KCE REPORT 238Cs

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

SYNTHESIS

CERVICAL CANCER SCREENING PROGRAM AND HUMAN PAPILLOMAVIRUS (HPV) TESTING, PART II: UPDATE ON HPV PRIMARY SCREENING

Belgian Health Care Knowledge Centre

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HEALTH TECHNOLOGY ASSESSMENT

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FOREWORD

Georgios Papanikolaou could be called the father of cancer screening. His first publication on the diagnosis of cervical cancer by means of a cervical smear is from 1928 but it is at the moment the book '*Diagnosis of Uterine Cancer by the Vaginal Smear'* was published in 1943 that the method was fully accepted. Better known as the '*Pap-smear',* the cervical smear is the standard method for periodic screening of cervical cancer, to a certain degree for lack of better, as the screening is not without problems. On top of the usual difficulties that screening has, such as assuring a good participation of the target group, reproducibility of cytology is poor.

We know now that cervical cancer is caused by human papilloma virus (HPV), so it may seem logic to look directly for the virus instead of looking for abnormal cells. In 2006 we tried to answer the question whether a HPV test should replace cytology, but at that moment there was not sufficient evidence that the test would effectively lead to a decrease in the number of cases. Different partners asked KCE for an update of the study. It is also an issue in other countries, it is debated in some Scandinavian countries and it will be implemented in the Netherlands.

It would be nice if we could, besides improving the screening, save money, and it looks as if this is the case, as you can read in this report. The good old *Pap-smear* is not entirely abandoned, but put in second line. More important, a change in strategy causes a change in the role of different actors. The technical performance of the test alone is not enough to realize the full potential of screening, equally important is the way the screening algorithm is implemented in the field.

Christian LÉONARD
Deputy general director

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ABSTRACT

THE PROBLEM ADDRESSED BY THIS REPORT

This report is an update of the report KCE report vol. 38C[4] on the place of HPV in cervical screening. It assesses the impact of HPV screening compared to cytology screening

This report will therefore addresses 3 questions:

- What is the optimal algorithm for cervical cancer screening?
- What is the organisational impact of HPV screening and the way it is organized?
- What is the cost-impact of the introduction of a new screening algorithm?

KEY FINDINGS

- HPV testing is more sensitive for precancerous lesions CIN2 and CIN3 than cytology. The downside is that the transversal specificity is lower.
- The protective effect of HPV screening compared to cytology on the incidence of invasive cervical cancer is directly demonstrated in randomized trials.
- No protective effect is demonstrated under 30 years.
- The risk of CIN3+ or invasive cervical cancer after a negative hrHPV DNA test is significantly lower than after a negative Pap smear. This means that screening intervals can be extended safely up to five and more.
- A two-step triage scenario with twice cytology at cutoff ASC-US+ offers a good balance of efficiency (4 to 9 referrals to detect one CIN3+, ~40% of referral) and safety (risk of CIN3+ in triage-negative women of 0.5% to 0.9%).
- For the interpretation of cervical cytology specimen, there is no quality control programme yet.

- In Belgium, an ISO15189 accreditation (including participation in external quality assessments) for high-risk HPV detection in cervicovaginal samples using a molecular method - but not for cytopathology - is mandatory for reimbursement.
- The use of colposcopies in Belgium, with high numbers performed without previous cytology result is not in line with the internationally agreed recommendations, where colposcopies should be used to examine women with abnormal cytology findings.
- Proportions of abnormal cytology results varies widely between laboratories.
- It is unlikely that the introduction of HPV screening would lead to a large increase in confirmation tests in the Belgian context.
- HPV screening every 5 year is a dominant option, compared to current practice of cytology screening every 3 years.

SYNTHESIS

TABLE OF CONTENTS

1. INTRODUCTION

1.1. Background

1.1.1. Incidence

In 2011, 623 cases of cervical cancer were declared to the Belgian Cancer Registry for Belgium, with a crude rate of 11.2 per 100 000 woman per year and an age adjusted rate (European standard) of 9.7 per 100 000 woman per year. Stage distribution is dominantly TNM stage I (Table 1).

Table 1 – Stage distribution of cervical cancer in Belgium, 2011

Invasive (ICD10: C53)	Total
Total invasive	623
Stadium I	257
Stadium II	53
Stadium III	96
Stadium IV	63
Stadium unknown	154
In situ	2926

Cervical cancer is the 12th most frequent tumour in females (2.1%) in Belgium. Cancer of the cervix is the 3rd most frequently occurring gynaecological tumour. Cervical cancer is a rare cause of cancer death (1.7%). Mean age at diagnosis is 54 years. Incidence remained roughly stable over the last years.

1.1.2. Mass screening

The Pap test was invented in the 1940s by George Papanicolaou and was introduced as an effective mass screening test in the 1960s and is based on the cytological morphology assessment of exfoliated cervical cells. Organised screening programmes based on the Pap test have been successful in reducing the incidence and mortality from the disease, although cancer still does occur in women who regularly attend for screening. In the last two decades it has been established that cervical cancer has a strong causal relationship with persistent infection with high-risk human papillomavirus (HPV) types. Since then, research efforts have focused on the evaluation of a test for the detection of HPV deoxyribonucleic acid (DNA) as an alternative method of screening for cervical cancer precursors.[1]

Coverage of cervical screening is currently around 60 % in Belgium, with only marginal differences between the different communities, despite the fact that organisational modalities are different. Methods to improve this coverage are needed but require primary research and are out of scope of this report. Self-sampling is considered a way to improve coverage but was out of scope of the report.

1.1.3. Caused by HPV

Infection of the uterine cervix with the high-risk types of HPV is necessary for the development of cervical cancer, although the HPV infection alone is usually not sufficient to cause cancer. The presence of additional co-factors is required. Most high-risk HPV infections clear spontaneously but in a small proportion of women the infection persists. It is these women who are at risk of developing high-grade cervical intraepithelial neoplasia (CIN) grades 2 or 3 and adenocarcinoma in situ, which are cancer precursors. CIN2 and 3 can be effectively treated by excision or ablation of the lesion. Over a period of 30 years, untreated CIN3 has a risk of progressing to invasive disease in approximately 25% to 30% of cases.[1]

1.1.4. Pap test

Currently in the developed world screening for cervical cancer is carried out by means of cytological examination of a cervical smear (the Pap test). After visualization of the cervix with the use of a speculum the specimen is obtained with a sampling device (spatula combined with an endocervical brush or a single broom), usually a spatula and in some instances a brush, which is rotated on the cervix. The collected material is applied to a glass slide (for conventional cytology) or the sampling device is rinsed in a preservative solution (for liquid based cytology).[1] Attempts were made to improve the process, such as the introduction of automated screening, but the added value of these improvements remains unclear.

Cytologists reading the Pap tests usually follow the Bethesda classification system for reporting cervical cytologic diagnoses. In this system the smears are reported as negative for intraepithelial lesion or malignancy; atypical squamous cells of undetermined significance (ASC-US); atypical squamous cells, cannot exclude high grade lesion (ASC-H); low-grade squamous intraepithelial lesion (LSIL); high-grade squamous intraepithelial lesion (HSIL); squamous cell carcinoma; atypical glandular cells (AGC); adenocarcinoma in situ (AIS); or adenocarcinoma. Women with an abnormal Pap test should be referred for further investigation, which includes either repetition of the cytology, HPV triage or colposcopy.[1]

The test-validity, in particular the cross-sectional test sensitivity of the conventional Pap smear for CIN, is moderate: between 50 and 70% for CIN; but around 80% for high-grade CIN.[2] Reading of Pap smears is operator dependent and reproducibility is poor, in particular for ASC-US.

