of cervical cancer. There is growing support for the use of HPV testing on the basis of its greater sensitivity for detection of cervical neoplasia (CIN), its potential to extend the screening interval, and the decrease in the effectiveness of cytology as a primary screening tool in a HPV-vaccinated cohort. This chapter considers the key ethical issues that should be considered in relation to changing from LBC to HPV-based testing as the primary screening test in Ireland.

This chapter was developed broadly in line with the ethical framework process proposed by Kass.[258] To advance traditional public health goals while maximising individual liberties and furthering social justice, public health interventions should:

- reduce morbidity or mortality
- data must substantiate that a programme (or the series of programmes of which a programme is a part) will reduce morbidity or mortality
- burdens of the programme must be identified and minimised
- the programme must be implemented fairly and must, at times, minimise preexisting social injustices and
- fair procedures must be used to determine which burdens are acceptable to a community.

The public must feel confident that health professionals will offer only those interventions that will improve the health of the public, that proposed measures are minimally burdensome, and that a fair procedure has determined that the magnitude of the problem and the ensuing benefits justify overriding conflicting moral claims.

In assessing the ethical implications of potential changes to the national cervical screening service, issues were considered under six headings as identified by Kass. These are presented below.

7.1 What are the public health goals of the proposed programme?

The first step for any proposed public health programme is to identify the programme's goals. These goals generally ought to be expressed in terms of public health improvement, that is, in terms of reduction of morbidity or mortality.

In the context of cervical screening generally, the public health goals are clearly identifiable as the reduction in the incidence of and mortality from cervical cancer through early detection and treatment. The proposed change from LBC-based screening to HPV testing as the primary screening test is supported by evidence of its increased sensitivity. However, this has also led to concerns about lack of specificity which may result in over-referral to colposcopy, thus putting an additional strain on resources and potentially resulting in over-diagnosis and unnecessary treatment.

In 2010, quadrivalent vaccination against HPV 6, 11, 16 and 18 was introduced into the Irish national immunisation schedule for all girls in the first year of second level school, with a catch-up programme from 2011 to 2014. The first vaccinated cohort of young women is due to enter CervicalCheck – Ireland's National Cervical Screening programme in 2018-2019. Vaccination is anticipated to reduce the risk of developing cervical cancer by 70%, thus the potential for over-referral to colposcopy and over-diagnosis may be a particular issue for concern amongst vaccinated women.

7.2 How effective is the programme in achieving its stated goals?

Proposed interventions or programmes are based on certain assumptions that lead us to believe they will achieve their stated goals. What those assumptions are and what data exist to substantiate each of them must be examined.

A systematic review and meta-analysis performed in Chapter 4 concluded that the sensitivity of HPV testing is higher than cytology-based testing (LBC). Primary HPV screening compared with LBC testing would lead to fewer women receiving false negative results. However, the specificity of HPV-based testing was found to be lower, resulting in more false positive results which might result in an increase in referrals to colposcopy services. To avoid unnecessary referral, as well as the consequent over-use of resources and anxiety for women, those with a positive HPV test will require a cytology triage test. Triage testing has already been in place since May 2015, when CervicalCheck adopted HPV triage for women with identified low-grade cytological abnormalities following a primary LBC screen.

These data provide evidence that the proposed change from primary LBC screening to primary HPV screening will be effective in achieving the goals of moving to a screening programme which is based on increased sensitivity of the testing method. Although the new programme may lead to a higher false positive rate with potential over-referral of women to colposcopy services, the use of a triage test may serve to

allay ethical concerns about the potential for anxiety among the screened women and over-use of colposcopy resources.

7.3 What are the known or potential burdens of the programme?

If data suggest that a programme is reasonably likely to achieve its stated goals, then the next step of the framework is to identify burdens or harms that could occur.

The aim of a cervical screening programme is to reduce the incidence, morbidity and mortality from cervical cancer through detection and treatment of precancerous abnormalities and early stage invasive cervical cancer. However, no cervical screening programme can prevent all cervical cancers. Cervical screening tests are not 100% accurate. Women may be falsely reassured by a negative cervical test, which is a potential harm of any cervical screening programme. Cervical cancer may develop in the time interval between a negative screening test and a woman's next screening, which is another potential harm of any cervical screening programme.

The 2015 Kitchener report for the UK National Screening Committee[223] identifies the following additional potential harms to women as specific to the use of primary HPV screening:

1. Increased anxiety as a result of early recall for women who are HPV positive, but cytology negative.
2. Increased morbidity due to increased detection of precancerous abnormalities (CIN), some of which would not result in cancer.

The Kitchener report concludes that the theoretical harm that could occur from the knowledge of having a sexually transmitted infection has not been apparent and no problems have been identified in the pilot studies. It also points to the efforts that have been made to inform women, sample takers and doctors which have 'undoubtedly helped to avoid distress.'

A study by O'Connor et al[212] in the Irish context in 2014 sought to explore whether HPV testing could result in significant psychological burden for women. Participants had a HPV test in colposcopy in the previous six months following treatment for one or more low-grade cytological abnormalities or treatment for CIN. For most women, having a test for high-risk HPV types generated little negative or positive emotional impact. Adverse emotional responses related to HPV infection rather than HPV testing. In those women who reported a negative reaction, this was characterised by distress, shame and embarrassment, fear of stigmatisation, regret, self-blame and

anxiety. Testing HPV negative did not appear to be reassuring to these women whose primary concern was about their abnormal cytology. The authors of the study express concern as proposed HPV testing will result in less frequent and intensive follow up which this could result in higher levels of anxiety and distress. Although overall, the authors describe the potential emotional impact on women as 'modest', it is nonetheless an important aspect of the HTA to be taken into account.

Primary HPV testing may result in worry and anxiety for some women. Some women may experience distress upon learning that they have a HPV infection. Women may be embarrassed or angry about their sexual partners (past and present) from whom they might have acquired the infection. Women may experience distress and shame in disclosing their HPV infection to partners as there may be a sense of self-blame and regret in their perception of their contribution to the infection. The Irish Screening Research Consortium (CERVIVA) conducted exploratory, in-depth, semi-structured interviews with 27 women who had HPV testing in a colposcopy clinic in 2011 following treatment for CIN or as follow-up of low-grade cytological abnormalities.[247] Women expressed fear of testing positive for HPV because of the possible implications for their health, their relationships as well as fear of the unknown.

There is no treatment for HPV infection though women are currently advised to stop smoking. It is unusual to be diagnosed with an infection for which there is no treatment and this may exacerbate distress and anxiety for some women.[247]

Disclosure of HPV infection to insurance companies could have potentially significant effects if women were refused cover for cervical cancer or their premiums were loaded excessively as a result. However, this is viewed as a theoretical concern only given that infection with HPV is considered to be universal in sexually-active individuals.

As with any screening test there is a possibility of false negative results. Thus it is possible that despite the high sensitivity of HPV testing, a small number of women who develop CIN 3+ may receive a false negative result when tested with a HPV test who could have received a positive result if tested using cytology-based screening.[213]

Women who have been vaccinated against HPV might consider themselves to be at low risk of cervical cancer and may not present for cervical screening. The evidence around this is conflicting. Data from Australia indicate that young vaccinated women have a significantly lower rate of uptake of screening than unvaccinated women.[254] In contrast, emerging evidence from other high-income countries such as

Scotland[251] Wales[255], Sweden[256] and the US[257] suggest that the rate of uptake of screening may be higher in vaccinated women.

7.4 Can burdens be minimised? Are there alternative approaches?

This piece of the framework requires that burdens be minimised once they have been identified. There is an ethical obligation to determine whether the programme could be modified in ways that minimise the burdens while not reducing the programme's efficacy.

Some of the potential harms discussed above represent a risk for women who are not adequately informed about HPV testing. Therefore, the informed consent process will have to be carefully managed to ensure that women are given sufficient information about the new testing process and its potential risks and benefits in a way they can understand. Women should be reassured about the meaning of HPV infection and their concerns about transmission allayed as far as possible.

7.5 Is the programme implemented fairly?

This piece of the framework corresponds to the ethics principle of distributive justice, requiring the fair distribution of benefits and burdens.

Are there social inequities in the way that the programme is managed or availed of and if so, how can this be addressed? While changes are proposed to the choice of the primary screening test, the screening process will not change from the woman's perspective, so it is anticipated that that the existing social inequities will neither increase nor decrease.

The relative risk of cervical cancer rises with increasing population density, level of unemployment and lower educational attainment. There is ongoing concern about the inequitable burden of cervical cancer among the lowest socioeconomic class, who may also represent a cohort least likely to present for vaccination and for screening. Self-testing has not been examined as part of this HTA, however it has been shown to be an effective alternative for women who do not regularly attend screening[189] and as a strategy to improve low uptake rates.[227] This emerging tool could have future potential to reduce inequalities through increasing uptake in traditionally hard-to-reach populations and represents an advantage for HPV primary screening.

7.6 How can the benefits and burdens of a programme be fairly balanced?

If it is determined that a proposed public health intervention, policy, or programme is likely to achieve its stated goals, if its potential burdens are recognised and minimised, if participants are able to make an informed choice, and if the programme is expected to be implemented in a non-discriminatory way, a decision must be reached about whether the expected benefits justify the identified burdens.

For both the vaccinated and unvaccinated cohorts, the data presented in this report support the view that switching to a screening programme providing HPV as the primary screening test will be more efficient (due to a reduction in the average lifetime number of screens) and less costly than the current programme. More specifically, HPV primary testing followed by a liquid-based cytology (LBC) triage test at five-yearly screening intervals from age 25 to 60 was found to be cost-effective for both the vaccinated and unvaccinated cohorts. However, cost-effectiveness is only one aspect of the decision-making process in healthcare as other factors are also of crucial importance in considering the benefits and burdens of a proposed change. In particular, the effectiveness of a proposed change is clearly a significant issue to be taken into account.

In this HTA, the recommended approach provides comparable clinical efficacy to the current strategy in terms of the number of cancer cases, cancer deaths and quality-adjusted life years (QALYs), over the lifetime of a cohort. Other issues to be taken into account in the decision-making process include safety, public tolerance and acceptability of change, and the best use of public resources in population health measures.

7.7 Summary

Changing a population cancer screening programme raises a range of ethical issues which policy-makers need to consider. There is an ethical obligation to determine if the current cervical screening programme can be modified in a way that minimises potential burdens or harms without reducing the programme's efficiency. While governments have an obligation to protect the health and wellbeing of citizens, this must be achieved in a way that it is equitable, non-discriminatory, transparent and as far as possible non-coercive.

Since there is no treatment for HPV infection, HPV testing may result in some women experiencing anxiety and distress. In order to reduce this psychological burden, it is crucial that women are given sufficient information about the new

process and its potential risks and benefits in a way they can understand to enable informed consent.

The relative risk of cervical cancer rises with increasing population density, level of unemployment and lower educational attainment. There is ongoing concern about the inequitable burden of cervical cancer among women in lower socio-economic groups who may be less likely to present for vaccination and or screening than women in higher socio-economic groups. The change to primary HPV testing is not expected to increase or decrease the current social inequities related to cervical screening and or vaccination. Women who have been vaccinated against HPV might consider themselves to be at low risk of developing cervical cancer and may not present for cervical screening. Education and awareness campaigns will be needed to ensure adherence to the revised cervical screening programme.

Proposed changes to the screening programme will result in greater efficiency and lower costs compared with the current screening programme. This would free resources for use elsewhere in the healthcare system, allowing for further increases in overall population benefits.

The recommended approach provides comparable clinical efficacy in the number of cancer cases and cancer deaths and quality-adjusted life years (QALYs), over the lifetime of a cohort. Other issues to be taken into account in the decision-making process include safety, public tolerance and acceptability of change, and the best use of public resources in population health measures.

In choosing the time interval for the new screening programme, any potential for an increased rate of undetected cancer must be considered as well as the importance in maintaining public confidence in the screening system. While primary HPV screening was not found to be cost-effective in the vaccinated cohort, it may be beneficial to adopt five-yearly screening for this group until further evidence becomes available to support a longer screening interval.

7.8 Key messages

- HPV testing when used as a primary screening test for the prevention of cervical cancer, would lead a reduction in the false negatives compared with cytology as a primary screening test. To avoid unnecessary referral to colposcopy services, women with a positive HPV test will require a triage test. The combination of a HPV primary test followed by a cytology triage test would lead to a more favourable risk-benefit compared with cytology primary testing followed by HPV triage testing.
- Primary HPV testing may result in worry and anxiety for some women, with potential issues relating to fear of testing positive for HPV because of the possible implications for their health, their relationships and the inability to treat HPV.
- The informed consent process will have to be carefully managed to ensure that women are given sufficient information about the new testing process and its potential risks and benefits in a way they can understand.
- For women who test positive for HPV, they should be reassured about the meaning of HPV infection and their concerns about transmission allayed as far as possible.
- The screening process will not change from the woman's perspective, so we anticipate that the existing social inequities will neither increase nor decrease.
- Proposed changes to the screening programme will increase efficiency and lower costs compared with the current screening programme. This would free resources for use elsewhere in the healthcare system, allowing for further increases in overall population benefits.
- In considering the time interval to be used in the new screening programme, any potential for an increased rate of undetected cancer must be considered as well as the importance in maintaining public confidence in the screening system. Other issues to be taken into account in the decision-making process include safety, public tolerance and acceptability of change, and the best use of public resources in population health measures.

8 Discussion

The best cervical screening programme detects and treats as many women with precancerous abnormalities as possible. However, no cervical screening programme can prevent all cervical cancers and a balance needs to be struck between effectiveness and efficiency.

Cervical cancer is the eighth most common invasive cancer in women in Ireland. In 2012, the estimated incidence of cervical cancer in Ireland was 15.1 per 100,000 (European age-standardised rate [EASR]), compared with the incidence in the 27 European Union member states of 11.3 per 100,000. The estimated mortality from invasive cervical cancer in Ireland was 4.3 per 100,000 (EASR), compared with the EU-27 mortality of 3.7 per 100,000. There has been an increase in the incidence of cervical cancer in Ireland with further increases anticipated based on changes in sexual behaviour and demographic changes. However, well-organised screening programmes have been shown to reduce the incidence and mortality from cervical cancer by earlier detection and management of precancerous abnormalities.

Organised screening began in Ireland in September 2008 with the establishment of CervicalCheck – Ireland's National Cervical Screening Programme.

8.1 Rationale for proposed changes to CervicalCheck

Since CervicalCheck's inception there have been a series of developments that may provide an opportunity to increase the clinical and cost-effectiveness of the existing programme. Knowledge of the natural history of cervical cancer has increased, in particular since the causative role of 'oncogenic types' (so called high-risk human papillomavirus [HPV] or hrHPV genotypes) in the development of cervical cancer was confirmed in the 1990s. In the last decade, high quality evidence has been published to show that primary HPV screening has a higher sensitivity to detect precancerous abnormalities and early invasive cancer than primary liquid-based cytology (LBC) screening.

Evidence has also emerged of the potential to increase the screening interval with a HPV-based screening programme. The body of evidence has also increased to support newer laboratory technologies, such as HPV genotyping and molecular biomarkers, which can provide additional information regarding the clinical significance of hr-HPV. Since 2016, good-quality preliminary data have also become available from a study by the Irish Screening Research Consortium (CERVIVA) on the prevalence of hrHPV in women attending for a routine smear test. A final consideration is the issue of HPV vaccination which reduces the risk of cervical

cancer and decreases the efficiency of primary LBC screening in a HPV-vaccinated cohort. In Ireland, a national school-based vaccination programme commenced in 2010. The first cohort of schoolgirls vaccinated against HPV through the national vaccination programme will be eligible for CervicalCheck in 2018-2019. As the number of vaccinated women increases, they will represent a growing proportion of those eligible for screening through CervicalCheck. Given all these developments, it is evident that there is potential to improve the efficiency of CervicalCheck, particularly in the context of a growing HPV-vaccinated cohort.

8.2 Comparative effectiveness of HPV-based screening

Based on a systematic review of the literature, good-quality data were identified to support the effectiveness of primary HPV screening. Twenty-two cross-sectional studies and one randomised controlled trial (RCT) were included in the evidence synthesis of the diagnostic accuracy of primary HPV screening. Overall, the quality of these studies was rated as fair to good. Meta-analysis of studies undertaken in industrialised countries indicated that primary HPV screening is significantly more sensitive and less specific than primary cytology screening. The synthesised evidence was based on the HC2 HPV assay. Meta-analysis of the available evidence indicated a significantly higher sensitivity for HC2 in detecting CIN 2+ and CIN 3+ than cytology screening. Switching to primary HPV screening would result in fewer women receiving a false negative result, meaning that less women and clinicians will be falsely reassured that no precancerous changes exist.

Meta-analysis of the data indicate pooled specificity of HC2 in detecting CIN 2+ and CIN 3+ were significantly lower than achieved with cytology screening. Switching to primary HPV screening with HC2 would result in more women receiving a false positive result.

HC2 was the first assay to become commercially available and is the most commonly used assay reported in the literature. Since May 2015, CervicalCheck has used the Aptima and Cobas 4800 assays for all HPV testing. Both of these assays have been identified as meeting validation criteria (that they should be highly reproducible and at least as accurate as HC2) proposed by an international expert committee, so it plausible that the outcomes reported in these trials are also applicable to Ireland.

It is important to note that the meta-analysis presents data for a general screening population without widespread HPV vaccination. There is currently limited evidence about the performance of cytology or HPV testing in vaccinated cohorts. Limited Scottish data on younger women (under 25 years of age) suggest that the performance of different HPV tests may be differentially affected in a vaccinated

cohort, but that the sensitivity and specificity of cytology for either CIN 2+ or CIN 3+ do not differ between a vaccinated and an unvaccinated cohort.

While the systematic review demonstrated that at baseline, HPV testing is more sensitive than cytology in detecting CIN 2+ and CIN 3+, it does not necessarily follow, that this would lead to a reduction in the incidence of cervical cancer in the long-term compared with cytology-based screening. Evidence from long-term follow up of women with a negative screening result from four large European population-based RCTs has shown that a negative HPV test carries a lower risk of developing both CIN 3+ and invasive cervical cancer than a negative cytology test result.

The low specificity of primary HPV screening means that using it as a standalone test would lead to large numbers of women unnecessarily referred for colposcopy. It therefore needs to be combined with a triage test to minimise the false positive test results. Fifteen studies based on eight RCTs were included in the evidence synthesis of the diagnostic accuracy of seven triage strategies:

1. cytology;
2. partial genotyping for HPV 16 and 18;
3. sequential testing with partial genotyping for HPV 16 and 18 followed by liquid-based cytology;
4. co-testing with partial genotyping for HPV 16 and 18 and liquid-based cytology;
5. triage with $p16^{INK4a}$ and $p16^{INK4a}$ /Ki-67 dual staining;
6. sequential testing with partial genotyping for HPV 16 and 18 followed by $p16^{INK4a}$ /Ki-67;
7. and co-testing with partial genotyping for HPV 16 and 18 and $p16^{INK4a}$ /Ki-67).

These RCTs were typically large-scale trials conducted within population-based screening programmes. The quantity of data available for the various triage strategies was less than that available for primary HPV screening, with few comparable trials. A number of the strategies appear to be advantageous with longitudinal data to support that they may be safely used within a typical screening interval.

Based on the systematic review of the literature, there are insufficient data to date to determine which strategy is most suitable in the Irish context, particularly in light of the HPV vaccination programme which will lead to reductions in the prevalence of HPV and the background risk of disease.

8.3 Effectiveness modelling and economic evaluation

A decision analysis model was built to compare the costs and benefits associated with different primary HPV screening strategies for preventing cervical cancer in Ireland compared with the current strategy of primary liquid-based cytology (LBC) screening with HPV triage. Thirty-two screening strategies with various combinations of primary tests, triage tests, screening intervals and exit ages were proposed for inclusion in the economic evaluation. Each strategy was considered in both unvaccinated and (HPV 16 and 18) vaccinated cohorts.

In the unvaccinated cohort, the current strategy of primary LBC screening with HPV triage at three-yearly intervals from age 25 to 44 years and five-yearly intervals from 45 to 60 years was more costly and either less or equally effective, when compared with all other options (apart from extending the current strategy to age 65 and primary HPV screening followed by triage comprising co-testing with partial genotyping and p16INK4a/Ki-67 with screening extended to age 65). Relative to a willingness-to-pay threshold in the range of €20,000 to €45,000 per quality-adjusted life years (QALY), which is typically used in Ireland, primary HPV screening with LBC triage at five-yearly intervals from age 25 to 60 years was found to be cost-effective with an ICER of €29,788 per QALY. While this strategy provides comparable clinical efficacy to the current screening practice, a number of other strategies, although not cost-effective were found to be more effective, and would also lead to a reduction in costs compared with current practice.

In the vaccinated cohort, the current strategy was less effective and more costly compared with all other strategies (apart from extending the current strategy to age 65 years). For women who have been vaccinated against HPV 16 and 18, none of the modelled strategies were considered cost-effective compared with no screening at a willingness-to-pay threshold of €45,000 per QALY. The strategy with the lowest ICER (€58,745 per QALY) was primary HPV screening with liquid-based cytology triage, at five-yearly intervals from age 25 to 60 years.

Two subgroup analyses were conducted at the request of the Expert Advisory Group. The first considered extending the screening exit age from 60 to 65 years in a cohort who have not had the benefit of lifetime access to CervicalCheck from the age of 25 years (that is, for women who were 50 years old when CervicalCheck commenced in 2008). This analysis confirmed that extending the upper screening age limit from age 60 to age 65 years provides a clinical benefit, but is not cost-effective under willingness-to-pay thresholds in the range of €20,000 to €45,000 per QALY, irrespective of when access to organised screening starts (25 or 50 years). Given their historic underscreening, it may be considered appropriate to extend screening to age 65 years for these women for ethical reasons. However, to realise the

potential benefits of this additional screening round, a targeted campaign to maximise uptake of screening in those over 60 would be necessary given the lower uptake of screening in older women.

The second subgroup analysis considered how best to screen women under the age of 30 years who have not been vaccinated for HPV 16 and 18 in the context of primary HPV screening followed by liquid-based cytology triage at five-yearly intervals being adopted from age 30 years. Given a high prevalence of both HPV infection and cervical abnormalities in these women, there was concern that a switch to five-yearly screening could lead to an increased risk of interval cancers within this subgroup. It is noted however that infection is also more likely to clear spontaneously in this age group and, in the absence of persistent infection, cytological abnormalities will typically regress. The optimal screening strategy for this subgroup of unvaccinated women under the age of 30 years was found to be primary HPV screening followed by liquid-based cytology triage at five-yearly intervals from age 25 to age 60 years.

Providing three-yearly screening for women aged under 30 (that is, adding one more screening round) increases the effectiveness of this strategy, but also increases its cost. With an ICER of €48,501 per QALY, this would not be considered cost-effective under willingness-to-pay thresholds in the range of €20,000 to €45,000 per QALY. If three-yearly screening to age 30 is adopted for clinical reasons, ongoing evaluation and monitoring of its efficacy will be required, taking into consideration the proportion of the population vaccinated against HPV and the prevalence of HPV infection. Furthermore it must be noted that questions still remain as to how best to manage unvaccinated women aged less than 30 years who screen positive for HPV, but negative on liquid-based cytology triage. Two alternative referral pathways were considered in the subgroup analysis. In the first pathway, women who were HPV positive at 12 months were referred directly to colposcopy. In the second, women were only referred to colposcopy if positive on partial genotyping test for HPV 16 or 18 at 12 months. Both referral pathways lead to similar clinical outcomes and costs. The requirement for a positive partial genotyping test would reduce the number of colposcopy referrals in this age group, but lead to repeated annual screening and potentially high levels of anxiety for some women. The efficacy of screening in this cohort will therefore require ongoing evaluation.

In the basecase analysis, with an ICER of €29,788 per QALY, primary HPV screening with LBC triage at five-yearly intervals from age 25 to 60 years was identified as the optimal strategy in the context of a willingness-to-pay threshold of €20,000 to €45,000 per QALY. However, it was not the most effective strategy. Alternative strategies considered had the potential to provide additional QALY gains, albeit

minimal, over the lifetime of a screening cohort while still costing less than the current screening programme. QALYs account for the differences in the quantity and quality of life and therefore account for differences in the stage at diagnosis and also the duration of survival of those who die from cervical cancer. They also account for harms due to screening including overdiagnosis, that is, the identification of abnormalities that would not otherwise become clinically significant. Overdiagnosis may contribute to a loss of quality of life due to increased surveillance and or unnecessary treatment. Furthermore, QALY estimates are discounted to reflect society's preference for benefits to be realised sooner and undesirable effects to be realised further into the future.

A balance needs to be struck between screening too frequently (over-screening) and screening too infrequently (under-screening). Over-screening may result in both short-term and long-term effects associated with the screening test, examination at colposcopy, biopsy, overdiagnosis and unnecessary treatment. Under-screening results in higher numbers of interval cancers and cancer deaths. A change in the sequence of screening tests from primary LBC screening with HPV triage to primary HPV screening with LBC triage, together with an increase in the screening interval to five-yearly for all women aged 25 to 60 years, would result in a decrease in the average number of lifetime screens from eight to 5.9 per woman. The number of cervical cancer cases and deaths avoided per screen would be higher than it is with the current strategy, with a 30% increase in the numbers of cervical cancer cases and deaths avoided per screening test. This higher yield would increase the efficiency of CervicalCheck, that is, it would achieve comparable benefits with fewer lifetime screens.