1.1.5. HPV test

The HPV test is performed on exfoliated cervical cells, similar to the Pap test. Molecular technologies for the detection of HPV DNA or RNA can be broadly divided into methods with amplification and methods without amplification.. The tests mainly used in clinical research use amplification methods, which are further divided into signal amplified and target amplified. The main representative techniques of each category are the hybrid capture II (HC2, Digene Corporation, Gainthersburg, MD, USA) assay and polymerase chain reaction (PCR), respectively.

HC2 is a Food and Drug Administration (FDA) approved test for HPV detection. It can detect infection from any of 13 high-risk types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68) or 5 low-risk types (6, 11, 42, 43, 44) but exact typing is not routinely possible.[1]

In most studies HC2 or GP5+6+ PCR were used. The last couple of years data have been published on the performance of HPV-based screening with other HPV DNA or RNA detection systems (Cervista, Cobas-4800, HPVCare, Papillocheck, APTIMA, Pretect HPV Proofer and others).[3] HPV testing has a higher sensitivity for CIN lesions but a lower cross sectional specificity, mainly due to the fact that not all HPV infections evolve to CIN or invasive cancer and the fact that there is a time lag between infection and the appearance of CIN lesions.

1.2. The problem addressed by this report.

This report is an update of the report KCE report vol. 38C[4] on the place of HPV in cervical screening. In this report KCE did not recommend primary HPV screening, because despite its proven increased sensitivity, RCT's were ongoing at that moment to assess its utility. In the meantime new evidence emerged, mainly coming from RCTs assessing the impact of HPV screening compared to cytology screening and from cohort studies assessing the long(er) term implications of a positive/negative cytology or HPV screening result. Switching to HPV screening in the Belgian context has also a number of organisational implications and its feasibility and consequences depend on a number of organisational modalities, including procurement, degree of centralisation and quality control of primary and follow up tests.

This report will therefore address 3 questions:

- What is the optimal algorithm for cervical cancer screening?
- What is the organisational impact of HPV screening and the way it is organized?
- What is the cost-impact of the introduction of a new screening algorithm?

2. FINDINGS

2.1. What is the optimal screening algorithm for cervical cancer screening

2.1.1. Update on accuracy of HPV vs. cytology screening

A systematic review on the accuracy of HPV testing and cytology in primary cervical cancer screening had been published in 2012[5] and was updated for this report. The updated meta-analysis of the cross-sectional accuracy of HPV tests contains data from 60 studies, among which 9 randomised trials. In the large majority of studies, the HC2 or GP5+6+ PCR were used.

In European and North-American studies, the pooled sensitivity for CIN2+ was 96% (95% CI: 95-98%), whereas the pooled specificity was 91% (95% CI: 89-91%). The accuracy values of HC2 for CIN3+ were similar to those for CIN2+. On average, eleven percent (95% CI: 9-12%) of the screened population was hrHPV-positive.[5]

The updated meta-analysis reinforces that hrHPV testing is substantially more sensitive than cytology in identifying underlying CIN2+ and CIN3+. However, one drawback is the lower specificity. A wide spread of accuracy estimates is observed in certain developing countries possibly explainable by variability in the reference standard. Further variation is observed according to the intensity of verification and methods to adjust for verification bias.[6, 7]

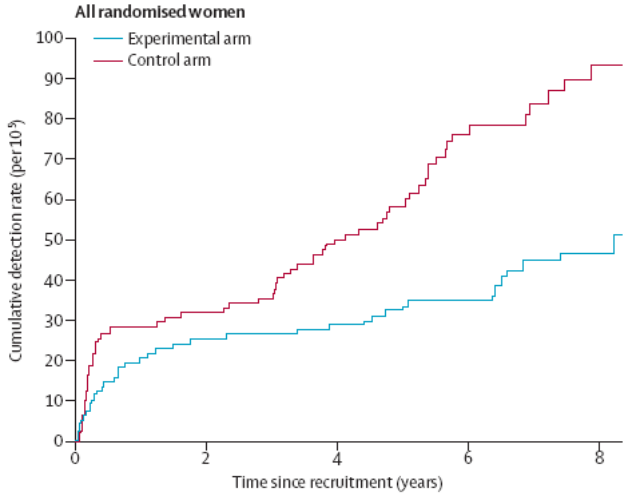
2.1.2. Efficacy of HPV-based compared to cytology-based screening

Higher cross-sectional sensitivity of hrHPV testing for detecting CIN2+ and CIN3+ provides insufficient evidence that HPV-based screening will decrease the incidence of cervical cancer more than cytology-based screening. Most CIN2 and CIN3 lesions clear and it cannot be excluded from cross-sectional studies that HPV tests just pick up more regressive disease. Therefore a review was conducted summarizing the longitudinal findings from randomized trials which compared cytology- with HPV-based screening.

Four trials were identified, a pooled analysis of the individual data from these trials was published,[8] which confirm findings of the previous meta-analysis of aggregated data (Figure 1).[5] This pooled analysis provided more details regarding the protection against invasive cervical cancer by HPV-based compared to cytology-based screening, such as:

- The protective effect was observed only 2.5 years after screening (relative protection of 0.45 (95% CI: 0.25–0.81) versus 0.79 (95% CI: 0.46–1.36) before 2.5 years), but increased with follow-up time;
- The protective effect was similar for early (stage 1A) or advanced (stages ≥ 1A) cervical cancer;
- The protective effect was observed both in the total screened group (relative protection of 0.60; 95% CI: 0.40–0.89) and in women with a negative screening test at base-line (relative protection of 0.30; 95% CI: 0.15–0.60);
- There was no protective effect observed in the age group of <30 years (relative protection of 0.98 (95% CI: 0.19–5.20);
- HPV-based screening protects more against adenocarcinoma (relative protection of 0.31; 95% CI: 0.14–0.69) than against squamous cancer (relative protection of 0.78; 95% CI: 0.49–1.25).

Figure 1 – Cumulative detection rate of invasive cervical cancer among women included in the experimental arm (blue curve) screened with a hrHPV DNA test versus those included in the control arm (red curve) screened with cytology



Source: Ronco, Lancet 2013[8]

There is strong evidence that HPV-based screening results in a lower incidence of cervical cancer.

2.1.3. Clinically validated HPV assays

Randomised trials have demonstrated that HPV-based screening using the HC2 assay or the GP5+/6+ PCR with EIA identification of 14 high-risk HPV types, is more effective in reducing the incidence of cervical cancer than cytology-based screening and therefore these assays should be considered as clinically validated.[5, 9] Experts have defined cross-sectional equivalency criteria allowing claims for other HPV DNA assays for use in primary screening.[10]

The candidate test should demonstrate non-inferior sensitivity and specificity compared to HC2 or GP5+/6+ PCR, with lower 95% confidence interval bounds of ≥0.90 and ≥0.98, respectively. A representative set of samples (minimally 60 CIN2+ cases, 800 ≤CIN1 cases) derived from a population-based screening cohort should be selected.[10] Moreover, a high reproducibility (≥ 87%) should be reached. A systematic search of published peer-reviewed references was performed using MEDLINE and Embase, completed with citations of the Meijer guideline, using www.scopus.com.