The budget impact analysis was conducted from the perspective the publicly-funded health and social care system. As any switch from a three-yearly to a five-yearly screening would required phased implementation, an eight-year timeframe was adopted for the budget impact analysis, as opposed to the five-year timeframe typically adopted in Irish health technology assessments. The incremental eight-year budget impact (2018 to 2025) of switching from the current strategy to primary HPV screening with LBC triage at five-yearly intervals from ages 25 to 60 years estimated a net saving of up to €32 million for the unvaccinated population, €3 million for the vaccinated population and up to €35 million for the entire CervicalCheck population. As noted in Chapter 6, due to phased implementation, no reduction in screening activity would occur until year four (2022). Screening activity and therefore costs would increase in the first three years due to surveillance of women identified as HPV-positive, but cytology-negative.

It is noted in the economic evaluation that a number of alternative screening strategies were identified with the potential to be more effective than the current screening programme while still costing less than it. However, these strategies were not found to be cost-effective when compared to primary HPV screening with LBC triage at five-yearly intervals from age 25 to 60 years.

It is important that public money is used efficiently. Value for money depends on the perspective taken and this HTA took the perspective of the publicly-funded health and social care system. Opportunity costs are associated with the investment of money from the health budget in a strategy where the incremental gain in effectiveness for the incremental increase in cost is not considered cost-effective. Using the willingness-to-pay threshold allows for comparison to be made across the entire health service and identifies when interventions can be considered good value for money. By applying the willingness-to-pay threshold to guide the choice in the optimal strategy we can ensure that where the health gains are small relative to the increase in costs, this is highlighted. Consideration can then be given to redistributing resources to elsewhere within the health system to maximise the benefit for the entire population.

8.3.1 Key uncertainties

As noted, the costs and benefits of a range of primary HPV-based screening strategies were estimated in a decision analysis model both for an unvaccinated and a vaccinated cohort. However, there is considerable uncertainty around a number of the model parameters. While CERVIVA data on the prevalence of HPV by genotype is available, cancer incidence by genotype is not. For the vaccinated cohort, the model was calibrated to predict a 70% reduction in cancer incidence relative to an unvaccinated cohort. However, this may not accurately predict the true cancer incidence in an Irish vaccinated cohort. It must also be noted that there is considerable uncertainty around how vaccinated women will progress through the precancerous states from HPV infection to cancer incidence as there is currently a lack of data on the longer term outcomes from HPV vaccination. In the model, progression was assumed to follow a similar, but slower pattern than for the unvaccinated cohort. An overestimate in the rate of progression will potentially have biased against the less intensive screening options, whereas if progression has been underestimated, it will potentially have biased towards the less intensive screening strategies.

Univariate sensitivity analysis was performed on a number of key model assumptions to assess the robustness of the model predictions. In an unvaccinated cohort, there were four parameters where the upper or lower bounds resulted in five-yearly primary HPV screening with LBC triage from age 25 to 60 years being more effective

than the current strategy. Lowering the sensitivity of LBC in the detection of CIN 2+ and CIN 3+, reduces the probability of progression from CIN 3 to undiagnosed FIGO stage I cervical cancer, and increasing the prevalence of CIN 3 at age 25 years made the strategy more effective than the current strategy. The cost of the primary screening tests was the most influence parameter on the estimates of the cost differences between strategies. In Ireland, unlike other countries the cost of primary LBC screening is similar to the cost of primary HPV screening, while the cost of primary HPV screening is higher in other published economic evaluations.

There is also additional uncertainty regarding the optimal screening strategy in the vaccinated cohort due to uncertainty regarding future uptake rates of HPV vaccination, vaccine efficacy and virus competition. These factors could influence the prevalence of HPV in the population, and or the impact of vaccination on the incidence of cervical cancer. In the absence of longer term data on the development of cervical cancer in vaccinated women, it is difficult to accurately predict the cost-effectiveness of cervical screening. Despite being found not to be cost-effective, a policy of five-yearly screening in this cohort is not unreasonable until further data emerge. Data on this cohort will need to be evaluated on an ongoing basis. Use of the nonavalent vaccine in the national vaccination programme, which has been estimated to reduce the incidence of cervical cancer by 90% compared to no vaccination, would affect the incidence of cervical cancer in this cohort. The varying prevalence of HPV, both overall and genotype specific, between populations may affect the external validity of the results of this economic evaluation.

8.4 Organisational and social implications

A change to the sequence of screening tests and the screening interval used by CervicalCheck would have implications for women, CervicalCheck, healthcare professionals, administrative staff, laboratory services and colposcopy services, some of which overlap. However, as CervicalCheck was only established in 2008 and was based on best international practice at the time, it has an advantage over many other national screening programmes with fewer legacy issues, minimising the disruption of the proposed changes.

A change to primary HPV screening would not impact the way the cervical screening sample is collected, as the test kit currently used by CervicalCheck is suitable for HPV testing (including partial genotyping) and cytology testing. Test processing has already been centralised in a small number of sites by CervicalCheck. This will continue to provide efficiency gains allowing a high throughput in the HPV testing platforms while ensuring that there is still sufficient cytology throughput to maintain staff expertise for quality assurance purposes.

Adopting primary HPV screening would allow all women to become aware of their current HPV status. This would have resource implications, including adaptation of literature and training resources for test takers and women in relation to the implications of positive and negative tests and an increase in the time to explain primary HPV screening to allow informed consent. When primary HPV screening is combined with LBC (cytology) triage, a new cohort would be identified for surveillance: woman who are HPV positive, but cytology negative. These women are at elevated risk of developing CIN 2+. In the absence of clinical trial data to identify the optimal management of these women, it was assumed in the base case analysis that they would be recalled for surveillance in one year, and at that point, a repeat positive HPV test would warrant referral to colposcopy. One alternative referral pathway for unvaccinated women aged less than 30 years who are HPV-positive, but cytology negative was included in a subgroup analysis. In this referral pathway, women who are HPV-positive, but cytology negative would only be referred to colposcopy at 12 months if positive also for HPV 16 and 18 on partial genotyping. The implementation of this strategy would have logistical implications for CervicalCheck's laboratory process pathways and would also mean that the information provided by CervicalCheck to women might need to be tailored to their age and HPV vaccination status.

Based on current screening uptake rates, changing to primary HPV screening and extending the screening interval to five-yearly screening for all women is estimated to result in over two fewer screens per lifetime (from an average of 8.0 to 5.9) on average. This would lead to a reduction in CervicalCheck screening activity and colposcopy referrals and increase the efficiency of the programme. Due to phased implementation, no reduction in screening activity would occur until year four, with screening activity estimated to increase in the first three years (due to surveillance of women identified as HPV positive, but cytology negative). The budget impact analysis estimated a net reduction of 15% in the total number of screening tests and 16% in colposcopy referrals between 2018 and 2025. Reduction in screening activity and colposcopy referrals is predicted for both vaccinated and unvaccinated cohorts with the reduction being greater in unvaccinated women. An implementation plan will be required for this transitional phase to avoid excessively large fluctuations in workload due to a change in the screening interval.

The impact of extending the screening interval from three to five years on programme coverage is not known, with speculation that adherence to screening could improve or disimprove. It has also been speculated that the perception of cervical cancer risk in women aged 50 and over might change if primary HPV screening is implemented. This issue would be particularly important in the context of any decision to extend screening to age 65 years as the potential benefits of an

additional screening round would only be realised if uptake could be increased in those aged over 60 years, particularly among those who have not previously attended or who are underscreened. Ongoing audit of programme coverage and tracking of non-responders will allow changes in adherence to be identified in a timely fashion. Switching to primary HPV screening could allow for self-sampling and may provide an opportunity to improve coverage through an initial engagement with eligible women who have not attended CervicalCheck or who are underscreened because they do not attend at the recommended screening intervals.

8.5 International developments

A recommendation to switch from primary cytology screening to primary HPV screening is in keeping with developments in other high-income countries. Australia, Italy, Netherlands, New Zealand, Sweden and the UK have all recommended the implementation of primary HPV screening.

In January 2017, the Netherlands was the first country with an organised cervical screening programme to fully transition from primary cytology screening to primary HPV screening. Since 1996, women between the ages of 30 and 60 years had been offered primary cytology screening at five-yearly intervals. Beginning in January 2017, primary HPV screening at five-yearly intervals is now offered to women aged 30 to 60 years in the Netherlands. The screening interval is extended to 10-yearly for HPV-negative women aged at least 40 years, based on predictions from cost-effectiveness models. Noting concerns about potential increases in the number of cancers that develop in the interval between screenings, these will be monitored closely under the new HPV-based screening programme. Australia plans to transition to primary HPV screening in December 2017 and women between the ages of 25 and 69 years will be invited for screening at five-yearly intervals. New Zealand plans to transition to this strategy in 2018.

Differences remain in the entrance and exit ages to national cervical screening programmes in various high-income countries. In adopting primary HPV screening, Australia and New Zealand will raise the age at which they start screening to 25 years (from 18 and 20 years, respectively). This is consistent with International Agency for Research on Cancer (IARC) recommendations and current practice in Ireland. The Netherlands offers screening from the age of 30. The screening exit age also differs: it is 69 years in both Australia and New Zealand, while in Ireland and the Netherlands the exit age is 60 years. Given the evidence to support extending the screening interval with primary HPV screening, a screening interval of five years is being adopted by Australia and New Zealand (increasing from two and three years currently). The Netherlands have moved from five-yearly cytology screening to five-

yearly primary HPV screening, with the interval increased to every 10 years in HPV-negative women aged at least 40 years.

In proposing to change the screening programme, it is important to examine the broader context and specifically the history of screening and level of engagement with primary prevention through HPV vaccination. CervicalCheck, which was established in 2008, is a relatively new national screening programme compared with countries such as the Netherlands, the UK, Australia and New Zealand where organised screening has been available for at least 25 to 30 years. There is a potential that a culture of screening is not as well embedded in Ireland. However, to date, the coverage rate for CervicalCheck (79.6% for the five years to 31 December 2016) compares well with coverage rates achieved elsewhere including Australia (82.7% for the period between 2010 and 2014) and the Netherlands (64% up to 2011 to 2102). In England reductions in the mortality from invasive cervical cancer of up to 70% have been observed as a result of a national cervical screening programme. In time, a similar reduction is expected in Ireland.

It is also important to consider the history and level of engagement with HPV vaccination when proposing changes to the screening programme as this will influence the prevalence of HPV infection and the risk of cervical cancer in the overall population. There are differences between Ireland and other high-income countries in HPV vaccination policies and vaccination uptake rates. Publicly-funded school-based access to HPV vaccination for girls aged 12 to 13 years started in Australia in 2007, with community-based vaccination for all females up to 26 years of age provided until the end of 2009. The Australian programme was extended to include boys in 2013. A national vaccination programme commenced for girls aged 12 to 13 years in the UK in 2008 and in 2010 in the Netherlands. New Zealand commenced a national HPV vaccination programme providing the quadrivalent vaccine to girls and young women up to 20 years of age in 2008. This was extended in January 2017, to include boys, young women and young men aged nine to 26 years, with the programme also switching to the nonavalent vaccine at that time.

Ireland has had a nationally funded girls-only HPV vaccination programme since 2010. The first cohort of vaccinated girls will be eligible for CervicalCheck in 2018. There is already experience of cervical screening in HPV-vaccinated women in countries such as Australia due to the initial provision of a catch-up programme for women up to 26 years of age. Uptake of HPV vaccination as part of the national immunisation programme in Ireland at 86.9% in 2014 to 2015 and 72.3% in 2015 to 2016 compared favourably with that seen elsewhere (61% in the Netherlands [2010]; 85.1% in the UK [2016]; and 77.8% and 67.0% in girls and boys, respectively in Australia [2015]). However, uptake in Ireland has declined in the last

two years due to high-profile negative publicity relating to concerns over the vaccine's safety.

8.6 Future research and developments

Evidence of the role of HPV infection and the potential benefits of HPV vaccination and different cervical screening strategies in the prevention of morbidity and mortality from cervical cancer continue to develop.

There is evidence that following a negative primary HPV screening test, the screening interval can be safely extended to six years. Further evidence is emerging that it is safe to extend the screening interval up to 10 years in women over the age of 40 years who have a negative primary HPV screening test in a national cervical screening programme. Given that organised screening was only established in Ireland in 2008, extending the screening intervals beyond five years was not considered appropriate at this time. However, a potential extension of the screening interval should be considered in the future when a five-yearly screening interval has been successfully embedded and more evidence becomes available to support an extension to the screening interval. Irrespective of the strategy adopted, close monitoring of the number of interval cancers will continue to be required.

There is currently limited evidence about the performance of cytology or HPV testing in vaccinated cohorts. Evaluation of these data as they become available will help to inform cervical screening programmes regarding the optimal strategy for a vaccinated cohort who have a substantially reduced risk of cervical cancer. This economic evaluation assumed use of the bivalent or quadrivalent vaccine, that is, a 70% reduction in the risk of cervical cancer associated with vaccination against HPV 16 and 18. Future adoption of the nonavalent vaccine will further lower the risk of cervical cancer in a vaccinated cohort and will require reevaluation of the potential benefits and harms of screening.

It is noted that the quantity of data available for the various triage strategies was less than that available for primary HPV screening, with few comparable trials. While a number of the strategies appear to be advantageous with longitudinal data to support that they may be safely used within a typical screening interval, further data from ongoing trials will help to further inform the choice of triage test. The ongoing advances in HPV testing techniques, including in the range of biomarkers that discriminate between transient acute infection and transforming infection, may also lead to further refinement in the triage strategy options.

Triage strategies have been implemented in national cervical screening programmes in an attempt to identify women's individual risk of developing cervical cancer. This

risk-based approach to cervical screening could improve efficiency, but it also increases complexity making it more challenging to maintain a high-quality screening programme. CervicalCheck already has a comprehensive linked screening registry and a call-recall based invitation system in place both of which are pre-requisites for a risk-based approach to screening. It also has an established link to the national HPV vaccination programme. This system will allow CervicalCheck to develop an ongoing evaluation process for HPV risk-based screening, and to validate the applicability of the international data in the Irish setting and the long-term safety of HPV-based strategies.

The success of a cervical screening programme depends in part on maximising participation in screening. In countries with long-established cervical screening programmes, it is noted that the majority of cervical cancers occur in women who do not participate in regular screening. Thus switching to primary HPV screening is not expected to lead to a substantial reduction in cervical cancer rates, unless participation in screening can be improved. Limited data regarding screening participation in vaccinated women provide conflicting evidence that attendance is higher and lower than in non-vaccinated cohorts. Moreover, it is not known how extending screening intervals will impact programme coverage, with speculation that five-year coverage could either improve or disimprove. Ongoing monitoring of programme coverage and also the number of interval cancers observed with a HPV-based screening programme will therefore be necessary.

8.7 Conclusion

Health technology assessment (HTA) supports evidence-based decision-making in making the best use of resources in healthcare services. Measured investment and disinvestment decisions are essential to ensuring that overall health gain in a population is maximised, particularly given constrained healthcare budgets and increasing demands for services provided.

Bearing in mind the estimates and assumptions that were used in this HTA, the following conclusions may be drawn.

This HTA carried out a systematic review of randomised controlled trials (RCTs). The evidence in this review suggests that primary HPV screening is significantly more sensitive than primary cytology screening, that is, it will result in fewer women receiving a false negative result compared with cytology-based screening. However, it would also result in more women receiving a false positive result, that is, it will result in more women receiving a false positive result compared with cytology-based screening. Therefore, it is important to triage

women who test positive for HPV to identify those at higher risk of precancerous abnormalities and early stage invasive cervical cancer.

An economic evaluation was undertaken to determine the cost-effectiveness and budget impact of changing to primary HPV screening in Ireland. Options for triage were also assessed, along with alternative screening intervals and age bands. All options were assessed both in a cohort of women vaccinated against HPV 16 and HPV 18 and in an unvaccinated cohort.

Taking into account the assumptions used in the economic model and the uncertainty of the parameter values, changing to a strategy of primary HPV screening followed by liquid-based cytology triage at five-yearly intervals for all eligible women aged 25 to 60 years would improve the efficiency of the CervicalCheck programme. Women would require fewer screenings in their lifetime to achieve the same benefits. This strategy provides similar efficacy to the current screening programme, and would lead to a net cost saving of up to €35 million over the first eight years of its implementation (2018 to 2025).

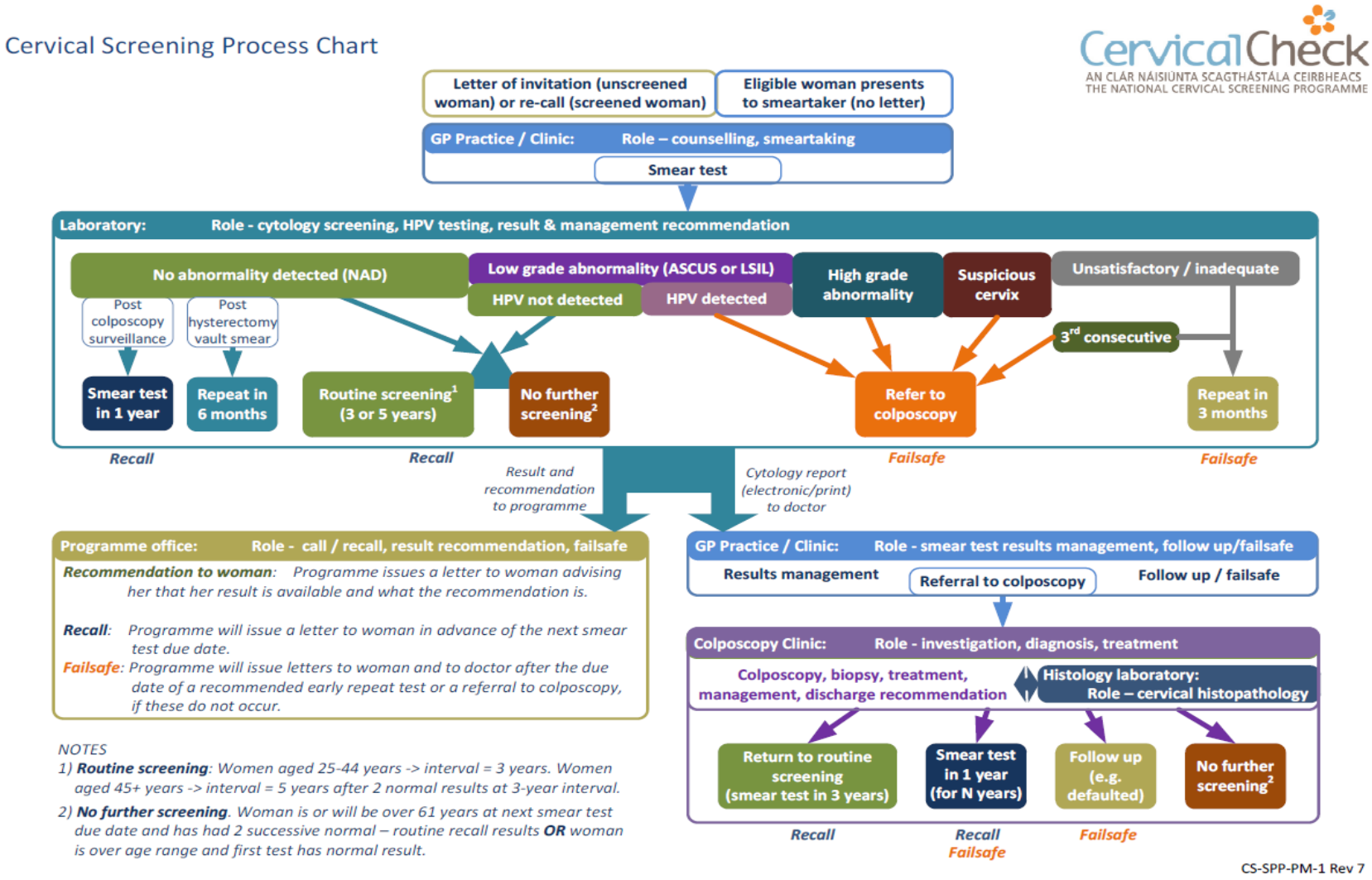
For women not vaccinated against HPV, a change to primary HPV screening followed by liquid-based cytology triage at five-yearly intervals for all eligible women aged 25 to 60 years would be cost-effective at the standard willingness-to-pay threshold of €20,000 to €45,000 per QALY,

For women who have only had access to organised screening from age 50, consideration should be given to extending screening to age 65 years. While not cost-effective, this would lead to improved clinical outcomes for this group. If implemented, it would need to be combined with a targeted campaign to increase the uptake of screening in those aged over 60 years.

Consideration should also be given to providing three-yearly primary HPV screening to women aged under 30 years who have not been vaccinated against HPV. While not cost-effective, this would lead to improved clinical outcomes for this group. Ongoing evaluation will be required to inform the future screening and surveillance of these women.

Given their lower risk of developing cervical cancer, screening women vaccinated against HPV at five-yearly intervals may not be cost-effective. However, given the uncertainty about this cohort, screening at five-yearly intervals should continue while giving consideration to increasing the screening interval as evidence emerges to support the long-term effectiveness of screening women vaccinated against HPV.

Appendix 1 – CervicalCheck screening process chart



Appendix 2 – FIGO staging of cervical cancer

Table App2.1 Féderation International de Gynecologie et d'Obstetrique (FIGO) classification system for staging cervical cancer

Stage			Description
I			Carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded).
	IA		Invasive cancer identified only microscopically. (All gross lesions even with superficial invasion are Stage IB cancers). Invasion is limited to measured stromal invasion with maximum depth of 5mm and maximum lateral spread of 7mm
		IA1	Measured stromal invasion ≤3mm in depth and ≤7mm spread.
		IA2	Measured stromal invasion 3mm<depth<5mm and ≤7mm spread.
	IB		Clinical lesions confined to the cervix, or preclinical lesions greater than Stage IA.
		IB1	Clinical lesions no greater than 4cm in size.
		IB2	Clinical lesions > 4cm in size.
II			Carcinoma extends beyond the cervix, but does not extend onto the pelvic wall. The carcinoma involves the vagina, but not as far as the lower third.
	IIA		
		IIA1	No obvious parametrial involvement. Involvement of up to two thirds of the vagina.
		IIA2	
	IIB		Clinically visible lesion ≤4cm in greatest dimension Clinically visible lesion >4cm in greatest dimension. Obvious parametrial involvement, but not onto the pelvic sidewall.
III			Carcinoma has extended onto the pelvic sidewall. On rectal examination, there is no cancer-free space between the tumour and the pelvic sidewall. The tumour involves the lower third of the vagina. All cases with a hydronephrosis or a non-functioning kidney are Stage III cancers unless shown to be due to other causes.
	IIIA		Involvement of the lower one-third of vagina, but no extension onto pelvic sidewall.
	IIIB		Extension **onto** the pelvic sidewall, or hydronephrosis/non-functioning kidney.
IV			Carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder and, or rectum.
	IVA		Spread to adjacent pelvic organs.
	IVB		Spread to distant organs.

Reference: Bermudez A, Bhatla N, Leung E 2015 http://www.sciencedirect.com/science/article/pii/S0020729215003756

Appendix 3 – Search details for clinical effectiveness

A search for studies relating to the diagnostic accuracy of HPV testing compared with cytology as the primary screening test for the prevention of cervical cancer was carried out. The systematic review updated a recent systematic review published by KCE in 2015[164] using the same search string. The databases searched were:

- PubMed
- EMBASE

The search string as applied in PubMed is shown in Table App3.1. The search was restricted to studies published since October 2013 and was completed in January 2016.

Table App3.1 Search string used in PubMed

Search string	Results
((Uterine Cervical Neoplasms [MeSH Terms] OR Uterine Cervical Dysplasia [MeSH Terms] OR Cervical Intraepithelial Neoplasia [MeSH Terms] OR ((cervix [tw] OR cervical [tw] OR cervico* [tw]) AND (cancer* [tw] OR carcinoma OR adenocarcinoma OR neoplas* [tw] OR dysplas* [tw] OR dyskaryos* [tw] OR squamous [tw] OR CIN [tw] OR CINII* [tw] OR CIN2* [tw] OR CINIII* [tw] OR CIN3* [tw] OR SIL [tw] OR HSIL [tw] OR H-SIL [tw] OR LSIL [tw] OR L-SIL [tw] OR ASCUS [tw] OR AS-CUS [tw]))) AND (papillomaviridae [MeSH:NoExp] OR alphapapillomavirus [MeSH Terms] OR "DNA, viral" [MeSH Terms] OR Papillomavirus Infections [MeSH Terms] OR Tumor Virus Infections [MeSH Terms] OR "Cervix Uteri/virology" [MeSH Terms] OR HPV [tw] OR "human papillomavirus" [tw] OR papillomaviridae [tw] OR PCR OR "hybrid capture*" [tw] OR HC2 [tw] OR HCII [tw] OR "HC 2" [tw] OR "HC II" [tw] OR ((viral [tw] OR virolog* [tw]) AND (DNA [tw]))) AND (Vaginal smears [MeSH Terms] OR Cytodiagnosis [MeSH Terms] OR Cell Transformation, Viral [MeSH Terms] OR Cytopathogenic Effect, Viral [MeSH Terms] OR ((pap [tw] OR papanicolaou [tw] OR vagina* [tw] OR cervical [tw] OR cervix [tw] OR cervico* [tw] OR cytolog* [tw]) AND (smear* OR test [tw] OR tests [tw] OR testing [tw] OR tested [tw] OR swab* OR scrap*))))	1,596

The bibliographic search returned 3,335 studies, which equated to 2,396 studies following removal of duplicates (Figure B.1). After removal of studies deemed not relevant based on the titles and abstract, 66 studies were identified for a full-text review. A further 55 studies were excluded (for reasons identified in Figure B.1) leaving 11 studies for inclusion. Quality appraisal and risk of bias assessment was conducted using QUADAS-2.[166]

Figure App3.2 Flow diagram of included studies

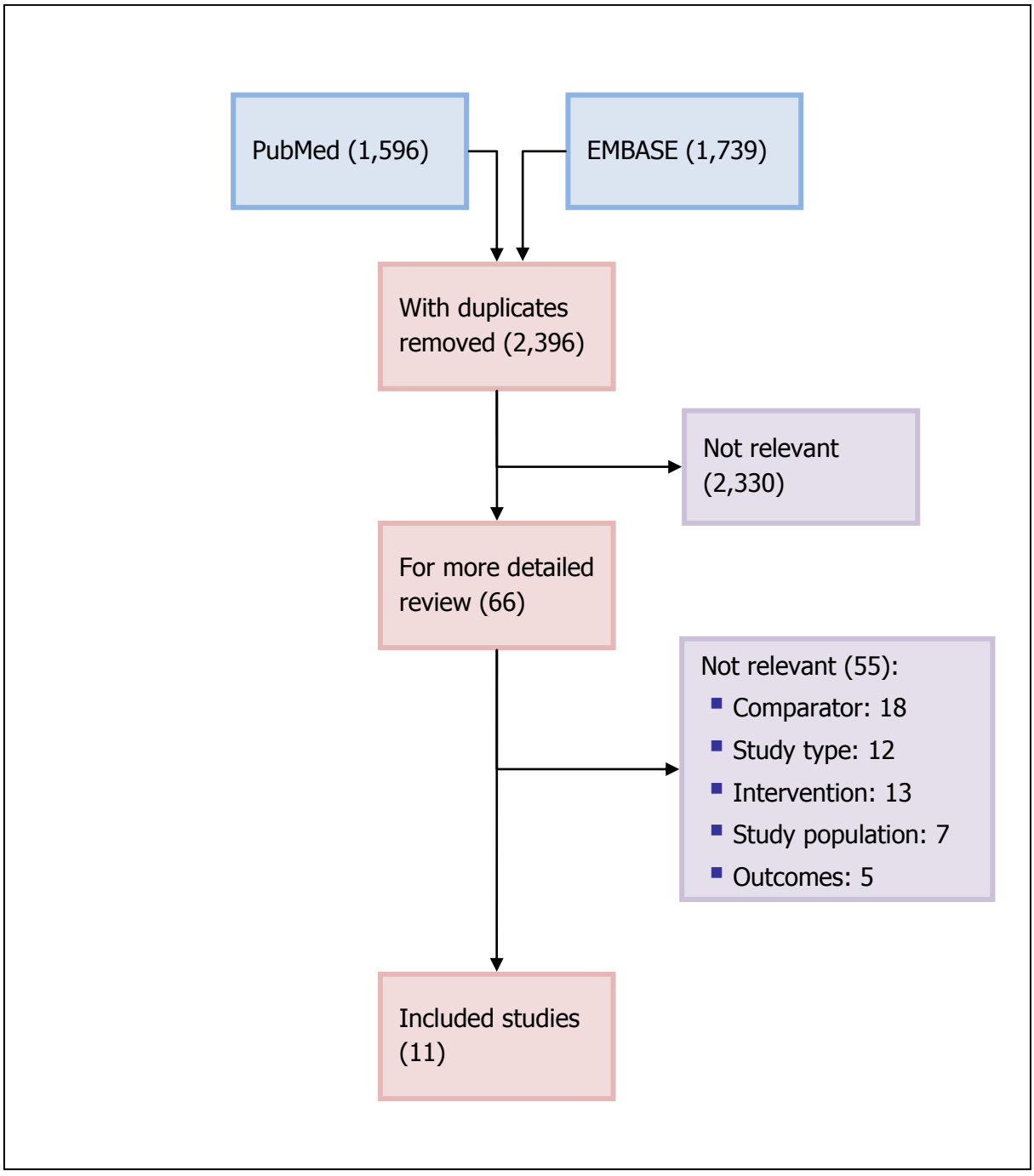


Table App3.2 Characteristics of studies from the review that were not included in the meta-analysis

Study	Reason for exclusion
Agorastos 2005[259]	Not HC2 (PCR-PGMY9/11)
Agorastos 2015[260]	Not HC2 (Roche Cobas 4800)
Almonte 2007[261]	Not industrialised country (Peru)
Anttila 2010[262]	Not concomitant testing (RCT)
Belinson 2001[263]	Not industrialised country (China)
Belinson 2003[264]	Not industrialised country (China)
Belinson 2010[265]	Not industrialised country (China)
Bellinson 2011[266]	Not industrialised country (China)
Bellinson 2012[267]	Not industrialised country (China)
Bian 2013[268]	Not industrialised country (China)
Blumenthal 2001[269]	Not industrialised country (Zimbabwe)
Bulkmans 2007[270]	Not HC2 (PCR-P5+/6+)
Cagle 2010[271]	Not industrialised country (China)
Castle 2011[30]	Not HC2 (Cobas®-4800)
Cuzick 1995[272]	Not HC2 (PCR-other)
Cuzick 1999[273]	Not HC2 (PCR-MY9/11)
Depuydt 2011[274]	Not HC2 (Real time PCR, ProExc)
Diamantopoulou 2013[275]	Not HC2 (CLART)
Girianelli 2006[276]	Not industrialised country (Brazil)
Gravitt 2010[277]	Not industrialised country (India)
Hovland 2010[278]	Not industrialised country (East Congo)
Jung 2016[279]	No cut off point – LSIL+
Kitchener 2009[207]	Kitchener 2014 is an update of this study
Kotaniemi-Talonen 2005[280]	Not concomitant testing (RCT)
Kuhn 2000[281]	Not industrialised country (South Africa)
Kulasingam 2002[282]	Not HC2 (PCR-MY9/11)
Leinonen 2009[283]	Not concomitant testing (RCT)
Leinonen 2012[284]	Not concomitant testing (RCT)
Li 2009[285]	Not industrialised country (China)
Li 2015[286]	Not industrialised country (China)
Longatto-Filho 2012[287]	Not industrialised country (Brazil, Argentina)
Mahmud 2012[288]	Not industrialised country (Congo)
Mayrand 2007[289]	Not HC2 (PCR)
Moy 2010[290]	Not industrialised country (China)

Naucler 2007[291]	Not HC2 (PCR-P5+/6+)
Nieves 2013[292]	Not industrialised country (Mexico)
Oh 2001[293]	Not industrialised country (Korea)
Paraskevaidis 2001[294]	Not HC2 (PCR-MY9/11)
Qiao 2008[295]	Not industrialised country (China)
Rijkaart 2012[296]	Not HC2 (PCR-P5+/6+)
Ronco 2008[297]	Not concomitant testing (RCT)
Ronco 2010[298]	no new data all contained in Ronco 2008
Salmeron 2003[299]	Not industrialised country (Mexico)
Sankaranarayanan 2004[300]	Not industrialised country (India)
Sankaranarayanan 2004[301]	Not industrialised country (India)
Sankaranarayanan 2005[302]	Not industrialised country (India)
Sankaranarayan 2009[303]	Not industrialised country (India)
Sarian 2005[304]	Not industrialised country (Latin America)
Schiffman 2000[305]	Not industrialised country (Costa Rica)
Schneider 2000[306]	Not HC2 (PCR-P5+/6+)
Wang 2013[307]	Not industrialised country (China)
Wright 2015[201]	Not HC2 (Roche Cobas 4800)
Wu 2010[308]	Not industrialised country (China)
Zhao 2012[226]	Not industrialised country (China)
Zhou 2016[309]	Not HC2 (Roche Cobas 4800)
Zong 2015[310]	Not industrialised country (China)

Abbreviations: RCT, randomised controlled trial; HC2, ; PCR,

A search for studies relating to the clinical effectiveness of triaging strategies for women with a positive HPV test was carried out. The systematic review updated a recent systematic review published by KCE in 2015[164] and the same search string was applied. The databases searched were:

- PubMed
- EMBASE

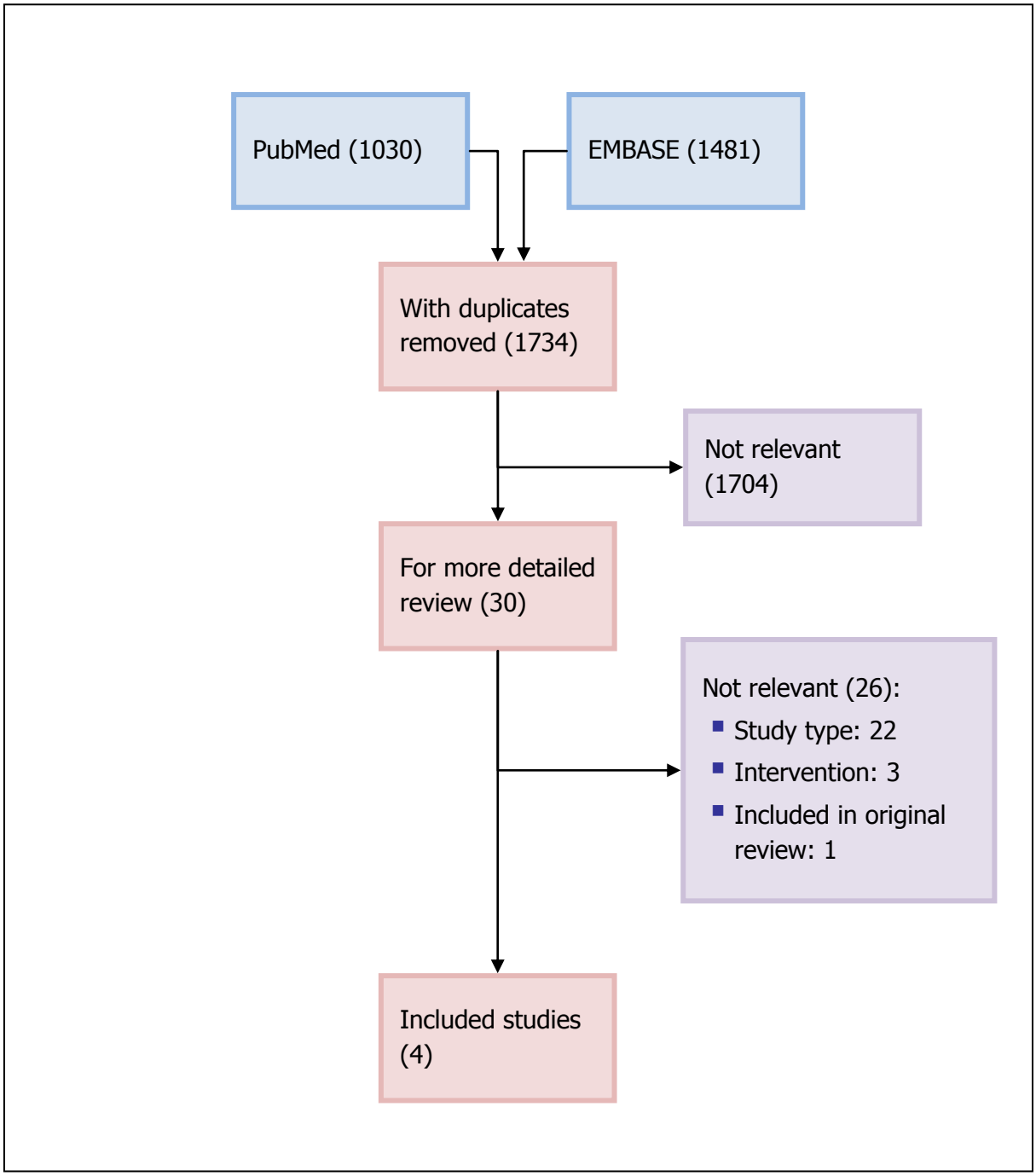
The search string as applied in PubMed is shown in Table App3.3. The search was restricted to studies published since October 2013 and updated to April 2016.

Table App3.3 Search string used in PubMed

Search string	Results
((Uterine Cervical Neoplasms [MeSH Terms] OR Uterine Cervical Dysplasia [MeSH Terms] OR Cervical Intraepithelial Neoplasia [MeSH Terms] OR ((cervix [tw] OR cervical [tw] OR cervico* [tw]) AND (cancer* [tw] OR carcinoma OR adenocarcinoma OR neoplas* [tw] OR dysplas* [tw] OR dyskaryos* [tw] OR squamous [tw] OR CIN [tw] OR CINII* [tw] OR CIN2* [tw] OR CINIII* [tw] OR CIN3* [tw] OR SIL [tw] OR HSIL [tw] OR H-SIL [tw] OR LSIL [tw] OR L-SIL [tw] OR ASCUS [tw] OR AS-CUS [tw]))) AND (papillomaviridae [MeSH:NoExp] OR alphapapillomavirus [MeSH Terms] OR "DNA, viral" [MeSH Terms] OR Papillomavirus Infections [MeSH Terms] OR Tumor Virus Infections [MeSH Terms] OR "Cervix Uteri/virology" [MeSH Terms] OR HPV [tw] OR "human papillomavirus" [tw] OR papillomaviridae [tw] OR PCR OR "hybrid capture*" [tw] OR HC2 [tw] OR HCII [tw] OR "HC 2" [tw] OR "HC II" [tw] OR ((viral [tw] OR virolog* [tw]) AND (DNA [tw]))) AND (Vaginal smears [MeSH Terms] OR Cytodiagnosis [MeSH Terms] OR Cell Transformation, Viral [MeSH Terms] OR Cytopathogenic Effect, Viral [MeSH Terms] OR ((pap [tw] OR papanicolaou [tw] OR vagina* [tw] OR cervical [tw] OR cervix [tw] OR cervico* [tw] OR cytolog* [tw]) AND (smear* OR test [tw] OR tests [tw] OR testing [tw] OR tested [tw] OR swab* OR scrap*)))) AND (triage OR management OR follow-up OR "follow up")	1,030

The bibliographic search returned 2,511 studies, which equated to 1,734 studies following removal of duplicates (Figure B.2). After removal of studies deemed not relevant based on the titles and abstract, 30 studies were identified for a full-text review. A further 26 studies were excluded (for reasons identified in Figure B.2) leaving four studies for inclusion. Quality appraisal and risk of bias assessment was conducted using QUADAS-2.[166]

Figure App3.2 Flow diagram of included studies



Appendix 4 – Search details for economic evaluations

Although a number systematic reviews of the economic literature have been published, none of these were considered to adequately address our question of interest. Thus a new systematic literature review was performed. The same search string that was applied in the search for clinical effectiveness data was used for the economic search. The timeframe was widened however to include studies published from 2008 to 21 January 2016, and a filter for economic studies was applied.

Studies were included if they compared HPV testing with LBC as the primary screening methodology for the prevention of cervical cancer. Following elimination of duplicates, removal of studies clearly not relevant based on title and abstract review, and exclusion of studies that did not meet the inclusion criteria, a total of six studies were identified for inclusion (Figure App4.1).

The relevance and credibility of the identified studies was assessed using the appropriate ISPOR questionnaire.[43] Reporting was generally adequate and considered to be fair and balanced.

Figure App4.1 Flow diagram of included studies

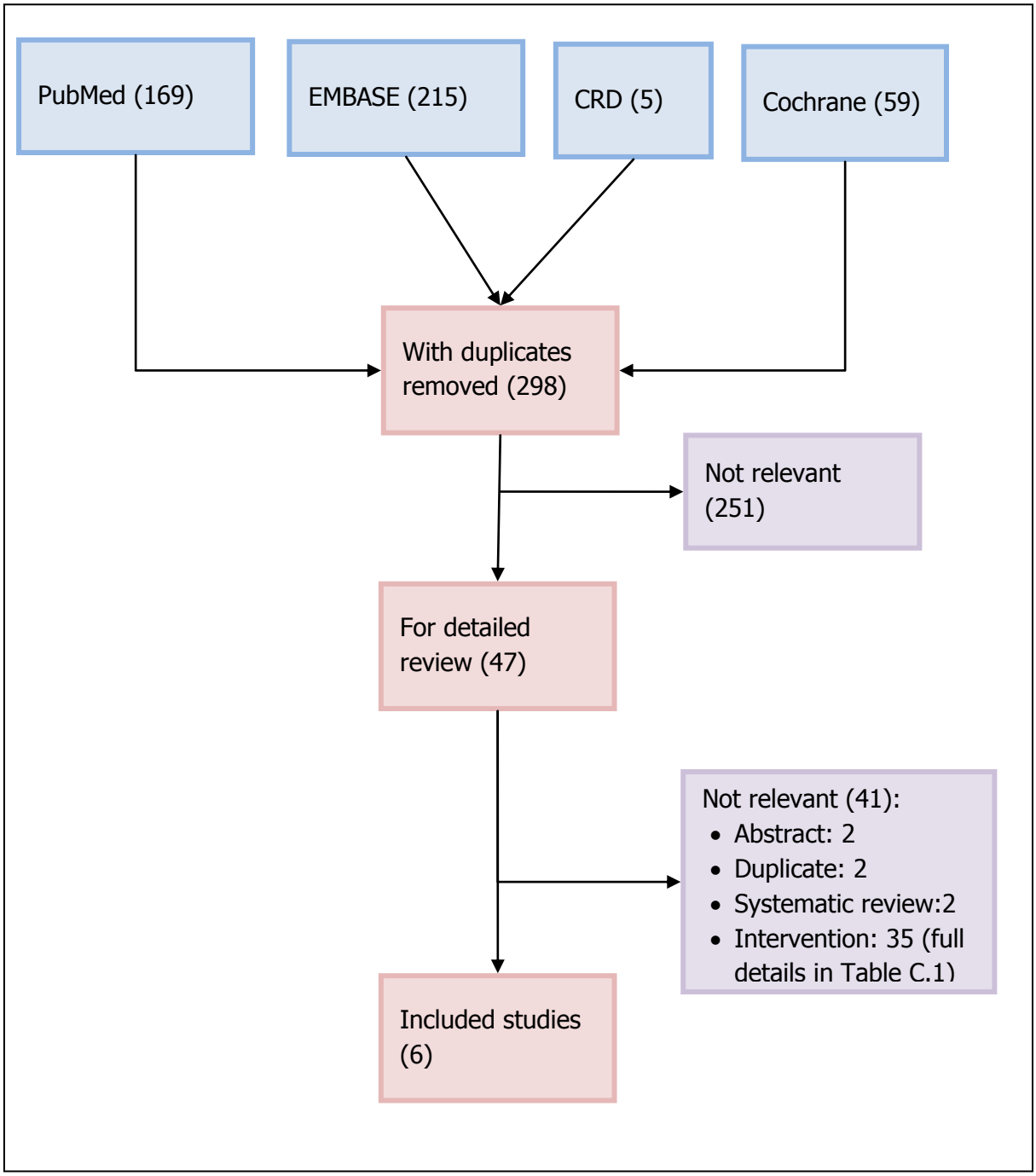


Table App4.1 Excluded studies

Study	Reason for exclusion
Accetta 2010[44]	The comparator is conventional cytology not liquid-based cytology.
Andres-Gamboa 2008[45]	The comparator is conventional cytology not liquid-based cytology.
Beal 2014[46]	Liquid-based cytology is not considered as a primary screening test, only included as a co-test option.
Berkhof 2013[47]	The comparator is conventional cytology not liquid-based cytology.
Berkhof 2010[48]	The comparator is conventional cytology not liquid-based cytology.
Bistoletti 2008[49]	The comparator is conventional cytology not liquid-based cytology.
Burger 2012[50]	Liquid-based cytology is not considered as a primary screening test.
Campos 2012[51]	The interventions compared were vaccination and HPV testing, cytology was not considered.
Canfell 2011[52]	The interventions compared were vaccination and HPV testing, cytology was not considered.
Chuck 2010[53]	Repeat of IHE 2009 publication.
Coupe 2009[54]	The comparator is conventional cytology not liquid-based cytology.
Coupe 2012[55]	Liquid-based cytology with HPV as triage not considered as a strategy option.
De Kok 2012[56]	The comparator is conventional cytology not liquid-based cytology.
Diaz 2010[57]	HPV testing is not considered as a primary screening test.
Diaz 2008[58]	Strategies considered are not relevant to our population.
Felix 2015[59]	Cytology is not considered as a primary screening test, only included as a co-test option.
Georgalis 2015[60]	Strategy options do not include any triaging options.
Ginsberg 2009 [61]	A high level global analysis, results not applicable to our situation.
Ginsberg 2013[62]	The comparator is conventional cytology not liquid-based cytology.
Goldhaber-Fiebert 2008[63]	The comparator is conventional cytology not liquid-based cytology.
Goldie 2012[64]	No alternative screening strategies considered, only the addition of vaccination.
Huh 2015[65]	The comparator is conventional cytology not liquid-based cytology.
Kim 2008[66]	No alternative screening strategies considered.
Kim 2008a[67]	No alternative screening strategies considered.

Kim 2009[68]	The comparator is conventional cytology not liquid-based cytology.
Kim 2015[69]	Considers improvements to current screening strategy not alternatives.
Kitchener 2009[70]	Updated in Kitchener 2014
Konno 2010[71]	No alternative screening strategies considered, only the addition of vaccination.
Kulasingam 2009 [72]	The comparator is conventional cytology not liquid-based cytology.
Levin 2010[73]	Strategy options do not include any triaging options.
Rogoza 2008[74]	HPV testing is not considered as a primary screening test.
Sharma 2012[75]	The comparator is conventional cytology not liquid-based cytology.
Sopina 2011[76]	Strategies did not include changing tests
Sroczynski 2010[77]	The comparator is conventional cytology not liquid-based cytology.
Sroczynski 2011[78]	The comparator is conventional cytology not liquid-based cytology.
Vijayaraghavan 2010[79]	The comparator is conventional cytology not liquid-based cytology.
Wiwanitkit 2009[80]	The comparator is conventional cytology not liquid-based cytology.

Appendix 5 – Details of model cost parameters

5.1 Screening

Current cervical screening and the associated costs were obtained from, CervicalCheck -Ireland's National Cervical Screening Programme.[55] Table App5.1 and Table App5.2 outline the costs of the primary screening tests of LBC and HPV. Following this there is a triage step using either liquid-based cytology (LBC), HPV, genotyping or dual staining $p16^{INK4a}$/Ki-67. Costs are broadly disaggregated into the cost of taking the screening test, the cost(s) of processing the test, and the cost of communicating the screening test result. Fully disaggregated costs are not included due to the commercial sensitivity of the test costs, this includes the triage test cost. Value added tax (VAT) (for example, 23% on consumables) is not included in the cost-effectiveness analysis, so where appropriate adjusted costs that exclude VAT are reported.

Primary screen

Cervical screening (outside of colposcopy settings) is mainly accessed through primary care (98.5%) with the remaining 1.5% accessed through secondary care (public gynaecology, GUM and STI services).

The cost of screening tests accessed through primary care includes the fee paid to the provider (exclusive of VAT), the cost of the consumables used (speculum and the screening test kit, the laboratory cost for processing the result, the cost of a letter and leaflet to the woman explaining the results, the costs associated with inadequate or unsatisfactory results (test repeated and all costs repaid) and the cost of an expired result (no fee paid, but other costs paid).

The cost for the small proportion of screening tests (1.5%) accessed through secondary care (public gynaecology, GUM and STI services) includes the same costs as that of primary care except that the fee is not paid. Regarding inadequate or unsatisfactory results, typically 1.8% of all screening tests are classified as this, meaning that the laboratory is unable to process them because the sample is unclear. In this case, it is recommended that a retest or repeat screening test is completed within three months. A small proportion (0.2%) are deemed 'expired' based on the samples or vials being expired. These values are based on the current test set-up using LBC and are very small, it is assumed that the same values apply for HPV.

Following a competitive tender, CervicalCheck currently outsources processing of approximately 90% of screening tests to two laboratories. The remaining 10% are processed in the National Cytopathology Training Centre based in the Cytology

Department of the Coombe Women and Infants University Hospital. The per-item fee paid by CervicalCheck for the processing of the LBC (ThinPrep®) sample and the consumables (Aptima or Cobas 4800 test kit) and processing of the HPV tests were obtained from CervicalCheck.

As some of the strategies modelled include a change in the screening interval, this results in a change in the number of lifetime screens per woman. The costs associated with communication of test results must therefore be included. The unit cost of a letter with the screening test result and an accompanying leaflet providing details on results were obtained from CervicalCheck. In addition, the unit cost for one reminder letter (no leaflet) was included, with the quantity based on the number of women who do not turn up to surveillance, see Table App5.1 and App5.2. The cost of this correspondence as obtained from CervicalCheck were as follows: a letter (letterhead, print, pack, envelope) has a cost of approximately €0.15 with a leaflet included and approximately €0.08 without a leaflet; and postage costs of €0.55 euro per letter (with or without leaflet) based on a bulk postage rate.[55]

In the following tables, some items are reported to apply to a percentage of women rather than all women. In these cases, the reported cost reflects the average contribution of the item to the cost of treatment. For example, in Table App5.7 the average weighted cost of a PET CT (100% of cases get 1 PET CT at a cost of approximately €992: 100% x 1 x €992) = €992 per patient) is listed as €992.