Besides the two assays evaluated in randomized trials (HC2 and GP5+6+ PCR), four other hrHPV DNA tests can be considered as clinically validated for use in cervical cancer screening (Abbott RT PCR, COBAS-4800, Papillo-Check, q E6-E7 PCR) since they fulfil the cross-sectional equivalency criteria for clinical validation. The APTIMA assay, detecting mRNA of the viral E6/E7 genes also fulfils these criteria, but more longitudinal data are needed, to demonstrate safety over five or more years after a negative mRNA test. The number of validated tests is increasing and an updated list should be consulted when deciding on what test should be used/allowed.

2.1.4. Screening interval: low risk of cervical pre-cancer and cancer after a negative hrHPV DNA test observed in screened cohorts

The screening interval should be defined taking into account the cumulative risk of significant disease after a previous negative screening test. The cumulative risk to develop CIN3+ in the next five years (pooled from 5 European[11-16] and two American screening cohorts[17, 18], completed with data obtained directly by the authors{Arbyn, 2012 #14}) is very low for HPV-negative women (0.2% and 1.2%, for women without or with cytological abnormalities, respectively). However, for women who were hrHPV positive, this risk was substantially higher: 6% or 12%, for women without or with ASC-US or worse cytology at baseline, respectively. In the Kaiser-Permanente cohort, where women of 30 years or older were screened by cytology and HC2, the 5 year cumulative incidence of invasive cervical cancer was: 0.90% if positive for both hrHPV and cytology, 0.54% if hrHPV positive and cytology-negative, 0.16% if hrHPV-negative and cytology positive and 0.016% if negative for both.[19] The 5-year cervical cancer risk corresponding with a negative hrHPV DNA result was 0.19% indicating that negative cytology does not stratify more the low-risk associated with one negative HPV test.

A recent pooled analysis of the individual data of four European randomised trials comparing cytology- with HPV-based screening showed a significantly lower risk after a negative hrHPV DNA test compared to a after negative cytology result.[8] The lower detection rate was only observable after two and a half years and remained observable up to eight years.

We can conclude from this:

- The risk of CIN3+ or invasive cervical cancer after a negative hrHPV DNA test is significantly lower than after a negative Pap smear. We can conclude from this and from additional data that screening intervals can be extended safely up to five and more.
- For reasons of safety and acceptability, the screening interval after a negative hrHPV test could be first defined at five years and extended further when the screening programme confirms the low longitudinal risk.
- A negative co-test (negative cytology and negative HPV test) shows only marginally smaller risk than a negative HPV test alone. Therefore contesting does not offer additional safety allowing for even longer intervals than after a sole negative HPV test.

2.1.5. Age to start HPV screening

2.1.5.1. Influence of age on screening efficacy

Pooling of the individual data of four randomised clinical trials comparing HPV- with cytology-based screening, conducted in Europe, allowed addressing the effect modification by age group on screening efficacy (Table 2). It shows that before the age of 30 shifting from cytology to HPV as primary testhas no effect on the incidence of cervical cancer. In Belgium the recommended age to start screening is currently 25 years.

Table 2 – Relative risk or protective effect (reduction in incidence of invasive cervical cancer) in women screened with HPV testing vs. cytology, according to age at enrolment

Age at enrolment (years)	RR	95% CI	I2	p for heterogeneity (inter-study)
<30	0.98	(0.19–5.20)	0.00%	0.34
30-34	0.36	(0·14–0·94)	7.20%	0.36
35-49	0.64	(0.37–1.10)	0.00%	0.55
>=50	0.68	(0.30–1.52)	36.50%	0.21

Source: Ronco, Lancet 2013[8]

2.1.5.2. Accuracy of hrHPV DNA testing by age group

In developed countries, the prevalence of HPV infections peaks shortly after onset of sexual activity and typically peaks in older teenagers and women in their early 20ies. Thereafter, the prevalence decreases progressively by age with sometimes a discrete peak around 45-55 years.[20-22]

Table 3 – Sensitivity and specificity of hrHPV DNA testing and cytology (at ASC-US+) to detect CIN2+ and CIN3+ in women attending cervical cancer screening, by age group. Relative sensitivity and specificity of the two tests (adapted from Cuzick, IJC 2006)[23]

Age (years)		<35	35-49	50+	Trend
Absolute accuracy of hrHPV DNA testing					
Sensitivity	CIN2+	98.4 (96.3-100)	95.2 (91.4-99.1)	99.3 (92.7-100.0)	0.13
	CIN3+	98.8 (96.5-100)	94.5 (89.5-99.0)	100.0 (93.2-100.0)	0.86
Specificity	CIN2+	88.4 (84.9-92.0)	93.5 (91.5-95.5)	94.4 (91.8-97.1)	<0.001
	CIN3+	86.4 (82.6-90.3)	93.1 (91.0-95.2)	94.1 (91.4-96.9)	<0.001
Absolute accuracy of cytology at ASC-US+					
Sensitivity	CIN2+	46.4 (25.9-66.8)	50.5 (34.9-66.1)	80.1 (67.5-92.7)	<0.001
	CIN3+	49.4 (29.8-69.0)	49.0 (33.3-64.6)	80.8 (67.5-94.1)	0.01
Specificity	CIN2+	95.7 (9379-97.7)	97.3 (96.2-98.4)	98.1 (96.9-99.24)	<0.001
	CIN3+	94.7 (92.2-97.1)	97.0 (95.8-98.2)	97.9 (96.6-99.2)	<0.001

2.1.5.3. Age-specific adverse effects related to treatment of screen-detected lesions

Data from recent meta-analyses show higher rates of adverse pregnancy outcomes in women with a prior history of excisional treatment of cervical pre-cancer than in the general population,[24-26] in particular when the excision is deep or a large proportion of cervical tissue is excised.[27] Adverse pregnancy outcomes may be induced by cervical incompetence or decreased protection against ascending infections and include preterm premature rupture of the membranes, preterm delivery (<37 weeks of gestation) and low birth weight (<2500 gr). Shallow excision of the transformation zone might be free of adverse obstetrical effects as suggested from recent reports where excisions probably were less aggressive.[28, 29] Birth rates are highest in the groups between 25 and 35 years old. This implies that in young women overdiagnosis of regressive CIN lesions should be avoided. There are indications from RCT that HPV screening may lead to overdiagnosis at younger age but this is not proven.

2.1.5.4. Conclusion

HPV-based screening should not start before the age of 30 (lack of evidence of health benefit, high prevalence of transient infections, there may be a risk of over-diagnosis and an increased risk of obstetrical adverse effects). In the age group 30 to 35, HPV screening is more effective compared to cytology screening but is less specific.

2.1.6. Triage algorithms

The higher sensitivity for CIN2+ and CIN3+ of HPV screening is associated with a drop in specificity, which results in a decreased cross-sectional positive predictive value (PPV) and may lead to unnecessary follow-up of screen-positive women and over-management of patients. As a consequence, the triage of hrHPV positive women is needed to limit the burden of follow-up and to avoid over-diagnosis and over-treatment as much as possible. By the use of appropriate triage of HPV+ women and by extended screening intervals, longitudinal specificity of HPV-based screening may exceed that of cytology-based screening.

The Unit Cancer Epidemiology of IPH did a literature review, restricted to large population-based trials comparing HPV-based with cytology-based screening to evaluate diverse triage methods that can be used to manage women with a positive hrHPV-DNA test at screening. Different triage options nested in large screening trials using an hrHPV assay as a primary screening test, enabled us to assess the accuracy of diverse strategies to manage hrHPV-positive women.

Studies addressing this issue are limited due to short follow up time, the fact that many scenarios of triage are documented in few and often even in only one study and the fact that the inter-study heterogeneity in the absolute accuracy values observed in multiple studies assessing a particular scenario often was large. Not all relevant triage information reported in secondary publications of the screening trials could be included in a formal meta-analysis since only proportions or rates were reported with different assumptions applied for adjustment for follow-up compliance. Adjustment for incomplete compliance could not be assessed statistically since it requires availability of the absolute data. Requesting data from authors will be done within the COCEAHR project, but cannot yet be included in the current review.

A two-step triage scenario with twice cytology at cut-off ASC-US+ offers a good balance of efficiency (4 to 9 referrals to detect one CIN3+, ~40% of referrals) and safety (risk of CIN3+ in triage-negative women of 0.5% to 0.9%). In the Netherlands, this scenario has been chosen for the future HPV-based screening policy, which will be applied over the whole country in 2016. The safety of this strategy can be increased by adding HPV16 or HPV16-18 genotyping, or by replacing in the second cytology triage test with a repeat hrHPV test. In these scenarios, safety criteria are obviously fulfilled, even when the background risk is high, but they are accompanied by a substantially increased referral rate (67% to 71%).

Two-step scenarios are characterised by a certain degree of drop-out of women under follow-up. Where this drop-out is important, more sensitive reflex triage scenarios could be favoured which involve reflex cytology combined with HPV16-18 genotyping. However, these one-step triage scenarios do not reach the safety criterion when the background risk is intermediate or high.

In conclusion, triage with reflex cytology and repeat cytology appeared to be an acceptable scenario. However, it should be mentioned that the quality of cytology in the field may be more heterogeneous than in the trials included in this review. Triage with objective bio-markers could reduce this variability.

2.2. Organisation of the cervical screening in Belgium

2.2.1. Organisation in general

The setup of a screening program is different over the country: whereas in the Flemish region a screening has been set up since 2013, no screening initiatives were taken in the French-speaking region and in Brussels. The current screening program is focused on the elaboration of a call-recall system, in which the woman is encouraged to make an appointment every 3 years for a PAP smear test. Only after a second positive reading of the cytological analysis, a reimbursement of a HPV test is foreseen.

2.2.2. Quality control of cytology

For cytopathology, laboratories must fulfil the quality criteria as described in the Royal Decree concerning the licensing of anatomic pathology laboratories that has been published in 2012 (Royal Decree of 5 December 2011, published on 13/02/2012 in Belgisch Staatsblad/Moniteur Belge, p. 10653-10663). A national external quality assessment program for various analyses, including cytopathology, is being initiated.

For the interpretation of cervical cytology specimen, there is no quality control programme yet. According to the Royal Decree, the Scientific Institute of Public Health is mandated to start up a national external quality control programme for diverse activities performed in cytopathology laboratories as defined by the Commission for Pathological Anatomy. Laboratories are obligated to participate for the tests and examinations which are performed in their laboratory.

In order to have an idea on how this is done in practice, we looked in literature and contacted a small sample of laboratories. The variety in quality control procedures between laboratories, the lack of evaluation of current procedures and the lack of clear instructions on the rescreening of negative cases, show that the quality control management for cytological analyses is still under development.

2.2.3. Quality control of HPV

In Belgium, an ISO15189 accreditation (including participation in external quality assessments) for high-risk HPV detection in cervicovaginal samples is mandatory for reimbursement. This International Standard specifies the quality requirements and competence that are particular for medical laboratories. A medical laboratory's fulfilment of the requirements of this International Standard means the laboratory meets both the technical competence requirements and the management system requirements that are necessary for it to consistently deliver technically valid results.

The Scientific Institute of Public Health organizes an external control procedure for HPV DNA testing via QCMD. Samples are prepared from cell cultures infected with HPV and fixed in PreservCyt (ThinPrep, Hologic). Belgian laboratories requesting reimbursement for bio-molecular testing for HPV must have an ISO15189 accreditation and participate in an external quality control programme. In 2013, 44 Belgian laboratories participated in this QC programme.

Recently (in 2009) the WHO has developed a technical manual for laboratories on HPV testing. Moreover, the WHO also recommends setting up national HPV reference laboratories per country within an international network. In Belgium, an ISO15189 accreditation for HPV detection is mandatory for reimbursement. However, a national reference laboratory for HPV tests is not (yet) assigned. The specific tasks of this HPV reference laboratory cover following domains: surveillance, quality control (e.g. validation of HPV assays, definition of list of HPV tests, set up of a quality assurance system); (international) collaboration with health authorities (and other services specialized in surveillance); education and training (e.g. training of personnel, continuously update of scientific and technical knowledge).

2.3. Cervical screening in Belgium

2.3.1. Introduction

In order to document the current situation in Belgium, we analysed IMA data and coupled these to the cyto-histo pathology register (CHP). We describe shortly the databases. Complete results are given in the full scientific report, for this synthesis we only report the results we think most relevant for the question if and under what condition HPV screening should be introduced.

2.3.1.1. IMA database

The IMA database contains the list of nomenclature codes of all reimbursed medical acts related to cervix and performed in Belgium from the year 2008 to the first semester of 2013. The database contains the following information: Social Security Number (SSN) of patients, date of medical act, nomenclature codes of medical acts and codes identifying the laboratory where the samples were analysed.

2.3.1.2. Cyto-histo pathology register (CHP)

The cyto-histo pathology register (CHP), managed by the Belgian Cancer Register (BCR), contains the diagnosis/result of all analyses (reimbursed and not reimbursed) performed on cervix samples by anatomopathological laboratories in Belgium. The database contains information such as the SSN of patient, date of analysis, result/diagnosis of the analysis, laboratory and nomenclature codes. Those data are delivered by the laboratories to the BCR. After receiving the data, they are treated by internal software. For this study only a part of the data of year 2011 has been treated by BCR. In order to increase the exhaustivity of HPV tests in CHP, a priority was given during data treatment to the laboratories performing HPV tests and encoding HPV results. Of the 91 laboratories that delivered data of cervical samples, data of 62 laboratories were treated and are available in the CHP for this study.

2.3.1.3. Coupling

The IMA data were coupled to the CHP data. Thanks to this coupling, the diagnosis/result of cytological analyses and HPV tests registered in the IMA database will be known. Since the CHP currently contains data of 2011, only the medical acts performed in 2011 have been selected for coupling. Details of the coupling are given in the scientific report.