Triage

The additional laboratory costs associated with a triage step are included for the options of LBC, HPV, genotyping or $p16^{INK4a}$/Ki-67 triage. Fully disaggregated costs are not included due to the commercial sensitivity of the test costs. LBC and HPV costs were obtained from CervicalCheck based on their current use. Estimated genotyping costs were also obtained from CervicalCheck based on its expected use. If the machine used for HPV testing includes genotyping probes for 16/18 then these results can be processed simultaneously, alternatively a second machine is used. With sufficient test volumes it is expected that there will be a minimal cost associated with the additional genotyping step. The costs associated with $p16^{INK4a}$/Ki-67 were based on expert opinion and include the test kit cost, the cost to make a slide, the cost to review a slide including the cost to review positive slides based on a 28% rate of referral to colposcopy, see Table App5.3.[202] The associated pay-related staff costs were included after adjustment for non-pay costs including employers' PRSI, superannuation, and general overheads in accordance with national guidelines.[225]

Table App5.1 Cost parameters – primary screening using LBC

Item	Cost
Non-colposcopy settings - PC*	
Fee (no VAT)	
Screening test kit (less VAT 23%)	
Speculum (less VAT 23%)	
Lab cost LBC	
Letter + leaflet - results	
Inadequate/Unsatisfactory LBC (repeat, all paid)	
Expired LBC (repeat, no fee, lab + consumables paid)	
Non-colposcopy settings - other**	
Screening test kit cost	
Lab cost LBC	
Letter + leaflet - results	
Inadequate/Unsatisfactory LBC (repeat, all paid)	
Expired LBC (repeat, no fee, lab + consumables paid)	
LBC primary screen total per patient cost	**€79.02**

Note: The total and disaggregated costs are not included based on the commercial sensitivity of the test costs.
Abbreviations: HPV, Human papillomavirus; LBC, liquid-based cytology; PC, Primary Care.

Table App5.2 Cost parameters – primary screening using HPV

Item	Cost
Non-colposcopy settings - PC*	
Fee (no VAT)	
Screening test kit (less VAT 23%)	
Speculum (less VAT 23%)	
Lab cost HPV	
Letter + leaflet - results	
Inadequate/Unsatisfactory HPV (repeat, all paid)	
Expired HPV (repeat, no fee, lab + consumables paid)	
Non-colposcopy settings - other**	
Screening test kit cost	
Lab cost HPV	
Letter + leaflet - results	
Inadequate/Unsatisfactory HPV (repeat, all paid)	
Expired HPV (repeat, no fee, lab + consumables paid)	
HPV primary screen total per patient cost	**€78.71**

Note: The total and disaggregated costs are not included based on the commercial sensitivity of the test costs.
Abbreviations: HPV, Human papillomavirus; LBC, liquid-based cytology; PC, Primary Care.

Table App5.3 Cost parameters – triage using dual staining p16^{INK4a}/Ki-67

Item	Cost
Lab cost	
Test kit costs	
Cost to make slide (€5 + technician time)	
Cost to review slide (3min/slide, medical scientist)	
Cost to review slide (5min/slide, senior medical scientist)	
Cost to review positive slides (3min/slide, consultant medical pathologist)	
p16^{INK4a}/Ki-67 triage total per patient cost	**€66.23**

5.2 Diagnosis and treatment of CIN

In cases where no CIN is detected at colposcopy, costs include colposcopy testing, a letter detailing results and the cost of a letter to recall to routine screening, see Table App5.4. These costs were obtained from CervicalCheck and were derived using a payment-model based upon a total national capacity of 19,500 new referrals per annum (range 500 – 3,000 per individual hospital; 15 hospitals).[55] The total payment for colposcopy per annum is €6,269,750. The average unit cost is therefore

calculated as €322.23 (range €287 - €436) and is independent of whether a person requires follow-up or not.

Table App5.4 Cost parameters – No CIN

Item	Cost
Diagnosis	
Colposcopy (includes follow-up, letters)	€321.53
Communication	
Recall letter to screening + leaflet	€0.70
No CIN total per patient cost	**€322.23**

Abbreviations: CIN, Cervical intraepithelial neoplasia;

For CIN 1, the costs of diagnosis (colposcopy, follow-up if required, letter with results) are included as in no CIN above. CervicalCheck Guidance note 7 states that CIN 1 women who require no treatment should be offered a combined LBC and HPV test after 12 months in colposcopy, the costs for this was included but are not disaggregated based on commercial sensitivity, see Table App5.5.(ref) In addition, to reflect Guidance note 7, costs were calculated for the different test options, for example, HPV primary test followed by genotyping triage. The costs for a recall letter plus a leaflet were included for a percentage of patients who do not turn up at colposcopy.

Table App5.5 Cost parameters – CIN 1 – HPV and LBC triage

Item	Cost
Diagnosis	
Colposcopy (includes follow-up, letters)	€321.53
Repeat screening test in colposcopy at 12 months	
Screening test kit (less VAT 23%)	
Lab cost for LBC	
Lab cost for HPV	
Letter to recall for screening	
Recall letter plus leaflet	
CIN 1 total per patient cost	**€372.51**

Abbreviations: CIN, Cervical intraepithelial neoplasia;

For CIN 2 and CIN 3, the costs of diagnosis (colposcopy, histology) and treatment (in colposcopy clinic plus any follow-up required, further treatment outside of colposcopy clinic and out-patient appointment follow-up, results letter), the cost for a repeat screen at six months in colposcopy (based on CervicalCheck Guidance note 7) and the costs for a recall letter plus a reminder letter were included, see Table

App5.6. The average unit cost for colposcopy is as above (€321.52). The average unit cost for histology plus treatment and follow-up, where required, was also provided by CervicalCheck (€49.54). This is based on a payment model for histology based upon a total national capacity of 19,250 new referrals per annum. Of these, it is estimated that 86% are confirmed as abnormal screening tests of which 80% would typically receive a punch biopsy (€37) and 35% would receive LLETZ treatment (€80). The total payment for histology and follow-up per annum is €954,000. Costs for any additional treatment (e.g., trachelectomy, hysterectomy) plus follow-up appointments outside of the colposcopy clinic, which is infrequent, were included. These are based on (2014) DRG costs from HIPE. See Table App5.6 for details.

Table App5.6 Cost parameters – CIN 2 or CIN 3 – HPV and LBC triage

Item	Cost
Diagnosis	
Colposcopy (includes follow-up, letters)	€321.53
Histology & treatment in colposcopy	
Histology and treatment (includes follow-up, letter)	€49.54
Further treatment	
Hysterectomy	€62.61
Trachelectomy	€6.66
Outpatient follow-up	€0.86
Repeat screen in colposcopy at 6 months	
Screening test kit (less 23% VAT)	
Lab cost for LBC	
Lab cost for HPV	
Communication	
Recall letter (plus leaflet)	€0.00
CIN 2 or CIN 3 total per patient cost	**€489.64**

Abbreviations: CIN, Cervical intraepithelial neoplasia;

5.3 Stage I (IA1, IA2, IB1, IB2)

Since the treatment pathway and associated costs vary largely between Stage 1A1 and 1B2, an additional column is added to Table App5.7 to highlight whether, for example, the cost applies to all Stage 1 patients or just Stage 1A1.

Diagnosis and treatment planning

For all Stage I, diagnosis involves staging using a PET scan.[311, 312] For all Stage I, except Stage IA1, an MRI of the pelvis is also included. For all Stage I, planning requires one multidisciplinary team meeting, typically 1.5 hours long where approximately 25 cases are discussed.[311, 312] The MDT meeting is attended as a minimum by a consultant radiologist, a consultant pathologist, a consultant surgeon, a consultant oncologist, a consultant medical oncologist and a clinical nurse manager.[311, 312] The associated pay-related staff costs were included after adjustment for non-pay costs including employers' PRSI, superannuation, and general overheads in accordance with national guidelines.[225] See Table App5.7.

Treatment

Using National Cancer Registry Ireland (NCRI) data, we estimated that 95% of all Stage I cases undergo surgery (mainly cone biopsies for Stage IA1). In addition, pelvic lymph node sampling/dissection, para-aortic nodal sampling, hysterectomy, trachelectomy are typically carried out in Stage IA2 and IB1. NCRI data indicate that 25% of all Stage I are treated with radiotherapy and brachytherapy (mainly Stage IB2) and 11% are treated with chemotherapy (mainly Stage IB2), with some patients receiving more than one treatment modality. Costs associated with surgery, drugs costs and staff costs to administer drugs are included. For surgery, the number of procedures and costs were approximated from HIPE activity and DRG data. In addition, approximately 20% of all women with cervical cancer develop hydronephrosis as a result of tumour or lymph node encroachment, inflammation, or scarring at the pelvic rim.[313] The cost of ureteral stent placement to relieve this obstruction is included. It is estimated that 14% of Stage I patients require lifelong ureteral stent placement for hydronephrosis,[313] based on a weighted average this represents 2% of all patients treated for cervical cancer. Stents must be replaced every four to six months, replacement costs are included below. Drug costs for chemotherapy (cisplatin, 70mg/week x 4-6 weeks) and administration time costs were included for an average of five cycles. The drug cost included the labour time for compounding (senior pharmacist and a pharmaceutical technician) and the component drug cost.

Successful treatment

The proportion of patients achieving successful treatment is included based on the per-annum stage-related survival obtained from the NCRI.[314] For Stage IA1, repeat screening is recommended at six months based on CervicalCheck Guidance Note 7. Following successful treatment for Stage IA2, IB1, IB2, patients are routinely followed up in oncology outpatient clinics for five years. Based on current practice,

the frequency of follow-up is as follows: every three months (year 1), every four months (year 2), and every six months (year 3 – 5). Costs associated with outpatient attendance were included using HIPE costs (2014). Stent replacement costs are included for every four months for five years. Costs beyond the first year are discounted using the standard rate.[225]

Other costs

The costs for a recall letter and a reminder letter are included as documented previously. Some additional costs associated with complications of treatment (e.g., lower-limb lymphoedema) or the disease itself (pain control, thrombosis) are included.[240] These include drug costs for pain control, physiotherapy and drug costs for thrombosis and lymphoedema and compression garment costs.[315]

Stage	Item		Cost
Diagnosis and treatment planning			
All stage I	Diagnosis	PET scan	**€992.16**
IA2, IB1, IB2		MRI of pelvis	**€26.23**
All I	Planning	MDT meeting (1.5 hrs/week)	
		consultant radiologist	**€10.38**
		consultant pathologist	**€10.38**
		consultant surgeon	**€10.38**
		consultant radiation oncologist	**€10.38**
		consultant medical oncologist	**€10.38**
		CNM	**€3.24**
Treatment			
IA1	Surgery	Cone biopsy of cervix or repeat conisation	**€1,403.10**
IA2, IB1	Surgery	Ureteric stent placement	**€1,741.31**
		Pelvic lymph node sampling for staging	**€75.07**
		Pelvic lymph node dissection (laparoscopic or not)	**€75.07**
		Para-aortic nodal sampling	**€75.07**
		Hysterectomy	**€124.20**
		Trachelectomy	**€13.22**
IB2	Therapy	BT	**€153.00**
		CT scan	**€82.09**
		Nurse accompany for 24hr	**€686.57**
		RT	**€1,275.00**
		Chemotherapy	**€580.80**
		Cisplatin (70mg/week x 4-6 weeks)	**€0.00**
		Staff nurse to administer cisplatin (4-6 hours)	**€5.50**
Successful treatment			
IA1	Repeat screening at 6 months	Screening test kit (less VAT 23%)	
IA2, IB1	Follow-up	Oncology Repeat Attendance	**€57.78**
		Outpatient follow-up year 1 (every 3m, 4 visits)	**€71.61**
		Outpatient follow-up year 2 (every 4m, 3 visits)	**€50.84**
		Outpatient follow-up year 3-5 (every 6m, 6 visits)	**€90.07**
IA2, IB1	Treatment	Stent replacement (every 4-6m for lifetime)	**€2,786.38**
		Year 2	**€3,676.92**
		Year 3	**€3,449.34**
		Year 4	**€3,235.26**
		Year 5	**€3,081.10**
Communication			
All stage I		Results letter + leaflet	**€0.69**
		Reminder letter	**€0.00**
Complications of treatment or disease			
IA2, IB1, IB2			**€68.90**
		Thrombosis	**€12.52**
		Lymphoedema - DLT	**€2.19**
		Compression garments	**€4.41**
Stage I total cost per patient			**€20,870.45**

Abbreviations: BT, brachytherapy; CNM, clinical nurse manager; DLT, decongestive lymphatic therapy; MDT, multi-disciplinary meeting; MRI, Magnetic resonance imaging; PET, positron emission tomography; RT, radiotherapy.

5.4 FIGO Stage II (IIA1, IIA2, IIB)

Diagnosis and treatment planning

Diagnosis and treatment planning is the same as Stage I except that all Stage II patients have an MRI of the pelvis, see Table App5.8.

Treatment

The same method is used as in Stage I. NCRI data reported a breakdown that 45% of patients diagnosed with FIGO Stage II undergo surgery (pelvic lymph node dissection, hysterectomy or trachelectomy), 95% are treated with radiotherapy and brachytherapy and 74% with chemotherapy (treatment, drugs and staff costs to administer drugs are included). It is reported that 20% of Stage II patients require lifelong stent placement for hydronephrosis,[313] based on a weighted average these represent 3% of all patients treated for cervical cancer.

Successful treatment and other costs

The cost of follow-up following successful treatment and other costs are included using the same procedure as for FIGO Stage I with NCRI survival rates included for Stage II.

Other costs

Costs are included as per FIGO Stage I.

Table App5.8 Cost parameters – FIGO Stage II

Item		Cost
Diagnosis and treatment planning		
Diagnosis	PET scan	**992.16**
	MRI of pelvis	**193.03**
Planning	MDT meeting (1.5 hrs/week)	
	consultant radiologist	**€10.38**
	consultant pathologist	**€10.38**
	consultant surgeon	**€10.38**
	consultant radiation oncologist	**€10.38**
	consultant medical oncologist	**€10.38**
	CNM	**€3.24**
Treatment		
Surgery	Ureteric stent placement	**€2,432.86**
	Pelvic lymph node dissection (laparoscopic or not)	**€443.59**
	Hysterectomy (malig) +/- PLND	**€2,996.40**
	Trachelectomy	**€319.09**
Therapy	BT	**€581.40**
	CT scan	**€311.93**
	Nurse accompany for 24hr	**€2,608.97**
	RT	**€4,845.00**
	ChemoT	**€3,907.20**
	Cisplatin (70mg/week x 4-6 weeks)	**€164.41**
	Staff nurse to administer cisplatin (4-6 hours)	**€141.99**
Successful Treatment		
Follow-up	Oncology Repeat Attendance	**€408.53**
	Outpatient follow-up year 1 (every 3m, 4 visits)	**€506.35**
	Outpatient follow-up year 3 (every 4m, 3 visits)	**€650.96**
	Outpatient follow-up year 3-5 (every 6m, 6 visits)	**€525.15**
Treatment	Stent replacement (every 4-6m for lifetime)	**€3,740.84**
	Year 1	**€4,579.95**
	Year 2	**€3,876.60**
	Year 3	**€3,461.09**
	Year 4	**€3,076.12**
Communication		
	Results letter + leaflet	**€0.59**
	Reminder letter	**€0.00**
Complications of treatment or disease		
	Pain control	**€68.90**
	Thrombosis	**€12.52**
	Lymphoedema - DLT	**€2.19**
	Compression garments	**€4.41**
Stage II total cost per patient		**€40,907.38**

Abbreviations: BT, brachytherapy; ChemoT, chemotherapy; CNM, clinical nurse manager; DLT, decongestive lymphatic therapy; MDT, multi-disciplinary meeting; MRI, Magnetic resonance imaging; PET, positron emission tomography; RT, radiotherapy.

5.5 FIGO Stage III (IIIA, IIIB)

Diagnosis and treatment planning

Diagnosis and treatment planning is the same as FIGO Stage II, see Table App5.9.

Treatment

The same method is used as in FIGO Stage I and II. NCRI data reported a breakdown of 35% of Stage III undergoing surgery (salvage surgery, hysterectomy), 95% treated with radiotherapy and brachytherapy and 65% treated with chemotherapy. A weight was applied to ensure this breakdown for Stage III. It is reported that 46% of Stage II patients require lifelong stent placement for hydronephrosis.[313] Based on a weighted average these represent 7.4% of all patients treated for cervical cancer.

Successful treatment and other costs

Successful treatment and other costs are included using the same procedure as for FIGO Stage I and II with NCRI survival rates included for Stage III.

Other costs

Costs are included per FIGO Stage I and II. Although the costs are minimal, the costs associated with some additional complications.[240] These include drug costs for pain control, stenting costs for ureteric obstruction (complications may result in more frequent stent changing required),[240] physiotherapy and drug costs for thrombosis and lymphoedema, personal care costs[315] and fistula costs based on an average of 7.6% of patients with Stage II and IV disease developing fistulae.[316]

Table App5.9 Cost parameters – Stage III

Item		Cost
Diagnosis and treatment planning		
Same as Stage II		
Treatment		
Surgery	Ureteric stent placement	**€5,721.45**
	Salvage surgery	**€1,048.75**
	Hysterectomy (malig) +/- PLND	**€2,708.29**
Therapy	BT	**€581.40**
	CT scan	**€311.93**
	Nurse accompany for 24hr	**€2,608.97**
	RT	**€4,845.00**
	ChemoT	**€3,432.00**
	Cisplatin (70mg/week x 4-6 weeks)	**€144.42**
	Staff nurse to administer cysplatin (4-6 hours)	**€124.72**
Successful treatment		
Follow-up	Oncology Repeat Attendance	**€358.27**
	Outpatient follow-up year 1 (every 3m, 4 visits)	**€444.05**
	Outpatient follow-up year 2 (every 4m, 3 visits)	**€552.53**
	Outpatient follow-up year 3-5 (every 6m, 6 visits)	**€427.24**
Treatment	Stent replacement (every 4-6m for lifetime)	**€7,715.00**
	Year 2	**€9,142.11**
	Year 3	**€7,417.01**
	Year 4	**€6,566.00**
	Year 5	**€5,778.77**
Communication		
	Recall letter + leaflet	**€0.41**
	Reminder letter	**€0.00**
Complications of treatment or disease		
	Pain control	**€393.72**
	Ureteric stent replacement	**€1,503.96**
	Thrombosis	**€12.52**
	Bleeding	**€0.00**
	Malodorous vaginal discharge	**€21.20**
	Lymphoedema - DLT	**€5.01**
	Compression garments	**€10.08**
	Fistula (rare & late complication)	**€40.19**
Stage III total cost per patient		**€63,155.30**

Abbreviations: BT, brachytherapy; ChemoT, chemotherapy; CNM, clinical nurse manager; DLT, decongestive lymphatic therapy; RT, radiotherapy.

5.6 FIGO Stage IV (IVA, IVB)

Diagnosis and treatment planning

Diagnosis and treatment planning is the same as FIGO Stage II and III, see Table App5.10.

Treatment

The same method is used as in FIGO Stages I, II and II. NCRI data reported a breakdown that 27% of those diagnosed with Stage IV disease undergo surgery (salvage surgery), 71% are treated with radiotherapy and brachytherapy and 49% are treated with chemotherapy. A weight was applied to ensure this breakdown for Stage 4. In addition, Stage IV patients with metastatic cancer may also receive paclitaxel (135mg/m2 IV over 24 hours, x 6 cycles), carboplatin (x6) and bevacizumab (10mg/kg/2 weeks, x 3 cycles). Drug costs and administration time costs were included based on an average patient body mass index (BMI) / weight of 70 kg. The drug cost included the labour time for compounding (senior pharmacist and a pharmaceutical technician) and the actual drug cost. It is reported that 45% of Stage IV patients require lifelong stent placement for hydronephrosis,[313] based on a weighted average these represent 7.2% of all patients treated for cervical cancer.

Successful treatment and other costs

Successful treatment and other costs are included using the same procedure as for Stage III with annual stage-related survival based on NCRI survival rates for those diagnosed with FIGO Stage IV. Costs for ongoing pain control and end of life counselling is included. This is taken from the breakdown of palliative care costs using the allied health professional and medication costs only.[241]

Other costs

Costs are included per FIGO Stage I, II and III.

Table App5.10 Cost parameters – Stage IV

Item		Cost
Diagnosis and treatment planning		
Same as Stages II and III		
Treatment		
Surgery	Ureteric stent placement	**€5,597.07**
	Salvage surgery	**€3,026.67**
	BT	**€434.52**
	CT scan	**€233.13**
	Nurse accompany for 24hr	**€1,949.86**
	RT / RT boost / individualised RT	**€3,621.00**
	ChemoT	**€2,587.20**
	Cisplatin (70mg/week x 4-6 weeks)	**€108.87**
	Staff nurse to administer cisplatin (4-6 hours)	**€94.02**
Metastatic	Paclitaxel 135mg/m2 IV over 24 hours, x 6	**€203.26**
	Inpatient cost	**€727.65**
	Carboplatin x6	**€84.59**
	Bevacizumab (10mg/kg/2 weeks) 3 cycles	**€1,585.14**
Successful treatment		
Follow-up	Oncology Repeat Attendance	**€204.91**
	Outpatient follow-up year 1 (every 3m, 4 visits)	**€253.97**
	Outpatient follow-up year 2 (every 4m, 3 visits)	**€193.86**
	Outpatient follow-up year 3-5 (every 6m, 6 visits)	**€154.05**
Treatment	Stent replacement (every 4-6m for lifetime)	**€4,316.58**
	Year 2	**€4,505.26**
	Year 3	**€2,988.36**
	Year 4	**€2,491.78**
	Year 5	**€2,046.10**
Pain control / end of life counselling		**€1,244.74**
Communication		
	Results letter + leaflet	**€0.34**
	Reminder letter	**€0.00**
Complications of treatment or disease		
	Pain control	**€393.72**
	Ureteric stent replacement	**€1,503.96**
	Thrombosis	**€12.52**
	Bleeding	**€0.00**
	Malodorous vaginal discharge	**€21.20**
	Lymphoedema - DLT	**€5.01**
	Compression garments	**€10.08**
	Fistula (rare & late complication)	**€40.19**
Stage IV total cost per patient		**€41,879.90**

Abbreviations: BT, brachytherapy; ChemoT, chemotherapy; CNM, clinical nurse manager; DLT, decongestive lymphatic therapy; RT, radiotherapy.

5.7 Palliative care

A recent economic evaluation of palliative care in Ireland (2015) was used to inform the palliative care costs associated with cervical cancer.[241] This study reported the formal care costs for patients receiving palliative care over their last year of life. A sample for three areas in Ireland was stratified by diagnosis in the approximate ratio of 70:30 for cancer and non-cancer cases. Community services costs such as GP and home help costs, specialist palliative care costs such as physiotherapy, occupational therapy and allied health professional care costs, hospital costs, nursing home costs, medication costs and equipment costs such as home equipment, are included, see Table App5.11.

Table App5.11 Cost parameters – Palliative care, cost for 1 year before death

Item	Cost
Palliative care	€38,112.84
PC total cost per patient	**€38,112.84**

Abbreviations: PC, palliative care.

Appendix 6 – Details of model transition probabilities

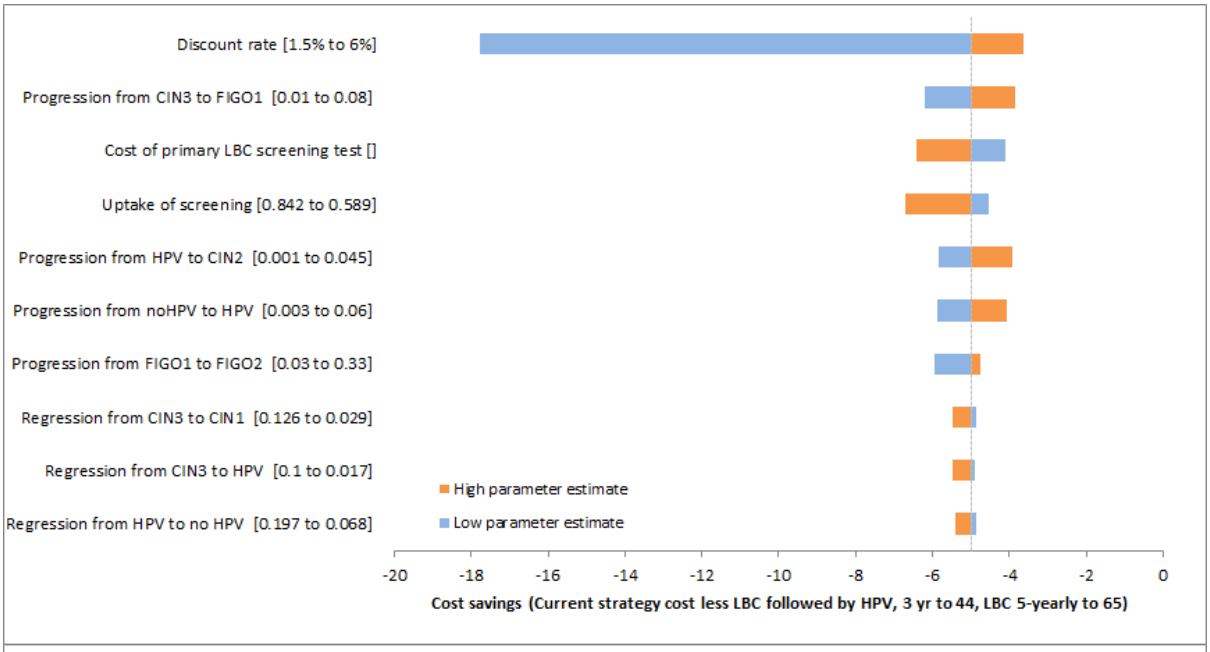
Table App6.1 highlights all possible transitions between states

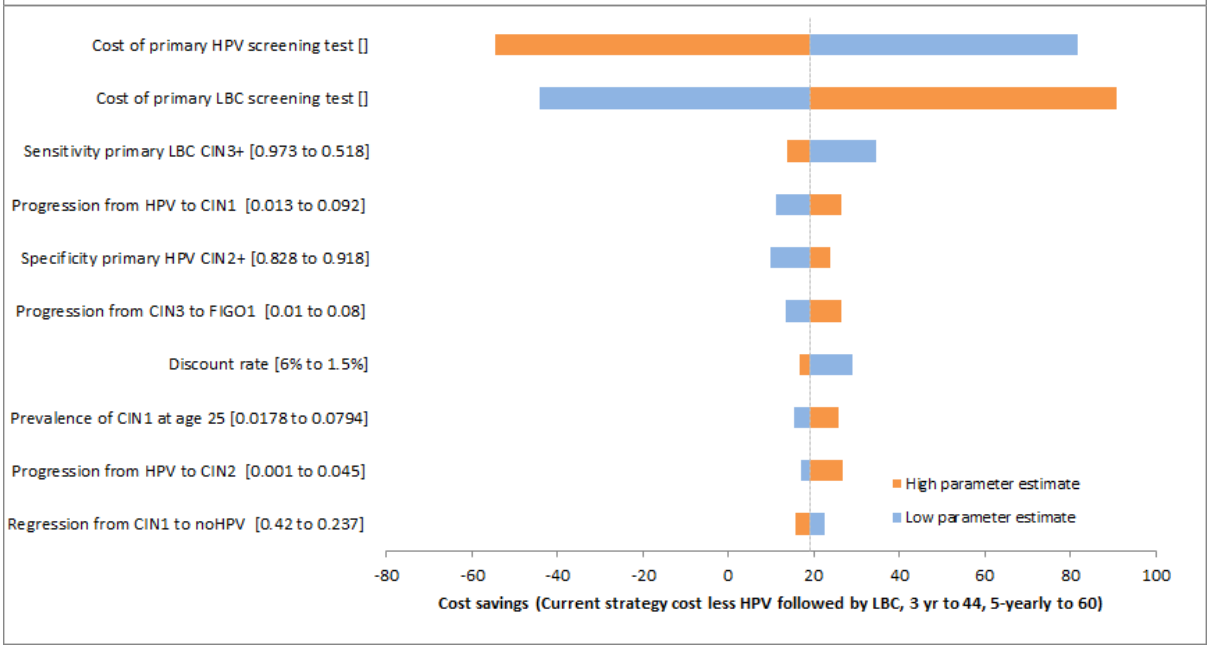
Table App6.1 Possible transitions between model states

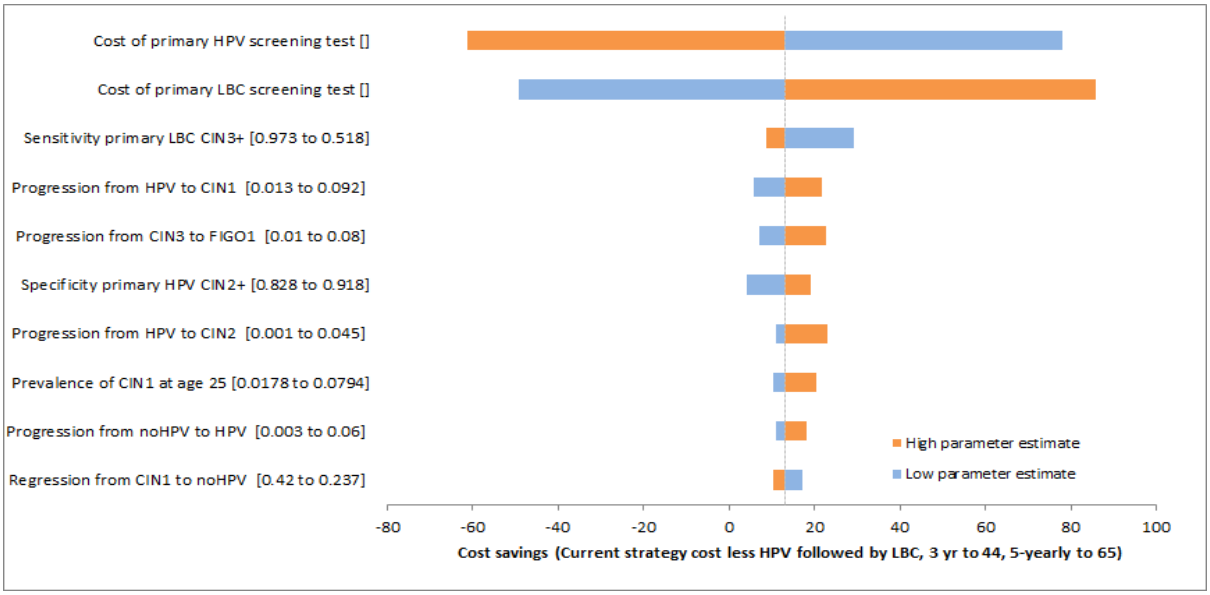
		To																								
	States	No HPV infection/no lesion	HPV infection/no lesion	Undetected CIN1	Undetected CIN2	Undetected CIN3	Cancer FIGO I, undiagnosed	Cancer FIGO II, undiagnosed	Cancer FIGO III, undiagnosed	Cancer FIGO IV, undiagnosed	Cancer survivor	Cervical Cancer death	Non cancer death	CIN1 surveillance	Treatment CIN2	Treatment CIN3	Benign Hysterectomy	Treatment Cancer FIGO I	Treatment Cancer FIGO II	Treatment Cancer FIGO III	Treatment Cancer FIGO IV	Post colposcopy yr 1	Post colposcopy yr 2	Post colposcopy yr 3	Detected HPV/ no lesion	Detected HPV/ undetected CIN1	Detected HPV/ undetected CIN2	Detected HPV/ undetected CIN3
From	No HPV infection/no lesion	Y	Y										Y				Y											
	HPV infection/no lesion	Y	Y	Y	Y								Y				Y					Y			Y			
	Undetected CIN1	Y	Y	Y	Y								Y	Y			Y									Y		
	Undetected CIN2	Y	Y	Y	Y	Y							Y		Y		Y										Y	
	Undetected CIN3	Y	Y	Y	Y	Y	Y						Y			Y	Y											Y
	Cancer FIGO I, undiagnosed						Y	Y					Y					Y											
	Cancer FIGO II, undiagnosed							Y	Y				Y						Y										
	Cancer FIGO III, undiagnosed								Y	Y			Y							Y									
	Cancer FIGO IV, undiagnosed									Y			Y								Y								
	Cancer survivor										Y	Y	Y																
	Cervical Cancer death											Y																	
	Non cancer death												Y																
	CIN1 surveillance												Y	Y	Y		Y					Y							
	Treatment CIN2	Y											Y				Y					Y							
	Treatment CIN3	Y											Y				Y					Y							
	Benign Hysterectomy												Y				Y												
	Treatment Cancer FIGO I										Y	Y	Y																
	Treatment Cancer FIGO II										Y	Y	Y																
	Treatment Cancer FIGO III										Y	Y	Y																
	Treatment Cancer FIGO IV										Y	Y	Y																
	Post colposcopy yr 1												Y				Y						Y						
	Post colposcopy yr 2												Y				Y							Y					
	Post colposcopy yr 3	Y	Y	Y	Y	Y							Y	Y	Y	Y	Y					Y			Y	Y	Y	Y
	Detected HPV/ no lesion	Y	Y	Y	Y								Y				Y					Y			Y	Y	Y	
	Detected HPV/ undetected CIN1	Y	Y	Y	Y								Y	Y			Y								Y	Y	Y	
	Detected HPV/ undetected CIN2	Y	Y	Y	Y	Y							Y		Y		Y								Y	Y	Y	Y
	Detected HPV/ undetected CIN3	Y	Y	Y	Y	Y	Y						Y			Y	Y								Y	Y	Y	Y

Appendix 7 – Sensitivity analysis

Univariate sensitivity analysis comparing the difference in costs of the alternative strategies compared with current practice, for an unvaccinated cohort.