2.3.2. Consumption based on IMA data

In Table 4 the evolution of the number of screening tests in the years 2008-2013 is shown. 2013 is incomplete, as only the 6 first months are reported. It shows a moderate decline in number of tests performed, mainly due to changes in the nomenclature, as from 2009 screening is only reimbursed every 2 years, from 2013 it is only reimbursed every 3 years, impact of this on the decline cannot be fully seen yet. Around 10% of smears is taken by a general practitioner. Number of follow up test is important compared to number of first readings, varying from 10 to 12%. It has been rising slowly, it is possible that they partly reflect screening outside the 2 or 3 years interval but it may also be caused by the high proportion cytology positive women that in principle need follow up. HPV is used both in combination with screening tests and with follow up tests. Although in principle HPV test is only reimbursed after a second reading and should be used as triage for ASCUS (although it is also reimbursed for ASCH and AGLC), only part of the HPV tests is preceded by a second reading, this indicates that the rule is not respected in a consistent way. There is a high number of colposcopies, 50% of these are performed on the same day as a screening test. As reported in previous reports this is an indication that the use of colposcopies in Belgium is not in line with the internationally agreed recommendations, where colposcopies should be used to examine women with abnormal cytology findings. In 2013 rules for reimbursement became stricter, colposcopy can only be performed after abnormal cytology, or for follow up of lesions. It is stated that other EBM indications are allowed, but it is not clear what it means. Although we observe already a decline in the number of colposcopies, it is too early to see what the impact of these rules is. Note that colposcopies are reimbursed in Belgium at a very low price, so that the impact on the budget is limited, however, quality of these colposcopies may be compromised.

In general a rather erratic picture emerges of a screening that is not done according to internationally accepted guidelines, with high use of colposcopy and possibly of follow up testing. Large savings are possible by a better compliance with internationally accepted standards, and the actual situation cannot be considered optimal.

Table 4 – Consumption of screening tests, follow up tests, colposcopies and HPV tests

	Year					
	2008	2009	2010	2011	2012	2013
Number of first readings of screening tests - sampling - global	1 264 346	995 983	673 983	816 284	717 169	219 095
Number of first readings of screening tests - sampling - by general practitioner	114 036	95 418	66 505	71 973	63 542	2 063
Number of first readings of screening tests - sampling - by specialist	1 150 310	900 565	607 478	744 311	653 627	198 465
Number of second readings of screening tests - global		12 288	27 279	33 739	31 247	8 943
Number of colposcopies	360 321	327 432	279 098	281 231	269 716	51 644
Number of colposcopies performed on the same day than a sampling of a screening test		233 030	131 719	158 541	133 681	11 938
Number of colposcopies without any previous cervix smear		252 592	228 085	237 826	223 300	39 620
Number of colposcopies performed with at least one cervix smear in the previous year		7 484	51 013	43 405	46 416	12 024
Number of HPV tests, triage screening test (following abnormal screening test)		8 488	19 759	23 229	21 789	6 685
Number of HPV tests, triage of screening test that are preceded by a second reading		4 621	13 314	16 529	15 877	4 246
Number of follow up tests - sampling - global		33 978	84 800	87 748	89 901	38 597
Number of HPV tests as part of follow-up examination after treatment		7 649	19 464	23 192	25 680	8 968

2.3.3. General cytological and HPV results

2.3.3.1. Overall cytology results

Table 5 shows the results of the coupled cytology tests by type of test according to the IMA data. Only 88% is reported as normal. It shows a relatively high proportion of samples lacking diagnosis, which makes this figure difficult to interpret. 7% ASCUS or higher. 2% is reported as 'atypical', a code that is not in line with accepted standards but may be similar to ASCUS but this is partly contradicted by the HPV results, where the proportion HPV+ results (among those where the result is known) is 64% in the atypical group compared with 34% in the ASCUS group. It indicates that specificity in a real life setting is lower than those observed in the validation studies.

Table 5 – Frequency and percentage of cytological diagnoses in the treated CHP per type of medical act (year 2011)

Type of medical act	NILM	ASCU	ATYP	ASCH	LSIL	HSIL	AGLC	SQGL	IN SITU	INVASIVE	OTHER	NODIAGN	TOTAL
Raw numbers													
First reading	427024	10499	9864	771	7704	1842	1404	321	4	110	50	24858	484451
Second reading	3740	6552	3500	584	1417	900	526	253	4	16	9	869	18370
Follow-up	35330	4693	3100	497	7449	1560	235	117	2	20	19	2075	55097
Not coupled to IMA record	84500	4314	2730	375	2663	775	351	125	4	43	16	15258	111154
TOTAL	550594	26058	19194	2227	19233	5077	2516	816	14	189	94	43060	669072
Percentages													
First reading	88.1%	2.2%	2.0%	0.2%	1.6%	0.4%	0.3%	0.1%	0.0%	0.0%	0.0%	5,1%	100.0%
Second reading	20.4%	35.7%	19.1%	3.2%	7.7%	4.9%	2.9%	1.4%	0.0%	0.1%	0.0%	4.7%	100.0%
Follow-up	64.1%	8.5%	5.6%	0.9%	13.5%	2.8%	0.4%	0.2%	0.0%	0.0%	0.0%	3.8%	100.0%
Not coupled to IMA record	76.0%	3.9%	2.5%	0.3%	2.4%	0.7%	0.3%	0.1%	0.0%	0.0%	0.0%	13.7%	100.0%
TOTAL	82.3%	3.9%	2.9%	0.3%	2.9%	0.8%	0.4%	0.1%	0.0%	0.0%	0.0%	6.4%	100.0%

Cytological diagnosis	Meaning
NILM	Negative for intraepithelial lesion of malignancy
ASCU	Atypical squamous cells of undetermined significance
ATYP	Atypical cells, not otherwise specified
ASCH	Atypical squamous cells, cannot exclude HSIL
LSIL	Low-grade squamous intraepithelial lesion
HSIL	High-grade squamous intraepithelial lesion
AGLC	Atypical glandular cells
SQGL	Combination of AGLC with either ASCU, ASCH, LSIL or HSIL
IN SITU	Adenocarcinoma, adenosquamous carcinoma (in situ), exclusion of HSIL
INVASIVE	Squamous carcinoma, adenocarcinoma, adenosquamous carcinoma (invasive)
NODIAGN	No diagnosis

Underlying these overall results there is a large variability in practice and results between laboratories. Following boxplots (Figure 2, Figure 3,Figure 4) show the median, interquartile range and range of cytology results. Percentages vary widely. Also the proportions of ASCUS followed by a HPV test and proportions of HPV that are positive after ASCUS show large variability, both in practices and results.

The fact that reproducibility of cytology is low and cytology is operator dependent and the absence of a systematic quality control are the most likely explanation of this variability. Most laboratories (66%) use liquid based cytology, only 8% use conventional, the others use a combination of both

.

Figure 2 – Box plots: proportion of cytological diagnoses after first readings (NILM, NODIAGN, ASCU, ASCH, LSIL, HSIL, AGLC) in the treated CHP (as percentages, year 2011) per laboratory

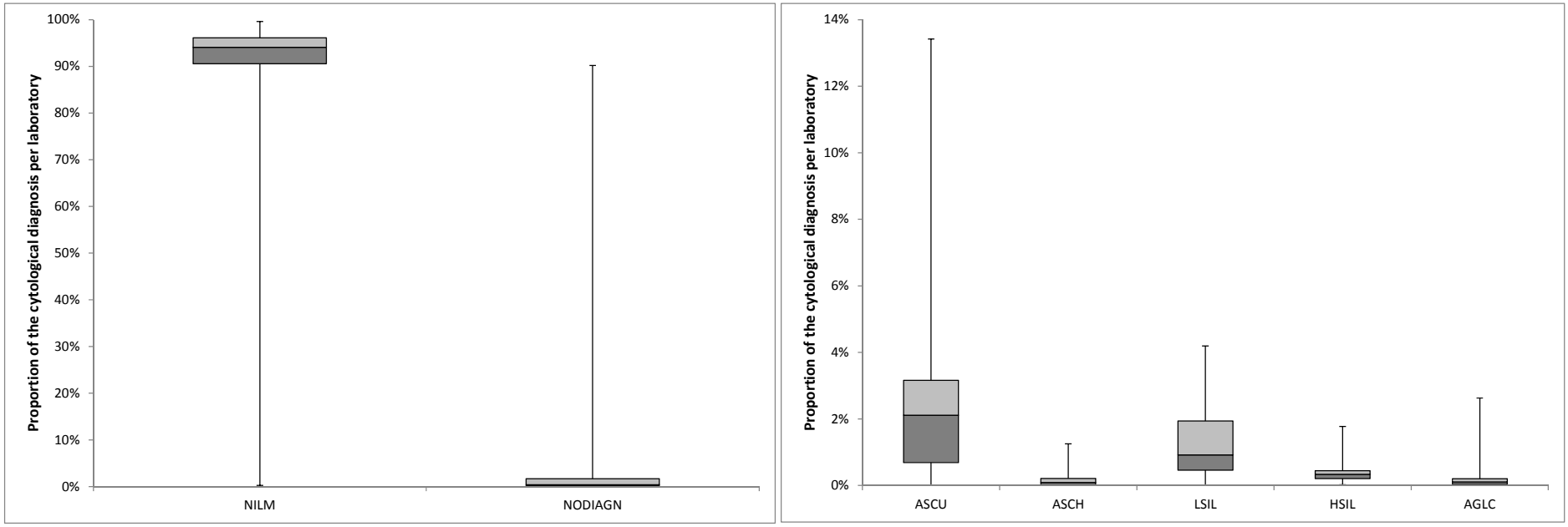


Figure 3 – Box plot: frequency of HPV tests after ASCU/ATYP in the CHP (first readings only, as percentages, year 2011) per laboratory

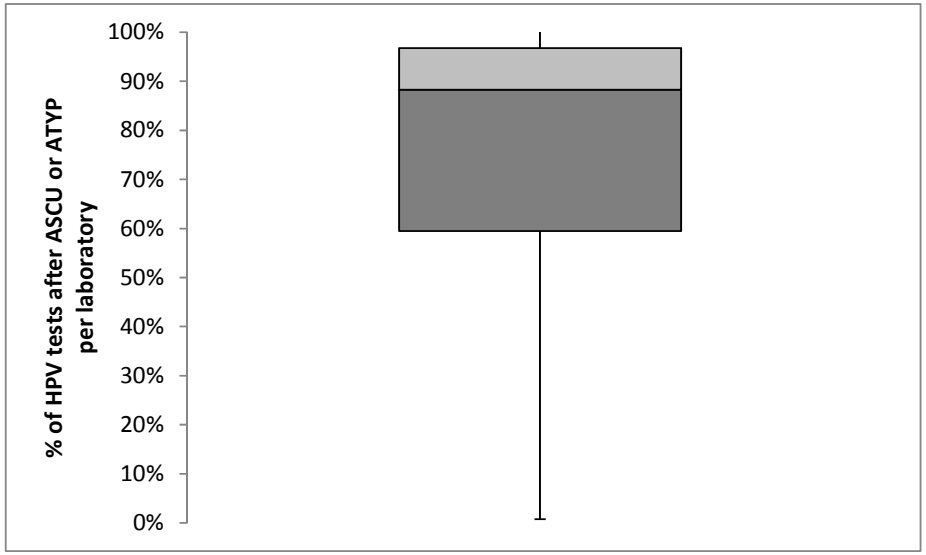
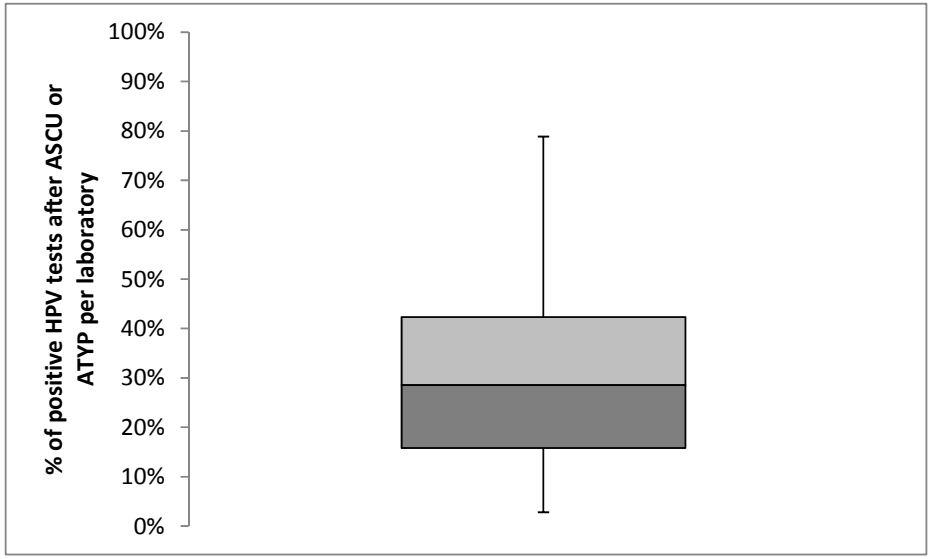


Figure 4 – Box plot: frequency of positive HPV tests after ASCU/ATYP in the treated CHP (first readings only, as percentages, year 2011) per laboratory



2.3.4. Cyto-virological relation

Table 6 shows the frequency of positive HPV test. 34% of ASCUS samples, where a HPV test is done and the result is known, are positive. This is lower than in the data reported by Riatol (60%). Other frequencies are comparable to the data of Riatol reported in chapter 6.