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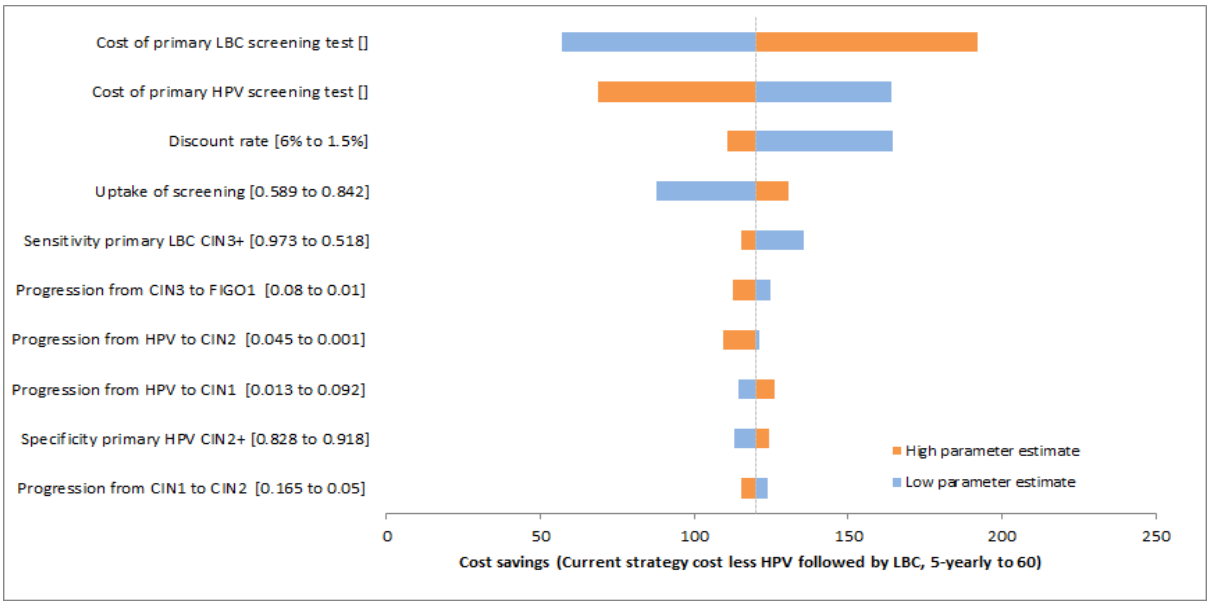
Progression from HPV to CIN1 [0.013 to 0.092]
Progression from CIN3 to FIGO1 [0.01 to 0.08]
Specificity primary HPV CIN2+ [0.828 to 0.918]
Progression from HPV to CIN2 [0.001 to 0.045]
Prevalence of CIN1 at age 25 [0.0178 to 0.0794]
Progression from noHPV to HPV [0.003 to 0.06]
Regression from CIN1 to noHPV [0.42 to 0.237]
High parameter estimate
Low parameter estimate
-80 -60 -40 -20 0 20 40 60 80 100
Cost savings (Current strategy cost less HPV followed by LBC, 3 yr to 44, 5-yearly to 65)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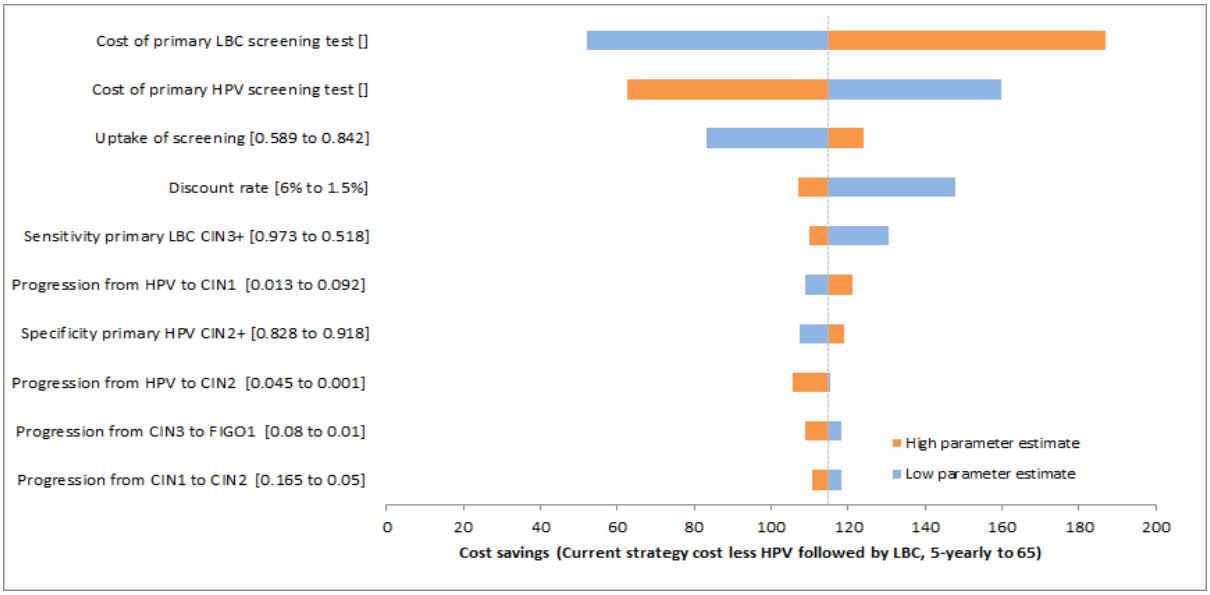
Discount rate [6% to 1.5%]
Uptake of screening [0.589 to 0.842]
Sensitivity primary LBC CIN3+ [0.973 to 0.518]
Progression from CIN3 to FIGO1 [0.08 to 0.01]
Progression from HPV to CIN2 [0.045 to 0.001]
Progression from HPV to CIN1 [0.013 to 0.092]
Specificity primary HPV CIN2+ [0.828 to 0.918]
Progression from CIN1 to CIN2 [0.165 to 0.05]
High parameter estimate
Low parameter estimate
0 50 100 150 200 250
Cost savings (Current strategy cost less HPV followed by LBC, 5-yearly to 60)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High parameter estimate
Low parameter estimate
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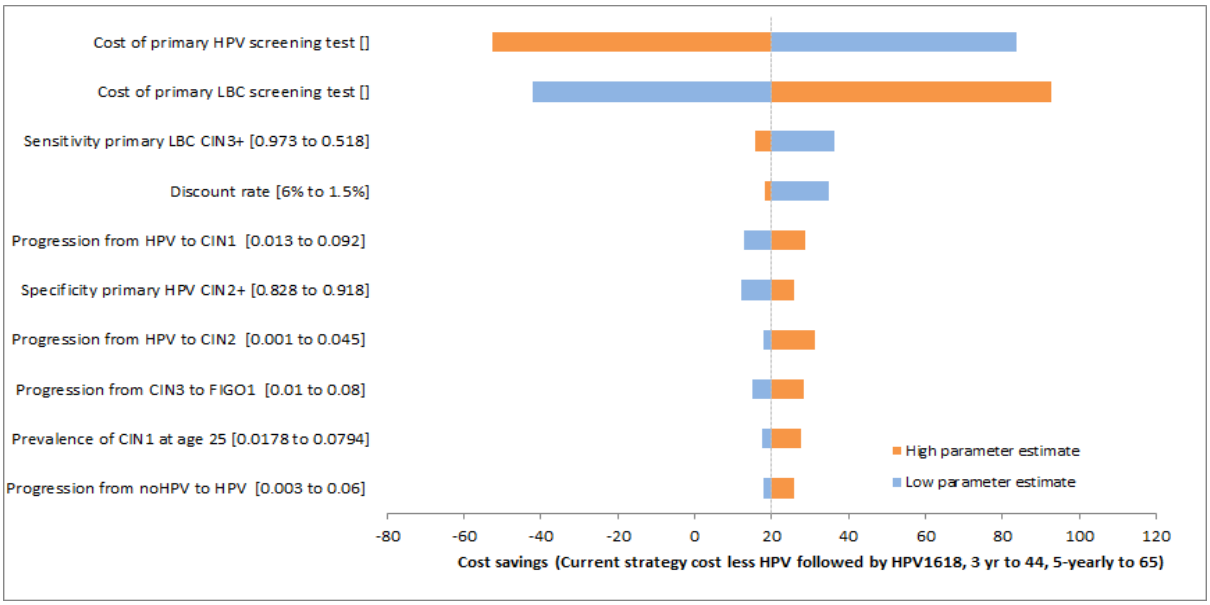
Cost savings (Current strategy cost less HPV followed by LBC, 5-yearly to 65)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Sensitivity primary LBC CIN3+ [0.973 to 0.518]
Discount rate [6% to 1.5%]
Progression from HPV to CIN1 [0.013 to 0.092]
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Progression from noHPV to HPV [0.003 to 0.06]
High parameter estimate
Low parameter estimate
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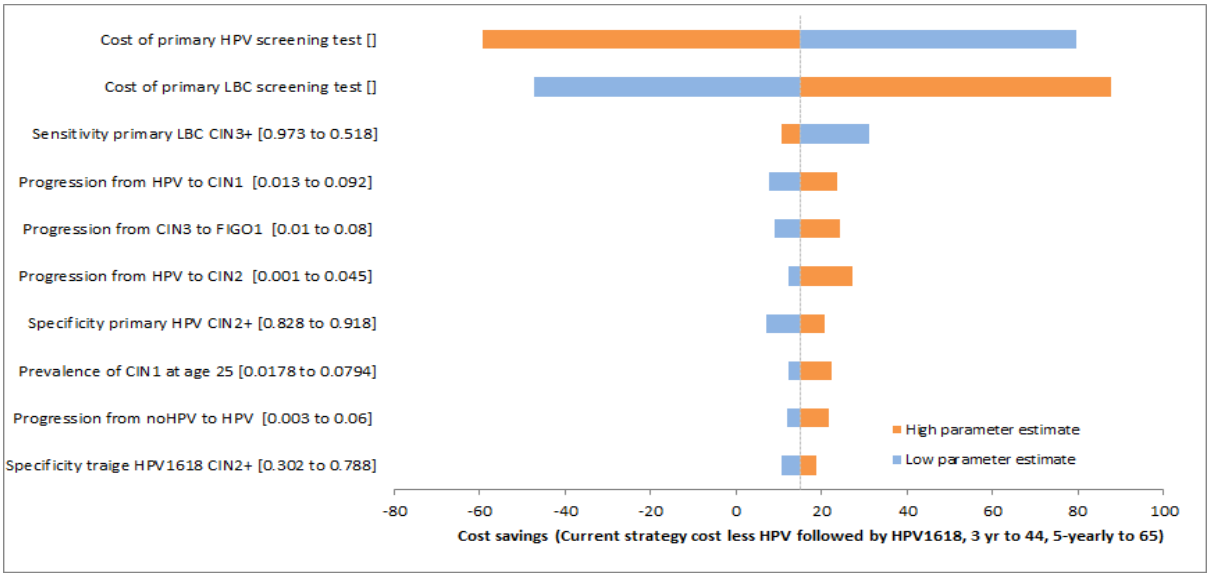
Cost savings (Current strategy cost less HPV followed by HPV1618, 3 yr to 44, 5-yearly to 65)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Specificity traige HPV1618 CIN2+ [0.302 to 0.788]
High parameter estimate
Low parameter estimate
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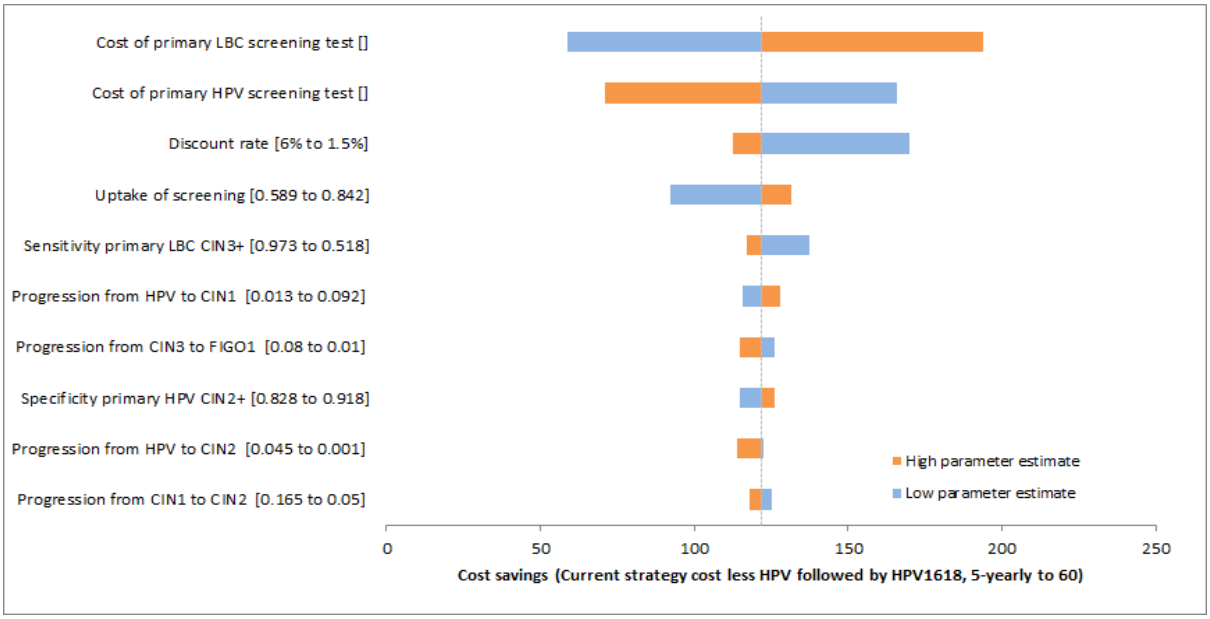
Cost savings (Current strategy cost less HPV followed by HPV1618, 3 yr to 44, 5-yearly to 65)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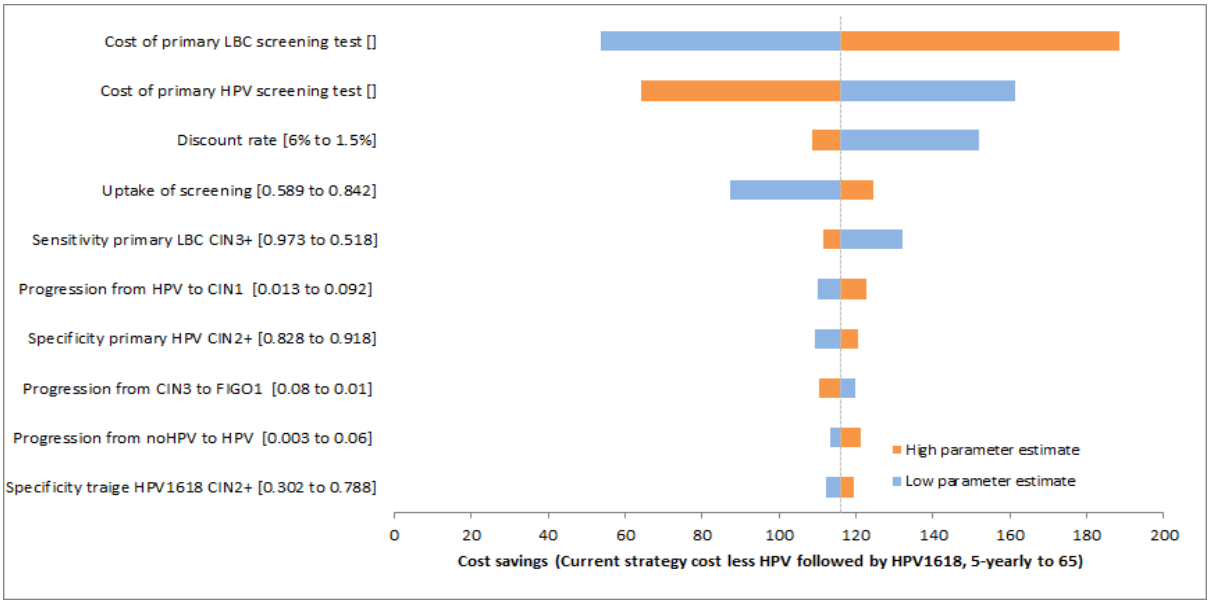
Low parameter estimate
0 50 100 150 200 250
Cost savings (Current strategy cost less HPV followed by HPV1618, 5-yearly to 60)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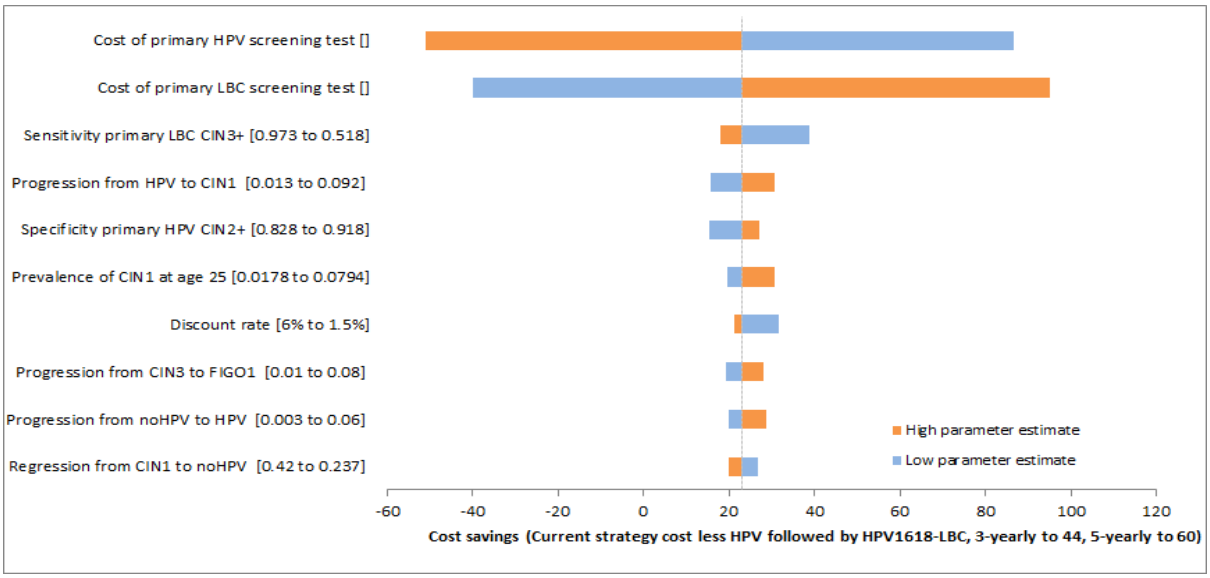
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Progression from noHPV to HPV [0.003 to 0.06]
Regression from CIN1 to noHPV [0.42 to 0.237]
High parameter estimate
Low parameter estimate
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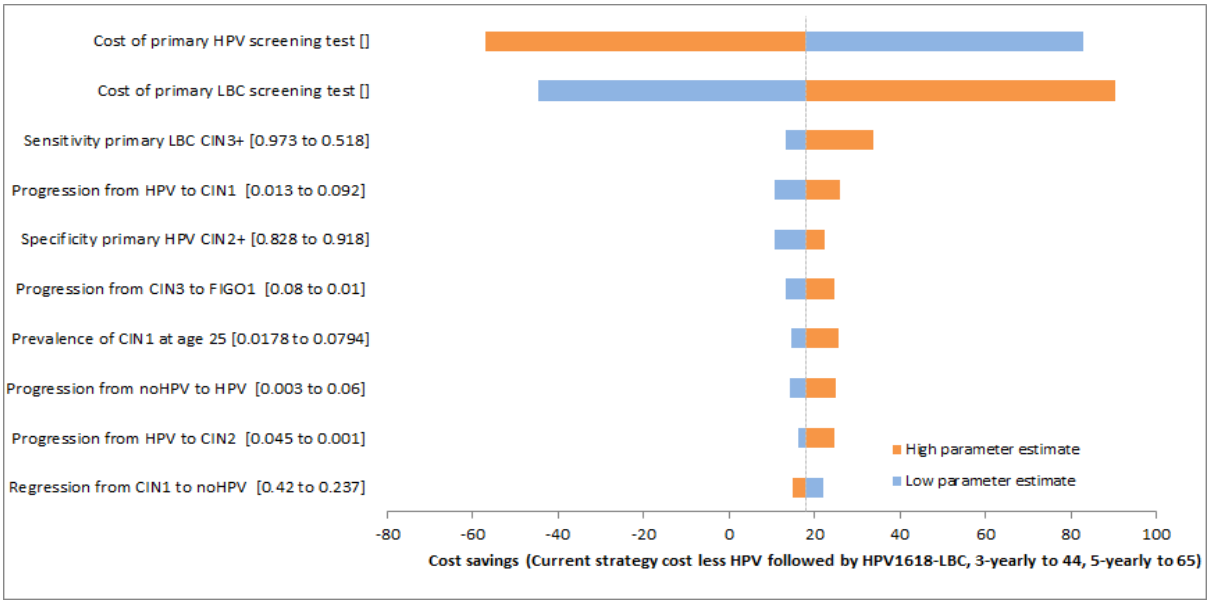
Cost savings (Current strategy cost less HPV followed by HPV1618-LBC, 3-yearly to 44, 5-yearly to 60)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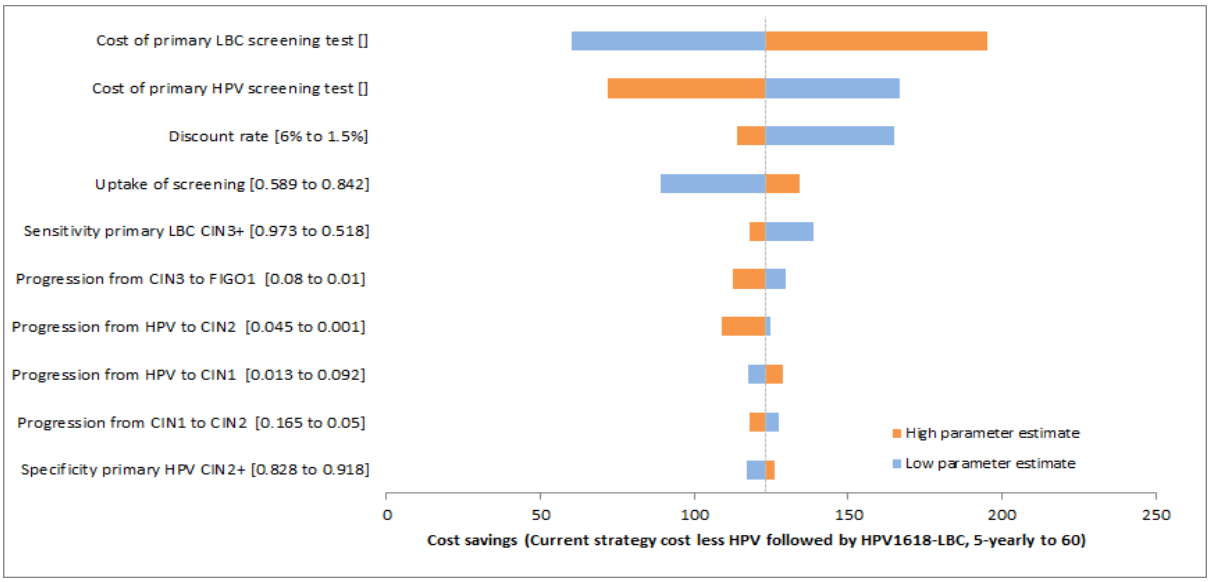
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Low parameter estimate
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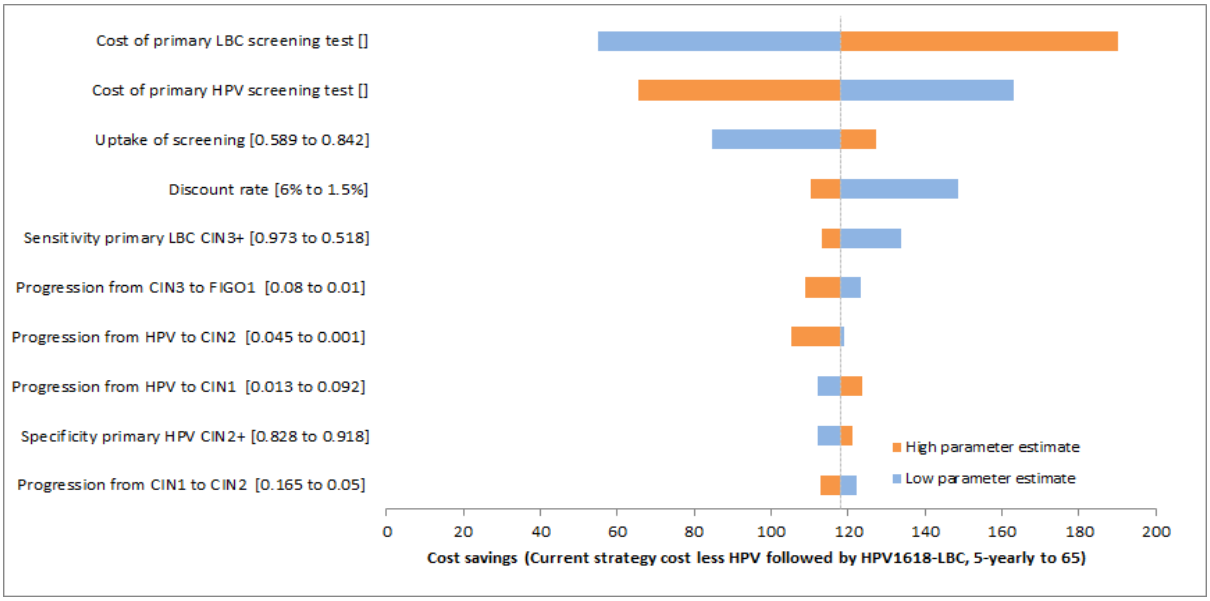
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High parameter estimate
Low parameter estimate
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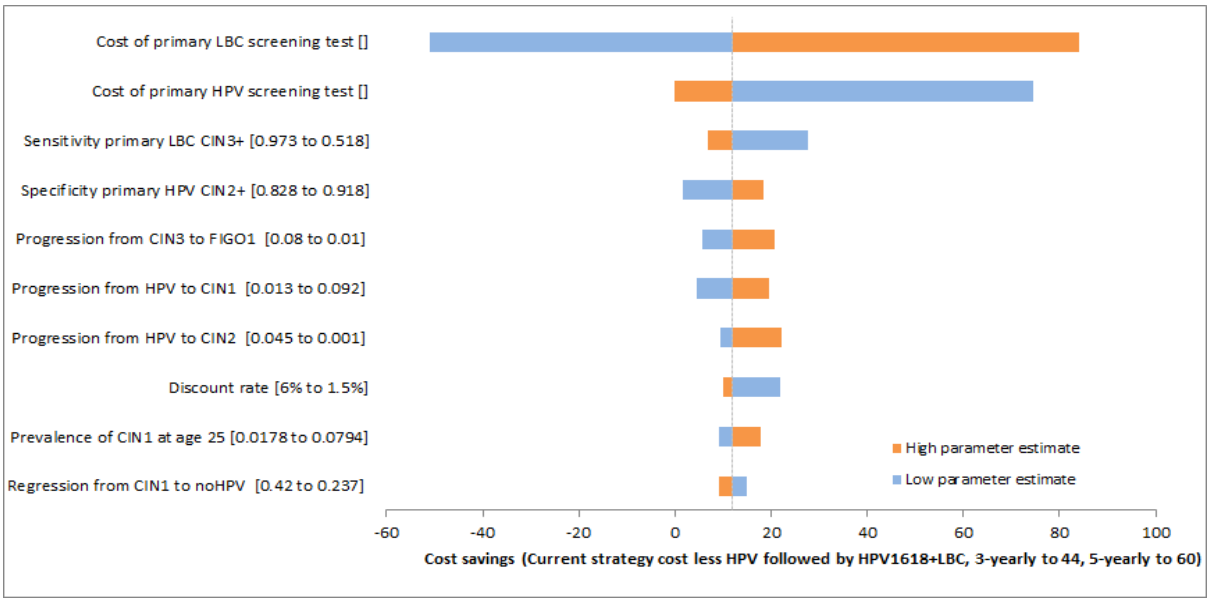
Cost savings (Current strategy cost less HPV followed by HPV1618-LBC, 5-yearly to 65)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Specificity primary HPV CIN2+ [0.828 to 0.918]
Progression from CIN3 to FIGO1 [0.08 to 0.01]
Progression from HPV to CIN1 [0.013 to 0.092]
Progression from HPV to CIN2 [0.045 to 0.001]
Discount rate [6% to 1.5%]
Prevalence of CIN1 at age 25 [0.0178 to 0.0794]
Regression from CIN1 to noHPV [0.42 to 0.237]
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Low parameter estimate
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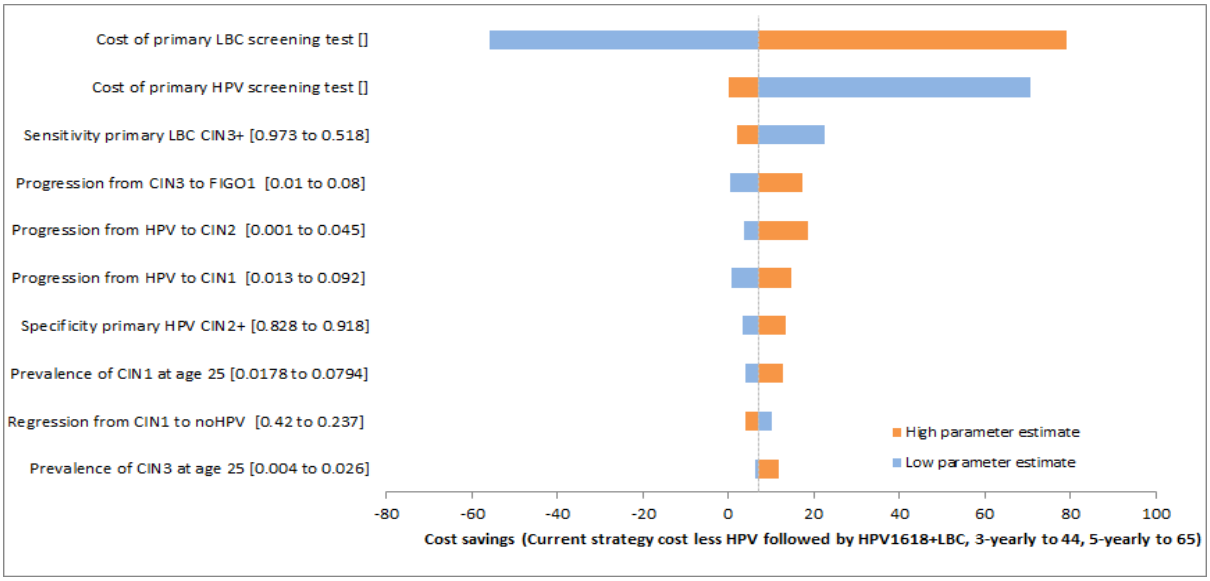
Cost savings (Current strategy cost less HPV followed by HPV1618+LBC, 3-yearly to 44, 5-yearly to 60)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Cost of primary HPV screening test []
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Progression from CIN3 to FIGO1 [0.01 to 0.08]
Progression from HPV to CIN2 [0.001 to 0.045]
Progression from HPV to CIN1 [0.013 to 0.092]
Specificity primary HPV CIN2+ [0.828 to 0.918]
Prevalence of CIN1 at age 25 [0.0178 to 0.0794]
Regression from CIN1 to noHPV [0.42 to 0.237]
Prevalence of CIN3 at age 25 [0.004 to 0.026]
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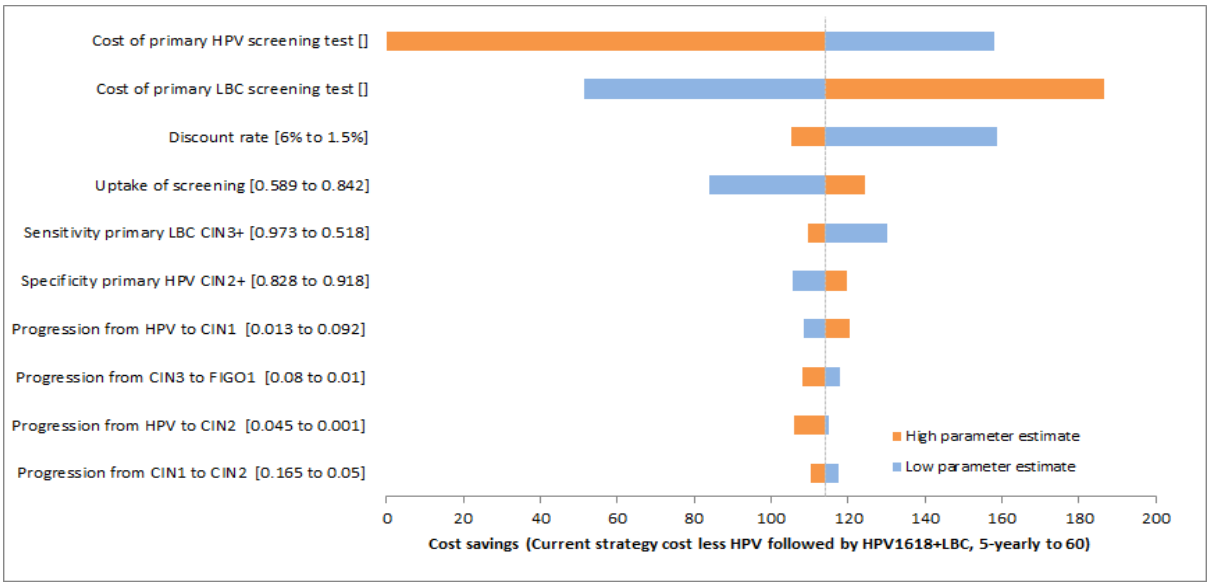
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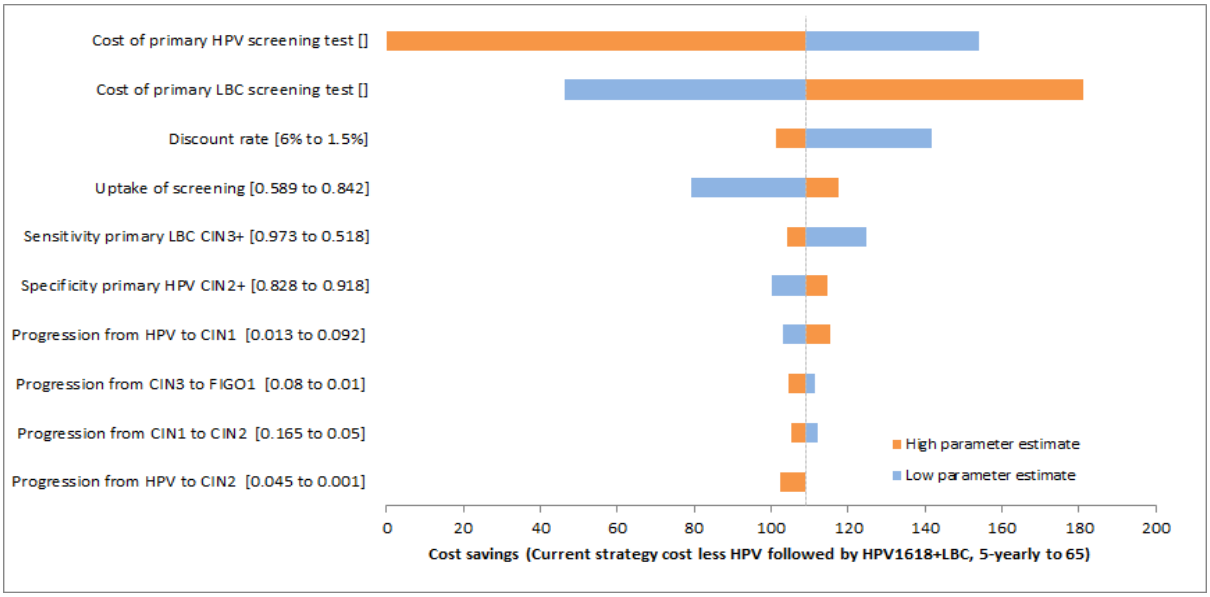
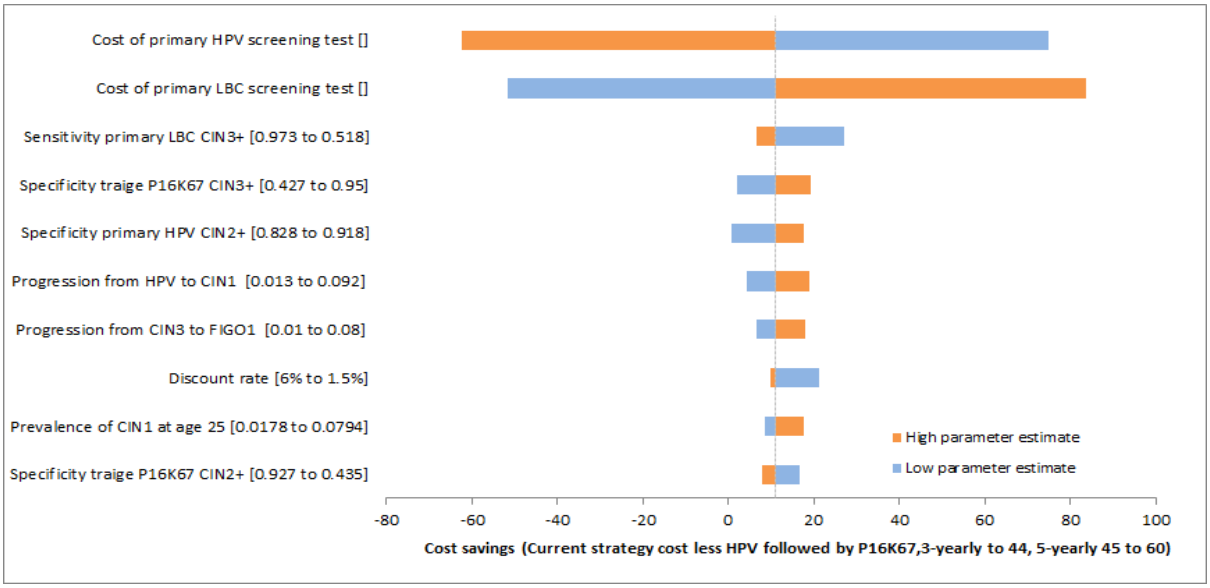
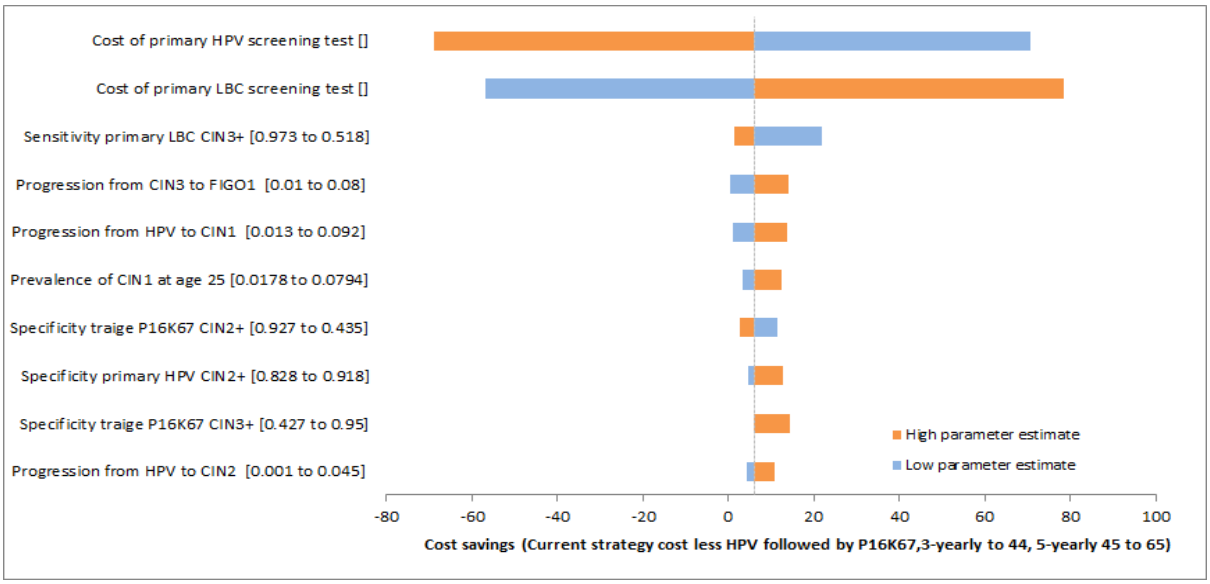
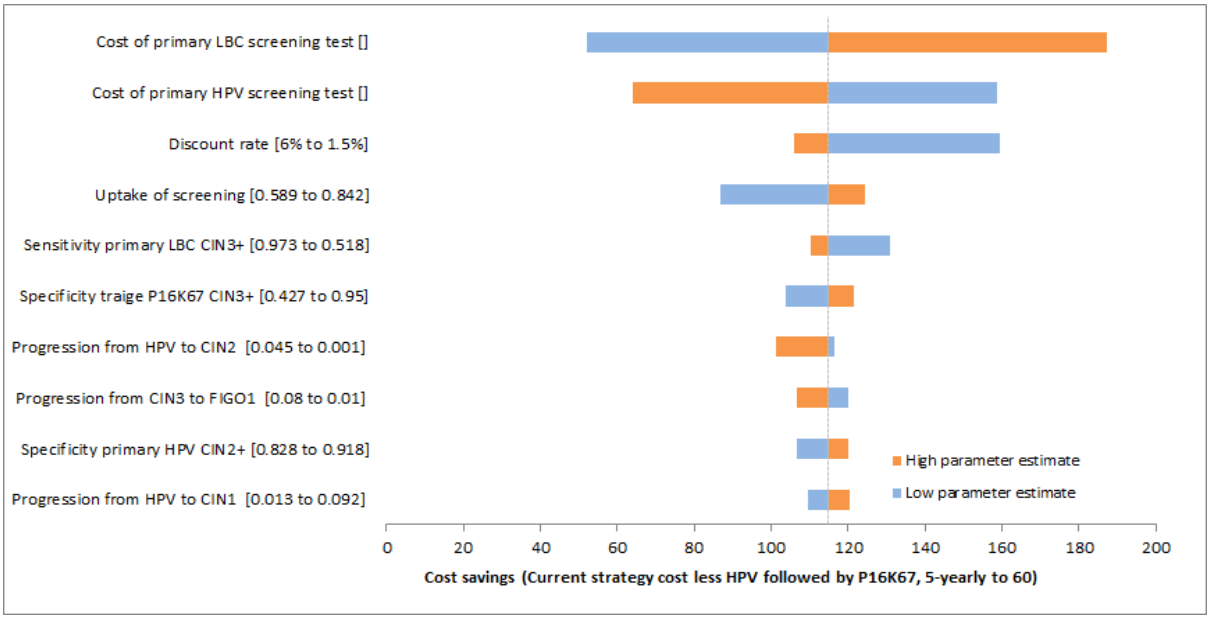
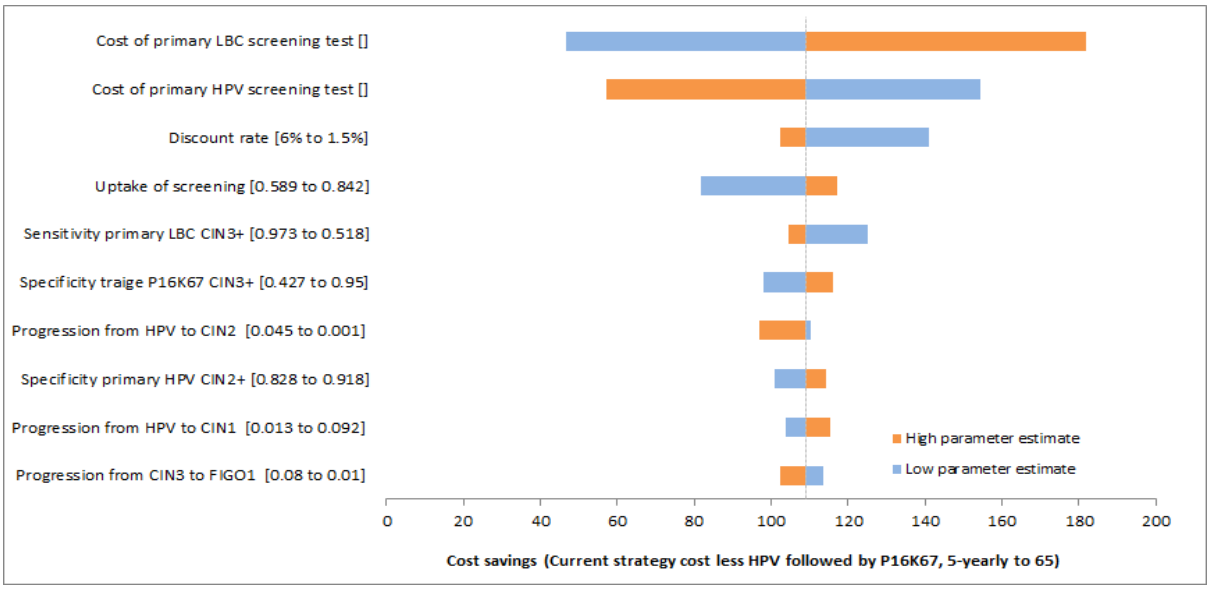
Progression from CIN3 to FIGO1 [0.08 to 0.01]
Progression from HPV to CIN2 [0.045 to 0.001]
Progression from CIN1 to CIN2 [0.165 to 0.05]
High parameter estimate
Low parameter estimate
0 20 40 60 80 100 120 140 160 180 200
Cost savings (Current strategy cost less HPV followed by HPV1618+LBC, 5-yearly to 60)