Table 6 – Frequency and % of positive (reimbursed) HPV tests after cytological diagnosis in the treated CHP, first reading (as percentages, year 2011)

Diagnosis		HPV+	HPV-	HPVi	HPV result unknown	No HPV	Total
NILM	N	6082	65 356	5	78	355 546	427 067
	%	1.42%	15.3%	0%	0.02%	83.25%	100%
ASCU	N	2528	4887	64	511	2511	10 501
	%	24.07%	46.54%	0.61%	4.87%	23.91%	100%
ATYP	N	2054	1137	2	313	6359	9865
	%	20.82%	11.53%	0.02%	3.17%	64.46%	100%
ASCH	N	288	237	9	23	214	771
	%	37.35%	30.74%	1.17%	2.98%	27.76%	100%
LSIL	N	2376	355	2	29	4946	7708
	%	30.83%	4.61%	0.03%	0.38%	64.17%	100%
HSIL	N	472	36	0	14	1.32	1842
	%	25.62%	1.95%	0.00%	0.76%	71.66%	100%
AGLC	N	80	410	4	23	888	1405
	%	5.69%	29.18%	0.28%	1.64%	63.2%	100%
SQGL	N	71	106	0	98	46	321
	%	22.12%	33.02%	0,00%	30.53%	14.33%	100%
IN SITU	N	0	0	0	0	4	4
	%	0.00%	0.00%	0.00%	0.00%	100%	100%
INVASIVE	N	6	2	0	3	149	160
	%	3.75%	1.25%	0.00%	1.88%	93.13%	100%
NODIAGN	N	35	138	2	6	24 682	24 863
	%	0.14%	0.56%	0.01%	0.02%	99.27%	100%
TOTAL	N	13 992	72 664	88	1098	396 665	484 507
	%	2.89%	15.00%	0.02%	0.23%	81.87%	100%

2.3.5. Cytohistological relation

Table 7 – Relation between the cytological diagnosis (after first readings only) and the first subsequent histological diagnosis within a time delay between 0 day and 3 months

Cytological diagnosis	Histological diagnosis													
	ABST/ NODIAGN		ATYP		Glandular lesion		CIN1+		Total		CIN2+		CIN3+	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
NILM	3358	91%	37	1%	1	0%	314	8%	3710	100%	131	4%	76	2%
NODIAGN	381	61%	33	5%	0	0%	209	34%	623	100%	125	20%	66	11%
ASCU/ATYP	1221	46%	78	3%	0	0%	1376	51%	2675	100%	507	19%	239	9%
ASCH	131	36%	12	3%	0	0%	222	61%	365	100%	154	42%	85	23%
LSIL	777	33%	30	1%	0	0%	1544	66%	2351	100%	520	22%	151	6%
HSIL	370	18%	21	1%	5	0%	1641	81%	2037	100%	137	7%	839	41%
AGLC	106	65%	6	4%	1	1%	49	30%	162	100%	30	19%	23	14%
SQGL	33	36%	1	1%	0	0%	58	63%	92	100%	36	39%	23	25%
IN SITU/INVASIVE	7	9%	0	0%	0	0%	75	91%	82	100%	74	90%	72	88%
Total	**6384**	53%	**218**	2%	**7**	0%	**5488**	45%	**12 097**	100%	**2947**	24%	**1574**	13%

Note that results are difficult to interpret in the Belgian context, as part of the histological confirmations are done because of a positive HPV test and part are done without or despite a negative HPV test.

Table 8 – Correlation between the cytological diagnosis (after first readings only), the result of the HPV test performed on the cytological sample and the first subsequent histological diagnosis within a time period of 3 months, including biopsies taken on the same day

CYTOLOGY		HISTOLOGY						
		NODIAGN	ABST	ATYP	CIN1	CIN2	CIN3+	Total
NODIAGN	HPV-/HPVi	12	38	7	16	2	2	77
	HPV+	23	48	0	41	34	14	160
NILM	HPV-/HPVi	274	308	4	34	5	6	631
	HPV+	40	119	0	42	14	12	227
ASCU	HPV-/HPVi	25	86	12	65	2	5	195
	HPV+	38	257	1	339	100	58	793
ATYP	HPV-/HPVi	27	37	1	12	1	0	78
	HPV+	65	301	0	198	84	81	729
LSIL	HPV-/HPVi	9	17	1	25	1	1	54
	HPV+	31	304	2	375	168	71	951
ASCH	HPV-/HPVi	8	14	5	16	7	2	52
	HPV+	7	50	0	26	37	51	171
HSIL	HPV-/HPVi	1	9	0	6	9	4	29
	HPV+	16	97	0	72	140	233	558
AGLC	HPV-/HPVi	3	28	3	4	1	3	42
	HPV+	8	17	1	9	5	9	49
Total		**587**	**1730**	**37**	**1280**	**610**	**552**	**4796**

2.4. Cost implications

2.4.1. Introduction

In order to assess the impact of introducing HPV screening in a Belgian context, we constructed a time dependent state transition cohort model with annual cycles. We compared two cohorts:

- A cohort of 100 000 women undergoing screening every 3 years with cytology as entry test ('cytology screening' strategy).
- A cohort of 100 000 women undergoing screening every 5 years with HPV as entry test ('HPV screening' strategy).

Women entered the model at age 30 years and were followed for 74 years, i.e. up to age 104 years where all women were assumed to have died. Future costs and benefits were discounted back to their present value. All costs are expressed in Euro from the year 2014. A discount rate of 3% was applied to costs and 1.5% was applied to benefits, as recommended by the Belgian guidelines on economic evaluations.[30]

We used data from the literature (e.g. for the effect of HPV screening as reported in RCT's) and Belgian sources (including data from the IMA-AIM and the BCR) to estimate the epidemiological parameters. Costs were valued under the perspective of the health care payer, including direct medical costs paid out of the health care budget (be it the federal government or the federated entities) and the patients' out-of-pocket expenses for health care. Costs were estimated from a recent Belgian study[31] and from the Belgian reimbursement scheme (the "nomenclature"), which contains the unit costs of all health care services reimbursed by the Belgian health care insurance including the patient share. The cost of an HPV test used in primary screening is currently unknown and was assumed to be €35.

Uncertainty around the model parameters was explored by running the model under a number of different scenarios (univariate and multivariate). In the univariate scenario analyses, the base case model was run by considering higher and/or lower values for a large range of uncertain clinical, epidemiological and screening parameters, separately. The cost of the HPV test used as primary screening, for which an assumption had to be made, was also varied in univariate scenario analyses. A multivariate scenario analysis, against HPV screening, was also performed by simultaneously

varying several parameters to their worst estimate (see below). Table 9 lists the scenario analyses performed on the base case model. A probabilistic sensitivity analysis was not performed because the data collected did not allow to inform a meaningful probability distribution for most of the parameters in the model. Details of the models and inputs are given in Chapter 8 of the main report.

Table 9 – Parameters varied in the scenario analyses

Parameter	Base case	Low scenario	High scenario
Values cytology screening			
Proportion ASCUS +	0.04	0.02	0.06
Proportion ASCUS + after re-reading	0.60	0.40	0.80
HPV+ among tested for triage	0.38	0.20	0.60
Proportion higher grade than ASCUS	0.03	0.02	0.06
Proportion CIN1 per screening round	0.004982	0.002	0.006
Proportion CIN2 per screening round	0.002788	0.002	0.006
Proportion CIN3 per screening round	0.002748	0.002	0.006
Proportion of women undergoing colposcopy where a biopsy is taken	0.50	0.20	0.80
Values HPV screening			
Proportion cytology triage + after HPV +	0.53	0.40	0.60
Proportion of women undergoing colposcopy where a biopsy is taken	0.50	0.20	0.80
Proportion CIN1 per screening round	0.008303	0.0058	0.0125
Proportion CIN2 per screening round	0.006040	0.0046	0.0084
Proportion CIN3 per screening round	0.004580	0.0039	0.0055
Effect HPV op cervical cancer incidence	0.45	0.30	0.80
Proportion hr-HPV persisting after one year	0.50	0.30	0.70
Cost of HPV test used in primary screening	€35	€20	€58.29
Common to two cohorts			
Effectiveness current screening (relative risk screened vs. unscreened)	0.50	0.40	0.60
Coverage rate of cervical cancer screening	0.60	0.40	0.80

2.4.2. Results

Table 10 shows the results of the base case analysis. If women undergo screening every 3 years with cytology as entry test ('cytology screening' strategy), the model predicts that 462 cervical cancer cases, resulting in 178 deaths, would occur over the lifetime of a cohort of 100 000 women with the cost of screening and treatment totalling €83 million.

If cytological primary screening is replaced by HPV primary screening, 240 cervical cancer cases and 95 deaths (or 2878 life years) could be prevented. HPV screening would further result in net savings (- €14 million), mainly due to the extension of the screening interval from 3 to 5 years. The base case analysis shows thus that HPV screening dominates cytology screening as it costs less and avoids more cervical cancer cases/deaths than cytology screening.

Table 10 – Results from the base case analysis (per cohort of 100 000 women)

	Cytology screening	HPV screening	Incremental outcomes
Cervical cancer cases	462	222	-240
Cervical cancer deaths	178	82	-95
Life years	5 337 361	5 340 240	2878
Life years (discounted)	3 658 751	3 660 369	1618
Total costs	€83 066 833	€68 179 074	- €14 887 760
Total costs (discounted)	€51 786 706	€46 004 382	- €5 782 324

Incremental outcomes are values for HPV screening minus values for cytologic screening. For discounted values, a discount rate of 3% was applied to costs and 1.5% was applied to benefits, as recommended by the Belgian guidelines on economic evaluations.

Switching to HPV screening remained both less costly and more clinically effective (i.e. HPV screening is dominant) under all univariate scenario analyses explored except one.

Results were most sensitive to the likely effect of the HPV test on the incidence of cervical cancer and to the cost of HPV testing. Increasing the effect of HPV on the incidence cervical cancer to 0.80 (instead of 0.45) resulted in a 64% decrease in the number of LY saved (from 2878 to 1047

LY gained), but HPV screening remained dominant. Even assuming that HPV has no additional beneficial effect over cytology (rate ratio of 1), the HPV strategy remained a dominant option. The only scenario in which HPV screening was no longer dominant is the scenario where HPV costs were assumed to be high at €58.29 (instead of €35), i.e. the current price of the HPV test as a follow-up test. However, the cost per LY gained of this scenario remained low at €4319.

Varying the baseline incidence of cervical cancer, by modifying the assumptions on the coverage rate and the effectiveness of cytology screening, had an important effect on the number of life years saved but only a modest effect on cost, such that HPV screening remained dominant.

In a multivariate scenario analysis penalizing HPV screening, in which it was assumed that 1) HPV screening had no additional beneficial effect on invasive cervical cancer, 2) the incidence of CIN 1, CIN2 and CIN3 are increased by 50%, 80% and 20%, respectively, 3) the number of false positives with HPV screening is increased by with 47% and 4) the number of false positives with cytology screening is reduced by 50% (i.e. cytology screening is much more specific), HPV screening still leads to net savings (of about €114 832 per cohort) with an equivalent number of life years saved compared to cytology screening.

2.4.3. Discussion and conclusion

The model suggests that net savings could be achieved in Belgium by switching from cytological to HPV screening, and that this would be associated with an increase in the number of cervical cancers cases and deaths avoided and life-years saved. There remains however considerable structural and parameter (mainly non-random) uncertainties around this model. Part of these uncertainties stem for the need to extrapolate RCTs far beyond their follow up time and uncertainties on the Belgian situation. The sensitivity analysis showed however that the conclusions hold under a broad range of plausible and even pessimistic assumptions.

3. KEY POINTS AND RECOMMENDATIONS

3.1. Key points

- HPV testing is more sensitive for precancerous lesions CIN2 and CIN3 than cytology. The downside is that the transversal specificity is lower.
- The protective effect of HPV screening compared to cytology on the incidence of invasive cervical cancer is directly demonstrated in randomized trials.
- No protective effect is demonstrated under 30 years.
- The risk of CIN3+ or invasive cervical cancer after a negative hrHPV DNA test is significantly lower than after a negative Pap smear. This means that screening intervals can be extended safely up to five to ten years.
- A two-step triage scenario with twice cytology at cutoff ASC-US+ offers a good balance of efficiency (4 to 9 referrals to detect one CIN3+, ~40% of referral) and safety (risk of CIN3+ in triage-negative women of 0.5% to 0.9%).
- For the interpretation of cervical cytology specimen, there is no quality control programme yet.
- In Belgium, an ISO15189 accreditation (including participation in external quality assessments) for high-risk HPV detection in cervicovaginal samples using a molecular method - but not for cytopathology - is mandatory for reimbursement.
- The use of colposcopies in Belgium, with high numbers performed without previous cytology result is not in line with the internationally agreed recommendations, where colposcopies should be used to examine women with abnormal cytology findings.
- Proportions of abnormal cytology results varies widely between laboratories.
- It is unlikely that the introduction of HPV screening would lead to a large increase in confirmation tests in the Belgian context.
- HPV screening every 5 year is a dominant option, compared to current practice of cytology screening every 3 years.

RECOMMENDATIONS[a]

To the Interministerial Conference on Public Health, the concerned "intercabinet working groups" and all authorities with screening competence:

- **HPV testing should replace cytology as the primary screening method as it affords better protection against cervical cancer than cytology from the age of 30 years onwards.**
- **Before the age of 30 years women should be screened with cytology followed by HPV triage as is currently recommended in Belgium**
- **Current policy of screening from 25 until 64 years should be maintained**
- **Only assays that are clinically validated for use in cervical cancer screening should be used.**
- **Screening interval should be extended to 5 years in case of HPV screening.**
- **To prevent unnecessary colposcopy referrals, hrHPV-positive women should not be offered colposcopy immediately. Triage should be done using cytology for this purpose. If cytological abnormalities (ASCUS+) are found, immediate referral should follow for diagnosis and, where appropriate, treatment. If no abnormalities are observed in triage, the subject should be offered follow-up testing (cytology) at six months.**
- **hrHPV positive women with double negative cytology should be offered hrHPV retesting after a year until they become negative.**
- **A quality control system should be set up for HPV testing as well as for colposcopy.**

To the competent authorities, the Commission for Pathological Anatomy, the Commission for Clinical Biology and the scientific societies of pathologists:

- **The impact of the screening program could be increased by harmonizing cytological analysis techniques. The current practice guideline on quality control procedures in cytological and histological analyses should be refined and minimum norms for quality control and evaluation should be set up by the Commission for Pathological Anatomy.**

To the NIHDI:

- **Next to the conventional cytology, also the liquid-based cytology should be reimbursed.**
- **An offical call addressed to manufacturers for price/quality offers could reduce costs of HPV tests and ensure high quality assays.**

[a] The KCE has sole responsibility for the recommendations.

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