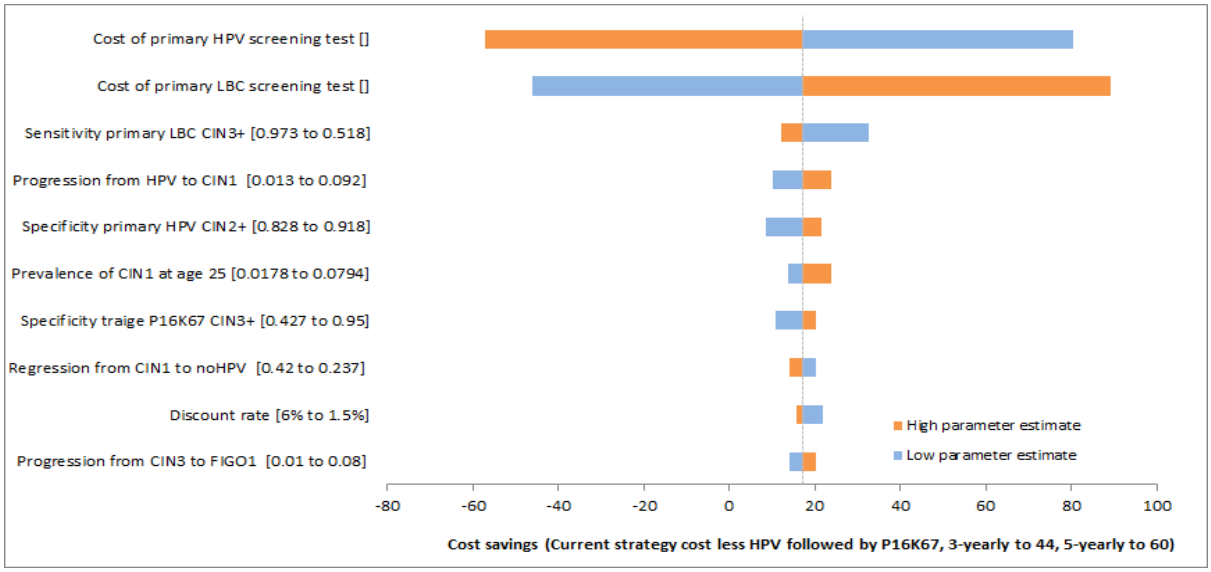

Cost of primary HPV screening test []
Cost of primary LBC screening test []
Discount rate [6% to 1.5%]
Uptake of screening [0.589 to 0.842]
Sensitivity primary LBC CIN3+ [0.973 to 0.518]
Specificity primary HPV CIN2+ [0.828 to 0.918]
Progression from HPV to CIN1 [0.013 to 0.092]
Progression from CIN3 to FIGO1 [0.08 to 0.01]
Progression from CIN1 to CIN2 [0.165 to 0.05]
Progression from HPV to CIN2 [0.045 to 0.001]
High parameter estimate
Low parameter estimate
0 20 40 60 80 100 120 140 160 180 200
Cost savings (Current strategy cost less HPV followed by HPV1618+LBC, 5-yearly to 65)

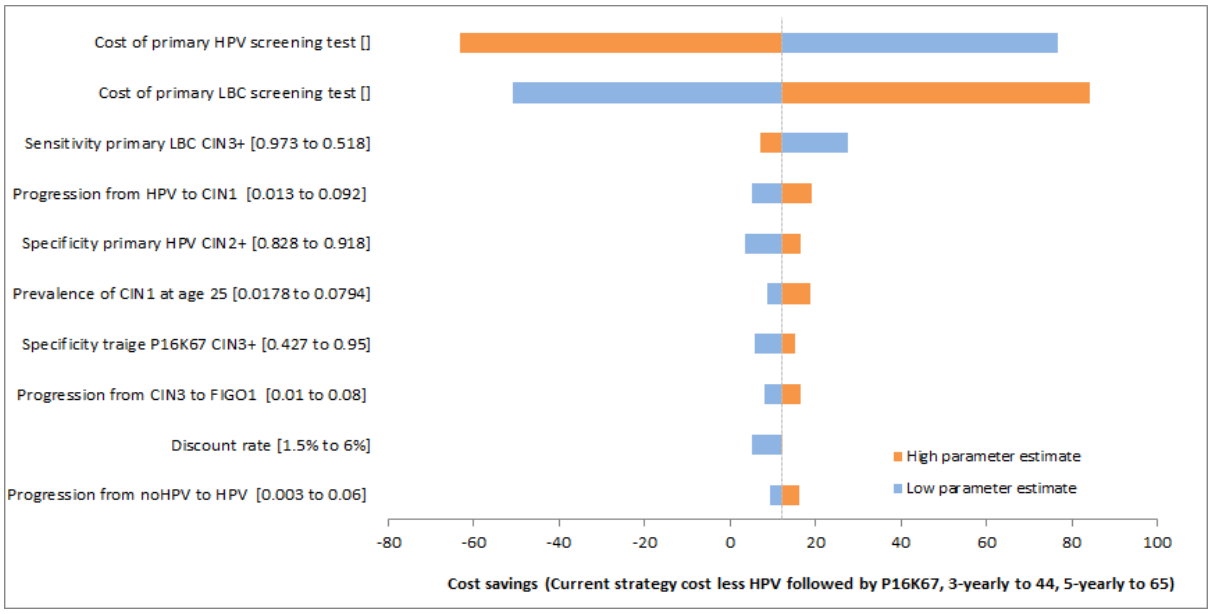

Cost of primary HPV screening test []
Cost of primary LBC screening test []
Sensitivity primary LBC CIN3+ [0.973 to 0.518]
Specificity traige P16K67 CIN3+ [0.427 to 0.95]
Specificity primary HPV CIN2+ [0.828 to 0.918]
Progression from HPV to CIN1 [0.013 to 0.092]
Progression from CIN3 to FIGO1 [0.01 to 0.08]
Discount rate [6% to 1.5%]
Prevalence of CIN1 at age 25 [0.0178 to 0.0794]
Specificity traige P16K67 CIN2+ [0.927 to 0.435]
High parameter estimate
Low parameter estimate
-80 -60 -40 -20 0 20 40 60 80 100
Cost savings (Current strategy cost less HPV followed by P16K67,3-yearly to 44, 5-yearly 45 to 60)

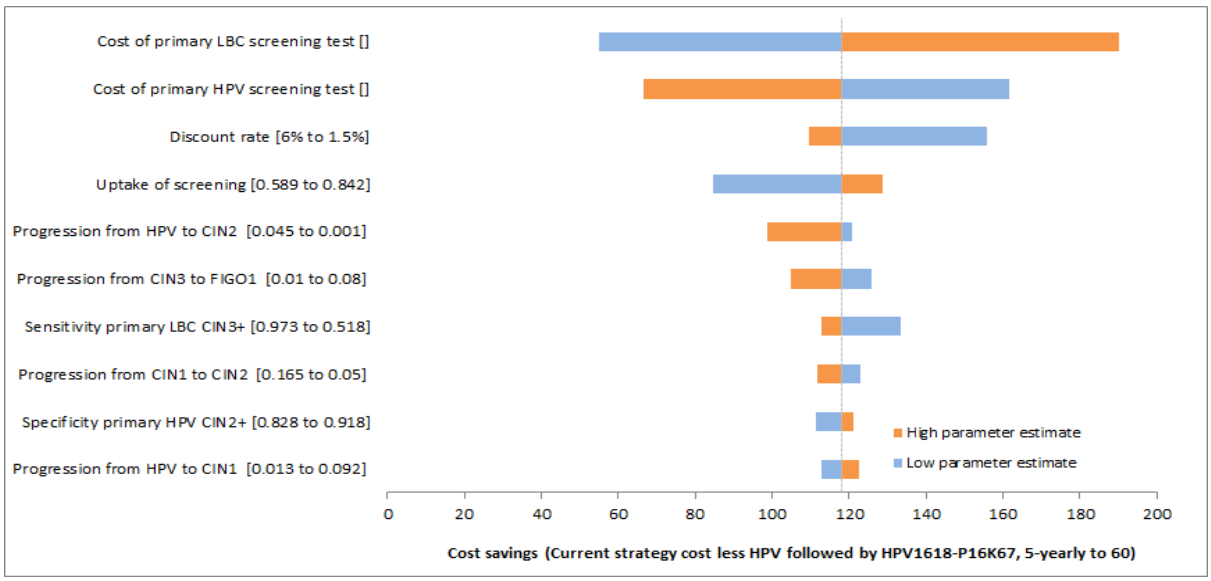

Cost of primary HPV screening test []
Cost of primary LBC screening test []
Sensitivity primary LBC CIN3+ [0.973 to 0.518]
Progression from CIN3 to FIGO1 [0.01 to 0.08]
Progression from HPV to CIN1 [0.013 to 0.092]
Prevalence of CIN1 at age 25 [0.0178 to 0.0794]
Specificity traige P16K67 CIN2+ [0.927 to 0.435]
Specificity primary HPV CIN2+ [0.828 to 0.918]
Specificity traige P16K67 CIN3+ [0.427 to 0.95]
Progression from HPV to CIN2 [0.001 to 0.045]
High parameter estimate
Low parameter estimate
-80 -60 -40 -20 0 20 40 60 80 100
Cost savings (Current strategy cost less HPV followed by P16K67,3-yearly to 44, 5-yearly 45 to 65)

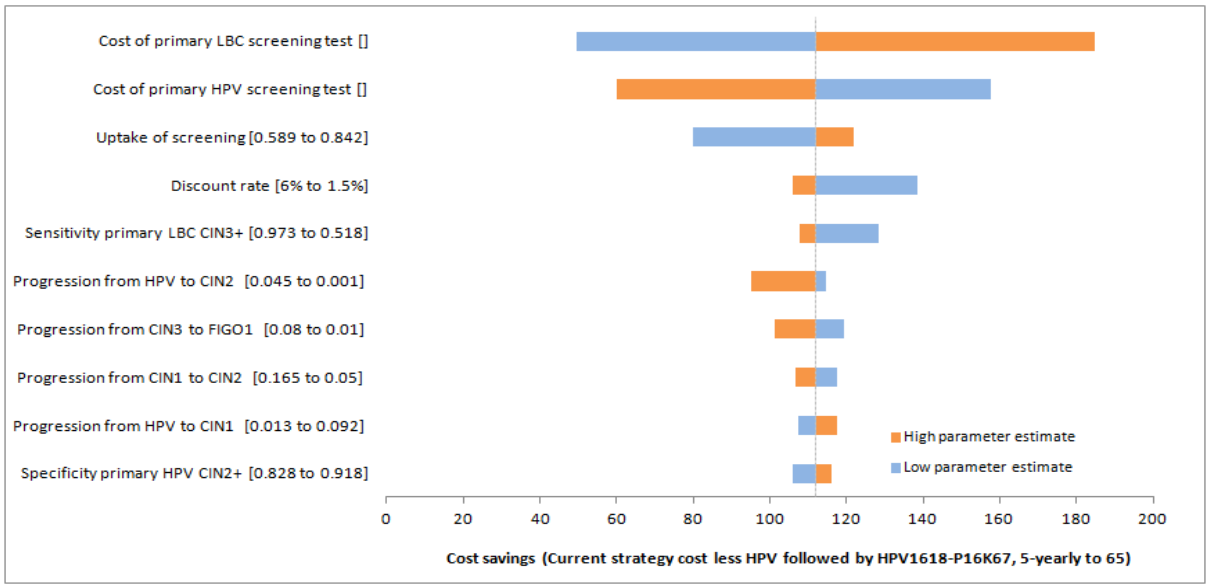

Cost of primary LBC screening test []
Cost of primary HPV screening test []
Discount rate [6% to 1.5%]
Uptake of screening [0.589 to 0.842]
Sensitivity primary LBC CIN3+ [0.973 to 0.518]
Specificity traige P16K67 CIN3+ [0.427 to 0.95]
Progression from HPV to CIN2 [0.045 to 0.001]
Progression from CIN3 to FIGO1 [0.08 to 0.01]
Specificity primary HPV CIN2+ [0.828 to 0.918]
Progression from HPV to CIN1 [0.013 to 0.092]
High parameter estimate
Low parameter estimate
0 20 40 60 80 100 120 140 160 180 200
Cost savings (Current strategy cost less HPV followed by P16K67, 5-yearly to 60)

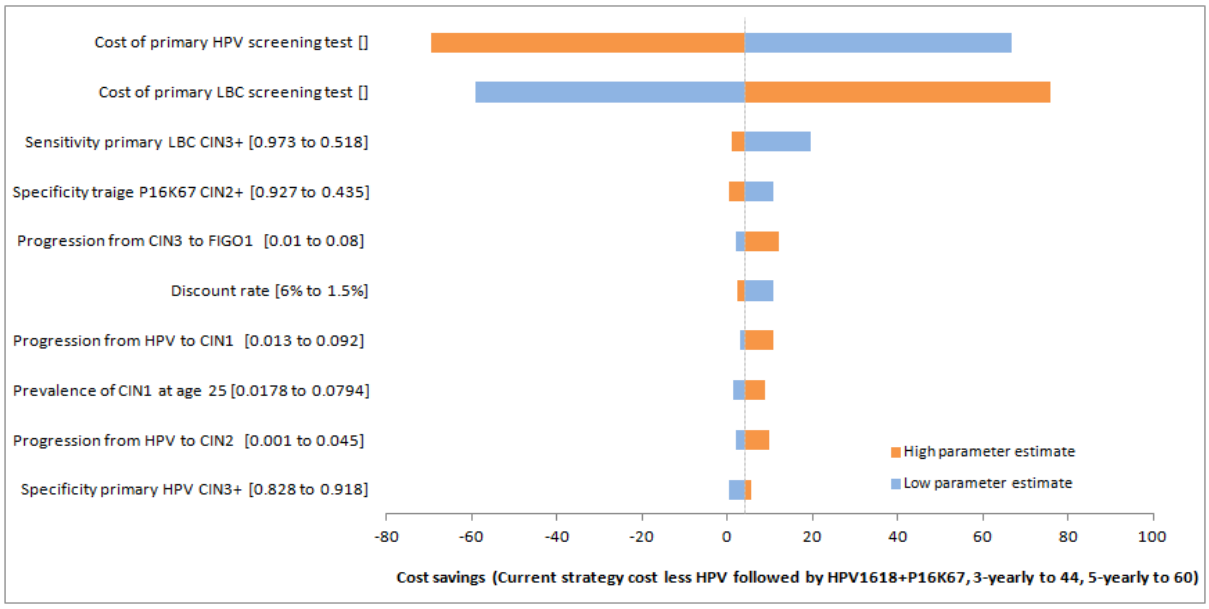

Cost of primary LBC screening test []
Cost of primary HPV screening test []
Discount rate [6% to 1.5%]
Uptake of screening [0.589 to 0.842]
Sensitivity primary LBC CIN3+ [0.973 to 0.518]
Specificity traige P16K67 CIN3+ [0.427 to 0.95]
Progression from HPV to CIN2 [0.045 to 0.001]
Specificity primary HPV CIN2+ [0.828 to 0.918]
Progression from HPV to CIN1 [0.013 to 0.092]
Progression from CIN3 to FIGO1 [0.08 to 0.01]
High parameter estimate
Low parameter estimate
0 20 40 60 80 100 120 140 160 180 200
Cost savings (Current strategy cost less HPV followed by P16K67, 5-yearly to 65)

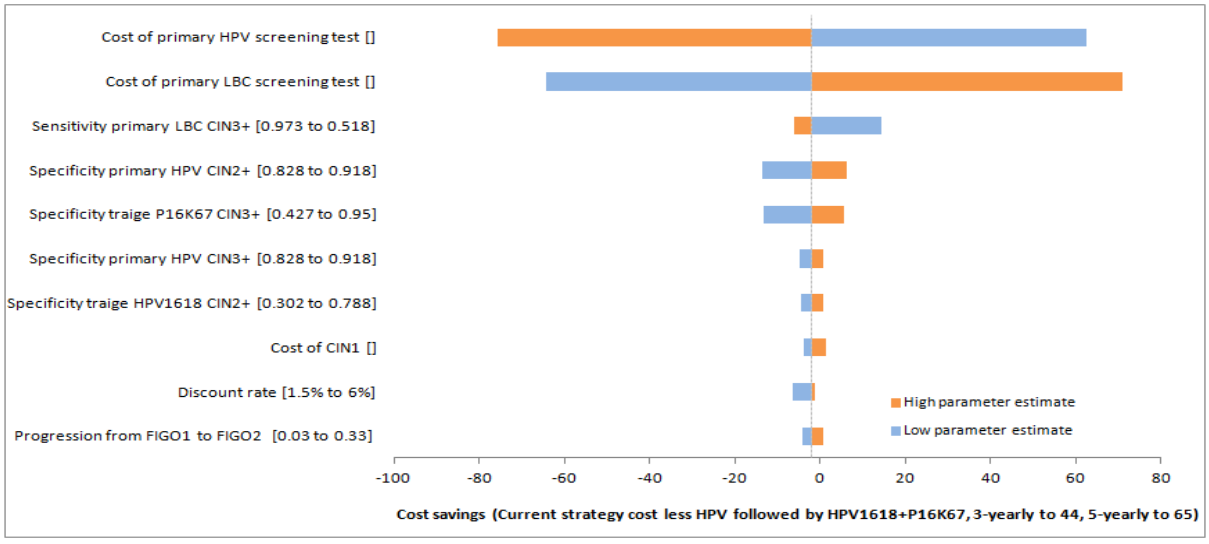

Cost of primary HPV screening test []
Cost of primary LBC screening test []
Sensitivity primary LBC CIN3+ [0.973 to 0.518]
Progression from HPV to CIN1 [0.013 to 0.092]
Specificity primary HPV CIN2+ [0.828 to 0.918]
Prevalence of CIN1 at age 25 [0.0178 to 0.0794]
Specificity traige P16K67 CIN3+ [0.427 to 0.95]
Regression from CIN1 to noHPV [0.42 to 0.237]
Discount rate [6% to 1.5%]
Progression from CIN3 to FIGO1 [0.01 to 0.08]
High parameter estimate
Low parameter estimate
-80 -60 -40 -20 0 20 40 60 80 100
Cost savings (Current strategy cost less HPV followed by P16K67, 3-yearly to 44, 5-yearly to 60)

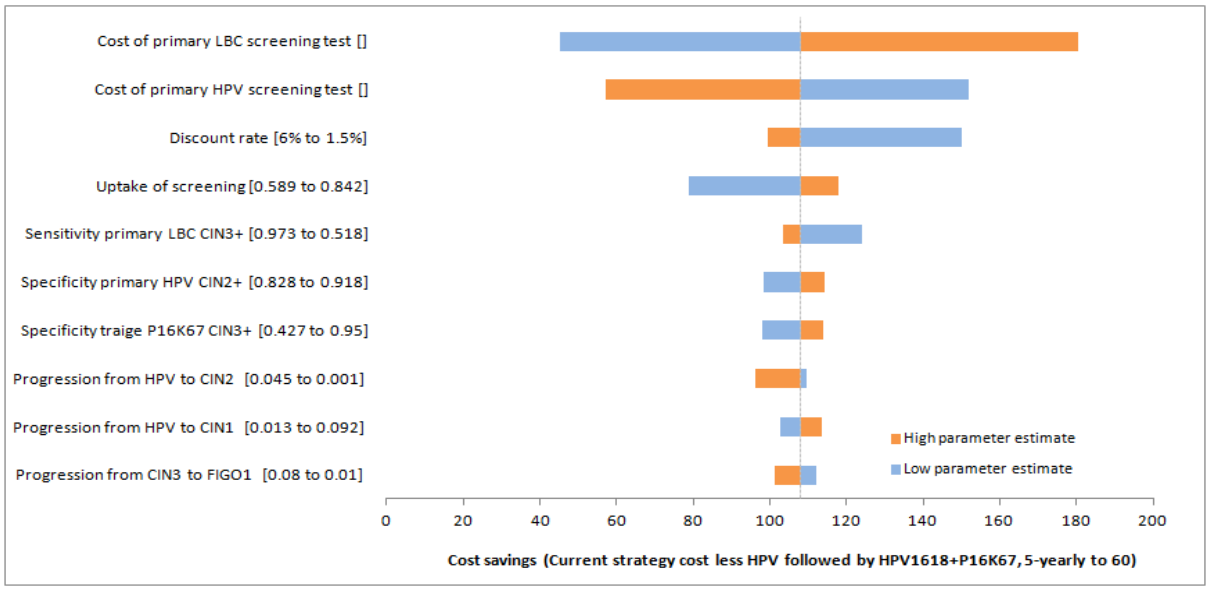

Cost of primary HPV screening test []
Cost of primary LBC screening test []
Sensitivity primary LBC CIN3+ [0.973 to 0.518]
Progression from HPV to CIN1 [0.013 to 0.092]
Specificity primary HPV CIN2+ [0.828 to 0.918]
Prevalence of CIN1 at age 25 [0.0178 to 0.0794]
Specificity traige P16K67 CIN3+ [0.427 to 0.95]
Progression from CIN3 to FIGO1 [0.01 to 0.08]
Discount rate [1.5% to 6%]
Progression from noHPV to HPV [0.003 to 0.06]
High parameter estimate
Low parameter estimate
-80 -60 -40 -20 0 20 40 60 80 100
Cost savings (Current strategy cost less HPV followed by P16K67, 3-yearly to 44, 5-yearly to 65)

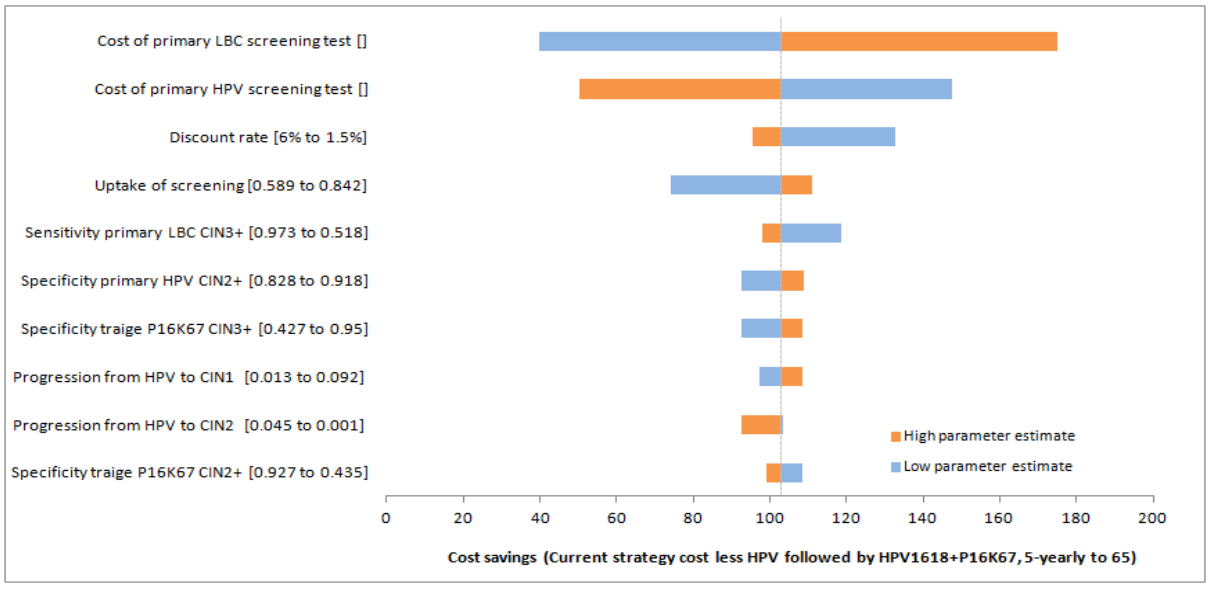

Cost of primary LBC screening test []
Cost of primary HPV screening test []
Discount rate [6% to 1.5%]
Uptake of screening [0.589 to 0.842]
Progression from HPV to CIN2 [0.045 to 0.001]
Progression from CIN3 to FIGO1 [0.01 to 0.08]
Sensitivity primary LBC CIN3+ [0.973 to 0.518]
Progression from CIN1 to CIN2 [0.165 to 0.05]
Specificity primary HPV CIN2+ [0.828 to 0.918]
Progression from HPV to CIN1 [0.013 to 0.092]
High parameter estimate
Low parameter estimate
0 20 40 60 80 100 120 140 160 180 200
Cost savings (Current strategy cost less HPV followed by HPV1618-P16K67, 5-yearly to 60)

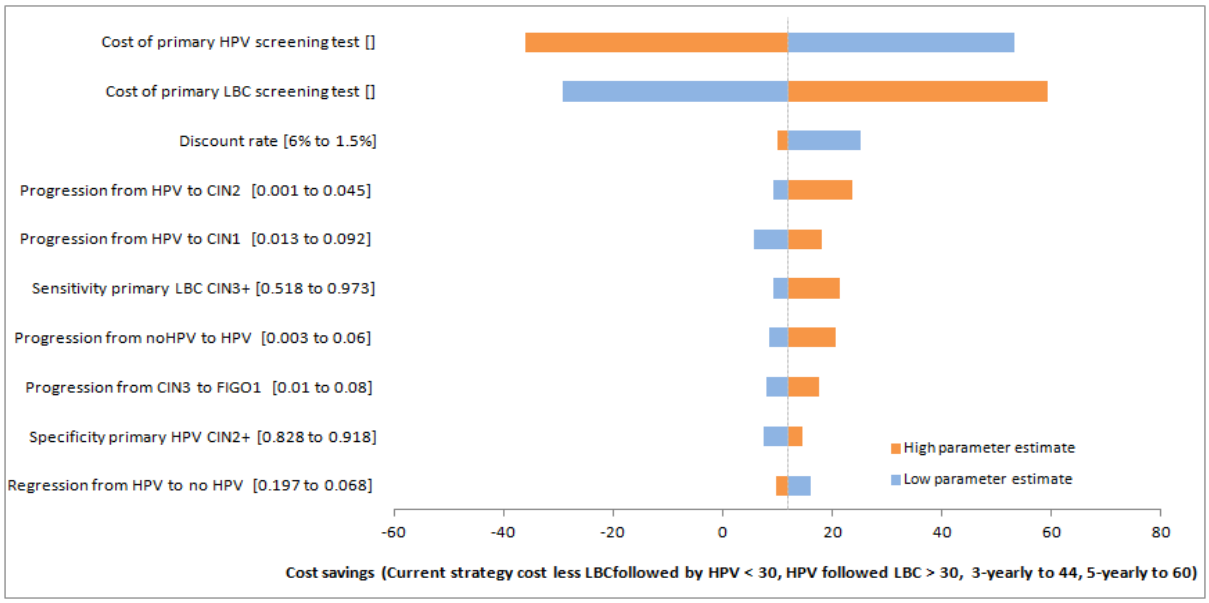

Cost of primary LBC screening test []
Cost of primary HPV screening test []
Uptake of screening [0.589 to 0.842]
Discount rate [6% to 1.5%]
Sensitivity primary LBC CIN3+ [0.973 to 0.518]
Progression from HPV to CIN2 [0.045 to 0.001]
Progression from CIN3 to FIGO1 [0.08 to 0.01]
Progression from CIN1 to CIN2 [0.165 to 0.05]
Progression from HPV to CIN1 [0.013 to 0.092]
Specificity primary HPV CIN2+ [0.828 to 0.918]
High parameter estimate
Low parameter estimate
0 20 40 60 80 100 120 140 160 180 200
Cost savings (Current strategy cost less HPV followed by HPV1618-P16K67, 5-yearly to 65)

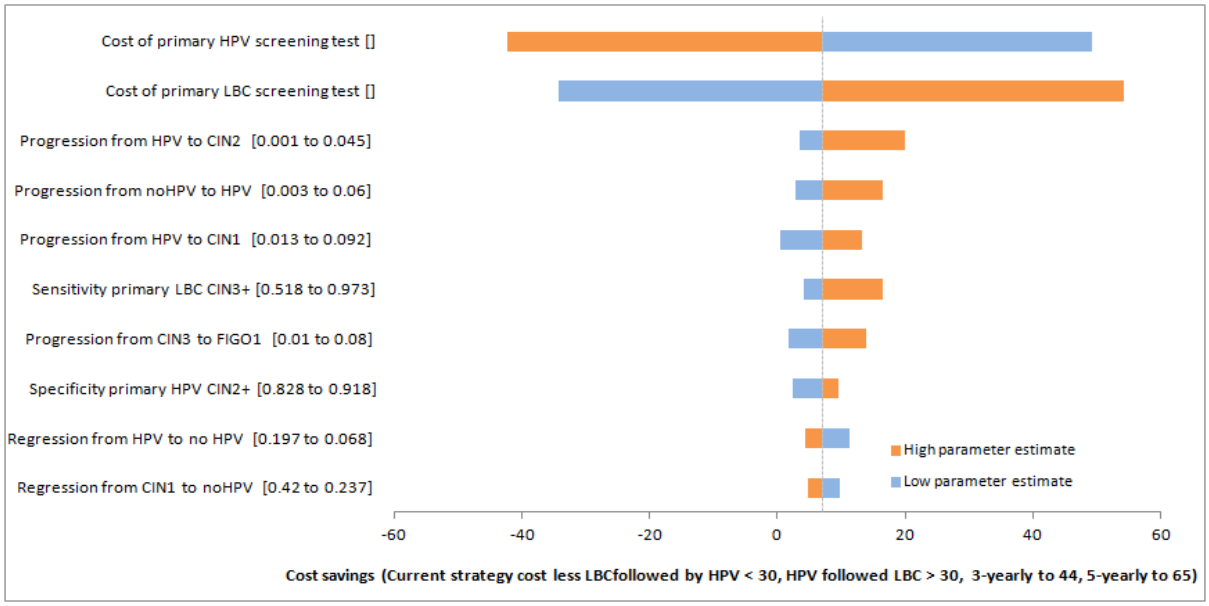

Cost of primary HPV screening test []
Cost of primary LBC screening test []
Sensitivity primary LBC CIN3+ [0.973 to 0.518]
Specificity traige P16K67 CIN2+ [0.927 to 0.435]
Progression from CIN3 to FIGO1 [0.01 to 0.08]
Discount rate [6% to 1.5%]
Progression from HPV to CIN1 [0.013 to 0.092]
Prevalence of CIN1 at age 25 [0.0178 to 0.0794]
Progression from HPV to CIN2 [0.001 to 0.045]
Specificity primary HPV CIN3+ [0.828 to 0.918]
High parameter estimate
Low parameter estimate
-80 -60 -40 -20 0 20 40 60 80 100
Cost savings (Current strategy cost less HPV followed by HPV1618+P16K67, 3-yearly to 44, 5-yearly to 60)


Cost of primary HPV screening test []
Cost of primary LBC screening test []
Sensitivity primary LBC CIN3+ [0.973 to 0.518]
Specificity primary HPV CIN2+ [0.828 to 0.918]
Specificity traige P16K67 CIN3+ [0.427 to 0.95]
Specificity primary HPV CIN3+ [0.828 to 0.918]
Specificity traige HPV1618 CIN2+ [0.302 to 0.788]
Cost of CIN1 []
Discount rate [1.5% to 6%]
Progression from FIGO1 to FIGO2 [0.03 to 0.33]
High parameter estimate
Low parameter estimate
-100 -80 -60 -40 -20 0 20 40 60 80
Cost savings (Current strategy cost less HPV followed by HPV1618+P16K67, 3-yearly to 44, 5-yearly to 65)


Cost of primary LBC screening test []
Cost of primary HPV screening test []
Discount rate [6% to 1.5%]
Uptake of screening [0.589 to 0.842]
Sensitivity primary LBC CIN3+ [0.973 to 0.518]
Specificity primary HPV CIN2+ [0.828 to 0.918]
Specificity traige P16K67 CIN3+ [0.427 to 0.95]
Progression from HPV to CIN2 [0.045 to 0.001]
Progression from HPV to CIN1 [0.013 to 0.092]
Progression from CIN3 to FIGO1 [0.08 to 0.01]
High parameter estimate
Low parameter estimate
0 20 40 60 80 100 120 140 160 180 200
Cost savings (Current strategy cost less HPV followed by HPV1618+P16K67, 5-yearly to 60)


Cost of primary LBC screening test []
Cost of primary HPV screening test []
Discount rate [6% to 1.5%]
Uptake of screening [0.589 to 0.842]
Sensitivity primary LBC CIN3+ [0.973 to 0.518]
Specificity primary HPV CIN2+ [0.828 to 0.918]
Specificity traige P16K67 CIN3+ [0.427 to 0.95]
Progression from HPV to CIN1 [0.013 to 0.092]
Progression from HPV to CIN2 [0.045 to 0.001]
Specificity traige P16K67 CIN2+ [0.927 to 0.435]
High parameter estimate
Low parameter estimate
0 20 40 60 80 100 120 140 160 180 200
Cost savings (Current strategy cost less HPV followed by HPV1618+P16K67, 5-yearly to 65)


Cost of primary HPV screening test []
Cost of primary LBC screening test []
Discount rate [6% to 1.5%]
Progression from HPV to CIN2 [0.001 to 0.045]
Progression from HPV to CIN1 [0.013 to 0.092]
Sensitivity primary LBC CIN3+ [0.518 to 0.973]
Progression from noHPV to HPV [0.003 to 0.06]
Progression from CIN3 to FIGO1 [0.01 to 0.08]
Specificity primary HPV CIN2+ [0.828 to 0.918]
Regression from HPV to no HPV [0.197 to 0.068]
High parameter estimate
Low parameter estimate
-60
-40
-20
0
20
40
60
80
Cost savings (Current strategy cost less LBCfollowed by HPV < 30, HPV followed LBC > 30, 3-yearly to 44, 5-yearly to 60)


Cost of primary HPV screening test []
Cost of primary LBC screening test []
Progression from HPV to CIN2 [0.001 to 0.045]
Progression from noHPV to HPV [0.003 to 0.06]
Progression from HPV to CIN1 [0.013 to 0.092]
Sensitivity primary LBC CIN3+ [0.518 to 0.973]
Progression from CIN3 to FIGO1 [0.01 to 0.08]
Specificity primary HPV CIN2+ [0.828 to 0.918]
Regression from HPV to no HPV [0.197 to 0.068]
Regression from CIN1 to noHPV [0.42 to 0.237]
High parameter estimate
Low parameter estimate
-60
-40
-20
0
20
40
60
Cost savings (Current strategy cost less LBCfollowed by HPV < 30, HPV followed LBC > 30, 3-yearly to 44, 5-yearly to 65)

Appendix 8 – Annual budget impact analysis for selected strategies

Table App8.1 Annual 8 year budget impact analysis for women who have not been vaccinated for HPV for selected strategies

Strategy	Year	Total cost (€)	Screening cost (€)	Treatment cost (€)	Screens (n)	Incremental screens	Incremental referrals	Incremental cost (€)
Current practice-LBC-HPV screen 3yr to 45,5yr to 60	**1**	**28,413,962**	**24,455,774**	**3,958,188**	**268,625**			
HPV-LBC screen 3yr to 29,5yr to 65	1	**27,996,326**	**23,886,522**	**4,109,804**	**268,825**	**199**	**-613**	**-417,636**
HPV-LBC screen 3yr to 29,5yr to 65 (referral includes HPV 1618)	**1**	**27,996,326**	**23,886,522**	**4,109,804**	**268,825**	**199**	**-613**	**-417,636**
Current practice-LBC-HPV screen 3yr to 45,5yr to 60	**2**	**30,053,200**	**25,633,104**	**4,420,097**	**268,680**	**-**		
HPV-LBC screen 3yr to 29,5yr to 65	2	**31,164,167**	**26,030,793**	**4,703,005**	**285,684**	**17,004**	**62**	**1,110,966**
HPV-LBC screen 3yr to 29,5yr to 65 (referral includes HPV 1618)	**2**	**31,162,048**	**26,030,793**	**4,703,005**	**285,684**	**17,004**	**15**	**1,108,848**
Current practice-LBC-HPV screen 3yr to 45,5yr to 60	**3**	**29,903,319**	**24,953,544**	**4,949,775**	**261,274**	**-**		
HPV-LBC screen 3yr to 29,5yr to 65	3	**31,122,127**	**25,346,633**	**5,247,964**	**279,248**	**17,974**	**227**	**1,218,807**
HPV-LBC screen 3yr to 29,5yr to 65 (referral includes HPV 1618)	**3**	**31,110,011**	**25,331,612**	**5,247,981**	**279,120**	**17,846**	**180**	**1,206,692**

Current practice-LBC-HPV screen 3yr to 45,5yr to 60	**4**	**27,118,292**	**23,249,150**	**3,869,141**	**247,070**	**-**		
HPV-LBC screen 3yr to 29,5yr to 65	4	**13,272,973**	**9,880,461**	**2,867,395**	**104,632**	**-142,439**	**-1,777**	**-13,845,318**
HPV-LBC screen 3yr to 29,5yr to 65 (referral includes HPV 1618)	**4**	**13,258,314**	**9,860,940**	**2,867,526**	**104,467**	**-142,604**	**-1,812**	**-13,859,978**
Current practice-LBC-HPV screen 3yr to 45,5yr to 60	**5**	**26,641,007**	**22,549,893**	**4,091,114**	**240,195**	**-**		
HPV-LBC screen 3yr to 29,5yr to 65	5	**12,091,763**	**8,801,773**	**3,019,898**	**98,274**	**-141,922**	**-2,003**	**-14,549,244**
HPV-LBC screen 3yr to 29,5yr to 65 (referral includes HPV 1618)	**5**	**12,085,909**	**8,793,215**	**3,020,017**	**98,233**	**-141,962**	**-2,031**	**-14,555,098**
Current practice-LBC-HPV screen 3yr to 45,5yr to 60	**6**	**25,994,623**	**21,577,156**	**4,417,467**	**231,338**			
HPV-LBC screen 3yr to 29,5yr to 65	6	**26,657,289**	**22,099,492**	**4,351,321**	**253,720**	**22,382**	**24**	**662,666**
HPV-LBC screen 3yr to 29,5yr to 65 (referral includes HPV 1618)	**6**	**26,658,316**	**22,098,316**	**4,351,494**	**253,758**	**22,421**	**3**	**663,693**
Current practice-LBC-HPV screen 3yr to 45,5yr to 60	**7**	**24,432,373**	**20,692,044**	**3,740,329**	**225,600**			
HPV-LBC screen 3yr to 29,5yr to 65	7	**26,743,260**	**22,056,293**	**4,371,158**	**250,785**	**25,184**	**397**	**2,310,887**
HPV-LBC screen 3yr to 29,5yr to 65 (referral includes HPV 1618)	**7**	**26,748,582**	**22,058,938**	**4,371,328**	**250,856**	**25,255**	**389**	**2,316,209**
Current practice-LBC-HPV screen 3yr to 45,5yr to 60	**8**	**24,280,977**	**20,573,363**	**3,707,614**	**218,276**			

HPV-LBC screen 3yr to 29,5yr to 65	8	**26,337,881**	**21,622,577**	**4,351,115**	**247,085**	**28,809**	**450**	**2,056,905**
HPV-LBC screen 3yr to 29,5yr to 65 (referral includes HPV 1618)	**8**	**26,331,209**	**21,614,463**	**4,351,249**	**247,017**	**28,741**	**440**	**2,050,232**

Table App8.2 Annual 8 year budget impact analysis for women who have been vaccinated for HPV for selected strategies

Strategy	Year	Total cost (€)	Screening cost (€)	Treatment cost (€)	Screens (n)	Incremental screens	Incremental referrals	Incremental cost (€)
Current practice-LBC-HPV screen 3yr to 45,5yr to 60	**1**	**204,712**	**199,644**	**5,067**	**2,215**			
HPV-LBC screen 5yr to 25 to 60	1	**198,663**	**193,140**	**5,523**	**2,215**	**0**	**-9**	**-6,048**
Current practice-LBC-HPV screen 3yr to 45,5yr to 60	**2**	**538,257**	**524,445**	**13,812**	**5,700**	**-**		
HPV-LBC screen 5yr to 25 to 60	2	**526,800**	**511,905**	**14,895**	**5,735**	**35**	**-18**	**-11,458**
Current practice-LBC-HPV screen 3yr to 45,5yr to 60	**3**	**1,180,090**	**1,148,493**	**31,597**	**12,465**	**-**		
HPV-LBC screen 5yr to 25 to 60	3	**1,153,188**	**1,119,562**	**33,625**	**12,564**	**99**	**-35**	**-26,902**
Current practice-LBC-HPV screen 3yr to 45,5yr to 60	**4**	**1,312,128**	**1,274,705**	**37,424**	**13,357**	**-**		
HPV-LBC screen 5yr to 25 to 60	4	**1,091,696**	**1,057,136**	**34,559**	**11,433**	**-1,924**	**-46**	**-220,433**

Current practice-LBC-HPV screen 3yr to 45,5yr to 60	**5**	**1,715,163**	**1,664,664**	**50,499**	**17,599**	**-**		
HPV-LBC screen 5yr to 25 to 60	5	**1,177,576**	**1,136,401**	**41,175**	**12,328**	**-5,271**	**-106**	**-537,587**
Current practice-LBC-HPV screen 3yr to 45,5yr to 60	**6**	**2,583,778**	**2,510,568**	**73,209**	**26,865**			
HPV-LBC screen 5yr to 25 to 60	6	**1,616,132**	**1,558,969**	**57,162**	**17,206**	**-9,659**	**-205**	**-967,646**
Current practice-LBC-HPV screen 3yr to 45,5yr to 60	**7**	**2,932,567**	**2,847,995**	**84,572**	**30,105**			
HPV-LBC screen 5yr to 25 to 60	7	**2,163,676**	**2,087,497**	**76,180**	**23,055**	**-7,051**	**-158**	**-768,891**
Current practice-LBC-HPV screen 3yr to 45,5yr to 60	**8**	**3,454,015**	**3,355,384**	**98,632**	**35,477**			
HPV-LBC screen 5yr to 25 to 60	8	**2,851,554**	**2,753,281**	**98,273**	**30,893**	**-4,584**	**-120**	**-602,461**

Table App8.3 Annual 8 year budget impact analysis for women the entire eligible population for selected strategies

Strategy	Year	Total cost (€)	Screening cost (€)	Treatment cost (€)	Screens (n)	Incremental screens	Incremental referrals	Incremental cost (€)
Current practice-LBC-HPV screen 3yr to 45,5yr to 60	**1**	**28,618,673**	**24,655,418**	**3,963,255**	**270,840**			
HPV-LBC screen 3yr to 29,5yr to 65	1	**28,194,989**	**24,079,661**	**4,115,328**	**271,039**	**199**	**-622**	**-423,685**

HPV-LBC screen 3yr to 29,5yr to 65 (referral includes HPV 1618)	**1**	**28,194,989**	**24,079,661**	**4,115,328**	**271,039**	**199**	**-622**	**-423,685**
Current practice-LBC-HPV screen 3yr to 45,5yr to 60	**2**	**30,591,458**	**26,157,549**	**4,433,909**	**274,380**	**-**		
HPV-LBC screen 3yr to 29,5yr to 65	2	**31,690,966**	**26,542,698**	**4,717,899**	**291,419**	**17,038**	**44**	**1,099,509**
HPV-LBC screen 3yr to 29,5yr to 65 (referral includes HPV 1618)	**2**	**31,688,848**	**26,542,698**	**4,717,899**	**291,419**	**17,038**	**-3**	**1,097,391**
Current practice-LBC-HPV screen 3yr to 45,5yr to 60	**3**	**31,083,409**	**26,102,038**	**4,981,372**	**273,739**	**-**		
HPV-LBC screen 3yr to 29,5yr to 65	3	**32,275,314**	**26,466,196**	**5,281,589**	**291,812**	**18,073**	**192**	**1,191,905**
HPV-LBC screen 3yr to 29,5yr to 65 (referral includes HPV 1618)	**3**	**32,263,199**	**26,451,174**	**5,281,606**	**291,685**	**17,945**	**144**	**1,179,790**
Current practice-LBC-HPV screen 3yr to 45,5yr to 60	**4**	**28,430,420**	**24,523,855**	**3,906,565**	**260,427**	**-**		
HPV-LBC screen 3yr to 29,5yr to 65	4	**14,364,669**	**10,937,597**	**2,901,955**	**116,065**	**-144,362**	**-1,823**	**-14,065,751**
HPV-LBC screen 3yr to 29,5yr to 65 (referral includes HPV 1618)	**4**	**14,350,010**	**10,918,076**	**2,902,086**	**115,900**	**-144,527**	**-1,858**	**-14,080,410**
Current practice-LBC-HPV screen 3yr to 45,5yr to 60	**5**	**28,356,170**	**24,214,556**	**4,141,613**	**257,794**	**-**		
HPV-LBC screen 3yr to 29,5yr to 65	5	**13,269,339**	**9,938,175**	**3,061,072**	**110,601**	**-147,193**	**-2,109**	**-15,086,831**
HPV-LBC screen 3yr to 29,5yr to 65 (referral includes HPV 1618)	**5**	**13,263,485**	**9,929,616**	**3,061,192**	**110,561**	**-147,234**	**-2,136**	**-15,092,684**

Current practice-LBC-HPV screen 3yr to 45,5yr to 60	**6**	**28,578,401**	**24,087,724**	**4,490,677**	**258,203**			
HPV-LBC screen 3yr to 29,5yr to 65	6	**28,273,421**	**23,658,461**	**4,408,483**	**270,926**	**12,723**	**-181**	**-304,980**
HPV-LBC screen 3yr to 29,5yr to 65 (referral includes HPV 1618)	**6**	**28,274,448**	**23,657,286**	**4,408,656**	**270,965**	**12,762**	**-202**	**-303,953**
Current practice-LBC-HPV screen 3yr to 45,5yr to 60	**7**	**27,364,940**	**23,540,039**	**3,824,901**	**255,706**			
HPV-LBC screen 3yr to 29,5yr to 65	7	**28,906,937**	**24,143,789**	**4,447,338**	**273,840**	**18,134**	**239**	**1,541,996**
HPV-LBC screen 3yr to 29,5yr to 65 (referral includes HPV 1618)	**7**	**28,912,258**	**24,146,434**	**4,447,508**	**273,911**	**18,205**	**231**	**1,547,318**
Current practice-LBC-HPV screen 3yr to 45,5yr to 60	**8**	**27,734,992**	**23,928,746**	**3,806,246**	**253,753**			
HPV-LBC screen 3yr to 29,5yr to 65	8	**29,189,435**	**24,375,858**	**4,449,388**	**277,978**	**24,225**	**330**	**1,454,443**
HPV-LBC screen 3yr to 29,5yr to 65 (referral includes HPV 1618)	**8**	**29,182,763**	**24,367,745**	**4,449,522**	**277,910**	**24,157**	**320**	**1,447,771**

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